NORTH CAROLINA
Psychiatric
Association

Science to Practice

Top Ten Research Findings of 2013-2014

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

Wrightsville Beach | Holiday Inn Resort
September 25-28, 2014

Science to Practice

Top Ten Research Findings of 2013-2014

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The Brody School of Medicine
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Vidant Medical Center, Greenville, NC

Science to Practice

Top Ten Research findings of 2013-2014

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 2013-2014 that have a direct bearing on the practice of clinical psychiatry.

*As identified by the methodology utilized for this presentation.

Disclosure

I, or any member of my immediate family, have no relevant financial relationship with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

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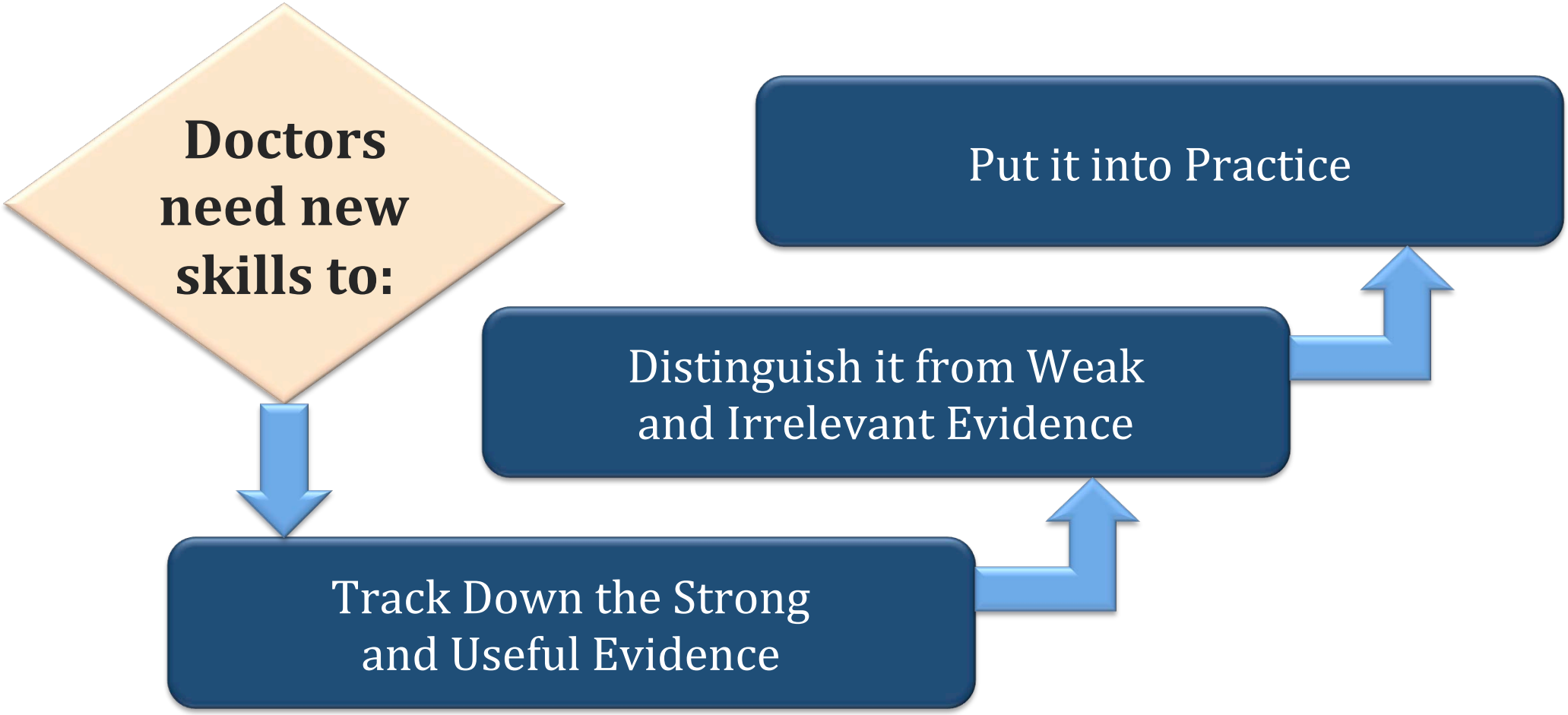
How much information in our midst is useful? How much of it gets in the way?

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

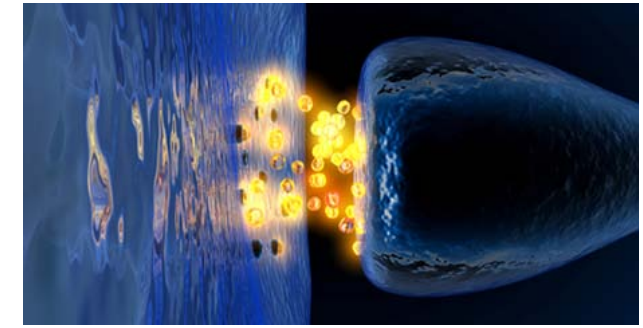
David Shenk. Data Smog: Surviving the Information Glut. San Francisco: Harper, 1998: 30.

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



Signal-to-Noise Ratio [SNR]

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

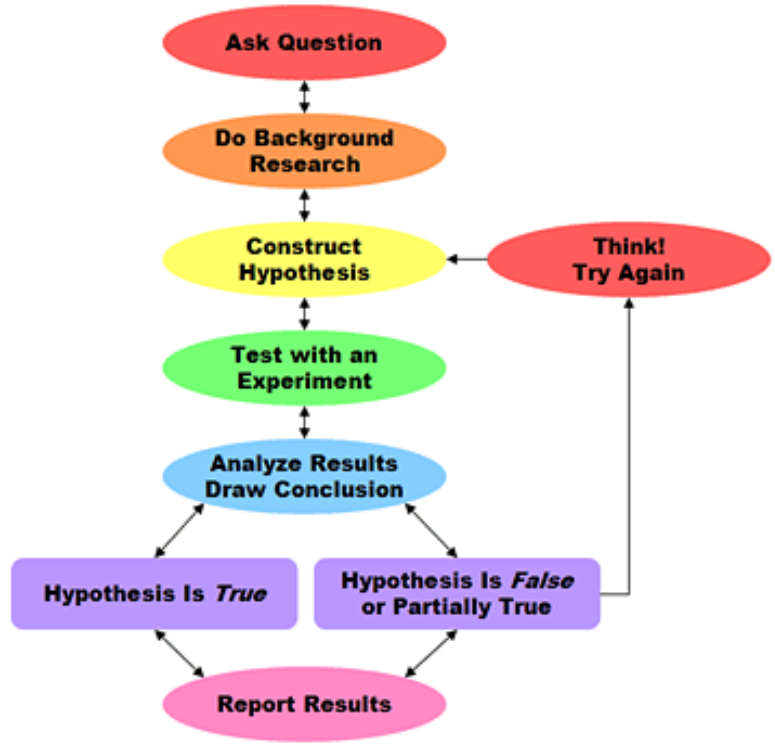


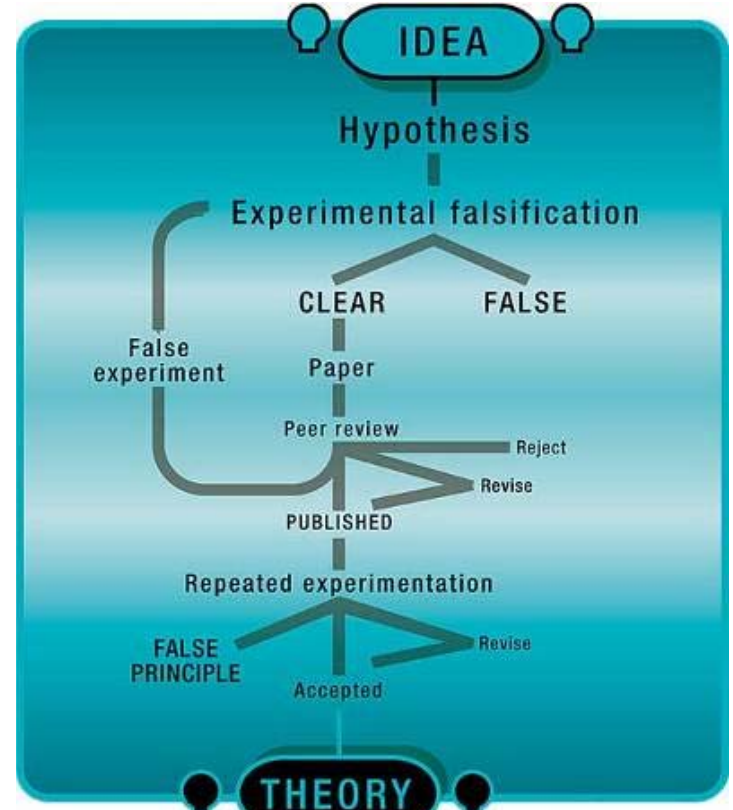
“It is wrong always, everywhere, and for anyone, to believe anything upon insufficient evidence.”

W.K. Clifford (1876): "The Ethics of Belief"

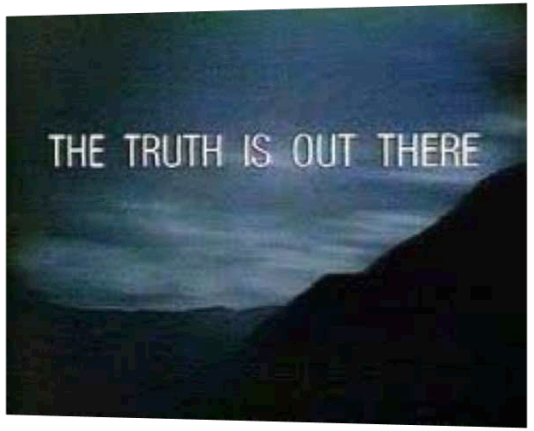
There is a long tortuous road to a "Scientific Truth"

YOU MUST ALWAYS OFFER EVIDENCE TO SUPPORT YOUR STATEMENTS.





All scientific truths are provisional!



Methodology

- Literature Search
- **Survey** [Question: *Amongst the papers published in the period July 1, 2013 to June 30, 2014, which ones in your opinion have [or likely to have or should have] impacted/ changed the clinical practice of psychiatry?*].
  - AACDP
  - AADPRT
  - AACP
  - AAPA
  - NCPA
  - GAP
  - Other Colleagues
- Faculty of 1000 Factor

Disclaimers

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


The NEW ENGLAND JOURNAL of MEDICINE
JAMA
ARCHIVES OF GENERAL PSYCHIATRY
THE AMERICAN JOURNAL OF PSYCHIATRY
THE JOURNAL OF NEUROPSYCHIATRY AND CLINICAL NEUROSCIENCES
nature
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BMJ
SUBCLINICAL vCJD: How common is it?
Science
American Journal of Psychotherapy
Journal of Abnormal Psychology
Journal of Clinical Psychopharmacology
PNAS
Potential Energy Landscapes
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THE LANCET
Journal of Psychotherapy Integration
ACADEMIC PSYCHIATRY
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Psychotherapy
Theory, Research, Practice, Training
Journal of the American Academy of CHILD & ADOLESCENT PSYCHIATRY
Behavioural Pharmacology
Psychiatry Research
Psychiatric Quarterly
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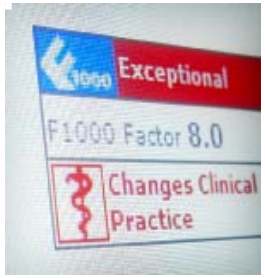
International Clinical Psychopharmacology



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Science to Practice

Top Ten Research Findings of 2013-2014

A Randomized Controlled Trial of 7-Day Intensive and Standard Weekly Cognitive Therapy for PTSD and Emotion-Focused Supportive Therapy

Anke Ehlers, Ph.D.

Ann Hackmann, D.Clin.Psy.

Nick Grey, D.Clin.Psy.

Jennifer Wild, D.Clin.Psy.

Sheena Liness, M.A.

Idit Albert, D.Clin.Psy.

Alicia Deale, Ph.D.

Richard Stott, D.Clin.Psy.

David M. Clark, D.Phil.

Objective: Psychological treatments for posttraumatic stress disorder (PTSD) are usually delivered once or twice a week over several months. It is unclear whether they can be successfully delivered over a shorter period of time. This clinical trial had two goals: to investigate the acceptability and efficacy of a 7-day intensive version of cognitive therapy for PTSD and to investigate whether cognitive therapy has specific treatment effects by comparing intensive and standard weekly cognitive therapy with an equally credible alternative treatment.

Method: Patients with chronic PTSD (N=121) were randomly allocated to 7-day intensive cognitive therapy for PTSD, 3 months of standard weekly cognitive therapy, 3 months of weekly emotion-focused supportive therapy, or a 14-week waiting list condition. The primary outcomes were change in PTSD symptoms and diagnosis as measured by independent assessor ratings and self-report. The secondary outcomes were change in disability, anxiety, depression, and quality of life. Evaluations were conducted at the baseline assessment and at 6 and 14 weeks (the posttreatment/wait assessment). For groups receiving treatment, evaluations were also conducted at 3 weeks and follow-up assessments at 27 and 40 weeks after randomization. All analyses were intent-to-treat.

Results: At the posttreatment/wait assessment, 73% of the intensive cognitive therapy group, 77% of the standard cognitive therapy group, 43% of the supportive therapy group, and 7% of the waiting list group had recovered from PTSD. All treatments were well tolerated and were superior to waiting list on nearly all outcome measures; no difference was observed between supportive therapy and waiting list on quality of life. For primary outcomes, disability, and general anxiety, intensive and standard cognitive therapy were superior to supportive therapy. Intensive cognitive therapy achieved faster symptom reduction and comparable overall outcomes to standard cognitive therapy.

Conclusions: Cognitive therapy for PTSD delivered intensively over little more than a week was as effective as cognitive therapy delivered over 3 months. Both had specific effects and were superior to supportive therapy. Intensive cognitive therapy for PTSD is a feasible and promising alternative to traditional weekly treatment.

