Science to Practice

Top Ten Research Findings of 2017-2018

Sy Atezaz Saeed, MD, MS, FACPsych,
Professor and Chair
Department of Psychiatry and Behavioral Medicine
Brody School of Medicine - East Carolina University

NORTH CAROLINA Psychiatric Association

Annual Meeting & Scientific Session
September 27-30, 2018 | Renaissance Asheville Hotel

Science to Practice

Top Ten Research findings of 2017-2018

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 2017-2018 that have a direct bearing on the practice of clinical psychiatry.

*As identified by the methodology utilized for this presentation.

Disclosure

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

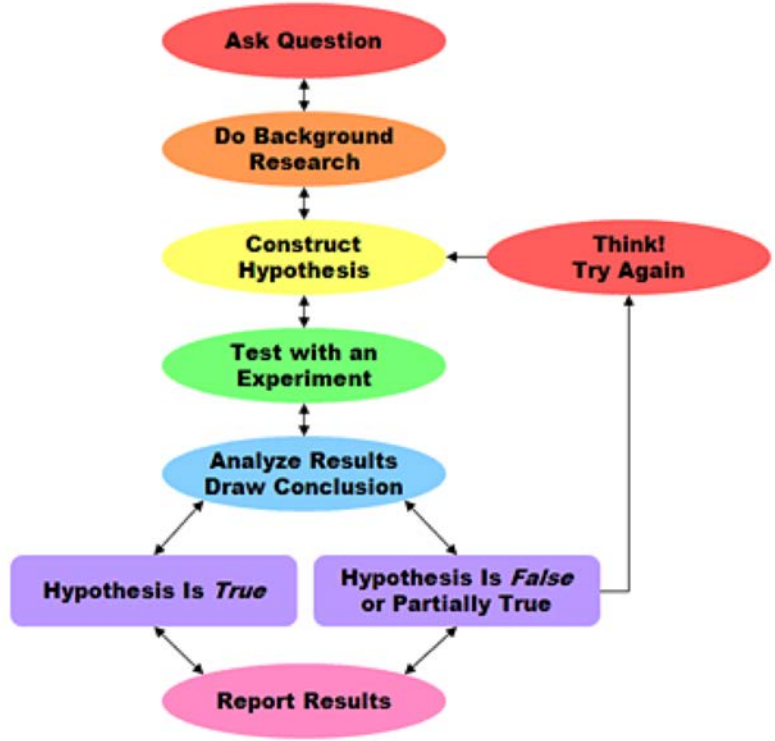
How much information in our midst is useful?
How much of it gets in the way?

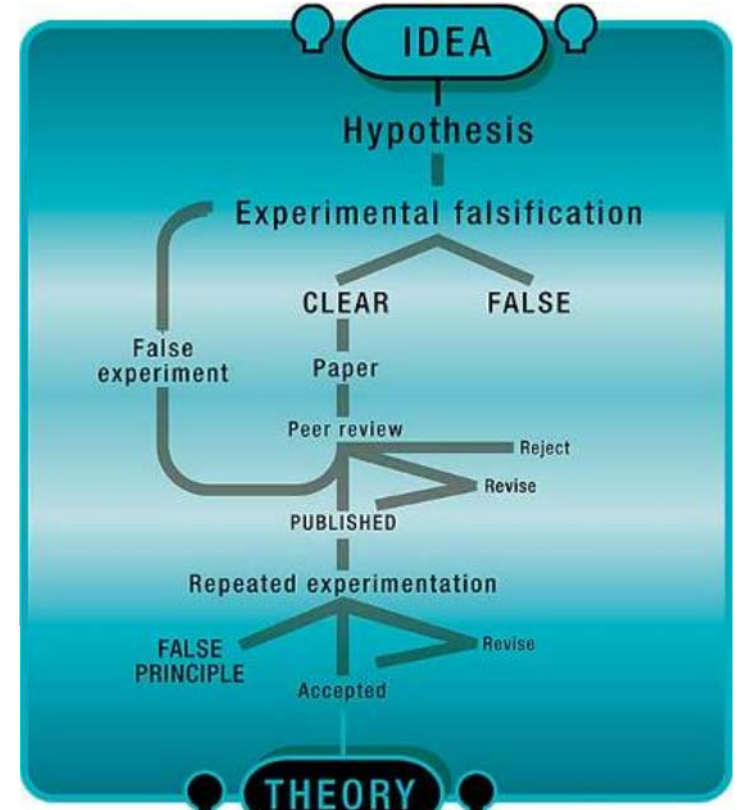
As we accrue more and more of it, information has emerged not only as a currency, but also as a pollutant.

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

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

YOU MUST ALWAYS OFFER EVIDENCE TO SUPPORT YOUR STATEMENTS.



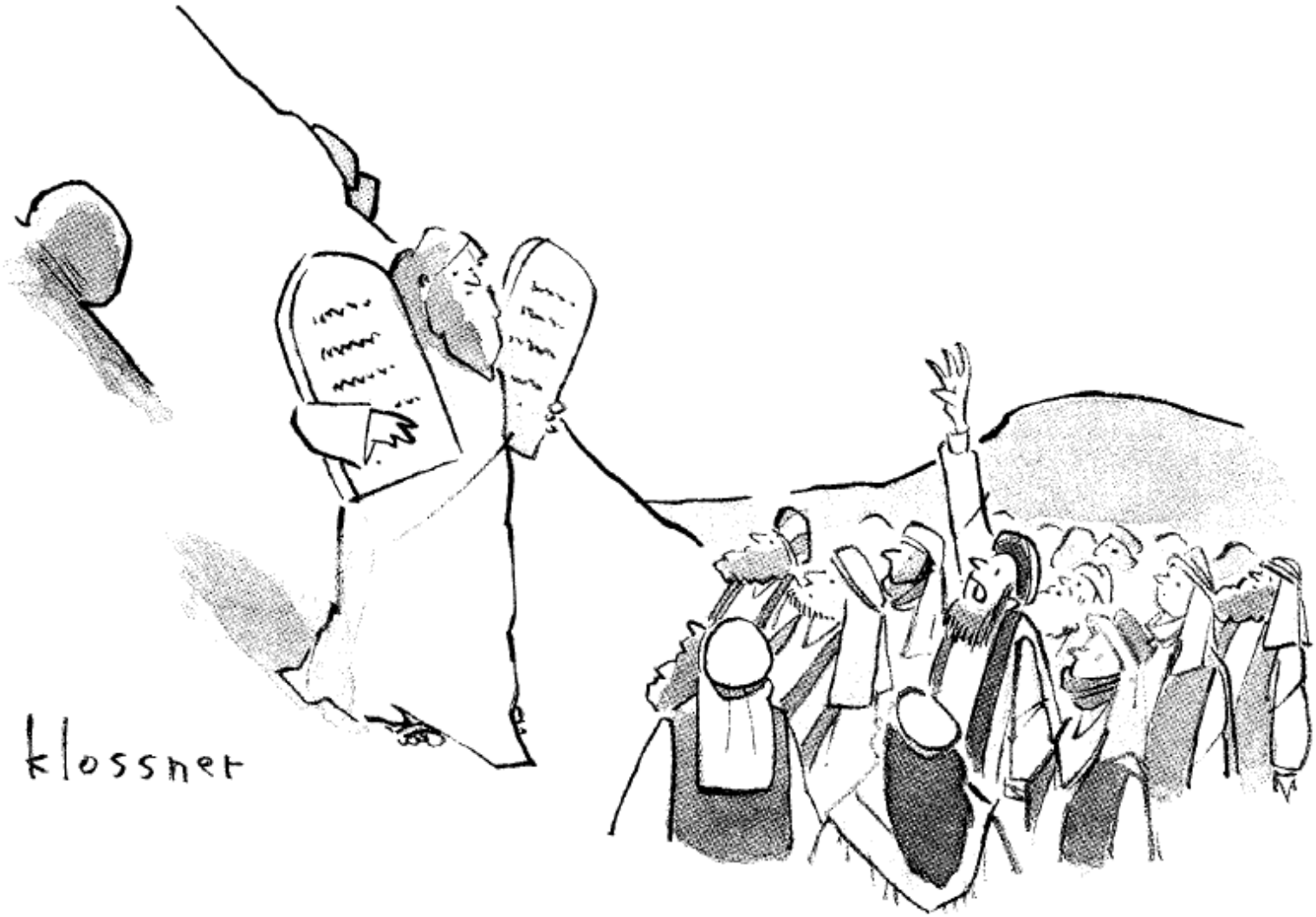


All scientific truths are provisional!

Methodology

- **Primary Literature Search**
- **Survey** [Question: *Amongst the papers published in the period July 1, 2017 to June 30, 2018, which ones in your opinion have [or likely to have or should have] impacted/changed the clinical practice of psychiatry?*].
  - AACDP
  - GAP
  - AACP
  - AAPA
  - NCPA
  - Other Colleagues
- **Secondary Literature**, e.g. Faculty of 1000 Factor, Cochrane, NEJM Journal Watch, etc.

THE NEW YORKER



"Are these the Top Ten Commandments?"

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

F1000 | FACULTY of 1000
POST-PUBLICATION PEER REVIEW

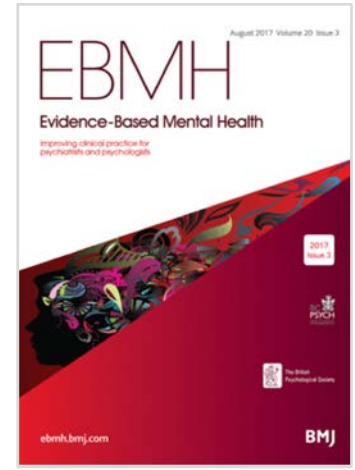
Cochrane Library

Cochrane Database of Systematic Reviews

CEBM | UNIVERSITY OF OXFORD

Centre for Evidence-Based Medicine

NEJM Journal Watch



ESSENTIAL EVIDENCE PLUS

BMJ Journals

Evidence-Based Mental Health

AHRQ
Agency for Healthcare Research and Quality

EvidenceAlerts | McMaster PLUS™ and *DynaMed Plus®*

Science to Practice

Top Ten Research Findings of 2017-2018

Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial

Dorothy K. Sit, M.D., James McGowan, B.A., Christopher Wiltrout, B.S., Rasim Somer Diler, M.D., John (Jesse) Dills, M.L.S., James Luther, M.A., Amy Yang, M.S., Jody D. Ciolino, Ph.D., Howard Seltman, M.D., Ph.D., Stephen R. Wisniewski, Ph.D., Michael Terman, Ph.D., Katherine L. Wisner, M.D., M.S.

Objective: Patients with bipolar disorder have recurrent major depression, residual mood symptoms, and limited treatment options. Building on promising pilot data, the authors conducted a 6-week randomized double-blind placebo-controlled trial to investigate the efficacy of adjunctive bright light therapy at midday for bipolar depression. The aims were to determine remission rate, depression symptom level, and rate of mood polarity switch, as well as to explore sleep quality.

Method: The study enrolled depressed adults with bipolar I or II disorder who were receiving stable dosages of antimanic medication (excluding patients with hypomania or mania, mixed symptoms, or rapid cycling). Patients were randomly assigned to treatment with either 7,000-lux bright white light or 50-lux dim red placebo light (N=23 for each group). Symptoms were assessed weekly with the Structured Interview Guide for the Hamilton Depression Scale With Atypical Depression Supplement (SIGH-ADS), the Mania Rating Scale, and the Pittsburgh Sleep Quality Index. Remission was defined as having a SIGH-ADS score of 8 or less.

Am J Psychiatry 175:2, February 2018

- Because medications for bipolar depression are often ineffective and frequently produce adverse effects, nonpharmacological approaches hold great interest.
- Morning light in patients with bipolar depression has had mixed results and induces occasional hypomania.
- Light therapy in this study was daily between noon and 2:30 p.m., gradually increasing to a target of 60 minutes daily (median achieved length, 46 minutes).

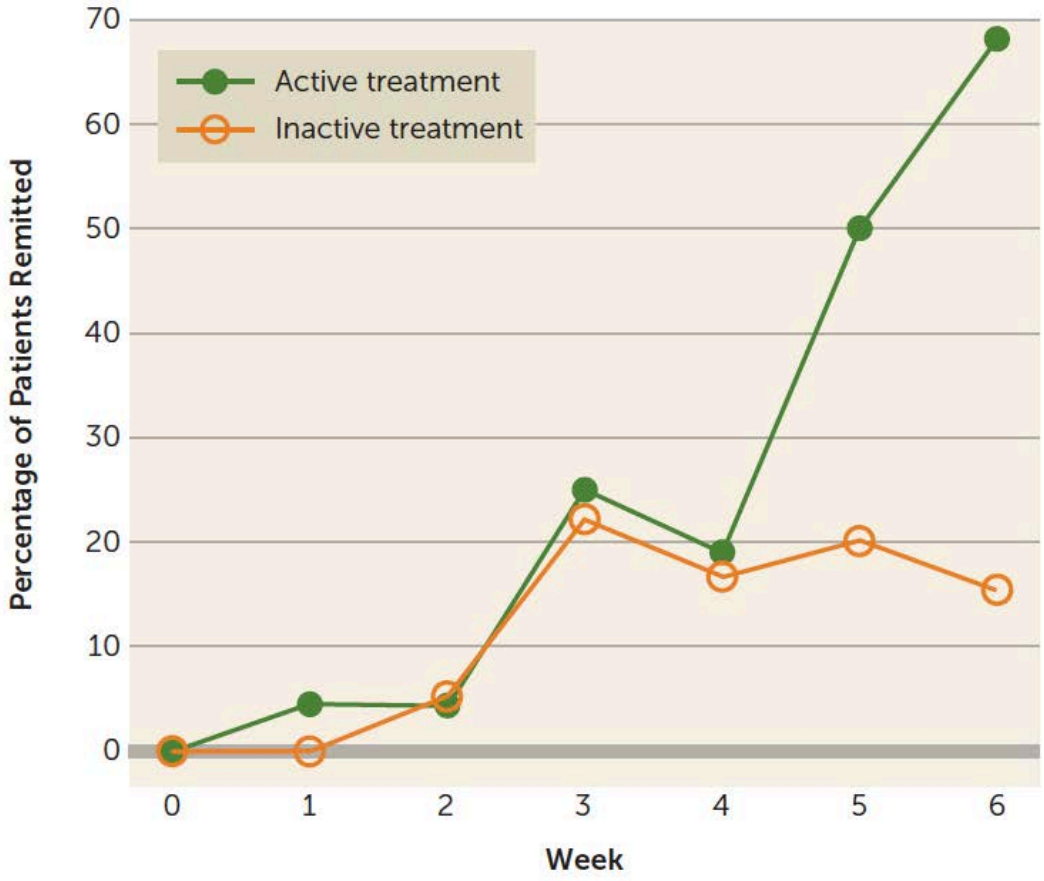
Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial

Dorothy K. Sit, M.D., James McGowan, B.A., Christopher Wiltrout, B.S., Rasim Somer Diler, M.D., John (Jesse) Dills, M.L.S., James Luther, M.A., Amy Yang, M.S., Jody D. Ciolino, Ph.D., Howard Seltman, M.D., Ph.D., Stephen R. Wisniewski, Ph.D., Michael Terman, Ph.D., Katherine L. Wisner, M.D., M.S.

Results: At baseline, both groups had moderate depression and no hypomanic or manic symptoms. Compared with the placebo light group, the group treated with bright white light experienced a significantly higher remission rate (68.2% compared with 22.2%) at weeks 4–6 and significantly lower depression scores (9.2 compared with14.9]) at the endpoint visit. No mood polarity switches were observed. Sleep quality improved in both groups and did not differ significantly between them.