(Am J Psychiatry 2014; 171:294–304)

A Randomized Controlled Trial of 7-Day Intensive and Standard Weekly Cognitive Therapy for PTSD and Emotion-Focused Supportive Therapy

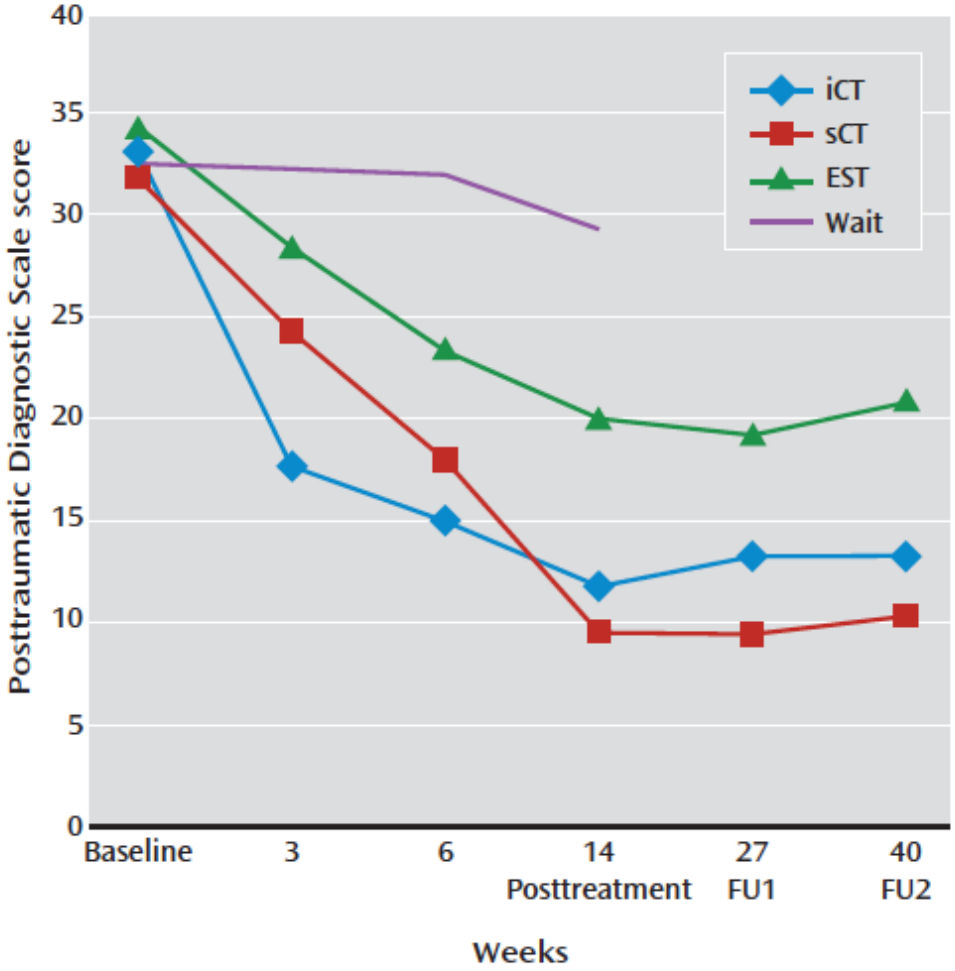
- Randomized controlled trial that evaluates the acceptability and efficacy of a rapid, intensive cognitive therapy delivered over a 7-day period compared with its established version, which involves once weekly therapy over approximately 3 months.
- In addition, the study evaluates the efficacy of these two cognitive therapies against a credible alternative treatment of emotion-focused supportive therapy.
- The study has four treatment arms: a 7-day intensive version of cognitive therapy, standard cognitive therapy, emotion-focused supportive therapy, and a waiting list.

A Randomized Controlled Trial of 7-Day Intensive and Standard Weekly Cognitive Therapy for PTSD and Emotion-Focused Supportive Therapy

Results

- At the post treatment/wait assessment, 73% of the intensive cognitive therapy group, 77% of the standard cognitive therapy group, 43% of the supportive therapy group, and 7% of the waiting list group had recovered from PTSD.
- All treatments were well tolerated and were superior to waiting list on nearly all outcome measures; no difference was observed between supportive therapy and waiting list on quality of life. For primary outcomes, disability, and general anxiety, intensive and standard cognitive therapy were superior to supportive therapy.
- Intensive cognitive therapy achieved faster symptom reduction and comparable overall outcomes to standard cognitive therapy.

FIGURE 2. Changes in PTSD Symptoms in a Randomized Controlled Trial of Cognitive and Supportive Therapies for PTSD[a]



[a] Scores were measured with the Posttraumatic Diagnostic Scale for 7-day intensive cognitive therapy (iCT, all patients), standard weekly cognitive therapy (sCT, all patients), weekly emotion-focused supportive therapy (EST), and waiting list. All patients completed the scale at baseline, 6 weeks, and 14 weeks (posttreatment/wait). Patients receiving therapy also completed the scale at 3 weeks, 27 weeks (follow-up 1, FU1), and 40 weeks (follow-up 2, FU2).

Am J Psychiatry 171:3, March 2014

A Randomized Controlled Trial of 7-Day Intensive and Standard Weekly Cognitive Therapy for PTSD and Emotion-Focused Supportive Therapy

Conclusions

- Cognitive therapy for PTSD delivered intensively over little more than a week was as effective as cognitive therapy delivered over 3 months.
- Both had specific effects and were superior to supportive therapy.
- Intensive cognitive therapy for PTSD is a feasible and promising alternative to traditional weekly treatment.

Preventive Effects of Ramelteon on Delirium
A Randomized Placebo-Controlled Trial

IMPORTANCE No highly effective interventions to prevent delirium have been identified.

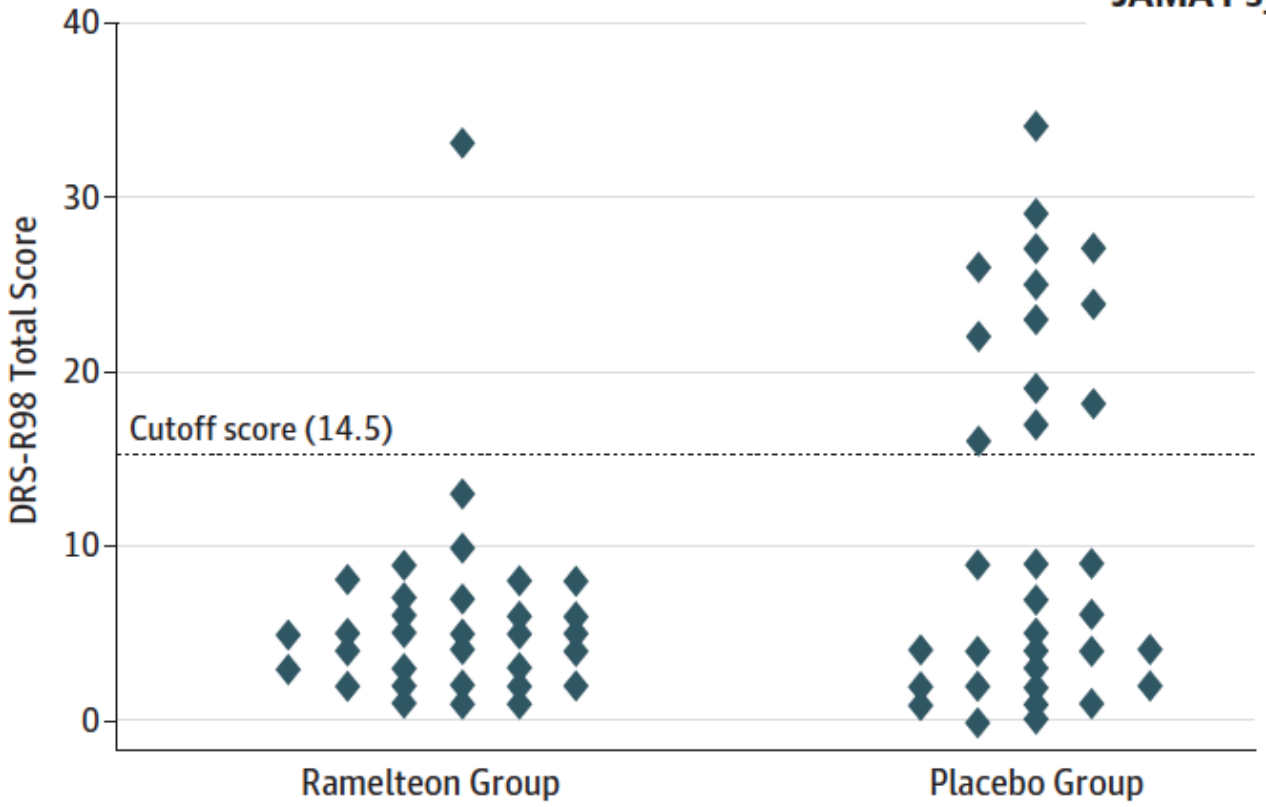
OBJECTIVE To examine whether ramelteon, a melatonin agonist, is effective for the prevention of delirium.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, rater-blinded, randomized placebo-controlled trial was performed in intensive care units and regular acute wards of 4 university hospitals and 1 general hospital. Eligible patients were 65 to 89 years old, newly admitted due to serious medical problems, and able to take medicine orally. Patients were excluded from the study if they had an expected stay or life expectancy of less than 48 hours.

INTERVENTIONS Sixty-seven patients were randomly assigned using the sealed envelope method to receive ramelteon (8 mg/d; 33 patients) or placebo (34 patients) every night for 7 days.

MAIN OUTCOMES AND MEASURES Incidence of delirium, as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).

Figure 2. Scattergrams of Each Patient's Highest Total Score on the Delirium Rating Scale–Revised-98 (DRS-R98)



Each patient was assessed until the development of delirium or up to 7 days. The cutoff score was 14.5. However, 2 patients with dementia in the placebo group had scores of 17 and 19 but did not have a delirium diagnosis according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[1]

Preventive Effects of Ramelteon on Delirium
A Randomized Placebo-Controlled Trial

RESULTS Ramelteon was associated with a lower risk of delirium (3% vs 32%; $P = .003$), with a relative risk of 0.09 (95% CI, 0.01-0.69). Even after risk factors were controlled for, ramelteon was still associated with a lower incidence of delirium ($P = .01$; odds ratio, 0.07 [95% CI, 0.008-0.54]). The Kaplan-Meier estimates of time to development of delirium were 6.94 (95% CI, 6.82-7.06) days for ramelteon and 5.74 (5.05-6.42) days for placebo. Comparison by log-rank test showed that the frequency of delirium was significantly lower in patients taking ramelteon than in those taking placebo ($\chi^2 = 9.83$; $P = .002$).

CONCLUSIONS AND RELEVANCE Ramelteon administered nightly to elderly patients admitted for acute care may provide protection against delirium. This finding supports a possible pathogenic role of melatonin neurotransmission in delirium.

Melatonin Prophylaxis in Delirium
Panacea or Paradigm Shift?

Sophia E. de Rooij, MD, PhD; Barbara C. van Munster, MD, PhD; Annemarieke de Jonghe, MD

Melatonin and ramelteon prevent delirium in acutely ill medical, elective surgical, and ICU patients.[8-10] It remains to be demonstrated whether this strategy is effective in other high-risk populations, such as patients with dementia or elderly patients undergoing hip surgery. Nevertheless, additional randomized clinical trials with more participants, using more physiologic doses of melatonin and controlling such environmental variables as light and noise, are required. Other issues that remain to be addressed are the pathophysiologic mechanisms responsible for the development of delirium and the effects of melatonin and/or melatonin receptor agonists on the long-term sequelae of delirium.

Melatonin Prophylaxis in Delirium
Panacea or Paradigm Shift?

Sophia E. de Rooij, MD, PhD; Barbara C. van Munster, MD, PhD; Annemarieke de Jonghe, MD

8. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. *Int J Geriatr Psychiatry*. 2011;26(7):687-694.

9. Sultan SS. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. *Saudi J Anaesth*. 2010;4(3):169-173.

10. Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial [published online February 19, 2014]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2013.3320.

Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings

A Systematic Review and Meta-analysis

Daniel E. Jonas, MD, MPH; Halle R. Amick, MSPH; Cynthia Feltner, MD, MPH; Georgiy Bobashev, PhD; Kathleen Thomas, PhD; Roberta Wines, MPH; Mimi M. Kim, PhD; Ellen Shanahan, MA; C. Elizabeth Gass, MPH; Cassandra J. Rowe, BA; James C. Garbutt, MD

IMPORTANCE Alcohol use disorders cause substantial morbidity and early mortality yet remain greatly undertreated. Medications are considerably underused.

OBJECTIVE To conduct a systematic review and meta-analysis of the benefits and harms of medications (US FDA-approved and others) for adults with alcohol use disorders.

DATA SOURCES PubMed, Cochrane Library, PsycINFO, CINAHL, EMBASE, FDA website, and clinical trials registries (January 1, 1970, to March 1, 2014).

STUDY SELECTION Two reviewers selected randomized clinical trials (RCTs) with at least 12 weeks' duration that reported eligible outcomes and head-to-head prospective cohort studies reporting health outcomes or harms.

DATA EXTRACTION AND SYNTHESIS We conducted meta-analyses using random-effects models and calculated numbers needed to treat for benefit (NNTs) or harm (NNHs).

MAIN OUTCOMES AND MEASURES Alcohol consumption, motor vehicle crashes, injuries, quality of life, function, mortality, and harms.

- The authors evaluated 122 randomized trials and 1 cohort study (total 22 803participants).
- Most of the studies assessed acamprosate (27 studies, n = 7519), naltrexone (53 studies, n = 9140), or both, which are approved by the US FDA for the treatment of AUD.
- Jonas and colleagues report that the efficacy of the oldest and best known FDA-approved medication for AUD—disulfiram—was not supported by randomized placebo-controlled trials.
- 4 medications—naltrexone, acamprosate, topiramate, and nalmefene—improved drinking outcomes.

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RESULTS We included 122 RCTs and 1 cohort study (total 22 803 participants). Most assessed acamprosate (27 studies, n = 7519), naltrexone (53 studies, n = 9140), or both. The NNT to prevent return to any drinking for acamprosate was 12 (95% CI, 8 to 26; risk difference [RD], −0.09; 95% CI, −0.14 to −0.04) and was 20 (95% CI, 11 to 500; RD, −0.05; 95% CI, −0.10 to −0.002) for oral naltrexone (50 mg/d). The NNT to prevent return to heavy drinking was 12 (95% CI, 8 to 26; RD −0.09; 95% CI, −0.13 to −0.04) for oral naltrexone (50 mg/d). Meta-analyses of trials comparing acamprosate to naltrexone found no statistically significant difference between them for return to any drinking (RD, 0.02; 95% CI, −0.03 to 0.08) or heavy drinking (RD, 0.01; 95% CI, −0.05 to 0.06). For injectable naltrexone, meta-analyses found no association with return to any drinking (RD, −0.04; 95% CI, −0.10 to 0.03) or heavy drinking (RD, −0.01; 95% CI, −0.14 to 0.13) but found an association with reduction in heavy drinking days (weighted mean difference [WMD], −4.6%; 95% CI, −8.5% to −0.56%). Among medications used off-label, moderate evidence supports an association with improvement in some consumption outcomes for nalmefene (heavy drinking days per month: WMD, −2.0; 95% CI, −3.0 to −1.0; drinks per drinking day: WMD, −1.02; 95% CI, −1.77 to −0.28) and topiramate (% heavy drinking days: WMD, −9.0%; 95% CI, −15.3% to −2.7%; drinks per drinking day: WMD, −1.0; 95% CI, −1.6 to −0.48). For naltrexone and nalmefene, NNHs for withdrawal from trials due to adverse events were 48 (95% CI, 30 to 112) and 12 (95% CI, 7 to 50), respectively; risk was not significantly increased for acamprosate or topiramate.

JAMA May 14, 2014 Volume 311, Number 18

Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings

A Systematic Review and Meta-analysis

Daniel E. Jonas, MD, MPH; Halle R. Amick, MSPH; Cynthia Feltner, MD, MPH; Georgiy Bobashev, PhD; Kathleen Thomas, PhD; Roberta Wines, MPH; Mimi M. Kim, PhD; Ellen Shanahan, MA; C. Elizabeth Gass, MPH; Cassandra J. Rowe, BA; James C. Garbutt, MD

CONCLUSIONS AND RELEVANCE Both acamprosate and oral naltrexone were associated with reduction in return to drinking. When directly compared with one another, no significant differences were found between acamprosate and naltrexone for controlling alcohol consumption. Factors such as dosing frequency, potential adverse events, and availability of treatments may guide medication choice.