Am J Psychiatry 175:2, February 2018

FIGURE 1. Remission Rates Across Study Weeks for Patients With Bipolar Depression Treated with Active (Bright White Light) or Inactive (Dim Red Light) Light Therapy[a]



[a] Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (odds ratio=7.50, 95% CI=1.80, 31.28, p=0.003; adjusted odds ratio=12.64, 95% CI=2.16, 74.08, p=0.004).

Bright light at midday for 6 weeks produced remission in 68% of participants, compared with 22% receiving dim red light, with no mood switches.

Am J Psychiatry 175:2, February 2018

Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial

Dorothy K. Sit, M.D., James McGowan, B.A., Christopher Wiltrout, B.S., Rasim Somer Diler, M.D., John (Jesse) Dills, M.L.S., James Luther, M.A., Amy Yang, M.S., Jody D. Ciolino, Ph.D., Howard Seltman, M.D., Ph.D., Stephen R. Wisniewski, Ph.D., Michael Terman, Ph.D., Katherine L. Wisner, M.D., M.S.

Conclusions: The data from this study provide robust evidence that supports the efficacy of midday bright light therapy for bipolar depression.

Am J Psychiatry 175:2, February 2018

While these findings require replication and extension with larger samples, they suggest that add-on bright-light therapy administered at midday can help achieve remission in carefully selected patients with bipolar depression who are insufficiently improved with medications.

JAMA | Original Investigation

Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment

The VAST-D Randomized Clinical Trial

Somaia Mohamed, MD, PhD; Gary R. Johnson, MS; Peijun Chen, MD, PhD, MPH; Paul B. Hicks, MD, PhD; Lori L. Davis, MD; Jean Yoon, PhD; Theresa C. Gleason, PhD; Julia E. Vertrees, PharmD, BCPP; Kimberly Weingart, PhD; Ilanit Tal, PhD; Alexandra Scrymgeour, PharmD; David D. Lawrence, MS; Beata Planeta, MS; Michael E. Thase, MD; Grant D. Huang, MPH, PhD; Sidney Zisook, MD; and the VAST-D Investigators

IMPORTANCE Less than one-third of patients with major depressive disorder (MDD) achieve remission with their first antidepressant.

OBJECTIVE To determine the relative effectiveness and safety of 3 common alternate treatments for MDD.

DESIGN, SETTING, AND PARTICIPANTS From December 2012 to May 2015, 1522 patients at 35 US Veterans Health Administration medical centers who were diagnosed with nonpsychotic MDD, unresponsive to at least 1 antidepressant course meeting minimal standards for treatment dose and duration, participated in the study. Patients were randomly assigned (1:1:1) to 1 of 3 treatments and evaluated for up to 36 weeks.

Key Points

Question Is there a difference among pharmacotherapeutic approaches for treating patients with depression unresponsive to an antidepressant course?

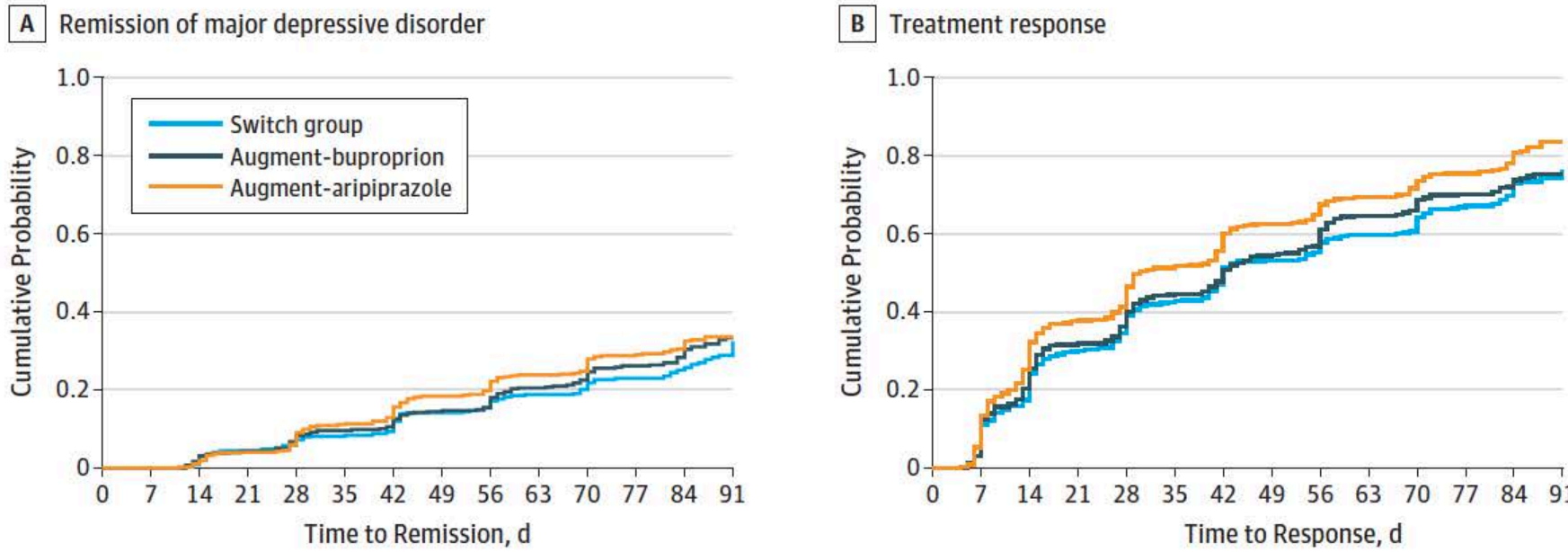
Findings In a 12-week follow-up of a randomized clinical trial of 1522 patients with major depressive disorder (85% men) unresponsive to previous antidepressant treatment, 29% achieved remission after augmenting their antidepressant with the antipsychotic aripiprazole vs 22% who switched to the antidepressant bupropion. Other remission comparisons were not significant.

Meaning Augmentation with aripiprazole resulted in a statistically significant, but only modestly increased, likelihood of remission during 12 weeks of treatment compared with switching to bupropion alone.

MAIN OUTCOMES AND MEASURES The primary outcome was remission during the acute treatment phase (16-item Quick Inventory of Depressive Symptomatology-Clinician Rated [QIDS-C_{16}] score ≤5 at 2 consecutive visits). Secondary outcomes included response (≥50% reduction in QIDS-C_{16} score or improvement on the Clinical Global Impression Improvement scale), relapse, and adverse effects.

RESULTS Among 1522 randomized patients (mean age, 54.4 years; men, 1296 [85.2%]), 1137 (74.7%) completed the acute treatment phase. Remission rates at 12 weeks were 22.3% (n = 114) for the switch group, 26.9% (n = 136)for the augment-bupropion group, and 28.9% (n = 146) for the augment-aripiprazole group. The augment-aripiprazole group exceeded the switch group in remission (relative risk [RR], 1.30 [95% CI, 1.05-1.60]; *P* = .02), but other remission comparisons were not significant. Response was greater for the augment-aripiprazole group (74.3%) than for either the switch group (62.4%; RR, 1.19 [95% CI, 1.09-1.29]) or the augment-bupropion group (65.6%; RR, 1.13 [95% CI, 1.04-1.23]). No significant treatment differences were observed for relapse. Anxiety was more frequent in the 2 bupropion groups (24.3% in the switch group [n = 124] vs 16.6% in the augment-aripiprazole group [n = 84]; and 22.5% in augment-bupropion group [n = 114]). Adverse effects more frequent in the augment-aripiprazole group included somnolence, akathisia, and weight gain.

Figure 2. Cumulative Probability of Remission and Response Among Patients With Antidepressant-Resistant Major Depressive Disorder, Acute Treatment Phase



No. at risk							
Switch group	511	477	428	379	331	292	221
Augment-buproprion	506	475	431	387	352	305	247
Augment-aripiprazole	505	467	427	383	341	307	245

511	395	294	218	173	141	77
506	386	292	223	174	124	79
505	357	272	198	149	116	72

CONCLUSIONS AND RELEVANCE Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. Given the small effect size and adverse effects associated with aripiprazole, further analysis including cost-effectiveness is needed to understand the net utility of this approach.

Lessons Learned From the VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) Study

Maurizio Fava, MD

In summary, the findings of the VAST-D study reported by Mohamed and colleagues in this issue of JAMA showed a modest yet significant advantage for the aripiprazole augmentation compared with switching to bupropion (in terms of both higher remission and response rates) and bupropion augmentation (in terms of higher response rates only) in a population of patients with MDD and inadequate response to antidepressant therapy. The VAST-D study was uniquely enriched by men and by those with PTSD comorbidity, and offers an important perspective on the role of treatment using augmentation with atypical antipsychotic agents in this population commonly seen in VA clinics.

PLOS ONE | August 21, 2017

Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: A meta-analysis

Ruey Chen[1], Pi-Tuan Chan[2], Hsin Chu[3,4,5], Yu-Cih Lin[1,6], Pi-Chen Chang[1], Chien-Yu Chen[6,7,8], Kuei-Ru Chou[1,9,10]*

Background

This is the first meta-analysis to compare the treatment effects and safety of administering donepezil alone versus a combination of memantine and donepezil to treat patients with moderate to severe Alzheimer Disease, particularly regarding cognitive functions, behavioral and psychological symptoms in dementia (BPSD), and global functions.

Methods

PubMed, Medline, Embase, PsycINFO, and Cochrane databases were used to search for English and non-English articles for inclusion in the meta-analysis to evaluate the effect size and incidence of adverse drug reactions of different treatments.

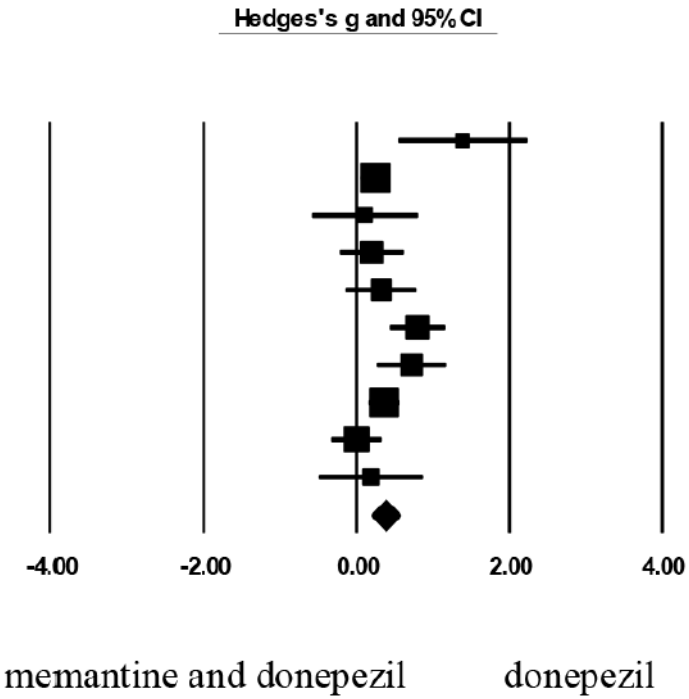
Results

Compared with patients who received donepezil alone, those who received donepezil in combination with memantine exhibited limited improvements in cognitive functions ($g = 0.378$, $p < .001$), BPSD ($g = -0.878$, $p < .001$) and global functions ($g = -0.585$, $p = .004$). Gradual titration of memantine plus a fixed dose and gradual titration of donepezil as well as a fixed dose and gradual titration of memantine resulted in limited improvements in cognitive functions($g = 0.371$, $p = .005$), BPSD($g = -0.913$, $p = .001$), and global functions($g = -0.371$, $p = .001$).

Conclusion

Both in the 24th week and at the final evaluation point, the combination of donepezil and memantine led to greater improvement in cognitive functions, BPSD, and global functions than did donepezil alone in patients with moderate to severe Alzheimer Disease.

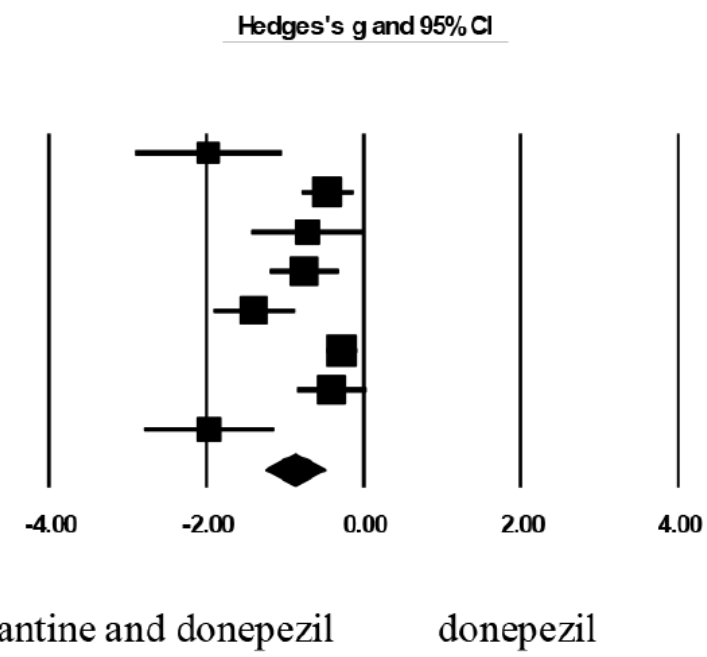
Study name	Comparison	Standard error	Hedges's g	Variance	Lower limit	Upper limit	Z-Value	p-Value
Araki 2014	MMSE	0.434	1.392	0.189	0.541	2.244	3.206	0.001
Doody 2012	MMSE	0.098	0.252	0.010	0.061	0.443	2.583	0.010
Kano 2013	MMSE	0.356	0.110	0.126	-0.587	0.807	0.309	0.757
M 2014	MMSE	0.214	0.200	0.046	-0.220	0.620	0.933	0.351
Peng 2015	MMSE	0.236	0.325	0.056	-0.138	0.788	1.375	0.169
Shao 2015	MMSE	0.186	0.804	0.034	0.440	1.168	4.332	0.000
Wang 2015	MMSE	0.232	0.723	0.054	0.269	1.177	3.123	0.002
Tariot 2004	SIB	0.101	0.356	0.010	0.157	0.554	3.509	0.000
Howard 2012	SMMSE	0.165	0.000	0.027	-0.323	0.323	0.000	1.000
Zheng 2011	MMSE	0.345	0.189	0.119	-0.488	0.866	0.548	0.584
		0.094	0.378	0.009	0.193	0.562	4.016	0.000



Forest plots to compare the combination therapy with the monotherapy: Cognitive functions

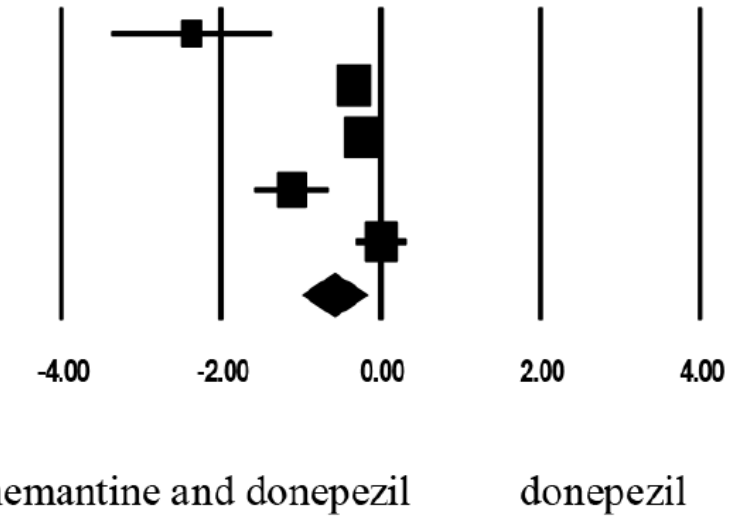
Behavioral and Psychological Symptoms in Dementia (BPSD)

Study name	Comparison	Statistics for each study						
		Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Araki 2014	NPI	-1.974	0.477	0.228	-2.909	-1.038	-4.135	0.000
Howard 2012	NPI	-0.459	0.167	0.028	-0.786	-0.132	-2.753	0.006
Kano 2013	CMAI	-0.716	0.367	0.135	-1.435	0.004	-1.950	0.051
M 2014	NPI	-0.756	0.221	0.049	-1.190	-0.322	-3.414	0.001
Peng 2015	NPI	-1.392	0.262	0.069	-1.906	-0.878	-5.307	0.000
Tariot 2004	NPI	-0.279	0.103	0.011	-0.480	-0.078	-2.715	0.007
Yang 2013	BEHAVE-AD	-0.408	0.224	0.050	-0.846	0.031	-1.821	0.069
Zheng 2011	NPI	-1.965	0.423	0.179	-2.795	-1.136	-4.643	0.000
		-0.878	0.193	0.037	-1.256	-0.500	-4.555	0.000



Forest plots to compare the combination therapy with the monotherapy: BPSD.