Prolonged Exposure vs Supportive Counseling for Sexual Abuse–Related PTSD in Adolescent Girls

A Randomized Clinical Trial

Edna B. Foa, PhD; Carmen P. McLean, PhD; Sandra Capaldi, PsyD; David Rosenfield, PhD

JAMA December 25, 2013 Volume 310, Number 24

IMPORTANCE Evidence-based treatments for posttraumatic stress disorder (PTSD) have not been established for adolescents despite high prevalence of PTSD in this population.

OBJECTIVE To examine the effects of counselor-delivered prolonged exposure therapy compared with supportive counseling for adolescents with PTSD.

DESIGN, SETTING, AND PARTICIPANTS A single-blind, randomized clinical trial of 61 adolescent girls with PTSD using a permuted block design. Counselors previously naive to prolonged exposure therapy provided the treatments in a community mental health clinic. Data collection lasted from February 2006 through March 2012.

INTERVENTIONS Participants received fourteen 60- to 90-minute sessions of prolonged exposure therapy (n = 31) or supportive counseling (n = 30).

Prolonged Exposure vs Supportive Counseling for Sexual Abuse–Related PTSD in Adolescent Girls
A Randomized Clinical Trial

Edna B. Foa, PhD; Carmen P. McLean, PhD; Sandra Capaldi, PsyD; David Rosenfield, PhD

MAIN OUTCOMES AND MEASURES All outcomes were assessed before treatment, at mid-treatment, and after treatment and at 3-, 6-, and 12-month follow-up. The primary outcome, PTSD symptom severity, was assessed by the Child PTSD Symptom Scale–Interview (range, 0-51; higher scores indicate greater severity). Secondary outcomes were presence or absence of PTSD diagnosis assessed by the *DSM-IV* Schedule for Affective Disorders and Schizophrenia for School-Age Children and functioning assessed by the Children's Global Assessment Scale (range, 1-100; higher scores indicate better functioning). Additional secondary measures, PTSD severity assessed by the Child PTSD Symptom Scale–Self-Report (range, 0-51; higher scores indicate greater severity) and depression severity assessed by the Children's Depression Inventory (range, 0-54; higher scores indicate greater severity), were also assessed weekly during treatment.

Prolonged Exposure vs Supportive Counseling for Sexual Abuse–Related PTSD in Adolescent Girls
A Randomized Clinical Trial

Edna B. Foa, PhD; Carmen P. McLean, PhD; Sandra Capaldi, PsyD; David Rosenfield, PhD

RESULTS Data were analyzed as intent to treat. During treatment, participants receiving prolonged exposure demonstrated greater improvement on the PTSD symptom severity scale (difference between treatments in improvement, 7.5; 95% CI, 2.5-12.5; $P < .001$) and on all secondary outcomes (loss of PTSD diagnosis: difference, 29.3%, 95% CI, 20.2%-41.2%; $P = .01$; self-reported PTSD severity: difference, 6.2; 95% CI, 1.2-11.2; $P = .02$; depression: difference, 4.9; 95% CI, 1.6-8.2; $P = .008$; global functioning: difference, 10.1; 95% CI, 3.4-16.8; $P = .008$). These treatment differences were maintained through the 12-month follow-up: for interviewer-assessed PTSD (difference, 6.0; 95% CI, 1.6-10.4; $P = .02$), loss of PTSD diagnosis (difference, 31.1; 95% CI, 14.7-34.8; $P = .01$), self-reported PTSD (difference, 9.3; 95% CI, 1.2-16.5; $P = .02$), depression (difference, 7.2; 95% CI, 1.4-13.0; $P = .02$), and global functioning (difference, 11.2; 95% CI, 4.5-17.9; $P = .01$).

Prolonged Exposure vs Supportive Counseling for Sexual Abuse–Related PTSD in Adolescent Girls
A Randomized Clinical Trial

Edna B. Foa, PhD; Carmen P. McLean, PhD; Sandra Capaldi, PsyD; David Rosenfield, PhD

CONCLUSION AND RELEVANCE Adolescents girls with sexual abuse–related PTSD experienced greater benefit from prolonged exposure therapy than from supportive counseling even when delivered by counselors who typically provide supportive counseling.

JAMA December 25, 2013 Volume 310, Number 24

Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

IMPORTANCE Approved medications for alcohol dependence are prescribed for less than 9% of US alcoholics.

OBJECTIVE To determine if gabapentin, a widely prescribed generic calcium channel/γ-aminobutyric acid–modulating medication, increases rates of sustained abstinence and no heavy drinking and decreases alcohol-related insomnia, dysphoria, and craving, in a dose-dependent manner.

DESIGN, PARTICIPANTS AND SETTING A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women older than 18 years with current alcohol dependence, conducted from 2004 through 2010 at a single-site, outpatient clinical research facility adjoining a general medical hospital.

INTERVENTIONS Oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling.

MAIN OUTCOMES AND MEASURES Rates of complete abstinence and no heavy drinking (coprimary) and changes in mood, sleep, and craving (secondary) over the 12-week study.

JAMA Intern Med. 2014;174(1):70-77

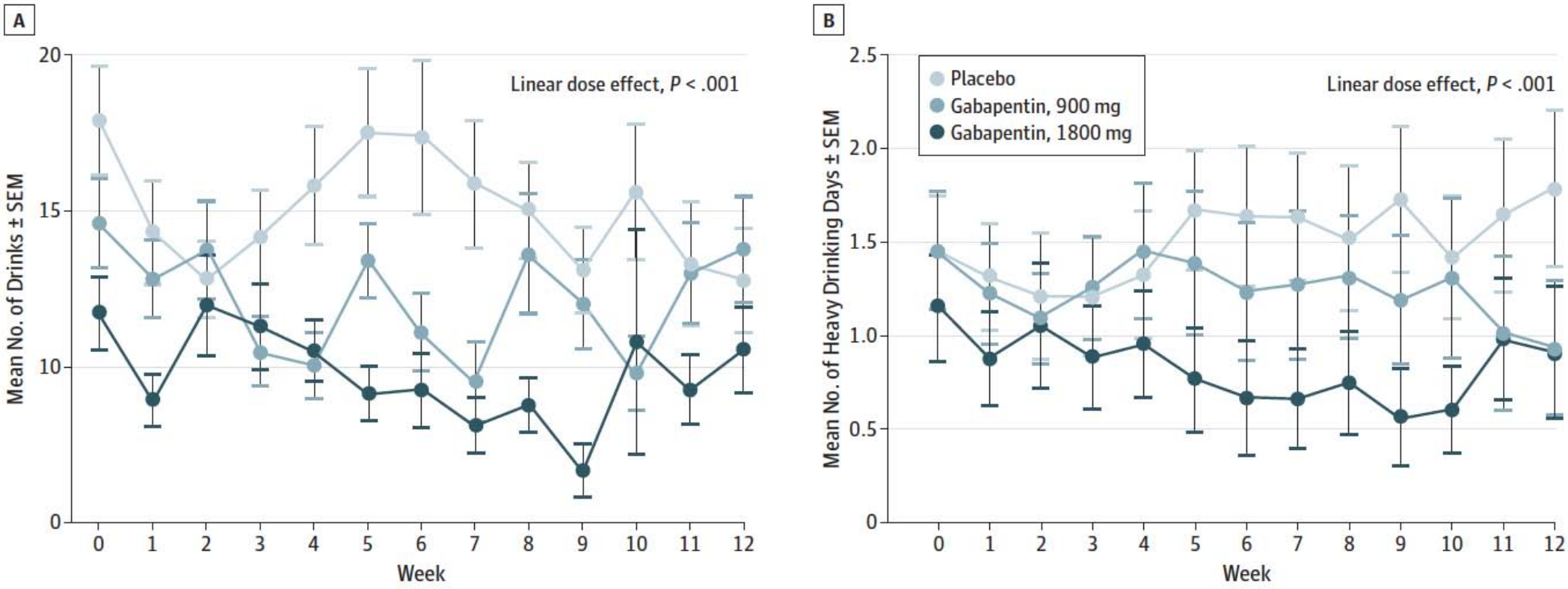
Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

RESULTS Gabapentin significantly improved the rates of abstinence and no heavy drinking. The abstinence rate was 4.1% (95% CI, 1.1%-13.7%) in the placebo group, 11.1% (95% CI, 5.2%-22.2%) in the 900-mg group, and 17.0% (95% CI, 8.9%-30.1%) in the 1800-mg group (P = .04 for linear dose effect; number needed to treat [NNT] = 8 for 1800 mg). The no heavy drinking rate was 22.5% (95% CI, 13.6%-37.2%) in the placebo group, 29.6% (95% CI, 19.1%-42.8%) in the 900-mg group, and 44.7% (95% CI, 31.4%-58.8%) in the 1800-mg group (P = .02 for linear dose effect; NNT = 5 for 1800 mg). Similar linear dose effects were obtained with measures of mood (F_2 = 7.37; P = .001), sleep (F_2 = 136; P < .001), and craving (F_2 = 3.56; P = .03). There were no serious drug-related adverse events, and terminations owing to adverse events (9 of 150 participants), time in the study (mean [SD], 9.1 [3.8] weeks), and rate of study completion (85 of 150 participants) did not differ among groups.

JAMA Intern Med. 2014;174(1):70-77

Figure 3. Gabapentin Effects on Number of Drinks per Week and Number of Heavy Drinking Days per Week During the 12-Week Study in the Intention-to-Treat Population



A, Number of drinks per week; B, number of heavy drinking days per week. Error bars indicate SEM. (N = 150.)

Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

CONCLUSIONS AND RELEVANCE Gabapentin (particularly the 1800-mg dosage) was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria, and craving, with a favorable safety profile. Increased implementation of pharmacological treatment of alcohol dependence in primary care may be a major benefit of gabapentin as a treatment option for alcohol dependence.

JAMA Intern Med. 2014;174(1):70-77

Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: Randomized double-blind placebo-controlled study

Amirhossein Modabbernia [a], Parvaneh Heidari [b], Robabeh Soleimani [b], Abdolrasoul Sobhani [c], Zahra Atrkar Roshan [d], Shervin Taslimi [a,e], Mandana Ashrafi [a], Mohammad Jafar Modabbernia [b,*]

1. Randomized double-blind placebo-controlled study aimed to determine the efficacy of melatonin 3 mg/day in prevention of olanzapine-induced metabolic side-effects.
2. 48 patients with first-episode schizophrenia who were eligible for olanzapine treatment, were randomly assigned to olanzapine plus either melatonin 3 mg/day or matched placebo for eight weeks.

Journal of Psychiatric Research 53 (2014) 133–140

Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: Randomized double-blind placebo-controlled study

Amirhossein Modabbernia [a], Parvaneh Heidari [b], Robabeh Soleimani [b], Abdolrasoul Sobhani [c], Zahra Atrkar Roshan [d], Shervin Taslimi [a,e], Mandana Ashrafi [a], Mohammad Jafar Modabbernia [b,*]

3. Anthropometric and metabolic parameters as well as psychiatric symptoms using PANSS were assessed at baseline, week 4, and 8.
4. Primary outcome measure was the change from baseline in weight at week 8.
5. Data were analyzed using t-test, Mann–Whitney U test, and mixed-effects model. Thirty-six patients had at least one post-baseline measurement.

Journal of Psychiatric Research 53 (2014) 133–140

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- At week eight, melatonin was associated with significantly less weight gain [mean difference (MD) = 3.2 kg, P = 0.023], increase in waist circumference [MD = 2.83 cm, P = 0.041] and triglyceride concentration [MD = 62 mg/dl, P = 0.090 (nearly significant)] than the placebo.
- Changes in cholesterol, insulin, and blood sugar concentrations did not differ significantly between the two groups. Patients in the melatonin group experienced significantly more reduction in their PANSS scores [MD = 12.9 points, P = 0.014] than the placebo group.
- No serious adverse events were reported.

Journal of Psychiatric Research 53 (2014) 133–140

Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: Randomized double-blind placebo-controlled study

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To summarize, in patients treated with olanzapine, short-term melatonin treatment

- Attenuates weight gain, abdominal obesity, and hypertriglyceridemia.
- It might also provide additional benefit for treatment of psychosis.

Journal of Psychiatric Research 53 (2014) 133–140

A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness

Gail L. Daumit, M.D., M.H.S., Faith B. Dickerson, Ph.D., M.P.H., Nae-Yuh Wang, Ph.D., Arlene Dalcin, R.D., Gerald J. Jerome, Ph.D., Cheryl A.M. Anderson, Ph.D., Deborah R. Young, Ph.D., Kevin D. Frick, Ph.D., Airong Yu, M.S., Joseph V. Gennusa III, Ph.D., R.D., L.D.N., Meghan Oefinger, B.S., Rosa M. Crum, M.D., M.H.S., Jeanne Charleston, R.N., Sarah S. Casagrande, Ph.D., Eliseo Guallar, M.D., Dr.P.H., M.P.H., Richard W. Goldberg, Ph.D., Leslie M. Campbell, B.A., and Lawrence J. Appel, M.D., M.P.H.

N ENGL J MED 368;17 NEJM.ORG APRIL 25, 2013

BACKGROUND

Overweight and obesity are epidemic among persons with serious mental illness, yet weight-loss trials systematically exclude this vulnerable population. Lifestyle interventions require adaptation in this group because psychiatric symptoms and cognitive impairment are highly prevalent. Our objective was to determine the effectiveness of an 18-month tailored behavioral weight-loss intervention in adults with serious mental illness.

METHODS

We recruited overweight or obese adults from 10 community psychiatric rehabilitation outpatient programs and randomly assigned them to an intervention or a control group. Participants in the intervention group received tailored group and individual weight-management sessions and group exercise sessions. Weight change was assessed at 6, 12, and 18 months.

A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness

RESULTS

Of 291 participants who underwent randomization, 58.1% had schizophrenia or a schizoaffective disorder, 22.0% had bipolar disorder, and 12.0% had major depression. At baseline, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 36.3, and the mean weight was 102.7 kg (225.9 lb). Data on weight at 18 months were obtained from 279 participants. Weight loss in the intervention group increased progressively over the 18-month study period and differed significantly from the control group at each follow-up visit. At 18 months, the mean between-group difference in weight (change in intervention group minus change in control group) was −3.2 kg (−7.0 lb, P=0.002); 37.8% of the participants in the intervention group lost 5% or more of their initial weight, as compared with 22.7% of those in the control group (P=0.009). There were no significant between-group differences in adverse events.