	Comparison	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Araki 2014	CGI	-2.367	0.512	0.262	-3.370	-1.364	-4.625	0.000
Doody 2012	CIBIC-Plus	-0.339	0.098	0.010	-0.532	-0.146	-3.448	0.001
Tariot 2004	CIBIC-Plus	-0.239	0.101	0.010	-0.436	-0.041	-2.369	0.018
Yang 2013	CGI	-1.115	0.238	0.057	-1.582	-0.648	-4.677	0.000
Howard 2012	GHQ-12	0.005	0.165	0.027	-0.318	0.328	0.030	0.976
		-0.585	0.202	0.041	-0.981	-0.188	-2.888	0.004



Forest plots to compare the combination therapy with the monotherapy: global functions.

The most crucial finding of the present study was that at the endpoint or in the 24th week of treatment for moderate to severe AD, the combination treatment group exhibited greater improvement in cognitive functions, BPSD, and global functions than did the control group. No significant difference was observed in adverse drug reactions, safety between the two groups.

Study heterogeneity was considerable, consistent with these medications' different mechanisms of action. Nevertheless, this meta-analysis suggests that combining donepezil and memantine results in greater improvements in cognition, behavior, and psychological symptoms for patients with moderate-to-severe Alzheimer disorder. Reassuringly, the findings also show that the combination does not increase adverse effects. Although overall improvement may still be modest, stakeholders might judge the potential benefits of pursuing combined treatment to be worth the expense.

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

Neeltje M Batelaan,[1,2] Renske C Bosman,[1] Anna Muntingh,[1,2] Willemijn D Scholten,[1,2] Klaas M Huijbregts,[1,2] Anton J L M van Balkom[1,2]

OBJECTIVES

To examine the risk of relapse and time to relapse after discontinuation of antidepressants in patients with anxiety disorder who responded to antidepressants, and to explore whether relapse risk is related to type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of treatment and follow-up, comorbidity, and allowance of psychotherapy.

DESIGN

Systematic review and meta-analyses of relapse prevention trials.

STUDY SELECTION

Eligible studies included patients with anxiety disorder who responded to antidepressants, randomised patients double blind to either continuing antidepressants or switching to placebo, and compared relapse rates or time to relapse.

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antidepressants are a first line treatment option for the acute treatment of anxiety disorders, but their benefits in optimising long term prognosis are less well known

International guidelines are therefore consensus based and advise continuing treatment for a variable time (six to 24 months) and subsequent tapering of the antidepressant

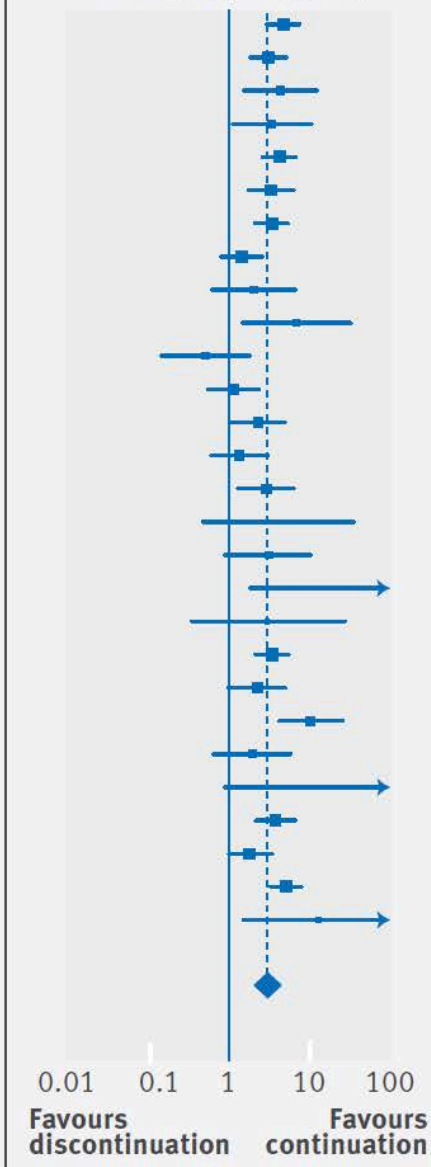
Previous studies have shown a high risk of relapse after discontinuation of antidepressants, but information on whether specific strategies influence relapse risk is scant and inconclusive

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

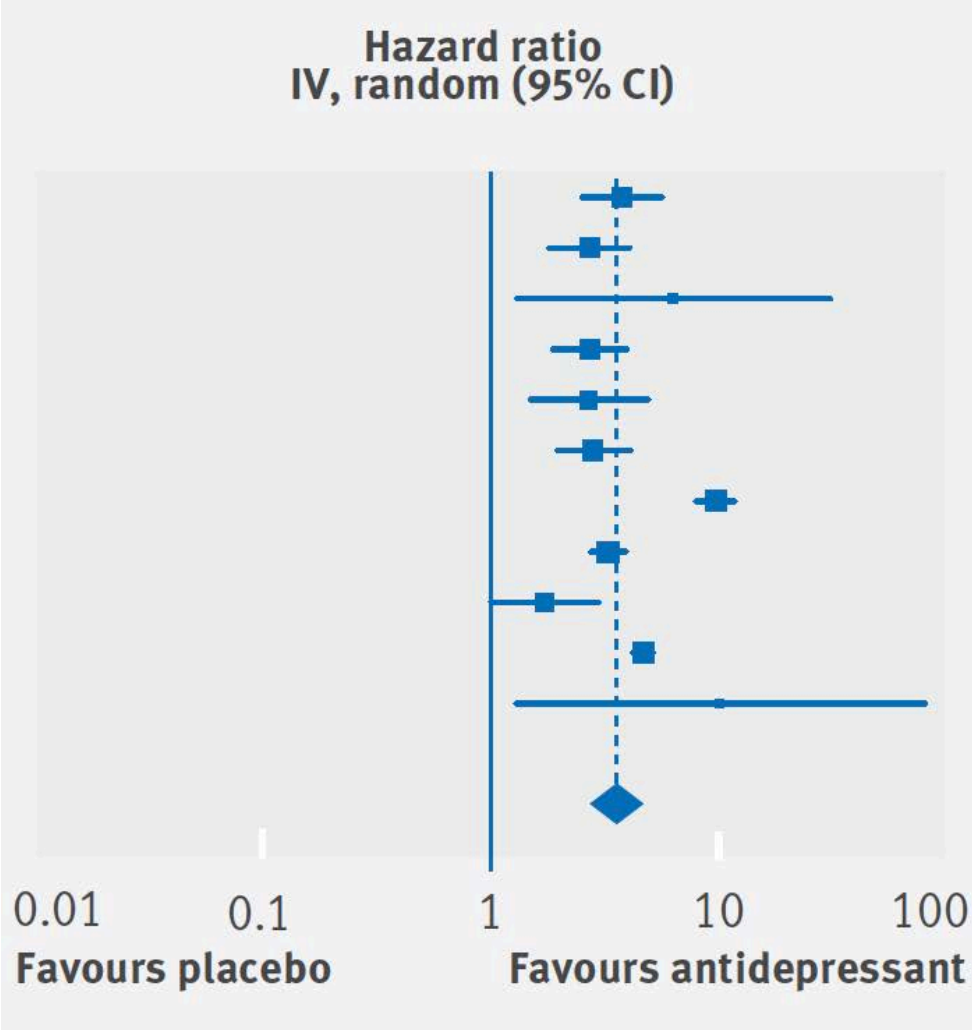
- A meta-analysis of 28 double-blind, placebo-controlled anti-depressant discontinuation studies in 5233 patients with any of five DSM-IV disorders (PD, GAD, SAD, OCD, and PTSD).
- The risk for relapse was three times greater in patients switched to placebo than in those who were continued on their antidepressants.
- Summary prevalence of relapse through the studies' follow-ups (range, 8-52 weeks) was 36% versus 16%.
- Diagnosis, duration of treatment, rapidity of discontinuation, or receipt of concomitant psychotherapy did not affect relapse rates.

Forest plot representing odds ratios of relapse per study

Study	Placebo Events	Placebo Total	Antidepressent Events	Antidepressent Total	Weight (%)	Odds ratio (95% CI)
Allgulander et al 2006	98	188	34	187	6.0	4.90 (3.07 to 7.83)
Baldwin et al 2012	66	227	26	224	5.7	3.12 (1.89 to 5.14)
Davidson et al 2001	21	46	6	38	2.8	4.48 (1.57 to 12.77)
Davidson et al 2005	15	32	6	30	2.6	3.53 (1.14 to 10.95)
Davidson et al 2008	84	213	28	216	5.9	4.37 (2.70 to 7.09)
Ferguson et al 2007	40	80	20	89	4.7	3.45 (1.78 to 6.70)
Fineberg et al 2007	81	157	38	163	5.9	3.51 (2.17 to 5.66)
Geller et al 2003	43	98	33	95	5.2	1.47 (0.82 to 2.63)
GSK-Study 127,1992—1994	14	24	8	20	2.2	2.10 (0.63 to 7.03)
GSK-Study 222,1993—1994	11	43	2	43	1.6	7.05 (1.46 to 34.07)
GSK-Study 470,1995—1996	5	28	8	27	2.2	0.52 (0.14 to 1.84)
GSK-Study 650,1999—2001	19	86	17	87	4.2	1.17 (0.56 to 2.44)
Hollander et al 2003	30	51	20	53	4.0	2.36 (1.07 to 5.18)
Kamijima et al 2005	16	121	12	119	3.9	1.36 (0.61 to 3.01)
Koran et al 2002	27	114	10	109	4.0	3.07 (1.41 to 6.71)
Koran et al 2005	5	8	2	7	0.9	4.17 (0.47 to 36.74)
Martenyi et al 2002	10	62	4	69	2.3	3.13 (0.93 to 10.54)
Mavissaklian et al 1999	10	27	1	29	0.9	16.47 (1.93 to 140.29)
Michelson et al 1999	4	50	1	38	0.9	3.22 (0.34 to 30.03)
Montgomery et al 2005	91	181	42	190	6.1	3.56 (2.27 to 5.59)
Rapaport et al 2001	21	89	11	92	3.9	2.27 (1.02 to 5.05)
Rickels et al 2010	29	54	8	82	3.4	10.73 (4.34 to 26.51)
Romano et al 2001	11	34	7	36	2.7	1.98 (0.66 to 5.92)
Stein et al 1996	5	8	1	8	0.7	11.67 (0.92 to 147.56)
Stein et al 2002	61	161	22	162	5.4	3.88 (2.24 to 6.73)
Stein et al 2012	35	114	22	113	5.0	1.83 (0.99 to 3.38)
Stocchi et al 2003	114	287	30	274	6.1	5.36 (3.43 to 8.38)
Walker et al 2000	9	25	1	25	0.9	13.50 (1.56 to 117.14)
Total (95% CI)		**2868**		**2625**	**100.0**	**3.11 (2.48 to 3.89)**
Total events:	975		420			



Forest plot representing hazard ratios of time to relapse per study



Weight (%)	Odds ratio (95% CI)
10.2	3.80 (2.54 to 5.69)
10.2	2.71 (1.80 to 4.08)
2.9	6.35 (1.32 to 30.52)
10.5	2.74 (1.89 to 3.98)
8.5	2.70 (1.51 to 4.83)
10.5	2.83 (1.95 to 4.11)
11.9	9.73 (8.05 to 11.76)
12.1	3.29 (2.80 to 3.87)
9.0	1.72 (1.01 to 2.93)
12.4	4.69 (4.28 to 5.15)
1.8	10.20 (1.29 to 80.36)
100.0	**3.63 (2.58 to 5.10)**

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

WHAT THIS STUDY ADDS

This meta-analysis of 28 relapse prevention trials in patients with remitted anxiety disorders found a clear benefit of continuing treatment up to one year for both relapse rate and time to relapse

Relapse risk was not significantly influenced by type of anxiety disorder, duration of previous treatment, duration of follow-up, mode of discontinuation, or concurrent psychotherapy

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

CONCLUSIONS

Up to one year of follow-up, discontinuation of antidepressant treatment results in higher relapse rates among responders compared with treatment continuation. The lack of evidence after a one year period should not be interpreted as explicit advice to discontinue antidepressants after one year. Given the chronicity of anxiety disorders, treatment should be directed by long term considerations, including relapse prevalence, side effects, and patients' preferences.

- This study clarifies the size of risk with discontinuation while highlighting that most patients who discontinue antidepressants do not relapse.
- Because of the few studies examined in this meta-analysis and the lack of direct comparisons, common clinician impressions are not confirmed, e.g.
  - that treatment discontinuation in obsessive-compulsive disorder is especially risky,
  - that gradual vs. rapid taper is safer, and
  - that longer treatment duration or concomitant psychotherapy may reduce relapse risk.

Predicting Suicide Attempts and Suicide Deaths Following Outpatient Visits Using Electronic Health Records

Gregory E. Simon, M.D., M.P.H., Eric Johnson, M.S., Jean M. Lawrence, Sc.D., Rebecca C. Rossom, M.D., M.S., Brian Ahmedani, Ph.D., Frances L. Lynch, Ph.D., Arne Beck, Ph.D., Beth Waitzfelder, Ph.D., Rebecca Ziebell, Robert B. Penfold, Ph.D., Susan M. Shortreed, Ph.D.

Objective: The authors sought to develop and validate models using electronic health records to predict suicide attempt and suicide death following an outpatient visit.

Method: Across seven health systems, 2,960,929 patients age 13 or older (mean age, 46 years; 62% female) made 10,275,853 specialty mental health visits and 9,685,206 primary care visits with mental health diagnoses between Jan. 1, 2009, and June 30, 2015. Health system records and state death certificate data identified suicide attempts (N=24,133) and suicide deaths (N=1,240) over 90 days following each visit. Potential predictors included 313 demographic and clinical characteristics extracted from records for up to 5 years before each visit: prior suicide attempts, mental health and substance use diagnoses, medical diagnoses, psychiatric medications dispensed, inpatient or emergency department care, and routinely administered depression questionnaires. Logistic regression models predicting suicide attempt and death were developed using penalized LASSO (least absolute shrinkage and selection operator) variable selection in a random sample of 65% of the visits and validated in the remaining 35%.

Published Online: 24 May 2018 https://doi.org/10.1176/appi.ajp.2018.17101167

Results: Mental health specialty visits with risk scores in the top 5% accounted for 43% of subsequent suicide attempts and 48% of suicide deaths. Of patients scoring in the top 5%, 5.4% attempted suicide and 0.26% died by suicide within 90 days. C-statistics (equivalent to area under the curve) for prediction of suicide attempt and suicide death were 0.851 (95% CI=0.848, 0.853) and 0.861 (95% CI=0.848, 0.875), respectively. Primary care visits with scores in the top 5% accounted for 48% of subsequent suicide attempts and 43% of suicide deaths. C-statistics for prediction of suicide attempt and suicide death were 0.853 (95% CI=0.849, 0.857) and 0.833 (95% CI=0.813, 0.853), respectively.

Conclusions: Prediction models incorporating both health record data and responses to self-report questionnaires substantially outperform existing suicide risk prediction tools.

Published Online: 24 May 2018 https://doi.org/10.1176/appi.ajp.2018.17101167

Clinical Characteristics Selected for Prediction of Suicide Attempt Within 90 Days of Visit in Seven Health Systems (2009–2015)

Listed in Order of Coefficients in Logistic Regression Models[a]

Suicide Attempt or Death, by Care Setting	
Suicide attempt following:	
Mental health specialty visit (of 94 predictors selected)	Primary care visit (of 102 predictors selected)
Depression diagnosis in past 5 years	Depression diagnosis in past 5 years
Drug abuse diagnosis in past 5 years	Suicide attempt diagnosis in past 5 years
PHQ-9 item 9 score=3 in past year	Drug abuse diagnosis in past 5 years
Alcohol use disorder diagnosis in past 5 years	Alcohol abuse diagnosis in past 5 years
Mental health inpatient stay in past year	PHQ-9 item 9 score=3 in past year
Benzodiazepine prescription in past 3 months	Suicide attempt diagnosis in past 3 months
Suicide attempt in past 3 months	Suicide attempt diagnosis in past year
Personality disorder diagnosis in past 5 years	Personality disorder diagnosis in past 5 years
Eating disorder diagnosis in past 5 years	Anxiety disorder diagnosis in past 5 years
Suicide attempt in past year	Suicide attempt diagnosis in past 5 years with schizophrenia diagnosis in past 5 years
Mental health emergency department visit in past 3 months	Benzodiazepine prescription in past 3 months
Self-inflicted cutting/piercing in past year	Eating disorder diagnosis in past 5 years
Suicide attempt in past 5 years	Mental health emergency department visit in past 3 months
Injury/poisoning diagnosis in past 3 months	Injury/poisoning diagnosis in past year
Antidepressant prescription in past 3 months	Mental health emergency department visit in past year

[a] Interaction terms are indicated by "with"; see Appendices 9B–9E in the online supplement for a complete list. PHQ-9=Patient Health Questionnaire; PHQ-8=Patient Health Questionnaire depression scale.

Published Online: 24 May 2018 https://doi.org/10.1176/appi.ajp.2018.17101167

Clinical Characteristics Selected for Prediction of Suicide Death Within 90 Days of Visit in Seven Health Systems (2009–2015)

Listed in Order of Coefficients in Logistic Regression Models[a]

Suicide death following:	
Mental health specialty visit (of 43 predictors selected)	Primary care visit (of 29 predictors selected)
Suicide attempt diagnosis in past year	Mental health emergency department visit in past 3 months
Benzodiazepine prescription in past 3 months	Alcohol abuse diagnosis in past 5 years
Mental health emergency department visit in past 3 months	Benzodiazepine prescription in past 3 months
Second-generation antipsychotic prescription in past 5 years	Depression diagnosis in past 5 years
Mental health inpatient stay in past 5 years	Mental health inpatient stay in past year
Mental health inpatient stay in past 3 months	Injury/poisoning diagnosis in past year
Mental health inpatient stay in past year	Anxiety disorder diagnosis in past 5 years
Alcohol use disorder diagnosis in past 5 years	PHQ-9 item 9 score=1 with PHQ-8 score
Antidepressant prescription in past 3 months	PHQ-9 item 9 score=3 with age
PHQ-9 item 9 score=3 with PHQ-8 score	Suicide attempt diagnosis in past 5 years with age
PHQ-9 item 9 score=1 with age	Mental health emergency department visit in past year
Depression diagnosis in past 5 years with age	PHQ-9 item 9 score=2 with age
Suicide attempt diagnosis in past 5 years with Charlson score	PHQ-9 item 9 score=3 with PHQ-8 score
PHQ-9 item 9 score=2 with age	Bipolar disorder diagnosis in past 5 years with age
Anxiety disorder diagnosis in past 5 years with age	Depression diagnosis in past 5 years with age

[a] Interaction terms are indicated by "with"; see Appendices 9B–9E in the online supplement for a complete list. PHQ-9=Patient Health Questionnaire; PHQ-8=Patient Health Questionnaire depression scale.

Published Online: 24 May 2018 https://doi.org/10.1176/appi.ajp.2018.17101167

Prediction models cannot replace clinical judgment, but risk scores can certainly inform both individual clinical decisions and quality improvement programs. Participating health systems now recommend completion of a structured suicide risk assessment after any response of “more than half the days” or “nearly every day” to PHQ-9 item 9—implying a 90-day risk of suicide attempt of 2%23%. A predicted 90-day risk exceeding 5% (i.e., above the 95th percentile for mental health specialty visits) would seem to warrant a similar level of additional assessment. A predicted 90-day suicide attempt risk exceeding 10% (i.e., above the 99th percentile for mental health specialty visits) should warrant creation of a personal safety plan and counseling regarding reducing access to means of self-harm.

Published Online: 24 May 2018 https://doi.org/10.1176/appi.ajp.2018.17101167

The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis

Samuel T. Wilkinson, M.D., Elizabeth D. Ballard, Ph.D., Michael H. Bloch, M.D., M.S., Sanjay J. Mathew, M.D., James W. Murrough, M.D., Ph.D., Adriana Feder, M.D., Peter Sos, M.D., Ph.D., Gang Wang, M.D., Carlos A. Zarate, Jr., M.D., Gerard Sanacora, M.D., Ph.D.

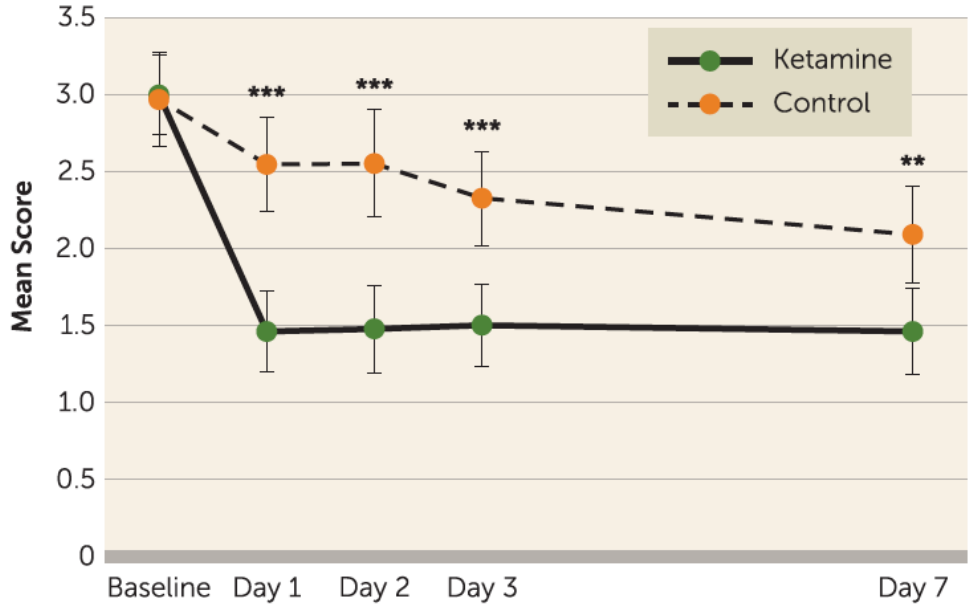
Objective: Suicide is a public health crisis with limited treatment options. The authors conducted a systematic review and individual participant data meta-analysis examining the effects of a single dose of ketamine on suicidal ideation.

Method: Individual participant data were obtained from 10 of 11 identified comparison intervention studies that used either saline or midazolam as a control treatment. The analysis included only participants who had suicidal ideation at baseline (N=167). A one-stage, individual participant data, meta-analytic procedure was employed using a mixed-effects, multilevel, general linear model. The primary outcome measures were the suicide items from clinician-administered (the Montgomery-Åsberg Depression Rating Scale [MADRS] or the Hamilton Depression Rating Scale [HAM-D]) and self-report scales (the Quick Inventory of Depressive Symptomatology–Self Report [QIDS-SR] or the Beck Depression Inventory [BDI]), obtained for up to 1 week after ketamine administration.

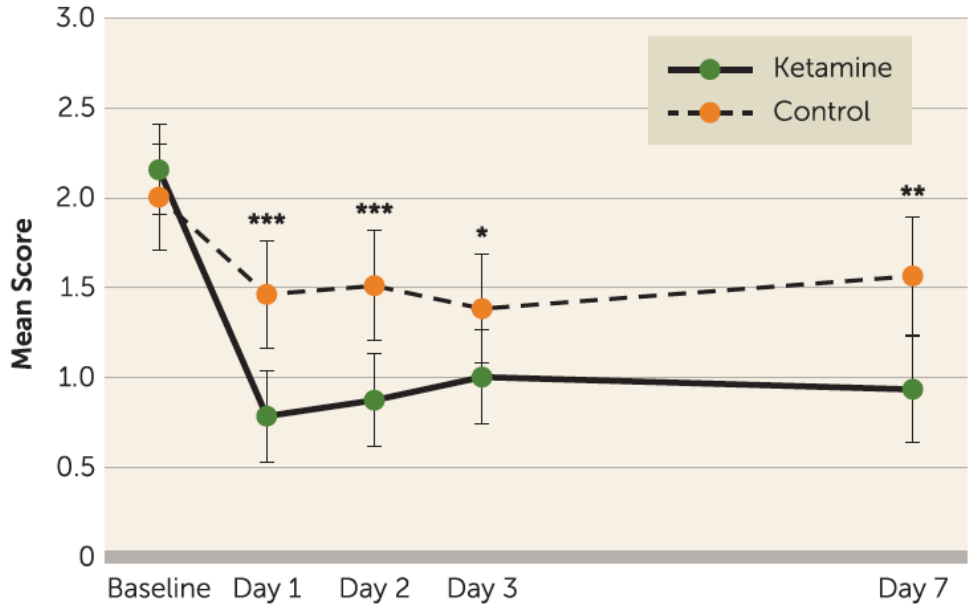
Results: Ketamine rapidly (within 1 day) reduced suicidal ideation significantly on both the clinician-administered and self-report outcome measures. Effect sizes were moderate to large (Cohen's d=0.48–0.85) at all time points after dosing. A sensitivity analysis demonstrated that compared with control treatments, ketamine had significant benefits on the individual suicide items of the MADRS, the HAM-D, and the QIDS-SR but not the BDI. Ketamine's effect on suicidal ideation remained significant after adjusting for concurrent changes in severity of depressive symptoms.

Am J Psychiatry 175:2, February 2018

B. MADRS Item 10

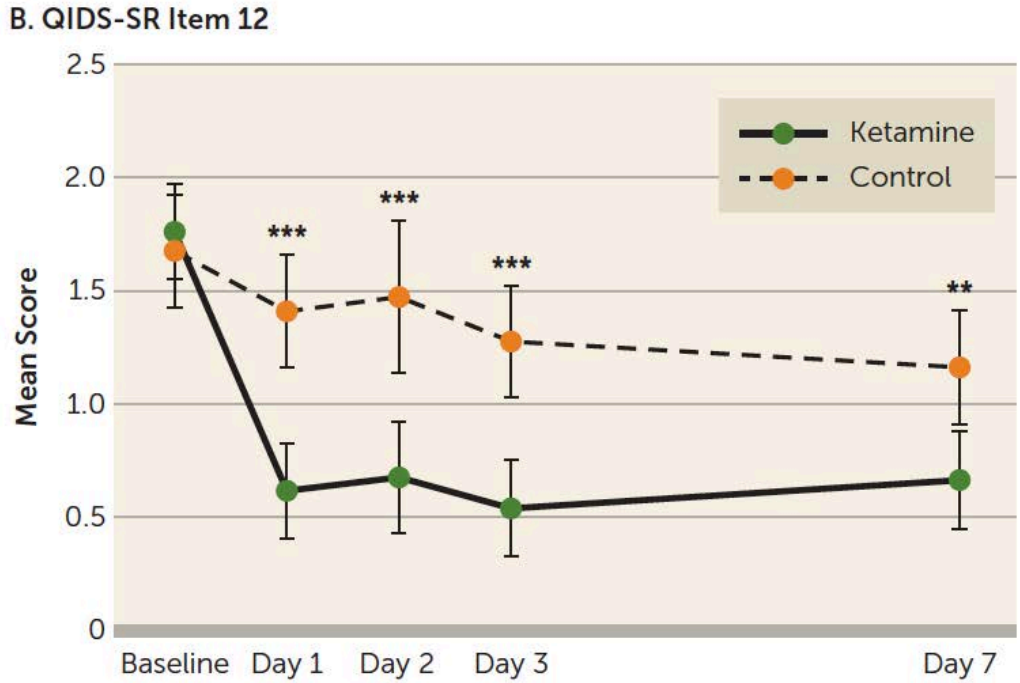


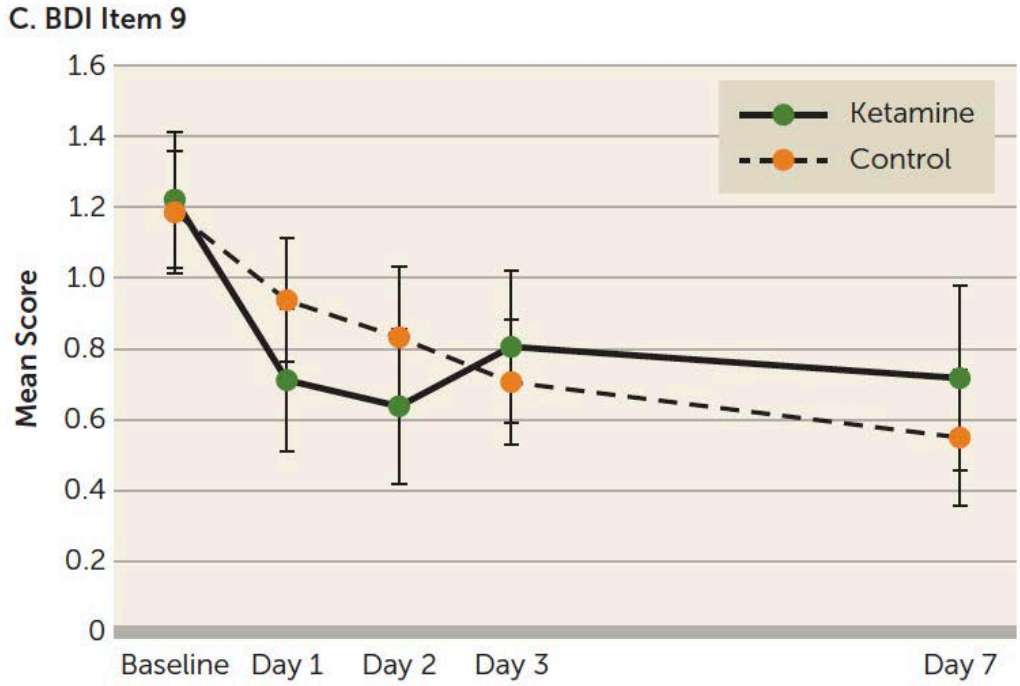
C. HAM-D Item 3



Effect of a Single Dose of Ketamine on Suicidal Ideation, as Indicated by Clinician-Administered Measures

Am J Psychiatry 175:2, February 2018





Effect of a Single Dose of Ketamine on Suicidal Ideation, as Indicated by Self-Report Measures

Am J Psychiatry 175:2, February 2018

The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis

Conclusions: Ketamine rapidly reduced suicidal thoughts, within 1 day and for up to 1 week in depressed patients with suicidal ideation. Ketamine's effects on suicidal ideation were partially independent of its effects on mood, although subsequent trials in transdiagnostic samples are required to confirm that ketamine exerts a specific effect on suicidal ideation. Additional research on ketamine's long-term safety and its efficacy in reducing suicide risk is needed before clinical implementation.