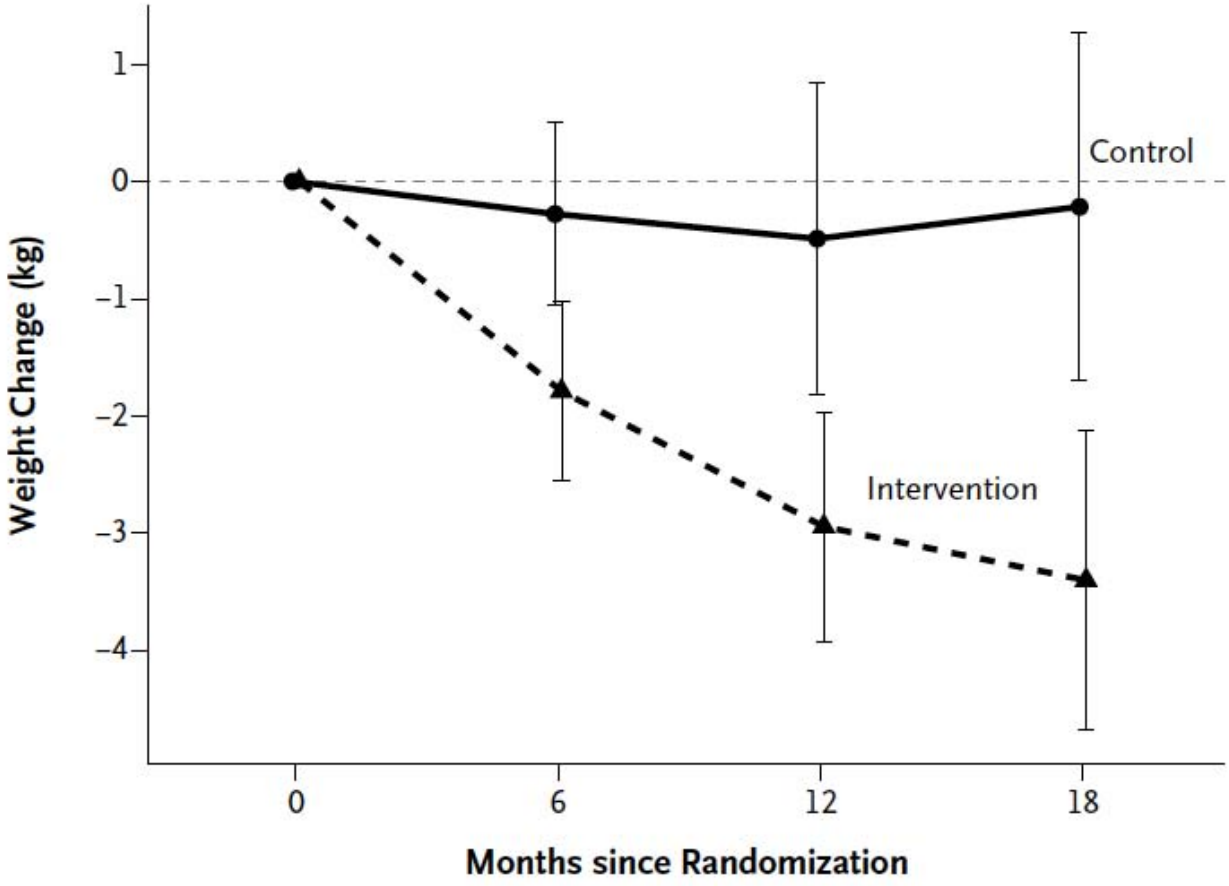

Figure 2. Mean Weight Change, According to Study Group.

The model-based estimates of the mean difference in changes in weight (the change in the intervention group minus the change in the control group) between the two groups at 6, 12, and 18 months were −1.5 kg (95% CI, −2.6 to −0.4; P=0.007), −2.5 kg (95% CI, −4.1 to −0.8; P=0.004), and −3.2 kg (95% CI, −5.1 to −1.2; P=0.002), respectively. To convert values for weight to pounds, multiply by 2.2.

A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness

CONCLUSIONS

A behavioral weight-loss intervention significantly reduced weight over a period of 18 months in overweight and obese adults with serious mental illness. Given the epidemic of obesity and weight-related disease among persons with serious mental illness, our findings support implementation of targeted behavioral weight-loss interventions in this high-risk population. (Funded by the National Institute of Mental Health; ACHIEVE ClinicalTrials.gov number, NCT00902694.)

Psychological Interventions for Psychosis: A Meta-Analysis of Comparative Outcome Studies

David Trevor Turner, M.Sc., M.Sc.Res.

Mark van der Gaag, Ph.D.

Eirini Karyotaki, M.Sc.Res.

Pim Cuijpers, Ph.D.

Objective: Meta-analyses have demonstrated the efficacy of various interventions for psychosis, and a small number of studies have compared such interventions. The aim of this study was to provide further insight into the relative efficacy of psychological interventions for psychosis.

Method: Forty-eight outcome trials comparing psychological interventions for psychosis were identified. The comparisons included 3,295 participants. Categorization of interventions resulted in six interventions being compared against other interventions pooled. Hedges' g was calculated for all comparisons. Risk of bias was assessed using four items of the Cochrane risk of bias tool, and sensitivity analyses were conducted. Researcher allegiance was assessed, and sensitivity analyses were conducted for robust significant findings.

Results: Cognitive-behavioral therapy (CBT) was significantly more efficacious than other interventions pooled in reducing positive symptoms (g=0.16). This finding was robust in all sensitivity analyses for risk of bias but lost significance in sensitivity analyses for researcher allegiance, which suffered from low power. Social skills training was significantly more efficacious in reducing negative symptoms (g=0.27). This finding was robust in sensitivity analyses for risk of bias and researcher allegiance. Significant findings for CBT, social skills training, and cognitive remediation for overall symptoms were not robust after sensitivity analyses. CBT was significantly more efficacious when compared directly with befriending for overall symptoms (g=0.42) and supportive counseling for positive symptoms (g=0.23).

Conclusions: There are small but reliable differences in efficacy between psychological interventions for psychosis, and they occur in a pattern consistent with the specific factors of particular interventions.

(Am J Psychiatry 2014; 171:523–538)

Psychological Interventions for Psychosis: A Meta-Analysis of Comparative Outcome Studies

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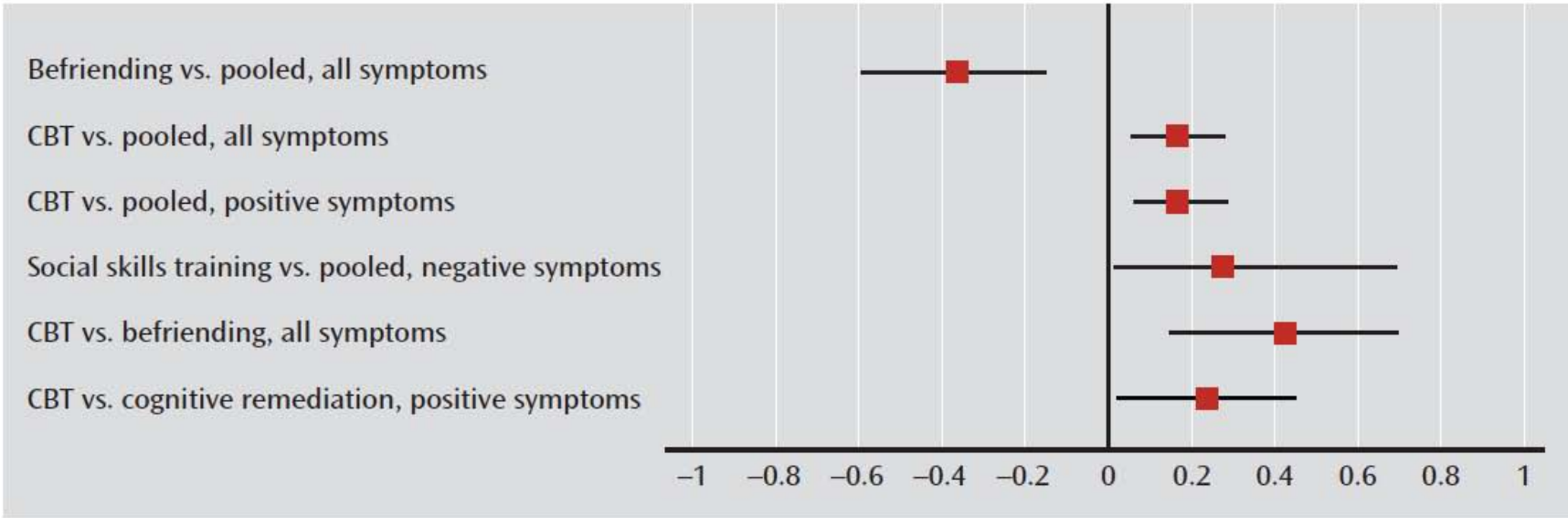
- CBT was significantly more efficacious than other interventions pooled in reducing positive symptoms (g=0.16).
- Social skills training was significantly more efficacious in reducing negative symptoms (g=0.27).
- Significant findings for CBT, social skills training, and cognitive remediation for overall symptoms were not robust after sensitivity analyses.
- CBT was significantly more efficacious when compared directly with befriending for overall symptoms (g=0.42) and supportive counseling for positive symptoms (g=0.23).

(Am J Psychiatry 2014; 171:523–538)

FIGURE 2. Main Results of Comparisons of Psychological Interventions for Psychotic Symptoms[a]



[a] The other main comparisons did not result in significant findings. This figure does not include sensitivity analyses for risk of bias or researcher allegiance; complete results are presented in Tables 3 and 4. CBT=cognitive-behavioral therapy.

Am J Psychiatry 171:5, May 2014

Psychological Interventions for Psychosis: A Meta-Analysis of Comparative Outcome Studies

David Trevor Turner, M.Sc., M.Sc.Res.

Mark van der Gaag, Ph.D.

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Conclusions

There are small but reliable differences in efficacy between psychological interventions for psychosis, and they occur in a pattern consistent with the specific factors of particular interventions.

(Am J Psychiatry 2014; 171:523–538)

Psychological Interventions for Psychosis: A Meta-Analysis of Comparative Outcome Studies

Clinical Guidance: Psychological Interventions for Psychosis

Cognitive-behavioral therapy is superior to other psychological treatments for reducing positive symptoms, and social skills training is more efficacious for negative symptoms, according to a meta-analysis by Turner et al. Befriending is less helpful in ameliorating symptoms than other interventions. In his editorial, Strauss (p. 479) underscores the need to consider the diversity of treatment options in relation to the even greater diversity of patients with severe mental illness. Cognitive training focuses on neural systems rather than symptoms, and Keshavan et al. (p. 510) report that it can benefit patients with schizophrenia and may improve functioning when combined with other forms of rehabilitation and coaching. The editorial by Harvey (p. 482) notes that training in a global cognitive process, such as planning, exercises multiple basic skills, such as sustained attention.

Am J Psychiatry 171:5, May 2014

Efficacy of Initiating Tobacco Dependence Treatment in Inpatient Psychiatry: A Randomized Controlled Trial

Judith J. Prochaska, PhD, MPH, Stephen E. Hall, MD, Kevin Delucchi, PhD, and Sharon M. Hall, PhD

Objectives. We evaluated the efficacy of a motivational tobacco cessation treatment combined with nicotine replacement relative to usual care initiated in inpatient psychiatry.

Methods. We randomized participants (n = 224; 79% recruitment rate) recruited from a locked acute psychiatry unit with a 100% smoking ban to intervention or usual care. Prior to hospitalization, participants averaged 19 (SD = 12) cigarettes per day; only 16% intended to quit smoking in the next 30 days.

Efficacy of Initiating Tobacco Dependence Treatment in Inpatient Psychiatry: A Randomized Controlled Trial

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Results.

- Verified smoking 7-day point prevalence abstinence was significantly higher for intervention than usual care at month 3 (13.9% vs. 3.2%), 6 (14.4% vs. 6.5%), 12 (19.4% vs. 10.9%), and 18 (20.0% vs. 7.7%; odds ratio [OR] = 3.15; 95% confidence interval [CI] = 1.22, 8.14; P = .018; retention > 80%).
- Psychiatric measures did not predict abstinence; measures of motivation and tobacco dependence did.
- The usual care group had a significantly greater likelihood than the intervention group of psychiatric rehospitalization (adjusted OR = 1.92; 95% CI = 1.06, 3.49).

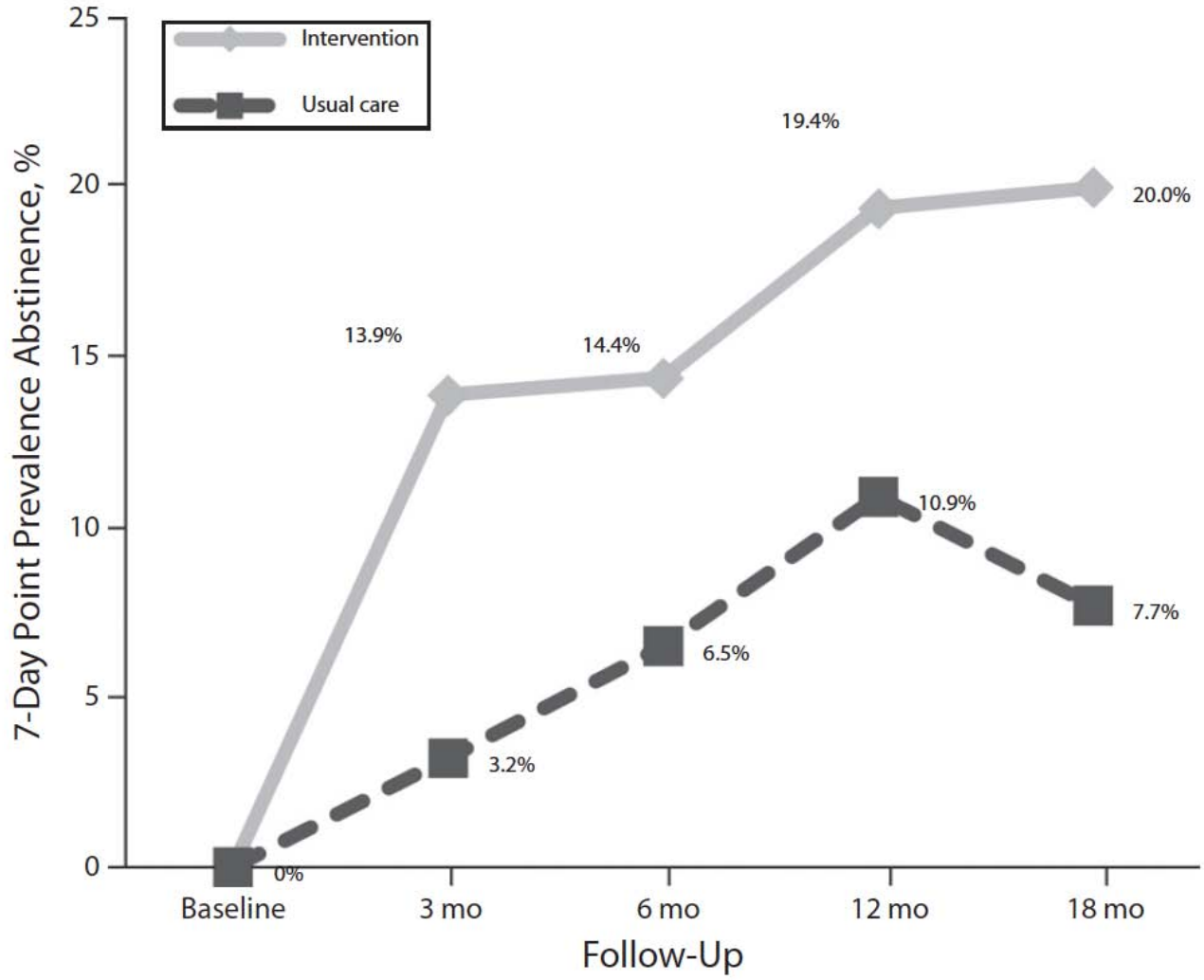

FIGURE 1—Verified point prevalence abstinence rates by treatment condition and time in a randomized controlled trial of a smoking cessation intervention among psychiatric inpatients: San Francisco, CA, July 2006–December 2008

Efficacy of Initiating Tobacco Dependence Treatment in Inpatient Psychiatry: A Randomized Controlled Trial

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Conclusions:

The findings support initiation of motivationally tailored tobacco cessation treatment during acute psychiatric hospitalization. Psychiatric severity did not moderate treatment efficacy, and cessation treatment appeared to decrease rehospitalization risk, perhaps by providing broader therapeutic benefit.