Am J Psychiatry 175:2, February 2018

The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis

1. The overall sample size is still relatively small.
2. Several of the trials specifically excluded participants with clinically serious suicidal risk.
3. The meta-analysis assesses outcomes that were restricted to suicidal ideation, which were single items within depression severity rating scales that are grossly inadequate for measuring suicide risk.
    - Measures of suicidal risk should incorporate assessment of the severity of suicidal ideation, its frequency and intensity, as well as associated risk factors for suicide.
4. More importantly, reduction in suicidal ideation is not equivalent to reduction in suicide attempt or death by suicide.

Am J Psychiatry 175:2, February 2018

Antisuicidal Effects of Ketamine: A Promising First Step

Madhukar H. Trivedi, M.D.

Ongoing clinical trials that are testing ketamine or similar rapid-acting antidepressants for suicidal ideation will need to include detailed assessments of suicidality as a key treatment outcome, rather than relying on single items from measures of depression severity.

Am J Psychiatry 175:2, February 2018

This first-ever meta-analysis using participant-level data on ketamine's anti-suicidality effects suggests that its rapid and persistent reduction in suicidal ideation is strongly, but not entirely, correlated with reduced depressive symptoms.

> For perspective, thrice-weekly ECT has been associated with freedom from suicidal ideation in 38% of patients after 1 week, 61% after 2 weeks, and 81% after a full course [average, 7.5 treatments]; Am J Psychiatry 2005; 162:977.

The meta-analysis did not assess suicidal behaviors; only one study included "imminently" suicidal patients. Although ketamine eventually might merit routine administration for suicidality in emergency settings, studies are first needed involving a broader diagnostic range (e.g., substance abuse, psychoses, borderline personality disorder, imminent risk), longer duration (to ascertain adverse effects; e.g., rebound suicidal ideation), and interactions with other therapies.

Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial

Michael F. Grunebaum, M.D., Hanga C. Galfalvy, Ph.D., Tse-Hwei Choo, M.P.H., John G. Keilp, Ph.D., Vivek K. Moitra, M.D., Michelle S. Parris, B.A., Julia E. Marver, B.A., Ainsley K. Burke, Ph.D., Matthew S. Milak, M.D., M. Elizabeth Sublette, M.D., Ph.D., Maria A. Oquendo, M.D., Ph.D., J. John Mann, M.D.

Objective: Pharmacotherapy to rapidly relieve suicidal ideation in depression may reduce suicide risk. Rapid reduction in suicidal thoughts after ketamine treatment has mostly been studied in patients with low levels of suicidal ideation. The authors tested the acute effect of adjunctive subanesthetic intravenous ketamine on clinically significant suicidal ideation in patients with major depressive disorder.

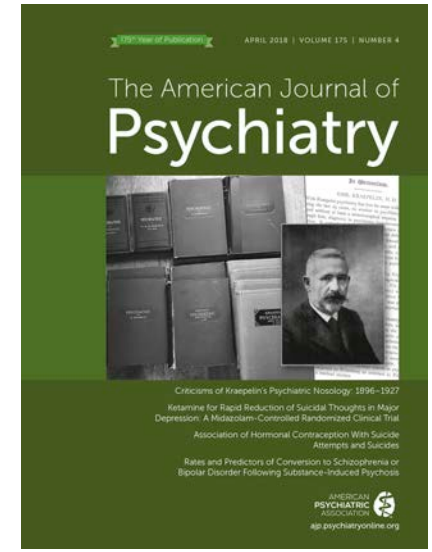
Method: In a randomized clinical trial, adults (N=80) with current major depressive disorder and a score ≥4 on the Scale for Suicidal Ideation (SSI), of whom 54% (N=43) were taking antidepressant medication, were randomly assigned to receive ketamine or midazolam infusion. The primary outcome measure was SSI score 24 hours after infusion (at day 1).

Am J Psychiatry 175:4, April 2018

Ketamine for Rapid Reduction of Suicidal Thoughts

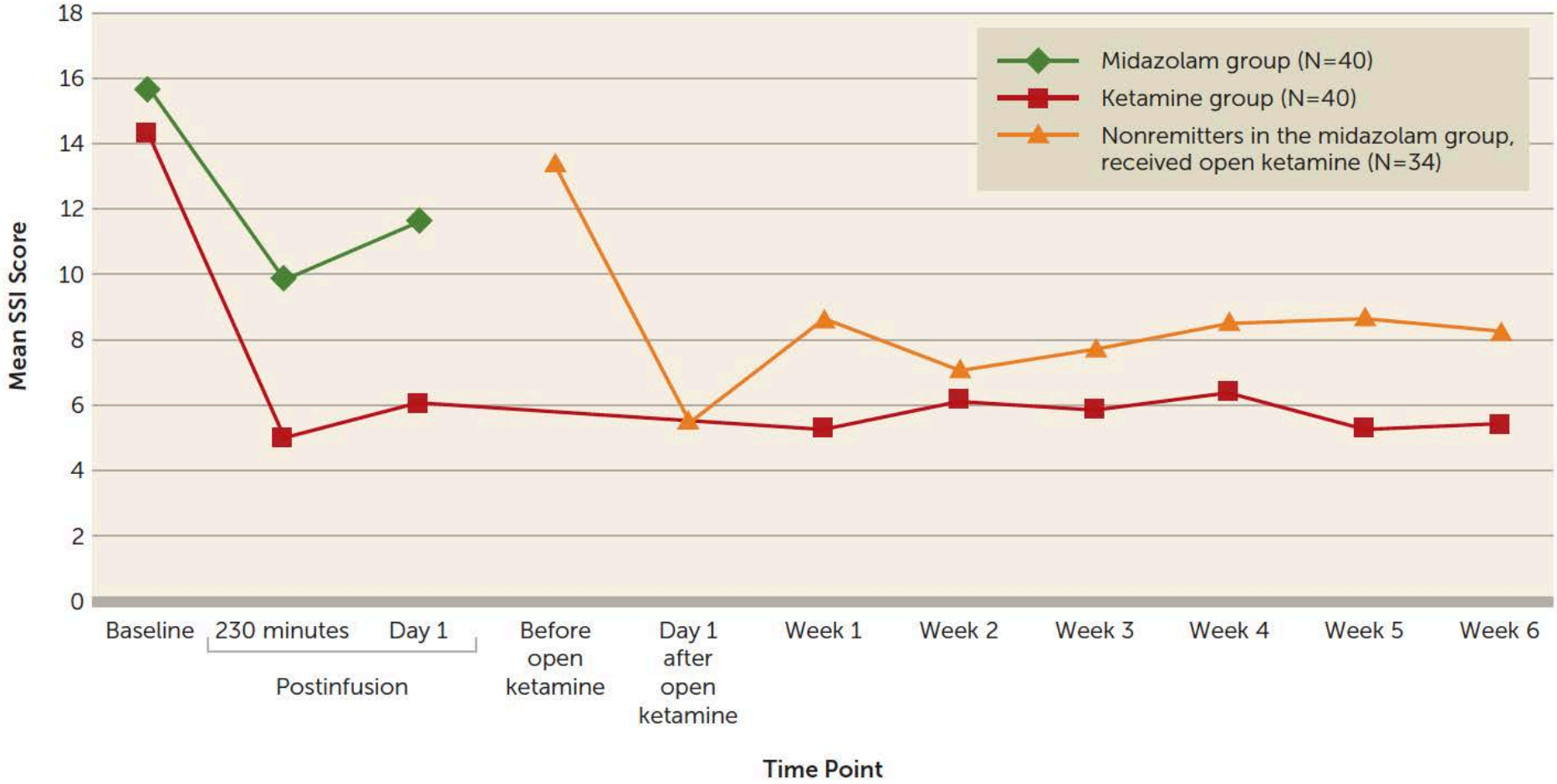
Results: The reduction in SSI score at day 1 was 4.96 points greater for the ketamine group compared with the midazolam group (95% CI=2.33, 7.59; Cohen's d=0.75). The proportion of responders (defined as having a reduction ≥50% in SSI score) at day 1 was 55% for the ketamine group and 30% for the midazolam group (odds ratio=2.85, 95% CI=1.14, 7.15; number needed to treat=4.0). Improvement in the Profile of Mood States depression subscale was greater at day 1 for the ketamine group compared with the midazolam group (estimate=7.65, 95% CI=1.36, 13.94), and this effect mediated 33.6% of ketamine's effect on SSI score. Side effects were short-lived, and clinical improvement was maintained for up to 6 weeks with additional optimized standard pharmacotherapy in an uncontrolled follow-up.

Conclusions: Adjunctive ketamine demonstrated a greater reduction in clinically significant suicidal ideation in depressed patients within 24 hours compared with midazolam, partially independently of antidepressant effect.



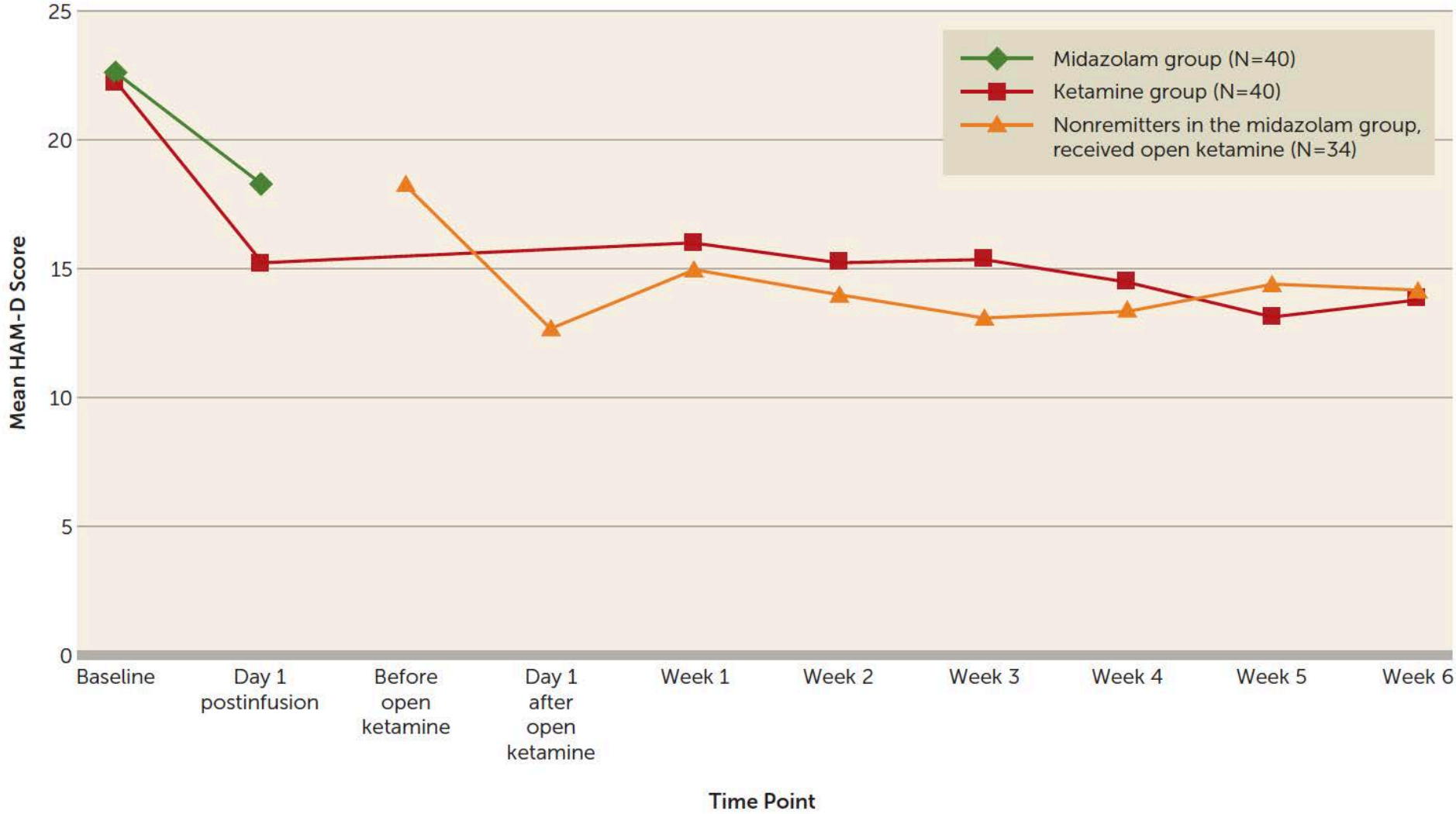
Am J Psychiatry 175:4, April 2018

FIGURE 1. Change in Suicidal Ideation Over Time in Suicidal Patients With Major Depression Treated With a Subanesthetic Infusion of Ketamine or Midazolam[a]



[a] The data are based on the modified intent-to-treat sample (N=40 per group). The primary outcome measure was score on the Scale for Suicidal Ideation (SSI) 24 hours after infusion (day 1); the reduction was greater for the ketamine group than for the midazolam group ($p<0.001$). SSI scores range from 0 to 38, with higher scores indicating greater severity. Remission was defined as an SSI score ≥50% below baseline at day 1 and less than the study eligibility threshold of 4. For nonremitters, the blind was broken and patients who were allocated to midazolam were offered an open ketamine infusion, usually the following day. Thirty-five midazolam nonremitters received an open ketamine infusion, and one withdrew from the study before the day 1 assessment.

FIGURE 2. Change in Depressive Symptoms Over Time in Suicidal Patients With Major Depression Treated With a Subanesthetic Infusion of Ketamine or Midazolam[a]



[a] The data are based on the modified intent-to-treat sample (N=40 per group). Score on the 17-Item Hamilton Depression Rating Scale (HAM-D) 24 hours after infusion (day 1) was a secondary outcome measure. Remission was defined as a Scale for Suicidal Ideation score ≥50% below baseline at day 1 and less than the study eligibility threshold of 4. For nonremitters, the blind was broken and patients who were allocated to midazolam were offered an open ketamine infusion, usually the following day. The reduction in HAM-D score was greater in the ketamine group compared with the midazolam group, but the difference fell short of statistical significance (p=0.06).

In summary, in this randomized trial in suicidal depressed patients, a single adjunctive subanesthetic ketamine infusion was associated with a clinically significant reduction in suicidal ideation at day 1 that was greater than with the midazolam control infusion. In the context of standard, optimized treatment after the ketamine infusion, this improvement appeared to persist for at least 6 weeks. The clinical applicability of our findings was improved with infusion administration by a psychiatrist and without a medication washout, as has been done in some studies. Research is needed to understand ketamine's mechanism of action and to investigate strategies and safety of longer-term treatment.

Am J Psychiatry 175:4, April 2018

Although ketamine has been shown to reduce suicidal ideation acutely, questions remain about these effects' duration and their relationship to ketamine's antidepressant qualities. To address these issues, investigators randomized 80 voluntary psychiatric inpatients with major depression and clinically significant suicidal ideation to receive blinded infusions of subanesthetic ketamine or low-dose midazolam (60% female; 92% white; mean age, 40; mean age at onset of depression, 15). There was no medication washout except for benzodiazepines.

Patients received optimized pharmacotherapy after infusion. Within 24 hours, ketamine was associated with lower suicidal ideation scores than midazolam, with a medium effect size (number needed to treat, 4); about one third of the effect was mediated by reduced depression scores. Midazolam recipients who were still suicidal after 24 hours (n=35) were given intravenous ketamine and had similarly improved suicidality scores. Improvements in both ketamine groups were largely maintained for 6 weeks. Adverse effects were mild to moderate and transient.