Efficacy of Initiating Tobacco Dependence Treatment in Inpatient Psychiatry: A Randomized Controlled Trial

Judith J. Prochaska, PhD, MPH, Stephen E. Hall, MD, Kevin Delucchi, PhD, and Sharon M. Hall, PhD

Conclusions

Our findings demonstrate that supporting people with serious mental illness in smoking cessation efforts during their hospital stay and beyond is feasible and worthwhile. It is possible to provide effective support across the hospital and community continuum, with little burden on services, with significant effects on cessation, and without harm to mental health recovery. ■

This is a very well done randomized trial of an important intervention targeting an important population at an important time (smoking cessation during inpatient psychiatric hospitalization). The successful 18-month follow up is a welcome addition to a psychiatric literature where 6- and 12-week trials are common. Clearly, more data on quit rates among homeless and marginally housed populations, and among persons with schizophrenia spectrum disorders, are needed. This trial suggests that integrating smoking cessation interventions into mental health treatment settings is feasible and effective.

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Tsai A: F1000Prime Recommendation of [Prochaska JJ et al., Am J Public Health 2013]. In F1000Prime, 19 Sep 2013; DOI: 10.3410/f.718080115.793483536. F1000Prime.com/718080115#eval793483536

Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: A meta-analysis

Chuan Shi [a,b,c,d], Xin Yu [c,d], Eric F.C. Cheung [e], David H.K. Shum [f], Raymond C.K. Chan [a,b,*]

Psychiatry Research 215 (2014) 505–513

A B S T R A C T

This study sought to determine the moderators in the treatment effect of repetitive transcranial magnetic stimulation (rTMS) on negative symptoms in schizophrenia. We performed a meta-analysis of prospective studies on the therapeutic application of rTMS in schizophrenia assessing the effects of both low-frequency and high-frequency rTMS on negative symptoms. Results indicate that rTMS is effective in alleviating negative symptoms in schizophrenia. The effect size was moderate (0.63 and 0.53, respectively). The effect size of rTMS on negative symptoms in sham-controlled trials was 0.80 as measured by the SANS and 0.41 as measured by the PANSS. A longer duration of illness was associated with poorer efficacy of rTMS on negative symptoms. A 10 Hz setting, at least 3 consecutive weeks of treatment, treatment site at the left dorsolateral prefrontal cortex (DLPFC) and a 110% motor threshold (MT) were found to be the best rTMS parameters for the treatment of negative symptoms. The results of our meta-analysis suggest that rTMS is an effective treatment option for negative symptoms in schizophrenia. The moderators of rTMS on negative symptoms included duration of illness, stimulus frequency, duration of illness, position and intensity of treatment as well as the type of outcome measures used.

Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: A meta-analysis

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- Despite limitations, this study provides strong evidence to support that rTMS is an efficacious add-on treatment for negative symptoms in schizophrenia, especially for individuals with early stage schizophrenia.
- The optimal parameters appear to be a frequency of 10Hz, stimulation at the left DLPFC, a 110% MT and at least 3 consecutive weeks of treatment.
- Further studies should be conducted to clarify if these parameters are more effective for schizophrenia patients with predominant negative symptoms.

Psychiatry Research 215 (2014) 505–513

Adult Diagnostic and Functional Outcomes of DSM-5 Disruptive Mood Dysregulation Disorder

William E. Copeland, Ph.D.

Lilly Shanahan, Ph.D.

Helen Egger, M.D.

Adrian Angold, M.R.C.Psych.

E. Jane Costello, Ph.D.

Objective: Disruptive mood dysregulation disorder (DMDD) is a new disorder for DSM-5 that is uncommon and frequently co-occurs with other psychiatric disorders. Here, the authors test whether meeting diagnostic criteria for this disorder in childhood predicts adult diagnostic and functional outcomes.

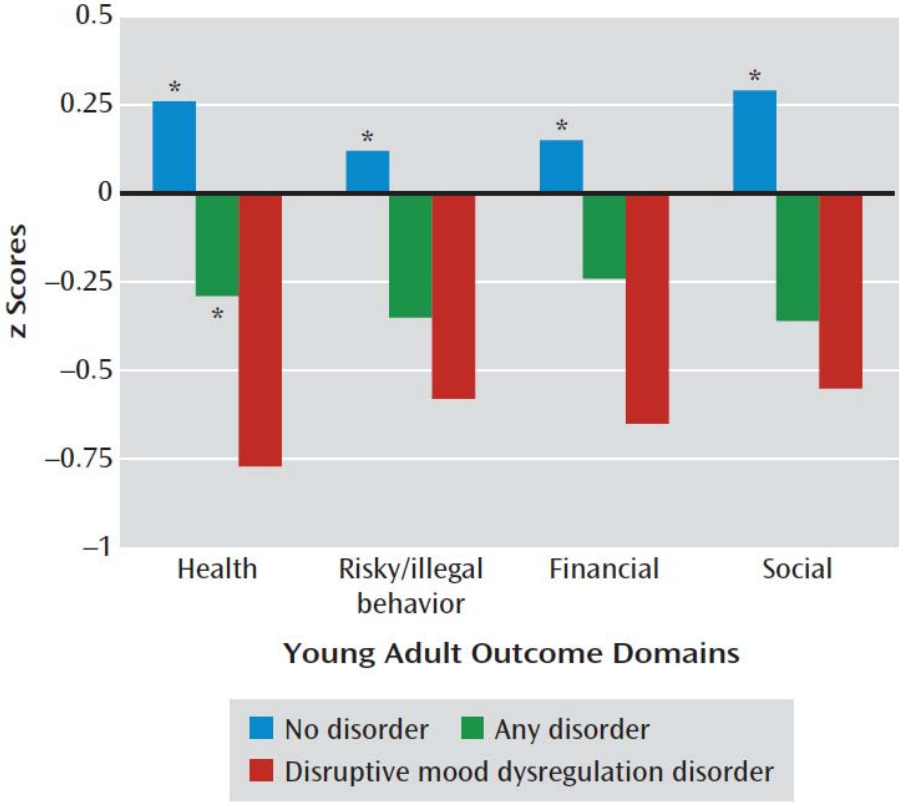
Method: In a prospective, population-based study, individuals were assessed with structured interviews up to six times in childhood and adolescence (ages 10 to 16 years; 5,336 observations of 1,420 youths) for symptoms of DMDD and three times in young adulthood (ages 19, 21, and 24–26 years; 3,215 observations of 1,273 young adults) for psychiatric and functional outcomes (health, risky/illegal behavior, financial/educational functioning, and social functioning).

Results: Young adults with a history of childhood DMDD had elevated rates of anxiety and depression and were more likely to meet criteria for more than one adult disorder relative to comparison subjects with no history of childhood psychiatric disorders (noncases) or individuals meeting criteria for psychiatric disorders other than DMDD in childhood or adolescence (psychiatric comparison subjects). Participants with a history of DMDD were more likely to have adverse health outcomes, be impoverished, have reported police contact, and have low educational attainment as adults compared with either psychiatric or noncase comparison subjects.

Conclusions: The long-term prognosis of children with DMDD is one of pervasive impaired functioning that in many cases is worse than that of other childhood psychiatric disorders.

(Am J Psychiatry 2014; 171:668–674)

FIGURE 1. Means Values for Adult Standardized Outcome Scales by Childhood Diagnostic Status[a]



Negative scores indicate more problems than the mean for the total sample. Asterisks indicate whether the comparison group was statistically different from the disruptive mood dysregulation disorder (DMDD) group ($p<0.05$). Children with DMDD had worse health outcomes than noncase comparison subjects (means ratio=2.8; 95% CI=1.8–2.1, $p<0.001$) and psychiatric comparison subjects (means ratio=1.6; 95% CI=1.0–2.5, $p=0.04$). DMDD case subjects had higher levels of all other outcomes compared with noncase comparison subjects (risky/illegal means ratio=2.0; 95% CI=1.1–3.6, $p=0.02$; financial/educational means ratio=2.3; 95% CI=1.6–3.3, $p<0.001$; and social means ratio=2.2; 95% CI=1.5–3.3, $p<0.001$). Relative to psychiatric comparison subjects, DMDD case subjects did not have worse risky/illegal behavior outcomes (means ratio=1.2; 95% CI=0.7–2.3, $p=0.45$) or financial/educational outcomes (means ratio=1.2; 95% CI=0.8–1.8, $p=0.34$), but had marginally worse social outcomes (means ratio=1.5; 95% CI=1.0–2.3, $p=0.06$).

Adult Diagnostic and Functional Outcomes of DSM-5 Disruptive Mood Dysregulation Disorder

Conclusions

Disruptive mood dysregulation disorder is a new disorder to DSM-5, and there is no question that research on irritability has increased dramatically over the last decade, but children with this constellation of symptoms have always been with us (24). Caspi et al. (5) described children with high levels of temper tantrums as "moving against the world" and documented their downward social mobility and turbulent social lives. Our analysis suggests that this bleak prognosis includes increased health problems, continued emotional distress, financial strain, and social isolation. For most children, development provides a constant series of opportunities for recovery and rehabilitation (25), but for children with DMDD, the accumulation of early failures may perpetuate a lifetime of limited opportunity and compromised well-being. As such, children with persistent irritable mood punctuated by frequent outbursts—regardless of what we call this cluster of symptoms—should be a priority for clinical care and treatment development.

Am J Psychiatry 171:6, June 2014

The new pediatric diagnosis in the DSM-5, disruptive mood dysregulation disorder (DMDD), is intriguing and not researched. This paper adds to its validity by describing its prognosis into adulthood. DMDD is different from bipolar disorder in kids in that there is a constant irritability with recurrent angry outbursts that appear before the age of 10. These kids lose their temper with tantrums and appear resentful. Out of a sample of 81 such kids in The Great Smoky Mountains Study (n=1420), 75 were re-interviewed at ages 19, 21 and 25. The authors found that the rate of psychiatric comorbidity into adulthood (chiefly anxiety and mood disorders) was 5-7 times elevated with a pervasive impaired function, including poverty. Irritability should be taken seriously.

Allgulander C: F1000 Prime Recommendation of [Copeland WE et al., Am J Psychiatry 2014, 171(6):668-74]. In F1000Prime, 15 Jul 2014; DOI: 10.3410/f.718369763.793497125. F1000Prime.com/718369763#eval793497125

Predictors of Natural and Unnatural Mortality among Patients with Personality Disorder: Evidence from a Large UK Case Register

Marcella Lei-Yee Fok[1]*, Robert Stewart[2], Richard D. Hayes[2¶], Paul Moran[1¶]

Background: People with personality disorder have reduced life expectancy, yet, within this population, little is known about the clinical predictors of natural and unnatural deaths. We set out to investigate this, using a large cohort of secondary mental health patients with personality disorder.

Methods: We identified patients with an ICD-10 diagnosis of personality disorder, aged ≥15 years in a large secondary mental healthcare case register. The case register was linked to national mortality tracing. Using Cox regression, we modelled the effect of a number of pre-specified clinical variables on all-cause, natural cause and unnatural cause mortality.

Predictors of Natural and Unnatural Mortality among Patients with Personality Disorder: Evidence from a Large UK Case Register

Marcella Lei-Yee Fok[1]*, Robert Stewart[2], Richard D. Hayes[2¶], Paul Moran[1¶]

Findings: 2,440 patients were identified. Eighty-five deaths (3.5% of cohort) occurred over a 5-year observation period, of which over 50% were from natural causes. All-cause mortality was associated with alcohol or drug use (adjusted Hazard Ratio [aHR] 2.3; 95% CI 1.3–4.1), physical illness (aHR 1.9; 95% CI 1.0–3.6), and functional impairment (aHR 1.9; 95% CI 1.0–3.6). Natural cause mortality was associated with mild problems of alcohol or drug use (aHR 3.4; 95% CI 1.5–7.4), and physical illness (aHR 2.4; 95% CI 1.0–5.6). Unnatural cause mortality was associated only with severe alcohol or drug use (aHR 3.1; 95% CI 1.3–7.3).

Interpretation: Alcohol and drug use, physical illness, and functional impairment are predictors of mortality in individuals with personality disorder. Clinicians should be aware of the existence of problems in these domains, even at mild levels, when assessing the needs of patients with personality disorder.

We know surprisingly little about the long-term progress of people with personality disorder. This study, which has some limitations, as clinical diagnoses of ICD-10 personality disorder are a little fuzzy, at least casts some light on the reasons for premature mortality. Interestingly, few died by suicide, and this is probably because this study is not focused, as most are in this area, on borderline personality disorder.

Tyrer P: F1000Prime Recommendation of [Fok ML et al., PLoS ONE 2014, 9(7):e100979]. In F1000Prime, 14 Jul 2014; DOI: 10.3410/f.718482674.793497051. F1000Prime.com/718482674#eval793497051

Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting

Daniel K. Hall-Flavin[a], Joel G. Winner[e,f], Josiah D. Allen[f], Joseph M. Carhart[f], Brian Proctor[d], Karen A. Snyder[a], Maureen S. Drews[b], Linda L. Eisterhold[a], Jennifer Geske[c] and David A. Mrazek[a]

Pharmacogenetics and Genomics 2013, **23**:535–548

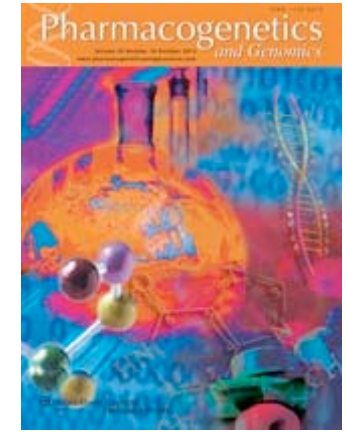
ABSTRACT

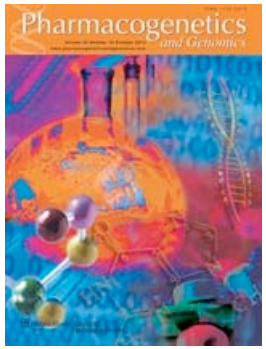
OBJECTIVE: The objective was to evaluate the potential benefit of an integrated, five-gene pharmacogenomic test and interpretive report (GeneSight) for the management of psychotropic medications used to treat major depression in an outpatient psychiatric practice.

METHODS: The open-label study was divided into two groups. In the first (unguided) group (n=113), pharmacogenomic information was not shared until all participants completed the study. In the second (guided) group (n=114), the pharmacogenomic report was provided to physicians for clinical use. Three depression ratings, the 17-item Hamilton Rating Scale for Depression (HAMD-17), the Quick Inventory of Depressive Symptomatology - Clinician Rated (QIDS-C16), and the Patient Health Questionnaire (PHQ-9), were collected at baseline, and at 2, 4, and 8 weeks.

RESULTS: The guided group experienced greater percent improvement in depression scores from baseline on all three depression instruments (HAMD-17, P<0.0001; QIDS-C16, P<0.0001; PHQ-9, P<0.0001) compared with the unguided group. Eight-week response rates were higher in the guided group than in the unguided group on all three measurements (HAMD-17, P=0.03; QIDS-C16, P=0.005; PHQ-9, P=0.01). Eight-week QIDS-C16 remission rates were higher in the guided group (P=0.03). Participants in the unguided group who at baseline were prescribed a medication that was most discordant with their genotype experienced the least improvement compared with other unguided participants (HAMD-17, P=0.007). Participants in the guided group and on a baseline medication most discordant with their genotype showed the greatest improvement compared with the unguided cohort participants (HAMD-17, P=0.01).