Adding to evidence suggesting the clinical usefulness of ketamine in managing acutely suicidal patients, this study conducted without medication washout had results lasting at least 6 weeks. Future studies should examine whether longer-term treatment in chronically suicidal patients might further extend these benefits.

A Brief Exposure-Based Treatment vs Cognitive Processing Therapy for Posttraumatic Stress Disorder: A Randomized Noninferiority Clinical Trial

Denise M. Sloan, PhD; Brian P. Marx, PhD; Daniel J. Lee, PhD; Patricia A. Resick, PhD

IMPORTANCE Written exposure therapy (WET), a 5-session intervention, has been shown to efficaciously treat posttraumatic stress disorder (PTSD). However, this treatment has not yet been directly compared with a first-line PTSD treatment such as cognitive processing therapy (CPT).

OBJECTIVE To determine if WET is noninferior to CPT in patients with PTSD.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial conducted at a Veterans Affairs medical facility between February 28, 2013, and November 6, 2016, 126 veteran and nonveteran adults were randomized to either WET or CPT. Inclusion criteria were a primary diagnosis of PTSD and stable medication therapy. Exclusion criteria included current psychotherapy for PTSD, high risk of suicide, diagnosis of psychosis, and unstable bipolar illness. Analysis was performed on an intent-to-treat basis.

INTERVENTIONS Participants assigned to CPT (n = 63) received 12 sessions and participants assigned to WET (n = 63) received 5 sessions. The CPT protocol that includes written accounts was delivered individually in 60-minute weekly sessions. The first WET session requires 60 minutes while the remaining 4 sessions require 40 minutes.

MAIN OUTCOMES AND MEASURES The primary outcome was the total score on the Clinician-Administered PTSD Scale for *DSM-5*; noninferiority was defined by a score of 10 points. Blinded evaluations were conducted at baseline and 6, 12, 24, and 36 weeks after the first treatment session. Treatment dropout was also examined.

RESULTS For the 126 participants (66 men and 60 women; mean [SD] age, 43.9 [14.6] years), improvements in PTSD symptoms in the WET condition were noninferior to improvements in the CPT condition at each of the assessment periods. The largest difference between treatments was observed at the 24-week assessment (mean difference, 4.31 points; 95% CI, -1.37 to 9.99). There were significantly fewer dropouts in the WET vs CPT condition (4 [6.4%] vs 25 [39.7%]; $\chi^2_1 = 12.84$, Cramer V = 0.40).

A Brief Exposure-Based Treatment vs Cognitive Processing Therapy for Posttraumatic Stress Disorder: A Randomized Noninferiority Clinical Trial

Denise M. Sloan, PhD; Brian P. Marx, PhD; Daniel J. Lee, PhD; Patricia A. Resick, PhD

Findings In this randomized noninferiority clinical trial of 126 adults who received a diagnosis of posttraumatic stress disorder, those treated with written exposure therapy, a 5-session treatment, and those treated with cognitive processing therapy improved significantly, with large effect sizes observed. Despite the substantial dose difference, written exposure therapy was noninferior to cognitive processing therapy.

CONCLUSIONS AND RELEVANCE Although WET involves fewer sessions, it was noninferior to CPT in reducing symptoms of PTSD. The findings suggest that WET is an efficacious and efficient PTSD treatment that may reduce attrition and transcend previously observed barriers to PTSD treatment for both patients and providers.

Meaning The findings provide evidence that written exposure therapy and cognitive processing therapy are effective for treatment of posttraumatic stress disorder, and that posttraumatic stress disorder can be effectively treated with a 5-session psychotherapy.

- The importance of this study is its demonstration of equivalence between an established PTSD therapy and a version of exposure therapy that is briefer and simpler and that requires less homework and less therapist training and expertise.
- Wider use of this "lower-dose" approach may improve access for the expanding number of patients requiring treatment for PTSD, especially in the VA system.

Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine

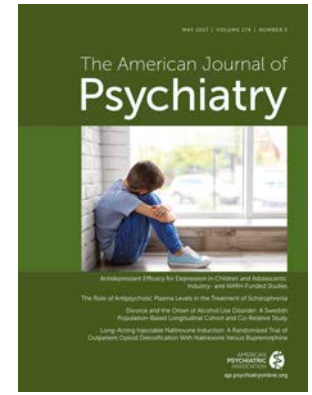
Maria Sullivan, M.D., Ph.D., Adam Bisaga, M.D., Martina Pavlicova, Ph.D., C. Jean Choi, M.S., Kaitlyn Mishlen, M.A., Kenneth M. Carpenter, Ph.D., Frances R. Levin, M.D., Elias Dakwar, M.D., John J. Mariani, M.D., Edward V. Nunes, M.D.

Objective: At present there is no established optimal approach for transitioning opioid-dependent adults to extended-release injection naltrexone (XR-naltrexone) while preventing relapse. The authors conducted a trial examining the efficacy of two methods of outpatient opioid detoxification for induction to XR-naltrexone.

Method: Participants were 150 opioid-dependent adults randomly assigned 2:1 to one of two outpatient detoxification regimens, naltrexone-assisted detoxification or buprenorphine-assisted detoxification, followed by an injection of XR-naltrexone. Naltrexone-assisted detoxification lasted 7 days and included a single day of buprenorphine followed by ascending doses of oral naltrexone along with clonidine and other adjunctive medications. Buprenorphine-assisted detoxification included a 7-day buprenorphine taper followed by a week-long delay before administration of XR-naltrexone, consistent with official prescribing information for XR-naltrexone. Participants from both groups received behavioral therapy focused on medication adherence and a second dose of XR-naltrexone.

Am J Psychiatry 174:5, May 2017

Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine



Results: Compared with participants in the buprenorphine-assisted detoxification condition, participants assigned to naltrexone-assisted detoxification were significantly more likely to be successfully inducted to XR-naltrexone (56.1% compared with 32.7%) and to receive the second injection at week 5 (50.0% compared with 26.9%). Both models adjusted for primary type of opioid use, route of opioid administration, and morphine equivalents at baseline.

Conclusions: These results demonstrate the safety, efficacy, and tolerability of low-dose naltrexone, in conjunction with single-day buprenorphine dosing and adjunctive nonopioid medications, for initiating adults with opioid dependence to XR-naltrexone. This strategy offers a promising alternative to the high rates of attrition and relapse currently observed with agonist tapers in both inpatient and outpatient settings.

Am J Psychiatry 174:5, May 2017

Current Progress in Opioid Treatment

George E. Woody, M.D.

These findings could represent a first step toward sustained remission but, as with many treatments, there remains plenty of room for improvement.

EDITORIALS

JAMA Psychiatry | Original Investigation

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence
A Randomized Clinical Noninferiority Trial

Lars Tanum, MD, DMSci; Kristin Klemmetsby Solli, MSc; Zill-e-Huma Latif, MD; Jūratė Šaltytė Benth, PhD; Arild Opheim, MSc; Kamni Sharma-Haase, MD; Peter Krajci, MD, PhD; Nikolaj Kunøe, MSc, PhD

IMPORTANCE To date, extended-release naltrexone hydrochloride has not previously been compared directly with opioid medication treatment (OMT), currently the most commonly prescribed treatment for opioid dependence.

OBJECTIVE To determine whether treatment with extended-release naltrexone will be as effective as daily buprenorphine hydrochloride with naloxone hydrochloride in maintaining abstinence from heroin and other illicit substances in newly detoxified individuals.

DESIGN, SETTING AND PARTICIPANTS A 12-week, multicenter, outpatient, open-label randomized clinical trial was conducted at 5 urban addiction clinics in Norway between November 1, 2012, and December 23, 2015; the last follow-up was performed on October 23, 2015. A total of 232 adult opioid-dependent (per *DSM-IV* criteria) individuals were recruited from outpatient addiction clinics and detoxification units and assessed for eligibility. Intention-to-treat analyses of efficacy end points were performed with all randomized participants.

JAMA Psychiatry | Original Investigation

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence

A Randomized Clinical Noninferiority Trial

Lars Tanum, MD, DMSci; Kristin Klemmetsby Solli, MSc; Zill-e-Huma Latif, MD; Jūratė Šaltytė Benth, PhD; Arild Opheim, MSc; Kamni Sharma-Haase, MD; Peter Krajci, MD, PhD; Nikolaj Kunøe, MSc, PhD

INTERVENTIONS Randomization to either daily oral flexible dose buprenorphine-naloxone, 4 to 24 mg/d, or extended-release naltrexone hydrochloride, 380 mg, administered intramuscularly every fourth week for 12 weeks.

MAIN OUTCOMES AND MEASURES Primary end points (protocol) were the randomized clinical trial completion rate, the proportion of opioid-negative urine drug tests, and number of days of use of heroin and other illicit opioids. Secondary end points included number of days of use of other illicit substances. Safety was assessed by adverse event reporting.

CONCLUSIONS AND RELEVANCE Extended-release naltrexone was as effective as buprenorphine-naloxone in maintaining short-term abstinence from heroin and other illicit substances and should be considered as a treatment option for opioid-dependent individuals.

Key Points

Question Are monthly intramuscular injections with extended-release naltrexone hydrochloride as effective as daily oral buprenorphine–naloxone hydrochloride in reducing the use of heroin and other illicit substances in newly detoxified, opioid-dependent individuals?

Findings In this 12-week, open-label randomized clinical trial including 159 opioid users, treatment with intramuscular extended-release naltrexone was as effective as oral buprenorphine-naloxone in reducing the use of heroin, opioids, and other illicit substances.

Meaning Maintaining short-term opioid abstinence with extended-release naltrexone should be considered an equal treatment alternative to buprenorphine-naloxone as medication-assisted treatment for opioid-dependent individuals.

Results from this Norwegian study, the first published prospective clinical trial comparing extended-release naltrexone (ERN) to buprenorphine-naloxone, indicate that ERN should be considered an equally efficacious treatment. Non-opioid OUD treatments are especially attractive for high-risk individuals who previously have had issues with diversion or for whom overdose is of greater concern, as in patients who also misuse benzodiazepines. Larger studies in other populations are needed to confirm these promising findings.

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Joshua D Lee, Edward V Nunes Jr, Patricia Novo, Ken Bachrach, Genie L Bailey, Snehal Bhatt, Sarah Farkas, Marc Fishman, Phoebe Gauthier, Candace C Hodgkins, Jacquie King, Robert Lindblad, David Liu, Abigail G Matthews, Jeanine May, K Michelle Peavy, Stephen Ross, Dagmar Salazar, Paul Schkolnik, Dikla Shmueli-Blumberg, Don Stablein, Geetha Subramaniam, John Rotrosen

Summary

Background Extended-release naltrexone (XR-NTX), an opioid antagonist, and sublingual buprenorphine-naloxone (BUP-NX), a partial opioid agonist, are pharmacologically and conceptually distinct interventions to prevent opioid relapse. We aimed to estimate the difference in opioid relapse-free survival between XR-NTX and BUP-NX.

Methods We initiated this 24 week, open-label, randomised controlled, comparative effectiveness trial at eight US community-based inpatient services and followed up participants as outpatients. Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and had used non-prescribed opioids in the past 30 days. We stratified participants by treatment site and opioid use severity and used a web-based permuted block design with random equally weighted block sizes of four and six for randomisation (1:1) to receive XR-NTX or BUP-NX. XR-NTX was monthly intramuscular injections (Vivitrol; Alkermes) and BUP-NX was daily self-administered buprenorphine-naloxone sublingual film (Suboxone; Indivior). The primary outcome was opioid relapse-free survival during 24 weeks of outpatient treatment. Relapse was 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use. This trial is registered with ClinicalTrials.gov, NCT02032433.

Findings Between Jan 30, 2014, and May 25, 2016, we randomly assigned 570 participants to receive XR-NTX (n=283) or BUP-NX (n=287). The last follow-up visit was Jan 31, 2017. As expected, XR-NTX had a substantial induction hurdle: fewer participants successfully initiated XR-NTX (204 [72%] of 283) than BUP-NX (270 [94%] of 287; p<0·0001). Among all participants who were randomly assigned (intention-to-treat population, n=570) 24 week relapse events were greater for XR-NTX (185 [65%] of 283) than for BUP-NX (163 [57%] of 287; hazard ratio [HR] 1·36, 95% CI 1·10–1·68), most or all of this difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures. Among participants successfully inducted (per-protocol population, n=474), 24 week relapse events were similar across study groups (p=0·44). Opioid-negative urine samples (p<0·0001) and opioid-abstinent days (p<0·0001) favoured BUP-NX compared with XR-NTX among the intention-to-treat population, but were similar across study groups among the per-protocol population. Self-reported opioid craving was initially less with XR-NTX than with BUP-NX (p=0·0012), then converged by week 24 (p=0·20). With the exception of mild-to-moderate XR-NTX injection site reactions, treatment-emergent adverse events including overdose did not differ between treatment groups. Five fatal overdoses occurred (two in the XR-NTX group and three in the BUP-NX group).

Interpretation In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective. Future work should focus on facilitating induction to XR-NTX and on improving treatment retention for both medications.

Funding NIDA Clinical Trials Network.

For treating opioid use disorder, both buprenorphine-naloxone combination (BN; suboxone) and extended-release naltrexone (ERN) can be prescribed in any clinic with minimal provider training, unlike methadone. A recent study showed similar efficacy for ERN and BN, but randomization occurred after detoxification (NEJM JW Psychiatry Dec 2017 and *JAMA Psychiatry* 2017 Oct 18; [e-pub]). As a full opioid antagonist, ERN can precipitate severe withdrawal, so patients need to be completely detoxified before starting ERN, unlike BN, which patients can start while still in mild withdrawal. Now, researchers report results from a multicenter study that randomized individuals before detoxification, allowing measurement of induction success.

In participants who present for treatment after completing withdrawal or who both succeed in getting through withdrawal and are off opioids, ERN should be considered a first-line treatment. ERN should also be seriously considered in residential settings and for patients with comorbid sedative-hypnotic use disorders, in whom the risk of overdose on BN is elevated. However, many individuals might not successfully complete the withdrawal process and thus cannot start ERN -- and this will likely limit widespread use of ERN. Using alternative detoxification protocols may increase induction success on ERN (NEJM JW Psychiatry Mar 2017; and *Am J Psychiatry* 2017; 174:459). Initiation challenges are likely to be greater in outpatient settings.

Extended-Release Naltrexone vs. Buprenorphine-Naloxone for Opioid Use Disorder

Claire Wilcox, MD

NEJM Journal Watch PSYCHIATRY

The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

Victor I. Reus, M.D., Laura J. Fochtmann, M.D., M.B.I., Oscar Bukstein, M.D., M.P.H., A. Evan Eyler, M.D., M.P.H., Donald M. Hilty, M.D., Marcela Horvitz-Lennon, M.D., M.P.H., Jane Mahoney, Ph.D., R.N., PMHCNS-B.C., Jagoda Pasic, M.D., Ph.D., Michael Weaver, M.D., Cheryl D. Wills, M.D., Jack McIntyre, M.D. (Consultant), Jeremy Kidd, M.D. (Consultant), Joel Yager, M.D. (Systematic Review), Seung-Hee Hong (Systematic Review)

- Focus on evidence-based pharmacological treatments for helping individuals reduce or stop their use of alcohol (not on treating withdrawal).
- Also includes statements related to assessment and treatment planning.
- Categorized by whether benefits of treatment outweigh harms and by the level of evidence.

Am J Psychiatry 175:1, January 2018

The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

Recommends (1B) that naltrexone or acamprosate be offered to patients with moderate to severe alcohol use disorder who

- have a goal of reducing alcohol consumption or achieving abstinence
- prefer pharmacotherapy or have not responded to non-pharmacological treatments alone
- have no contraindications to the use of these medications

Am J Psychiatry 175:1, January 2018

The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

- *Suggests* (2C) that disulfiram be offered to patients with moderate to severe alcohol use disorder who
  - have a goal of achieving abstinence
  - prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate
  - are capable of understanding the risks of alcohol consumption while taking disulfiram
  - have no contraindications to the use of this medication
- *Suggests* (2C) that topiramate or gabapentin be offered to patients with moderate to severe alcohol use disorder who
  - have a goal of reducing alcohol consumption or achieving abstinence
  - prefer topiramate or gabapentin or are intolerant to or have not responded to naltrexone and acamprosate
  - have no contraindications to the use of these medications.

Am J Psychiatry 175:1, January 2018

The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

- Avoid acamprosate if there is severe renal impairment.
- Avoid naltrexone if there is acute hepatitis, hepatic failure, or ongoing opioid use.
- Avoid benzodiazepines and antidepressants unless treating alcohol withdrawal or a comorbid disorder.
- Avoid pharmacological treatments in pregnant or breast-feeding women.

Am J Psychiatry 175:1, January 2018

- A systematic review and meta-analysis (**JAMA** May 14, 2014 Volume 311, Number 18) formed the basis for the guidelines. Expansions beyond this earlier publication occur in the suggestions regarding gabapentin (because of new data) and disulfiram (because of a newer meta-analysis with open-label trials plus a study using supervised medication delivery). The guidelines did not distinguish between depot and oral naltrexone because head-to-head studies have not been published.
- Most of the medication studies used to develop these guidelines provided evidence-based psychosocial interventions concurrently, which should be considered first-line AUD treatments.

Multisystemic therapy versus management as usual in the treatment of adolescent antisocial behaviour (START): a pragmatic, randomised controlled, superiority trial

Peter Fonagy, Stephen Butler, David Cottrell, Stephen Scott, Stephen Pilling, Ivan Eisler, Peter Fuggle, Abdullah Kraam, Sarah Byford, James Wason, Rachel Ellison, Elizabeth Simes, Poushali Ganguli, Elizabeth Allison, Ian M Goodyer

Summary

Background Adolescent antisocial behaviour is a major health and social problem. Studies in the USA have shown that multisystemic therapy reduces such behaviour and the number of criminal offences committed by this group. However, findings outside the USA are equivocal. We aimed to assess the effectiveness and cost-effectiveness of multisystemic therapy versus management as usual in the treatment of adolescent antisocial behaviour.

Methods We did an 18 month, multisite, pragmatic, randomised controlled, superiority trial in England. Eligible participants aged 11–17 years with moderate-to-severe antisocial behaviour had at least three severity criteria indicating past difficulties across several settings and one of five general inclusion criteria for antisocial behaviour. We randomly assigned families (1:1) using stochastic minimisation, stratifying for treatment centre, sex, age at enrolment to study, and age at onset of antisocial behaviour, to receive either management as usual or 3–5 months of multisystemic therapy followed by management as usual. Research assistants and investigators were masked to treatment allocation; the participants could not be masked. The primary outcome was out-of-home placement at 18 months. The primary analysis included all randomised participants for whom data were available. This trial is registered, number ISRCTN77132214. Follow-up of the trial is still ongoing.

Findings 1076 families were referred to nine multi-agency panels, 684 of whom were assigned to management as usual (n=342) or MST followed by management as usual (n=342). Management as usual was individualized to include social, parental, and school services. The MST group received 3 to 5 months of thrice-weekly family meetings with a trained and supervised therapist, followed by management as usual.

At 18 months, the proportion of participants in out-of-home placement was not significantly different between the groups (13% in the MST group vs 11% in the management-as-usual group). Time to first offense was similar between groups. MST had worse outcomes among children with earlier onset of conduct symptoms and among those with few delinquent peers. Outcomes were unaffected by comorbid psychiatric diagnoses.

Interpretation The findings do not support that multisystemic therapy should be used over management as usual as the intervention of choice for adolescents with moderate-to-severe antisocial behavior.

- We identified no long-term benefits in behavior, mental health, social care, forensics, or education, nor any economic advantage, for multisystemic therapy compared with management as usual.
- Multisystemic therapy appeared to worsen some of these outcomes for some young people; relative to management as usual, it did not reduce the likelihood of out-of-home placement, and even slightly increased this outcome.

Implications of all the available evidence

Previous evidence from the USA and some European countries suggested that multisystemic therapy was a promising treatment, but whether it would be similarly effective in the UK had not been fully investigated before this study. Our results do not provide strong evidence for the continued national rollout of multisystemic therapy in child and adolescent health and social services. We found no evidence that major savings would ensue from further implementation of the model. The substantial improvements observed in both groups reflect the effectiveness of routinely offered interventions for this group of young people, at least when observed via trial methodology. Further post-hoc analysis of differences in management-as-usual outcomes might provide suggestions for rational investment or disinvestment in this expensive domain of service provision.

In the U.S., multisystemic therapy (MST) has been found effective for childhood conduct disorders, but the studies were conducted by the therapy's developers and used noncomprehensive comparators, such as individual therapy. The current U.K. study marks the first to be performed by independent investigators and to use a comprehensive control.

These results support the effectiveness of usual care in the U.K. system. The results are contrary to studies in the U.S., where insurance companies typically restrict treatment to medication visits and thus limit comprehensive care.

Real-world Effectiveness of Pharmacologic Treatments for the Prevention of Rehospitalization in a Finnish Nationwide Cohort of Patients With Bipolar Disorder

Markku Lähteenvuo, MD, PhD; Antti Tanskanen, PhLic; Heidi Taipale, PhD; Fabian Hoti, PhD; Pia Vattulainen, MSc; Eduard Vieta, MD, PhD; Jari Tiihonen, MD, PhD

IMPORTANCE Mood stabilizers and antipsychotics are the main maintenance treatments for bipolar disorder. Lithium is considered to be the most effective mood stabilizer, but very little is known about overall health outcomes associated with specific treatments and the comparative long-term effectiveness of specific psychotropics or routes of administration in the prevention of rehospitalizations.

OBJECTIVE To study the comparative effectiveness of pharmacologic treatments in the prevention of rehospitalization in a nationwide cohort of patients with bipolar disorder.

DESIGN, SETTING, AND PARTICIPANTS This cohort study examined the risk of psychiatric, cardiovascular, and all-cause hospitalization from January 1, 1987, to December 31, 2012, among all patients in Finland who had been hospitalized for bipolar disorder (N = 18 018; mean follow-up time, 7.2 years) using prospectively gathered nationwide databases for hospitalization and dispensed medications. The primary analysis was within-individual analysis, in which each individual was used as his or her own control to eliminate selection bias. The study adjusted for the effect of concomitant psychotropic medications, duration of illness, and the temporal orders of exposure and nonexposure periods. Statistical analysis was conducted from January 1, 1996, to December 31, 2012.

MAIN OUTCOMES AND MEASURES Adjusted hazard ratios (HRs) for rehospitalization were calculated.

Question What is the comparative effectiveness of pharmacologic treatments in the prevention of rehospitalization in bipolar disorder?

Findings In this Finnish nationwide cohort study of 18 018 patients, lithium use was associated with the lowest risk of rehospitalization because of mental or somatic disorder. The risk of rehospitalization was about 30% lower during treatment with long-acting injections compared with treatment with their oral counterparts.

Meaning In bipolar disorder, lithium should remain the first line of treatment, and long-acting injections might offer a safe, effective option for patients in whom lithium is not suitable.

Real-world Effectiveness of Pharmacologic Treatments in Bipolar Disorder

Researchers studied prospective Finnish databases of 17,877 patients (mean age, 47) who had been hospitalized and discharged for bipolar disorder.

- 54.0% patients had at least 1 psychiatric rehospitalization.
- Lithium had the best track record for reducing the risk for psychiatric rehospitalization (by 33%) and for hospitalization for any reason (by 29%).

Real-world Effectiveness of Pharmacologic Treatments in Bipolar Disorder

- Carbamazepine and valproate were also effective.
- Long-acting injectable antipsychotics, compared with their oral counterparts, conveyed a significantly lower risk for psychiatric and all-cause hospitalization.
- Quetiapine had very modest benefit.
- Valproate and carbamazepine were associated with increased risks for cardiovascular hospitalization.
- Benzodiazepines increased the risks for psychiatric and all-cause hospitalizations.

JAMA Psychiatry April 2018 Volume 75, Number 4

- Although patients were used as their own controls, the outcome measure was hospitalization, and one cannot infer the effects of these medications on other important outcomes such as functioning, quality of life, and symptoms.
- However, at least for hospitalization, lithium still seems to be the superior maintenance medication.
- If antipsychotic drugs are to be used long-term, depot preparations might produce better results. However, this class of medication is usually reserved for severely nonadherent patients.
- Benzodiazepines should probably be used sparingly.

Mindfulness-based cognitive therapy *v.* treatment as usual in adults with ADHD: a multicentre, single-blind, randomised controlled trial

Lotte Janssen[1], Cornelis C. Kan[1], Pieter J. Carpentier[2], Bram Sizoo[3], Sevket Hepark[1], Melanie P.J. Schellekens[1], A. Rogier T. Donders[4], Jan K. Buitelaar[5,6] and Anne E.M. Speckens[1]

Background. There is a high need for evidence-based psychosocial treatments for adult attention-deficit hyperactivity disorder (ADHD) to offer alongside treatment as usual (TAU). Mindfulness-based cognitive therapy (MBCT) is a promising psychosocial treatment. This trial investigated the efficacy of MBCT + TAU *v.* TAU in reducing core symptoms in adults with ADHD.

Methods. A multicentre, single-blind, randomised controlled trial (ClinicalTrials.gov: NCT02463396). Participants were randomly assigned to MBCT + TAU ($n = 60$), an 8-weekly group therapy including meditation exercises, psychoeducation and group discussions, or TAU only ($n = 60$), which reflected usual treatment in the Netherlands and included pharmacotherapy and/or psychoeducation. Primary outcome was ADHD symptoms rated by blinded clinicians. Secondary outcomes included self-reported ADHD symptoms, executive functioning, mindfulness skills, self-compassion, positive mental health and general functioning. Outcomes were assessed at baseline, post-treatment, 3- and 6-month follow-up. Post-treatment effects at group and individual level, and follow-up effects were examined.

Psychological Medicine First published online: February 2018

Mindfulness-based cognitive therapy

The program was primarily based on MBCT, consisting of 8-weekly sessions of 2.5 h and a 6 h silent day between the sixth and seventh sessions. The program included meditation exercises (body scan, sitting meditation, mindful movement) combined with psychoeducation, CBT techniques and group discussions. In addition to the group sessions, participants were instructed to practice 6 days a week at home for approximately 30 min a day with guided exercises. MBCT was taught in 10 groups with approximately nine individuals per group (consisting of both study and non-study participants with ADHD to strive for a group size of 8–12 patients) by four mindfulness teachers, who all met the advanced criteria of the internationally agreed good practice guidelines of the UK Network for Mindfulness-Based Teachers

Mindfulness-based cognitive therapy *v.* treatment as usual in adults with ADHD: a multicentre, single-blind, randomised controlled trial

Results. In MBCT + TAU patients, a significant reduction of clinician-rated ADHD symptoms was found at post-treatment [M difference = −3.44 (−5.75, −1.11), p = 0.004, d = 0.41]. This effect was maintained until 6-month follow-up. More MBCT + TAU (27%) than TAU participants (4%) showed a ⩽30% reduction of ADHD symptoms (p = 0.001). MBCT + TAU patients compared with TAU patients also reported significant improvements in ADHD symptoms, mindfulness skills, self-compassion and positive mental health at post-treatment, which were maintained until 6-month follow-up. Although patients in MBCT + TAU compared with TAU reported no improvement in executive functioning at post-treatment, they did report improvement at 6-month follow-up.

Conclusions. MBCT might be a valuable treatment option alongside TAU for adult ADHD aimed at alleviating symptoms.

Psychological Medicine First published online: February 2018

Among the study's limitations, researchers did not control for amount of treatment time and nonspecific therapeutic effects or compare MBCT to an effective active intervention such as CBT. However, most effects were larger at 6 months than at 8 weeks, and beneficial changes in objective and self-report measures were observed, indicating that MBCT holds promise for adult ADHD.

Clinicians now have more compelling evidence to suggest that patients add MBCT to their current treatment programs. Concurrent medication may enhance adherence to this intervention.

20-Year Nationwide Follow-Up Study on Discontinuation of Antipsychotic Treatment in First-Episode Schizophrenia

Jari Tiihonen, M.D., Ph.D., Antti Tanskanen, Phil.Lic., Heidi Taipale, Ph.D.

Objective: It is generally believed that after the first episode of schizophrenia, the risk of relapse decreases with time in patients who are stabilized. Many treatment guidelines recommend that after stabilization, antipsychotic treatment should be continued for 1–5 years, and longer exposure should be avoided if possible. However, there is no published evidence to substantiate this view. The authors used nationwide databases to investigate this issue.

Method: Prospectively gathered nationwide register data were used to study the risk of treatment failure (psychiatric rehospitalization or death) after discontinuation of antipsychotic treatment. Multivariate Cox regression was used to assess outcomes among all patients hospitalized for the first time with a schizophrenia diagnosis in Finland during the period of 1996–2014 (N=8,719).

Am J Psychiatry 175:8, August 2018

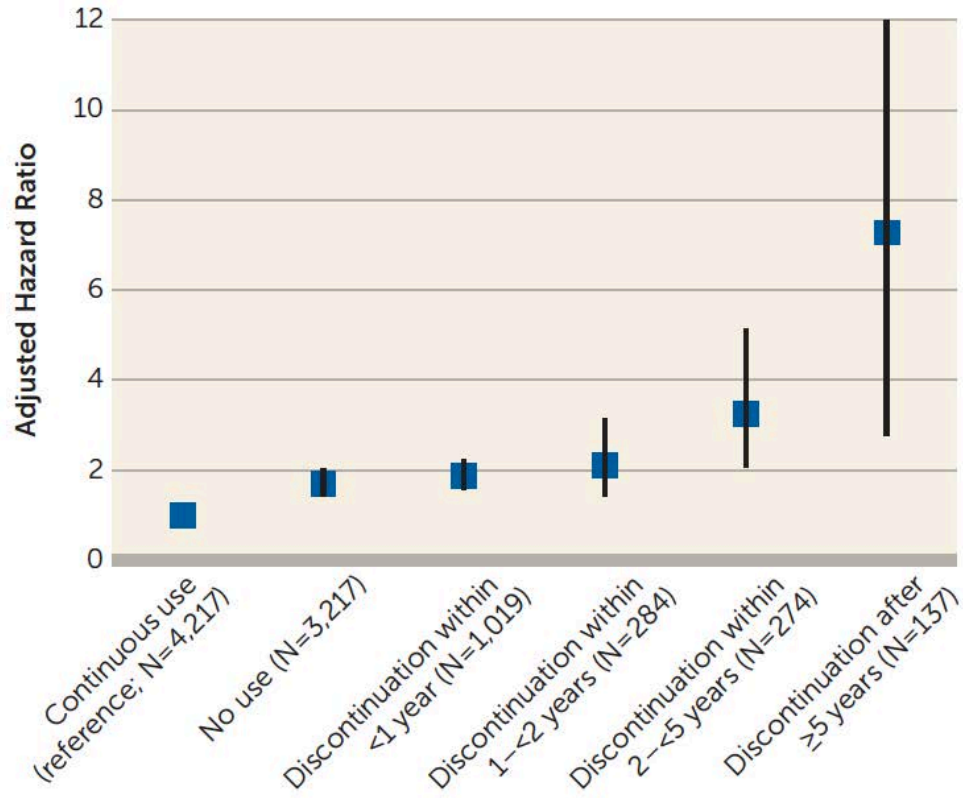
- Finnish national registries to identify patients first hospitalized for schizophrenia in 1996-2014 who had not used antipsychotics in the previous year.
- Starting 30 days post discharge, patients were divided into 4217 "users" who initiated antipsychotic use and 3217 "nonusers" who did not initiate antipsychotic use.
- Within the user group, 1714 "discontinuers" were classified by time on antipsychotics before discontinuation (maximum, 20 years).
    - At each of four comparison points (from <1 year to ≥5 years), discontinuers were matched to users on age, sex, and length of initial hospitalization.
- Adjusted hazard ratios for treatment failure (rehospitalization or death) after antipsychotic discontinuation climbed steadily from 2.24 (≤1 year) to 2.90 (2-5 years) to 8.24 (≥5 years). Overall risk for death was 214% higher among nonusers and 174% higher among discontinuers than among continuous users; this risk progressively increased through follow-up.
- Treatment resistance (i.e., clozapine use) was associated with early discontinuation, but poor treatment adherence (i.e., use of long-acting injectables) was not.