CONCLUSION: These findings replicate previous studies and demonstrate significantly improved depression outcomes with use of GeneSight, an integrated, multigenetic pharmacogenomic testing platform. « less





Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting

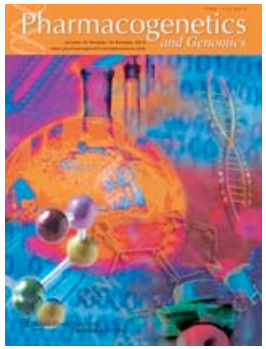
Daniel K. Hall-Flavin[a], Joel G. Winner[e,f], Josiah D. Allen[f], Joseph M. Carhart[f], Brian Proctor[d], Karen A. Snyder[a], Maureen S. Drews[b], Linda L. Eisterhold[a], Jennifer Geske[c] and David A. Mrazek[a]

- Several different gene products handling antidepressants in the body (like metabolizing enzymes and transporters, and their targets) are polymorphic, and these polymorphisms might influence the response to treatment.
- This study assessed the value of a five-gene (CYP2D6, CYP2C19, CYP1A2, SLCA4 and HTR2A) pharmacogenomic test and interpretive report (GeneSight) for the management of psychotropic medications (n=26) used to treat major depression in an outpatient psychiatric practice.

Objective.

To evaluate the potential benefit of an integrated, five-gene pharmacogenomic test and interpretive report (GeneSight) for the management of psychotropic medications used to treat major depression in an outpatient psychiatric practice.

Pharmacogenetics and Genomics 2013, 23:535–548



Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting

Daniel K. Hall-Flavin[a], Joel G. Winner[e,f], Josiah D. Allen[f], Joseph M. Carhart[f], Brian Proctor[d], Karen A. Snyder[a], Maureen S. Drews[b], Linda L. Eisterhold[a], Jennifer Geske[c] and David A. Mrazek[a]

Methods:

- Open-label study, divided into two groups. In the first (unguided) group (n =113), pharmacogenomic information was not shared until all participants completed the study. In the second (guided) group (n= 114), the pharmacogenomic report was provided to physicians for clinical use.
- Three depression ratings, the 17-item Hamilton Rating Scale for Depression (HAMD-17), the Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C16), and the Patient Health Questionnaire (PHQ-9), were collected at baseline, and at 2, 4, and 8 weeks.

Pharmacogenetics and Genomics 2013, 23:535–548

Antidepressants

Use as directed	Use with caution	Use with increased caution and with more frequent monitoring
Citalopram (Celexa) Desvenlafaxine (Pristiq) Escitalopram (Lexapro) Fluvoxamine (Luvox) Selegiline (Emsam) Sertraline (Zoloft)	Duloxetine (Cymbalta) [1] Miratazapine (Remeron) [1] Trazodone (Desyrel) [1]	Amitriptyline (Elavil) [6] Bupropion (Wellbutrin) [6] Clomipramine (Anafranil) [6] Desipramine (Norpramin) [6] Fluoxetine (Prozac) [6] Imipramine (Tofranil) [6] Nortriptyline (Pamelor) [6] Paroxetine (Paxil) [6] Venlafaxine (Effexor) [6]

Antipsychotics

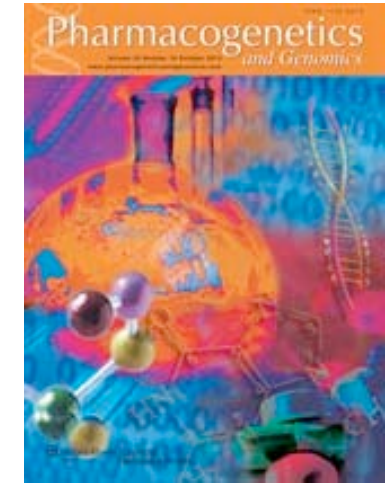
Use as directed	Use with caution	Use with increased caution and with more frequent monitoring
Quetiapine (Seroquel) Ziprasidone (Geodon)	Clozapine (Clozaril) [1] Olanzapine (Zyprexa) [1] Risperidone (Risperdal) [1]	Aripiprazole (Abilify) [6] Haloperidol (Haldol) [6] Perphenazine (Trilafon) [6]

[1] Serum level may be too high, lower doses may be required.
[6] Use of this drug is associated with an increased risk of side effects.

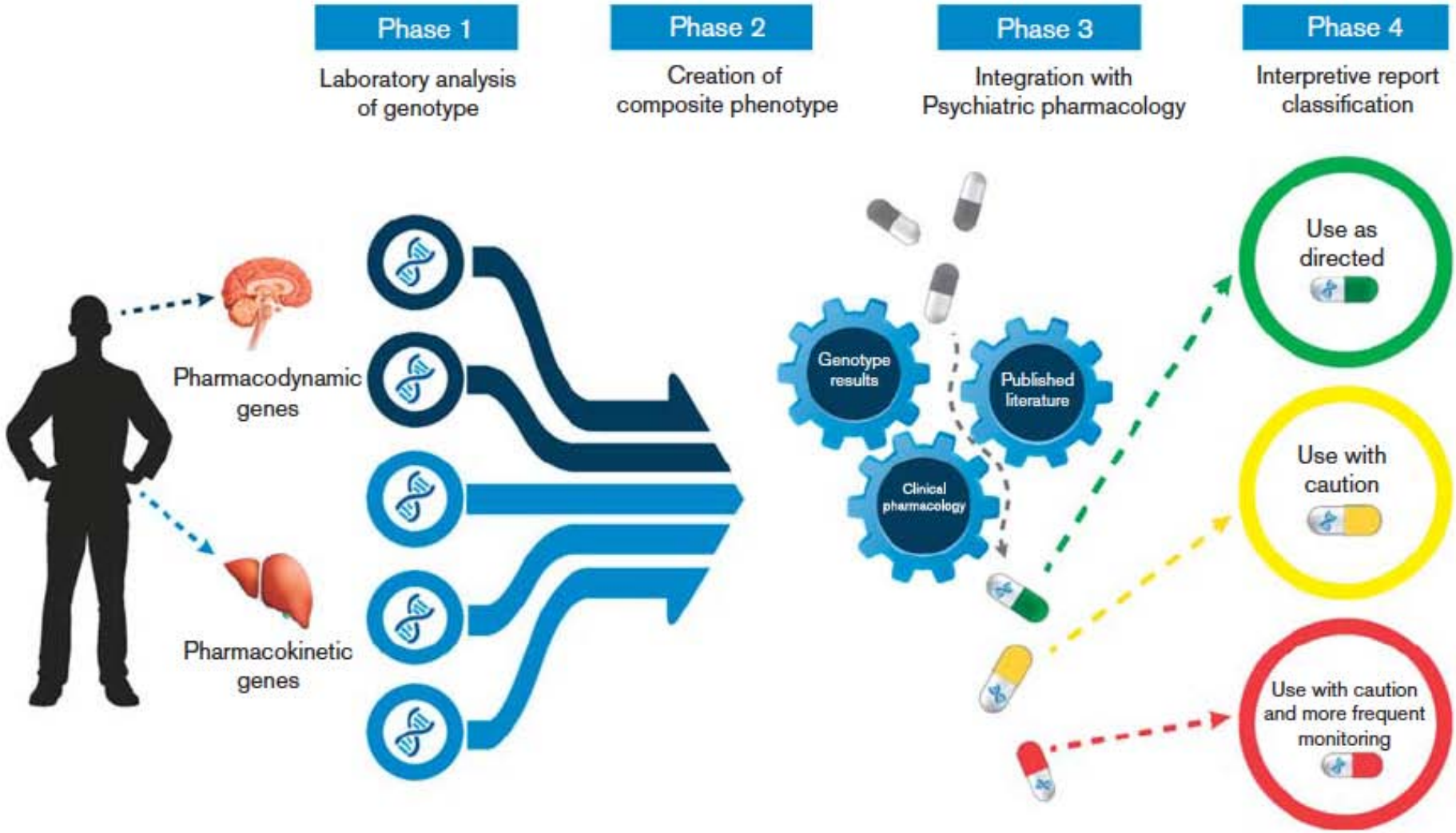
Patient genotypes and phenotypes

Gene	Genotype	Predicted phenotype
CYP2D6	*4/*4	Poor metabolizer
CYP2C19	*1/*1	Extensive metabolizer
CYP1A2	–163C>A – C/A	Extensive metabolizer
SLC6A4	L/L	High activity
HTR2A	C/C	Reduced activity

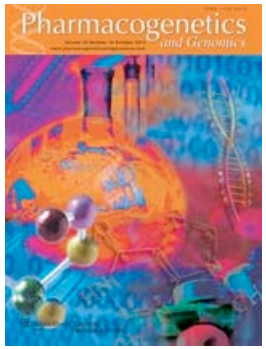
An example of a pharmacogenomic interpretive report for one individual participant. Pharmacogenomic test results are used to categorize medications based on the individual pharmacokinetic and pharmacodynamic factors that are salient to each medication.



Pharmacogenetics and Genomics 2013, **23**:535–548



Medication binning methodology of the GeneSight interpretive report.



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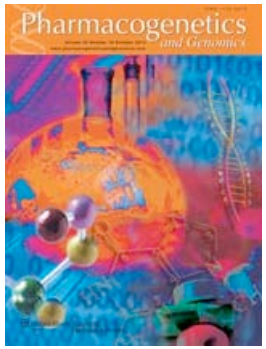
Results:

The guided group experienced 20-55% better improvement in depression scores from baseline on all three depression instruments ($P<0.0001$) compared with the unguided group.

- The guided group experienced greater percent improvement in depression scores from baseline on all three depression instruments compared with the unguided group.
- Eight-week response rates were higher in the guided group than in the unguided group on all three measurements.
- Eight-week QIDS-C16 remission rates were higher in the guided group.
- Participants in the unguided group who at baseline were prescribed a medication that was most discordant with their genotype experienced the least improvement compared with other unguided participants.
- Participants in the guided group and on a baseline medication most discordant with their genotype showed the greatest improvement compared with the unguided cohort participants.

Pharmacogenetics and Genomics 2013, 23:535–548



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Conclusion:

These findings replicate previous studies and demonstrate significantly improved depression outcomes with use of GeneSight, an integrated, multigenetic pharmacogenomic testing platform.

Pharmacogenetics and Genomics 2013, 23:535–548

- The results are surprisingly good, but biasing factors might have been involved:
  - some of the authors are employed by the company manufacturing GeneSight, and
  - the senior author developed the intellectual property [IP] licensed to the company.
- Number of gene variations (five) measured by the test is small
- Impacts of the CYP1A2, SLC6A4 (serotonin transporter) and HTR2A (serotonin receptor) polymorphisms in the treatment of major depression are not really validated.
- There were many more drop outs in the guided group, of an unclear basis.

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Ingelman-Sundberg M: F1000Prime Recommendation of [Hall-Flavin DK et al., Pharmacogenet Genomics 2013, 23(10):535-48]. In F1000Prime, 30 Sep 2013; DOI: 10.3410/f.718116166.793484201. F1000Prime.com/718116166#eval793484201

Nevertheless, this study should be followed up by other studies in this area, to cast light on the question of whether the treatment of major depression is indeed improved by genotype-assisted dosing regimens.

F1000 FACULTY of 1000

Ingelman-Sundberg M: F1000Prime Recommendation of [Hall-Flavin DK et al., Pharmacogenet Genomics 2013, 23(10):535-48]. In F1000Prime, 30 Sep 2013; DOI: 10.3410/f.718116166.793484201. F1000Prime.com/718116166#eval793484201

Maintenance Treatment With Varenicline for Smoking Cessation in Patients With Schizophrenia and Bipolar Disorder
A Randomized Clinical Trial

A. Eden Evins, MD, MPH; Corinne Cather, PhD; Sarah A. Pratt, PhD; Gladys N. Pachas, MD; Susanne S. Hoeppner, PhD; Donald C. Goff, MD; Eric D. Achtyes, MD, MS; David Ayer, PhD; David A. Schoenfeld, PhD

IMPORTANCE It is estimated that more than half of those with serious mental illness smoke tobacco regularly. Standard courses of pharmacotherapeutic cessation aids improve short-term abstinence, but most who attain abstinence relapse rapidly after discontinuation of pharmacotherapy.

OBJECTIVE To determine whether smokers diagnosed with schizophrenia and bipolar disease have higher rates of prolonged tobacco abstinence with maintenance pharmacotherapy than with standard treatment.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled, parallel-group, relapse-prevention clinical trial conducted in 10 community mental-health centers. Of 247 smokers with schizophrenia or bipolar disease recruited from March 2008-April 2012, 203 received 12-weeks' open-label varenicline and cognitive behavioral therapy and 87 met abstinence criteria to enter the relapse prevention intervention.

INTERVENTIONS Participants who had 2 weeks or more of continuous abstinence at week 12 of open treatment were randomly assigned to receive cognitive behavioral therapy and double-blind varenicline (1 mg, 2 per day) or placebo from weeks 12 to 52. Participants then discontinued study treatment and were followed up to week 76.

JAMA January 8, 2014 Volume 311, Number 2

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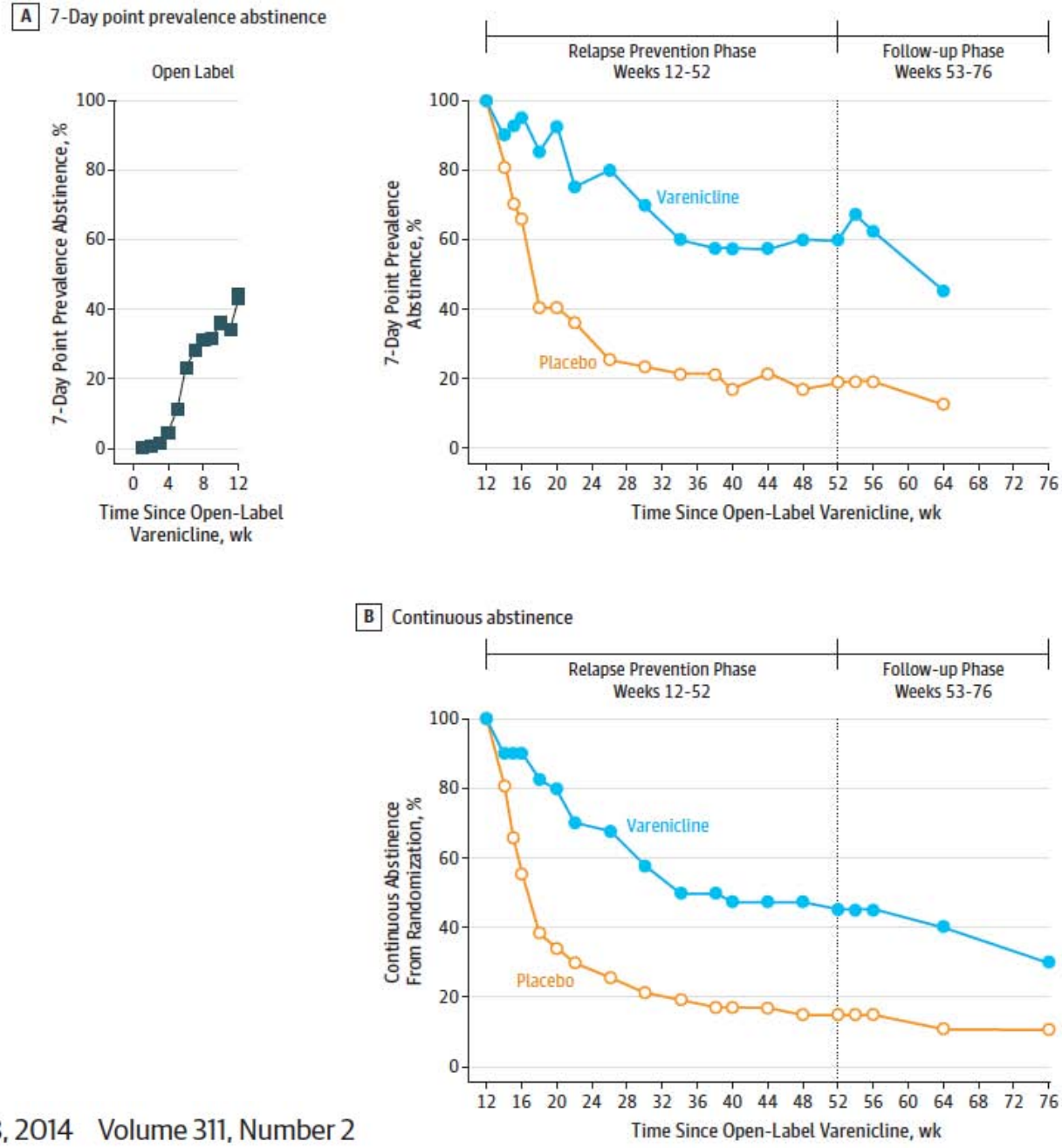
MAIN OUTCOMES AND MEASURES Seven-day rate of continuous abstinence at study week 52, the end of the relapse-prevention phase, confirmed by exhaled carbon monoxide. Secondary outcomes were continuous abstinence rates for weeks 12 through 64 based on biochemically verified abstinence and weeks 12 through 76, based on self-reported smoking behavior.

RESULTS Sixty-one participants completed the relapse-prevention phase; 26 discontinued participation (7 varenicline, 19 placebo) and were considered to have relapsed for the analyses; 18 of these had relapsed prior to dropout. At week 52, point-prevalence abstinence rates were 60% in the varenicline group (24 of 40) vs 19% (9 of 47) in the placebo group (odds ratio [OR], 6.2; 95% CI, 2.2-19.2; $P < .001$). From weeks 12 through 64, 45% (18 of 40) among those in the varenicline group vs 15% (7 of 47) in the placebo group were continuously abstinent (OR, 4.6; 95% CI, 1.5-15.7; $P = .004$), and from weeks 12 through 76, 30% (12 of 40) in the varenicline group vs 11% (5 of 47) in the placebo group were continuously abstinent (OR, 3.4; 95% CI, 1.02-13.6; $P = .03$). There were no significant treatment effects on psychiatric symptom ratings or psychiatric adverse events.

Figure 2. Point-Prevalence and Continuous Abstinence Rates During Study Treatment and Follow-up Phases



At week 16, cognitive behavioral therapy sessions were tapered to twice a month; at week 20, to once a month. *P* values are based on Fisher exact tests. Seven-day point-prevalence was higher for those assigned to varenicline at week 52 ($P < .001$) and at week 64 ($P < .01$). Continuous abstinence was higher for those assigned to the varenicline group from weeks 12 through 52 ($P < .01$), weeks 12 through 64 ($P < .01$), and weeks 12 through 76 ($P < .05$). There were 40 participants in the varenicline and 47 in the placebo group throughout the relapse-prevention and follow-up phases, and there were 203 participants in the open-label phase.

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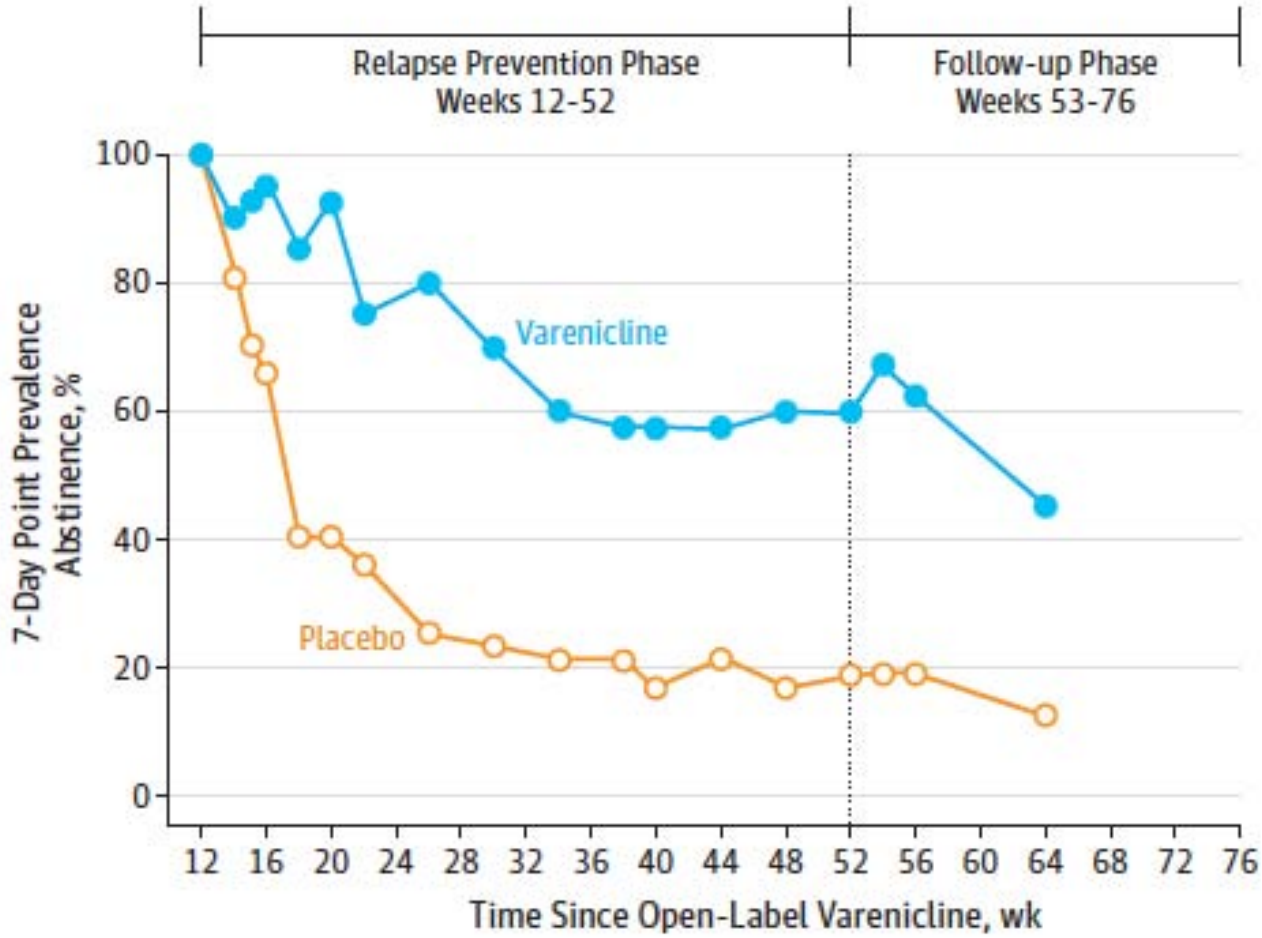

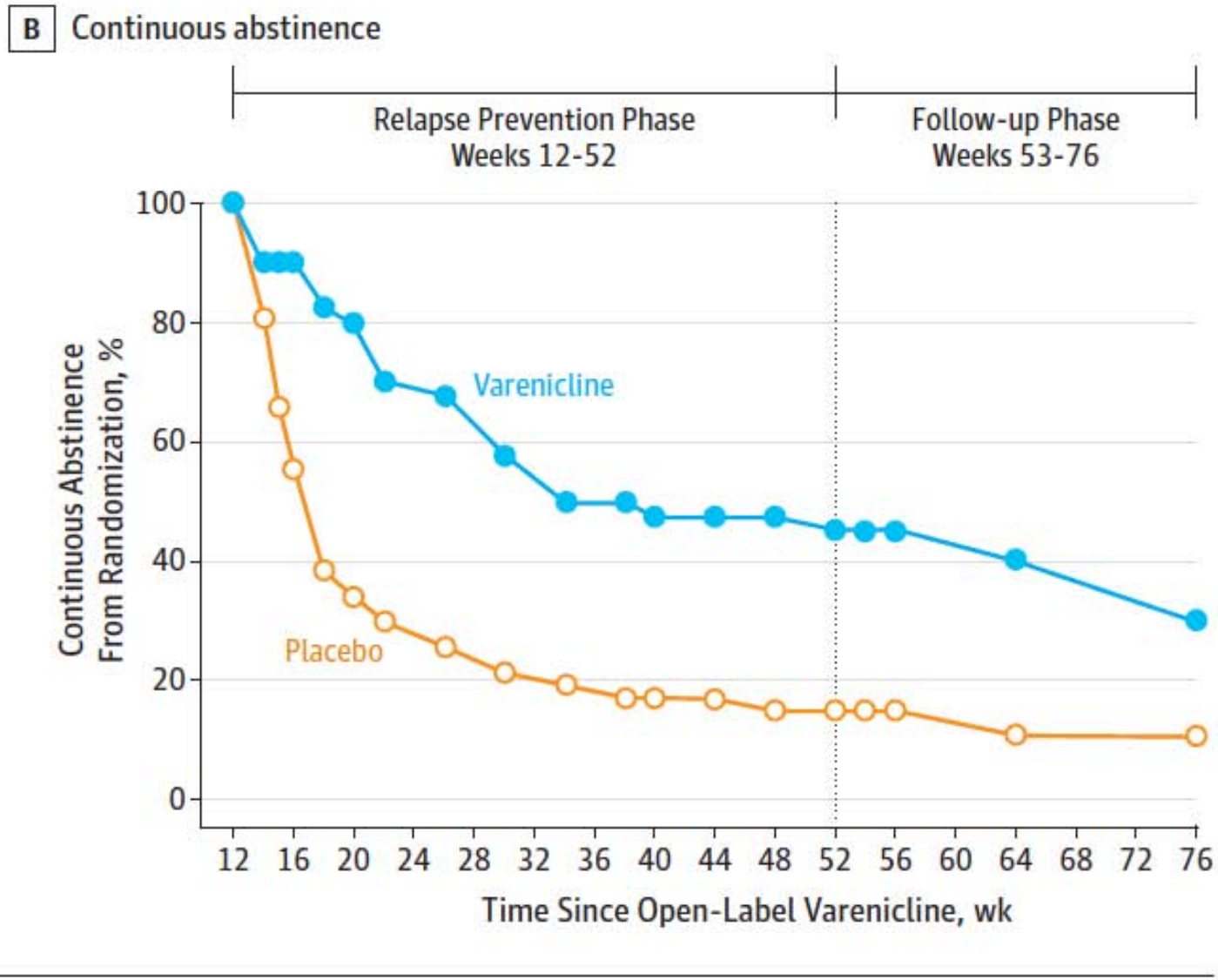

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Maintenance Treatment With Varenicline for Smoking Cessation in Patients With Schizophrenia and Bipolar Disorder

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CONCLUSIONS AND RELEVANCE Among smokers with serious mental illness who attained initial abstinence with standard treatment, maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates compared with cognitive behavioral therapy alone after 1 year of treatment and at 6 months after treatment discontinuation.

Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder
A Randomized Clinical Trial

JAMA Psychiatry June 2014 Volume 71, Number 6

Adriana Feder, MD; Michael K. Parides, PhD; James W. Murrough, MD; Andrew M. Perez, MD; Julia E. Morgan, BA; Shireen Saxena, MScPH; Katherine Kirkwood, MS; Marije aan het Rot, PhD; Kyle A. B. Lapidus, MD, PhD; Le-Ben Wan, MD, PhD; Dan Iosifescu, MD; Dennis S. Charney, MD

IMPORTANCE Few pharmacotherapies have demonstrated sufficient efficacy in the treatment of posttraumatic stress disorder (PTSD), a chronic and disabling condition.

OBJECTIVE To test the efficacy and safety of a single intravenous subanesthetic dose of ketamine for the treatment of PTSD and associated depressive symptoms in patients with chronic PTSD.

DESIGN, SETTING, AND PARTICIPANTS Proof-of-concept, randomized, double-blind, crossover trial comparing ketamine with an active placebo control, midazolam, conducted at a single site (Icahn School of Medicine at Mount Sinai, New York, New York). Forty-one patients with chronic PTSD related to a range of trauma exposures were recruited via advertisements.

INTERVENTIONS Intravenous infusion of ketamine hydrochloride (0.5 mg/kg) and midazolam (0.045 mg/kg).

MAIN OUTCOMES AND MEASURES The primary outcome measure was change in PTSD symptom severity, measured using the Impact of Event Scale–Revised. Secondary outcome measures included the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impression–Severity and –Improvement scales, and adverse effect measures, including the Clinician-Administered Dissociative States Scale, the Brief Psychiatric Rating Scale, and the Young Mania Rating Scale.

Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder

A Randomized Clinical Trial

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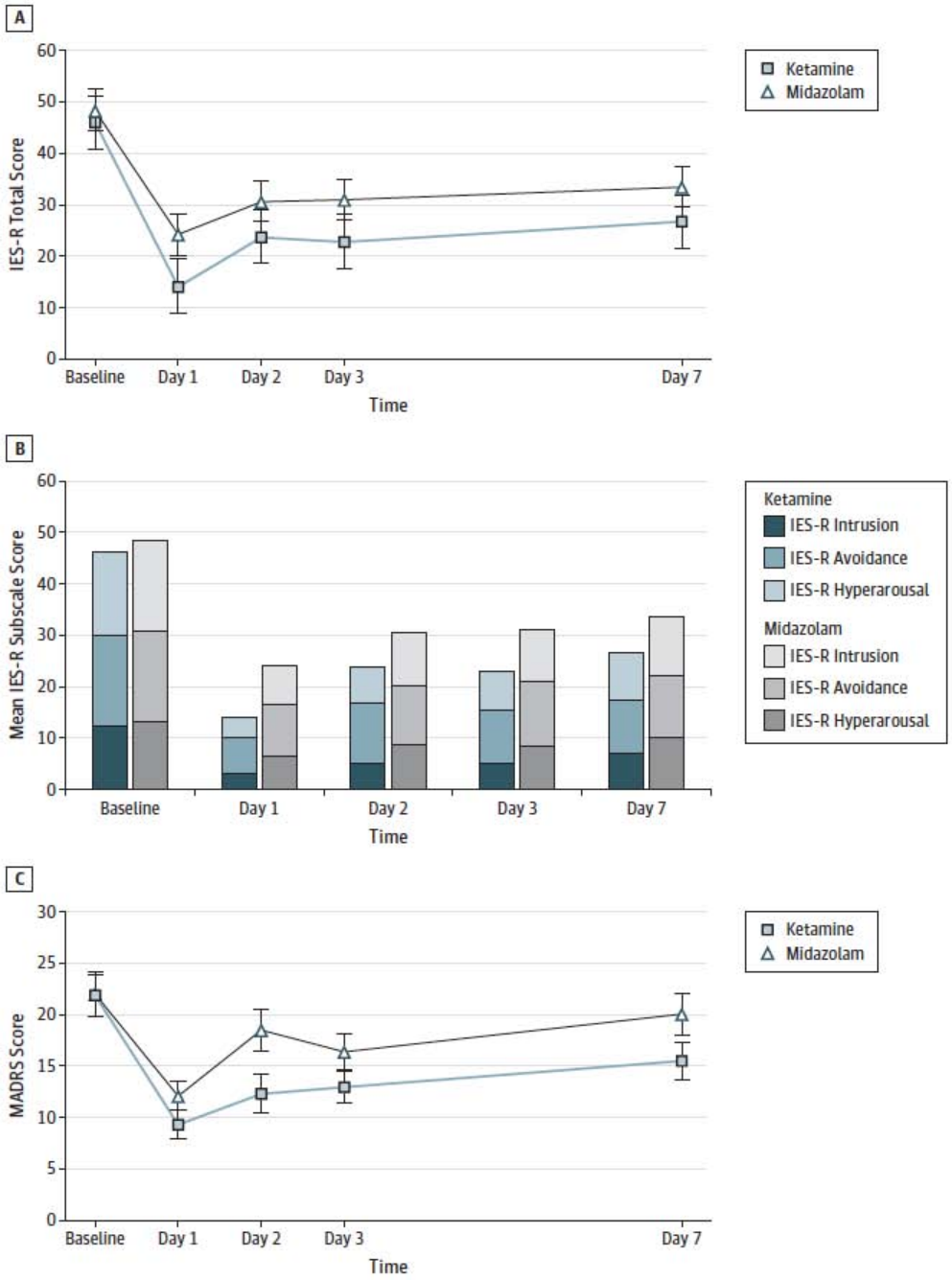
RESULTS Ketamine infusion was associated with significant and rapid reduction in PTSD symptom severity, compared with midazolam, when assessed 24 hours after infusion (mean difference in Impact of Event Scale–Revised score, 12.7 [95% CI, 2.5-22.8]; $P = .02$). Greater reduction of PTSD symptoms following treatment with ketamine was evident in both crossover and first-period analyses, and remained significant after adjusting for baseline and 24-hour depressive symptom severity. Ketamine was also associated with reduction in comorbid depressive symptoms and with improvement in overall clinical presentation. Ketamine was generally well tolerated without clinically significant persistent dissociative symptoms.