Am J Psychiatry 175:8, August 2018

This study addresses two highly relevant questions:

1. Is antipsychotic prophylaxis still needed after the first 5 years of illness, even in patients who have been doing well?
2. What is the effect of antipsychotics on mortality in patients with schizophrenia who have been followed from their first episode?
    - Especially relevant in view of the claims that continuous use of antipsychotics may increase mortality among schizophrenia patients.

FIGURE 1. Adjusted Hazard Ratios for Treatment Failure (Psychiatric Rehospitalization or Death) as a Function of Duration of Antipsychotic Use Prior to Discontinuation[a]



[a] The risk of rehospitalization or death increases when the duration of antipsychotic treatment before discontinuation increases ($p<0.05$, Spearman correlation, two-tailed). Among the patient group with discontinuation after ≥5 years, the median duration of treatment before discontinuation was 7.9 years (interquartile range, 5.8–10.4 years). The hazard ratios and 95% confidence intervals are listed in Table 1. "No use" indicates that the patients have not used antipsychotics in outpatient care after discharge from hospital. Error bars indicate 95% confidence interval.

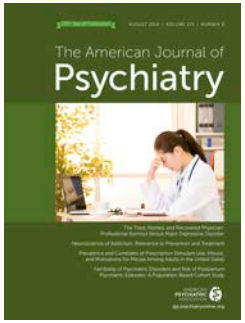
Results:

The lowest risk of rehospitalization or death was observed for patients who received antipsychotic treatment continuously (adjusted hazard ratio=1.00), followed by patients who discontinued antipsychotic use immediately after discharge from the first hospital treatment (hazard ratio=1.63, 95% CI=1.52–1.75), within 1 year (hazard ratio=1.88, 95% CI=1.57–2.24), within 1–2 years (hazard ratio=2.12, 95% CI=1.43–3.14), within 2–5 years (hazard ratio=3.26, 95% CI=2.07–5.13), and after 5 years (a median of 7.9 years) (hazard ratio=7.28, 95% CI=2.78–19.05). Risk of death was 174%- 214% higher among nonusers and patients with early discontinuation of antipsychotics compared with patients who received antipsychotic treatment continuously for up to 16.4 years.

Am J Psychiatry 175:8, August 2018

Over the entire follow-up period, the risk of hospitalization increased after discontinuation of antipsychotics. That finding is not new. What is new is the counterintuitive finding that the risk of relapse increases in proportion to the duration of prior treatment: the lowest risk of rehospitalization was observed for patients using antipsychotics continuously followed by patients discontinuing antipsychotics immediately after discharge from their first inpatient treatment (a relative risk of 1.63). The risk increased sevenfold when the period of prior treatment had been 5 years or longer. Indeed, the longer the duration of treatment, the higher the risk for relapse after discontinuation of antipsychotic medication after the first episode.

ANTIPSYCHOTIC TREATMENT IN FIRST-EPISODE SCHIZOPHRENIA



Conclusions: Whatever the underlying mechanisms, these results provide evidence that, contrary to general belief, the risk of treatment failure or relapse after discontinuation of antipsychotic use does not decrease as a function of time during the first 8 years of illness, and that long-term antipsychotic treatment is associated with increased survival.

On the Continued Benefit of Antipsychotics After the First Episode of Schizophrenia

René S. Kahn, M.D., Ph.D.

This study may help close the debate on the risk-benefit ratio of antipsychotics in schizophrenia: the results unequivocally indicate that antipsychotics substantially decrease, not increase, the risk of death after the first episode and that continuous antipsychotic treatment in first-episode patients materially decreases the risk of relapse, especially in the long term. Because this study included only medication- naive schizophrenia patients, the clinical usefulness and relevance of the data were meaningfully enhanced, because it is at that moment in the illness that the physician needs to make the difficult decision to treat, and for how long. This decision has been made easier by the Tiihonen et al. study. As the authors summarize, “long-lasting continuous anti- psychotic treatment is beneficial for the majority of patients with first-episode schizophrenia” — a message that is as clinically relevant as it is timely.

Am J Psychiatry 175:8, August 2018

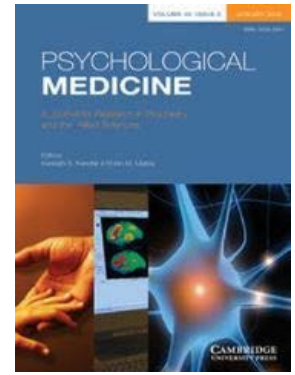
On the Continued Benefit of Antipsychotics After the First Episode of Schizophrenia

René S. Kahn, M.D., Ph.D.

Although the finding that antipsychotics reduce mortality is not new, this is the first study to use longitudinal data from first-episode antipsychotic-naive patients.

Conceivably, the longer that brains are treated, the harder it is to discontinue medication.

Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis



Alessandro Pompoli[1], Toshi A. Furukawa[2], Orestis Efthimiou[3,4], Hissei Imai[2], Aran Tajika[2] and Georgia Salanti[3,4]

Cognitive-behaviour therapy (CBT) for panic disorder may consist of different combinations of several therapeutic components such as relaxation, breathing retraining, cognitive restructuring, interoceptive exposure and/or in vivo exposure. It is therefore important both theoretically and clinically to examine whether specific components of CBT or their combinations are superior to others in the treatment of panic disorder.

Component network meta-analysis (NMA) is an extension of standard NMA that can be used to disentangle the treatment effects of different components included in composite interventions.

We searched MEDLINE, EMBASE, PsycINFO and Cochrane Central, with supplementary searches of reference lists and clinical trial registries, for all randomized controlled trials comparing different CBT-based psychological therapies for panic disorder with each other or with control interventions..

Psychological Medicine First published online: 25 January 2018

- Cognitive-behavioral therapy (CBT) is the most efficacious of the psychotherapies, according to a Cochrane review.
  - However, CBT is complex and can involve many strategies, including support, psychoeducation, breathing retraining, muscle relaxation, cognitive restructuring, interoceptive exposure to bodily sensations that accompany panic, in vivo exposure, virtual reality exposure, mindfulness, and self-help.
- Identifying which components work best could simplify CBT, thereby streamlining training, decreasing costs, and improving accessibility.

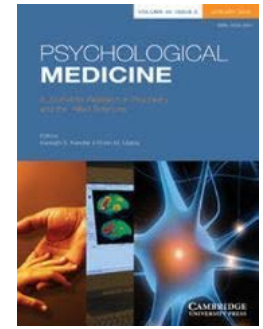
Table 1. List of included components and their definitions

Component		Description
w	Waiting component	Participants are aware that they will receive an active treatment after a waiting phase. This component was considered present even when non-specific psychotherapy was provided while the participants were aware that they could receive the 'active' intervention after the waiting period was over
pl	Placebo effect	Effect of an intervention due to the patients' belief that they are receiving some form of treatment
ps	Psychological support	Effect of an intervention due to various non-specific techniques (e.g. encouragement, rationalizing and reframing, anticipatory guidance, etc.) administered within the context of a therapeutic alliance (Winston *et al.* 2004). Considered present even in self-help format if personal encouragement was provided to proceed with the self-help material
pe	Psychoeducation	It consists in providing patients information about their psychological disease
br	Breathing retraining	It consists in teaching patients various techniques aimed at correcting those respiratory patterns thought to elicit or sustain panic attacks
mr	Progressive/applied muscle relaxation	*Progressive muscle relaxation* is aimed at reducing general tension and achieving a body state that lowers the risk for stressors to provoke a panic attack (Bernstein & Borkovec, 1973). In the so-called *applied relaxation* (Ost, 1987), relaxation training and exposure are combined
cr	Cognitive restructuring	Psychotherapeutic process of learning to identify and modify irrational or maladaptive thoughts (such as catastrophic misinterpretation of bodily sensations) using strategies such as Socratic questioning, thought recording and guided imagery
ine	Interoceptive exposure	Graded exposure to bodily sensations that accompany panic
ive	*In vivo* exposure	Graded exposure to real-life situations perceived as threatening
vre	Virtual reality exposure	Graded exposure to virtual reality simulations reproducing real-life situations perceived as threatening
3w	Third wave components	Various techniques aimed at helping patients to develop more adaptive emotional responses to situations, such as the ability to observe symptomatic processes without overly identifying with them or without reacting to them in ways that cause further distress (Roemer *et al.* 2008)
ftf	Face-to-face setting	Administration of therapeutic components in a face-to-face setting (rather than through self-help means)

Group format was not considered a component because in a previous review and NMA comparing various psychological therapies for the treatment of panic disorder (Pompoli et al, 2016), we did not detect any association between the relative treatment effects and the difference of therapy delivery (individual *v.* group) format.

Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis

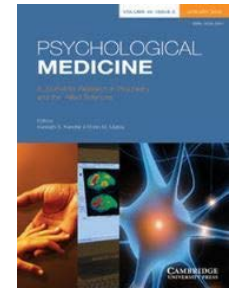
Alessandro Pompoli[1], Toshi A. Furukawa[2], Orestis Efthimiou[3,4], Hissei Imai[2], Aran Tajika[2] and Georgia Salanti[3,4]



We applied component NMA to disentangle the treatment effects of different components included in these interventions.

After reviewing 2526 references, we included 72 studies with 4064 participants. Interoceptive exposure and face-to-face setting were associated with better treatment efficacy and acceptability. Muscle relaxation and virtual-reality exposure were associated with significantly lower efficacy. Components such as breathing retraining and in vivo exposure appeared to improve treatment acceptability while having small effects on efficacy. The comparison of the most v. the least efficacious combination, both of which may be provided as 'evidence-based CBT,' yielded an odds ratio for the remission of 7.69 (95% credible interval: 1.75 to 33.33). Effective CBT packages for panic disorder would include face-to-face and interoceptive exposure components, while excluding muscle relaxation and virtual-reality exposure

Psychological Medicine First published online: 25 January 2018



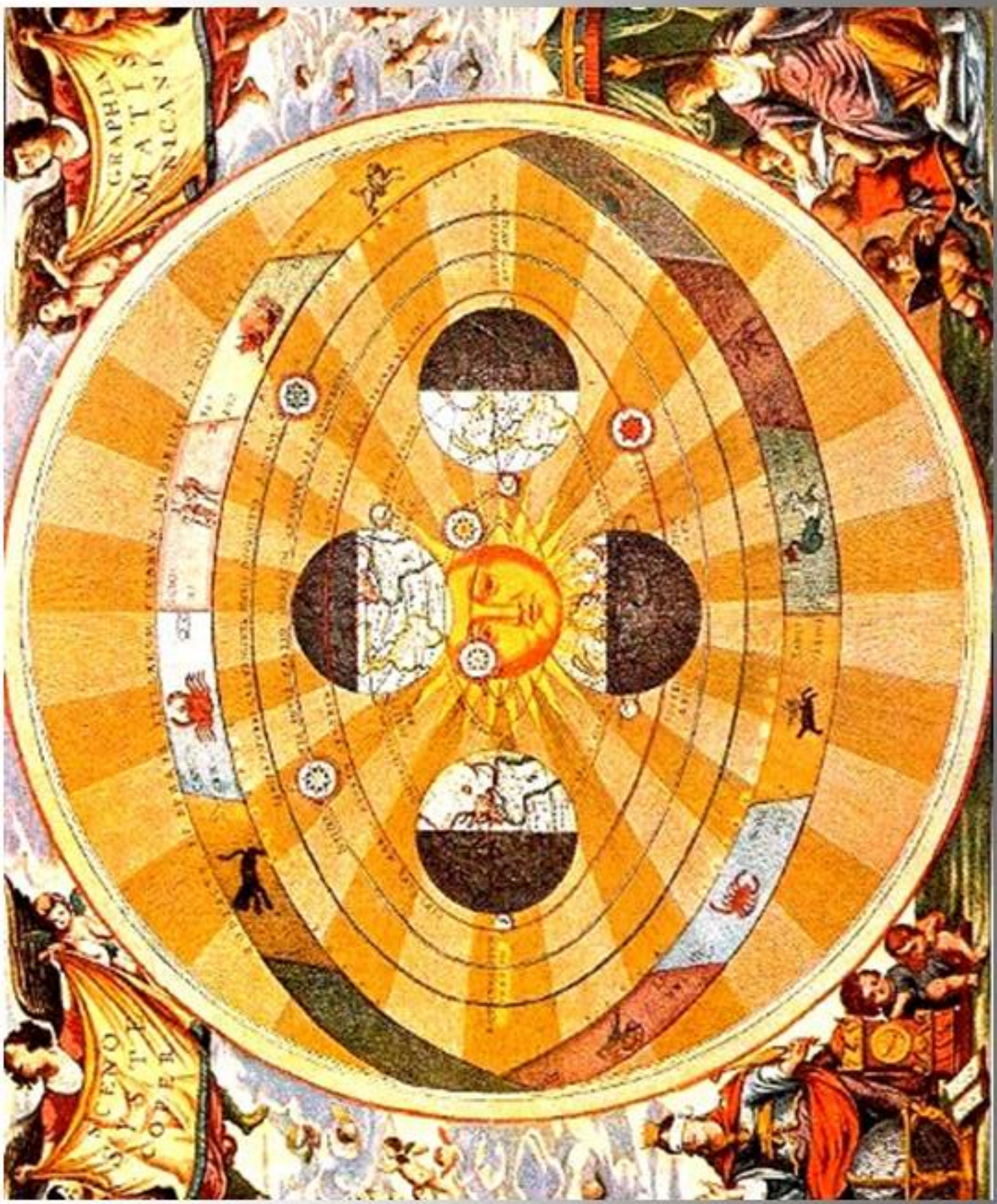
Findings:

- Interoceptive exposure and face-to-face setting were each associated with elevated odds of remission and response
- Cognitive restructuring was associated with elevated remission odds.
- Muscle relaxation and virtual reality worsened likelihood of both remission and response.
- Breathing retraining, psychoeducation, in vivo exposure, and psychological support reduced the odds of remission.
- Dropout was lower with breathing retraining and in vivo exposure and higher with psychological support and virtual reality.

Psychological Medicine First published online: 25 January 2018

Findings from this rigorous meta-analysis have high practical utility. Which CBT components are used might significantly alter its efficacy and acceptability in patients with panic disorder. The "most efficacious CBT" would include cognitive restructuring and interoceptive exposure in a face-to-face setting. Breathing retraining, muscle relaxation, and virtual reality may have a minimal or even negative impact.

Thanks



Science to Practice

Top Ten Research Findings of 2017-2018

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

Q and A

NORTH CAROLINA
Psychiatric
Association

Annual Meeting & Scientific Session
September 27-30, 2018 | Renaissance Asheville Hotel