CONCLUSIONS AND RELEVANCE This study provides the first evidence for rapid reduction in symptom severity following ketamine infusion in patients with chronic PTSD. If replicated, these findings may lead to novel approaches to the pharmacologic treatment of patients with this disabling condition.

Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A Randomized Clinical Trial

Figure 2. Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First Period



Change in the Impact of Event Scale–Revised (IES-R) total score, the IES-R mean subscale scores, and the Montgomery-Asberg Depression Rating Scale (MADRS) score over 1 week for the first period (n = 41). Error bars represent standard errors. For this study, the IES-R was modified to inquire about symptoms over the previous 24 hours (instead of the previous 7 days).

Commentary

A Word to the Wise About Ketamine

Until we know more, clinicians should be wary about embarking on a slippery ketamine slope.

ALAN F. SCHATZBERG, M.D.

Am J Psychiatry 171:3, March 2014

Adverse Health Effects of Marijuana Use

Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D., and Susan R.B. Weiss, Ph.D.

In light of the rapidly shifting landscape regarding the legalization of marijuana for medical and recreational purposes, patients may be more likely to ask physicians about its potential adverse and beneficial effects on health. The popular notion seems to be that marijuana is a harmless pleasure, access to which should not be regulated or considered illegal. Currently, marijuana is the most commonly used "illicit" drug in the United States, with about 12% of people 12 years of age or older reporting use in the past year and particularly high rates of use among young people.[1] The most common route of administration is inhalation. The greenish-gray shredded leaves and flowers of the *Cannabis sativa* plant are smoked (along with stems and seeds) in cigarettes, cigars, pipes, water pipes, or "blunts" (marijuana rolled in the tobacco-leaf wrapper from a cigar). Hashish is a related product created from the resin of marijuana flowers and is usually smoked (by itself or in a mixture with tobacco) but can be ingested orally. Marijuana can also be used to brew tea, and its oil-based extract can be mixed into food products.

The regular use of marijuana during adolescence is of particular concern, since use by this age group is associated with an increased likelihood of deleterious consequences[2] (Table 1). Although multiple studies have reported detrimental effects, others have not, and the question of whether marijuana is harmful remains the subject of heated debate. Here we review the current state of the science related to the adverse health effects of the recreational use of marijuana, focusing on those areas for which the evidence is strongest.

N Engl J Med 2014;370:2219-27.

Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Effects of short-term use
Impaired short-term memory, making it difficult to learn and to retain information
Impaired motor coordination, interfering with driving skills and increasing the risk of injuries
Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases
In high doses, paranoia and psychosis
Effects of long-term or heavy use
Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*
Altered brain development*
Poor educational outcome, with increased likelihood of dropping out of school*
Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*
Symptoms of chronic bronchitis
Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence.

Adverse Health Effects of Marijuana Use

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The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2014;370:2219-27.

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2014;370:2219-27.

Schizophrenia—Time to Commit to Policy Change

W. Wolfgang Fleischhacker*[,1], Celso Arango[2], Paul Arteel[3], Thomas R. E. Barnes[4], William Carpenter[5], Ken Duckworth[6], Silvana Galderisi[7], Lisa Halpern[8], Martin Knapp[9], Stephen R. Marder[10], Mary Moller[11], Norman Sartorius[12], and Peter Woodruff[13]

Care and outcomes for people with schizophrenia have improved in recent years, but further progress is needed to help more individuals achieve an independent and fulfilled life. This report sets out the current need, informs policy makers and all relevant stakeholders who influence care quality, and supports their commitment to creating a better future. The authors recommend the following policy actions, based on research evidence, stakeholder consultation, and examples of best practice worldwide.

Schizophrenia Bulletin vol. 40 suppl. no. 3 pp. S165–S194, 2014

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Recommendations for Policy Change. Schizophrenia Has a Profound Personal, Social, and Economic Impact. Furthermore, Public Attitudes Toward Schizophrenia Lead to Prejudice and Discrimination. The Authors of This Report Recommend the Following Policy Actions to Local, National, and Regional Policy Makers.

1. Provide an evidence-based, integrated care package for people with schizophrenia that addresses their mental and physical health needs. This should be underpinned with an integrated approach by their health care professionals and supported by the national health care system and by educational and research facilities.
2. Provide support for people with schizophrenia to enter and to remain in their community, and develop mechanisms to help guide them through the often complex benefit and employment systems to enhance recovery. Guidelines and educational programs should be developed and implemented to support the inclusion of people with schizophrenia in their community, workplace or school.
3. Provide concrete support, information and educational programs to families and carers on how to enhance care for an individual living with schizophrenia in a manner that entails minimal disruption to their own personal lives.

Schizophrenia—Time to Commit to Policy Change

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4. Consult with health care professionals and other stakeholders directly involved in the management of schizophrenia, including organizations that support people living with schizophrenia, their families and their carers, in order to regularly revise, update and improve policy on the management of schizophrenia.
5. Provide support, which is proportionate to the impact of the disease, for research and development of new treatments that improve the overall outlook for people with schizophrenia, including those that target negative symptoms and cognitive impairment.
6. Establish adequately funded, ongoing and regular awareness-raising campaigns to: increase the understanding of schizophrenia among the general public; emphasize the importance of positive societal attitudes toward mental illnesses; highlight available support for the management of schizophrenia; and deter discriminatory attitudes and actions. Such campaigns should form an integral part of routine plans of action.

Our recommendations are based on research evidence, stakeholder consultation, and examples of best practice worldwide.

Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside

A Randomized, Double-blind, Placebo-Controlled Trial

Jaime E. C. Hallak, MD, PhD; Joao Paulo Maia-de-Oliveira, MD; Joao Abrao, MD, PhD; Paulo R. Evora, MD, PhD; Antonio W. Zuardi, MD, PhD; Jose A. S. Crippa, MD, PhD; Paulo Belmonte-de-Abreu, MD; Glen B. Baker, PhD, DSc; Serdar M. Dursun, MD, PhD, FRCPC

IMPORTANCE The treatment of schizophrenia remains a challenge, and the currently available antipsychotic drugs are slow acting and produce a number of adverse effects.

OBJECTIVE To examine the effectiveness and safety of a single intravenous administration of sodium nitroprusside (0.5 μg/kg/min for 4 hours) on the positive, negative, anxiety, and depressive symptoms in patients with schizophrenia.

DESIGN Single-center, randomized, double-blind, placebo-controlled trial performed from March 9, 2007, to March 12, 2009.

SETTING University teaching hospital in São Paulo, Brazil.

PARTICIPANTS Twenty inpatients aged 19 to 40 years with a diagnosis of schizophrenia who were in the first 5 years of the disease who are taking antipsychotics.

INTERVENTION Sodium nitroprusside administration.

Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside

A Randomized, Double-blind, Placebo-Controlled Trial

Jaime E. C. Hallak, MD, PhD; Joao Paulo Maia-de-Oliveira, MD; Joao Abrao, MD, PhD; Paulo R. Evora, MD, PhD; Antonio W. Zuardi, MD, PhD; Jose A. S. Crippa, MD, PhD; Paulo Belmonte-de-Abreu, MD; Glen B. Baker, PhD, DSc; Serdar M. Dursun, MD, PhD, FRCPC

MAIN OUTCOME MEASURES The 18-item Brief Psychiatric Rating Scale and the negative subscale of the Positive and Negative Syndrome Scale.

RESULTS After the infusion of sodium nitroprusside, a rapid (within 4 hours) improvement of symptoms was observed. The placebo and experimental groups had significant differences in the 18-item Brief Psychiatric Rating Scale total score and subscale scores, which persisted for 4 weeks after infusion.

CONCLUSIONS The results clearly show a therapeutic effect of sodium nitroprusside. If this drug is approved for routine clinical use in patients with schizophrenia, this discovery will be an important advance in the pharmacologic treatment of this devastating disorder.

This is an important proof-of-concept study in that it investigates a novel approach to the management of schizophrenia, albeit building on the well-established glutamate hypothesis. We desperately need new treatments for schizophrenia and the finding that intravenous sodium nitroprusside ameliorated psychotic symptoms not only acutely (within four hours) but also that some effects persisted for up to four weeks, is very exciting. Of course much more work is required before such findings may translate into a clinically useful intervention, but this can be seen as a 'next step' after animal work, which showed the utility of sodium nitroprusside in abolishing behavioural effects (and c-fos expression) of phencyclidine in a psychosis 'model' {Blockade of phencyclidine-induced effects by a nitric oxide donor. {Bujas-Bobanovic M, Bird DC, Robertson HA, Dursun SM. Br J Pharmacol 2000 Jul; 130(5):1005-12}.

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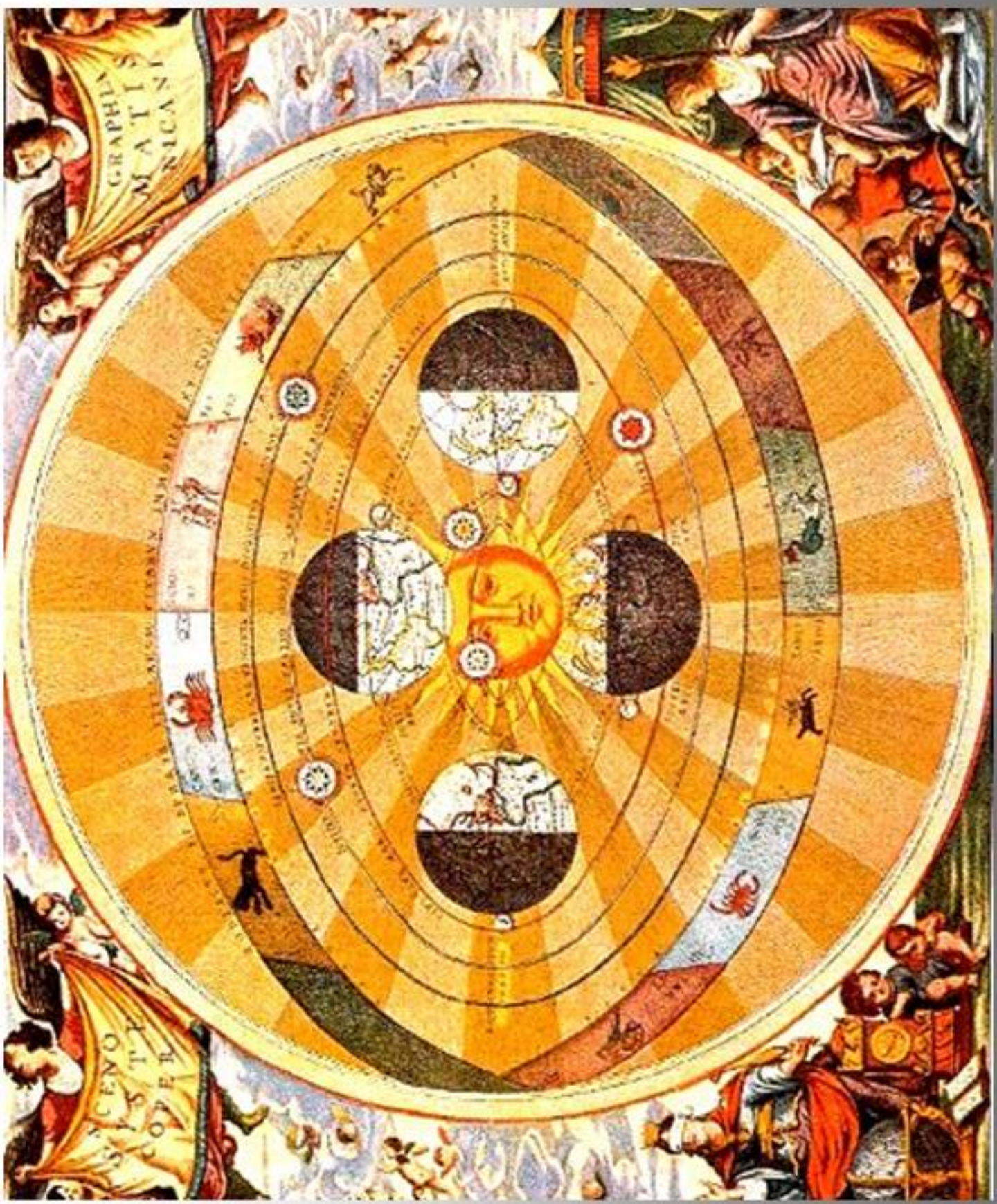
Castle D: F1000Prime Recommendation of [Hallak JE et al., JAMA Psychiatry 2013, 70(7):668-76]. In F1000Prime, 19 Aug 2013; DOI: 10.3410/f. 718058146.793481545. F1000Prime.com/718058146#eval793481545

Nitric Oxide and Symptom Reduction in Schizophrenia

Joseph T. Coyle, MD

the finding that a treatment that augments the levels of nitric oxide, a signaling molecule downstream from the NMDA receptor, can reduce symptoms in schizophrenia provides additional evidence of NMDA receptor hypofunction in schizophrenia. Thus, these results are consistent with the therapeutic effects of NMDA-positive allosteric modulators, the schizophrenogenic effects of NMDA receptor antagonists, and the development of a schizophrenic phenotype in an autoimmune disorder in which anti-NMDA receptor antibodies are generated. However, caution must be exercised until sufficiently powered clinical trials of nitroprusside are performed in patients with schizophrenia.

Thanks



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