Science to Practice

Top Ten Research Findings of 2014-2015

Sy Saeed, MD, MS, FAC*Psych*

Professor and Chairman

Department of Psychiatry and Behavioral Medicine
Brody School of Medicine | East Carolina University

Chief of Psychiatry
Vidant Medical Center,
Greenville, NC

NORTH CAROLINA
Psychiatric
Association

Winston-Salem, NC | Twin City Quarter
October 1-4, 2015

Science to Practice

Top Ten Research findings of 2014-2015

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 2014-2015 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.

VIDANT™ Medical Center

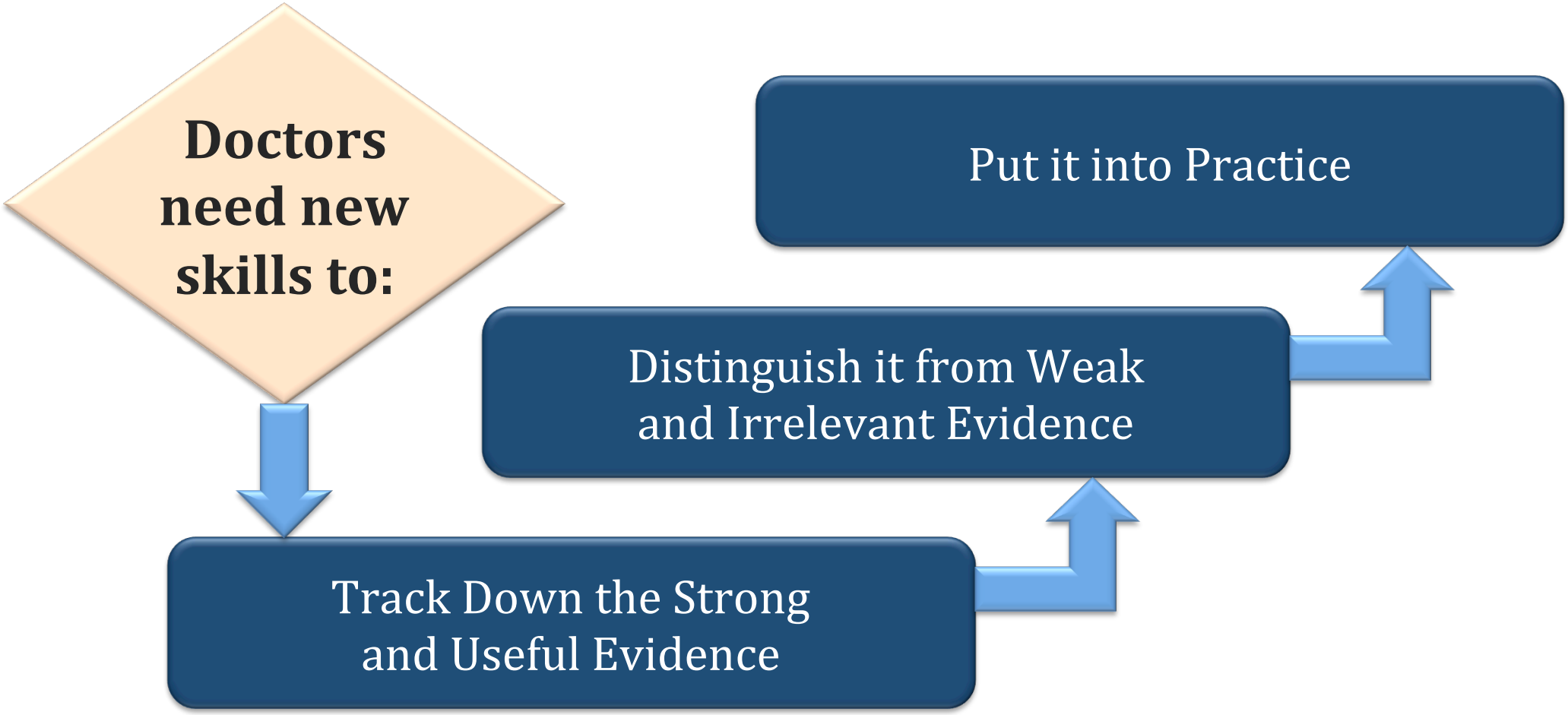
East Carolina UNIVERSITY

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

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

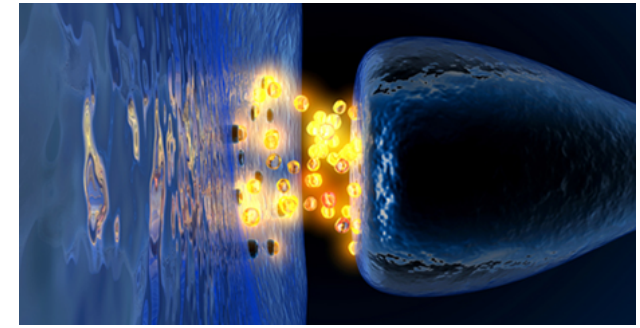
David Shenk. Data Smog: Surviving the Information Glut. San Francisco: Harper, 1998: 30.

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



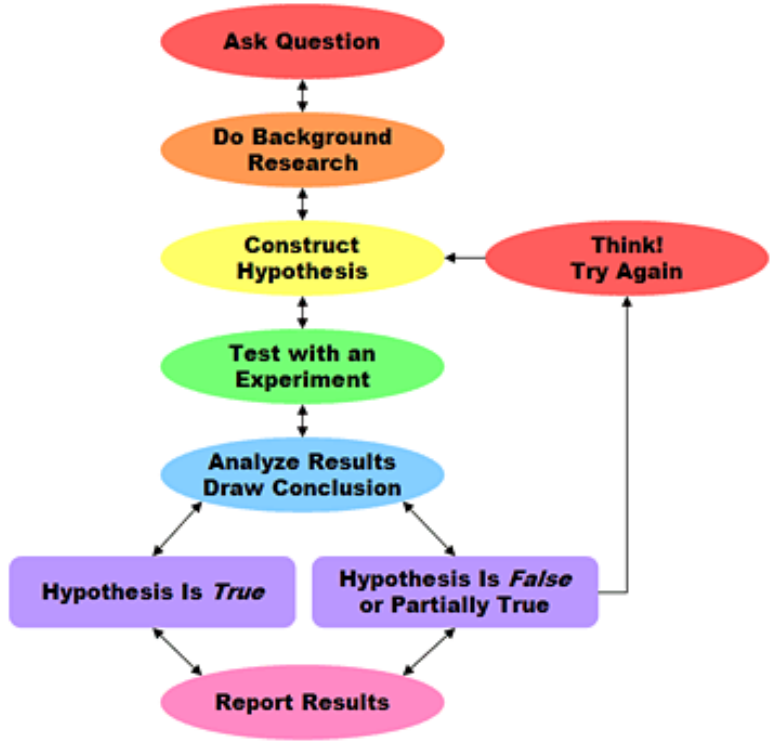
Signal-to-Noise Ratio [SNR]

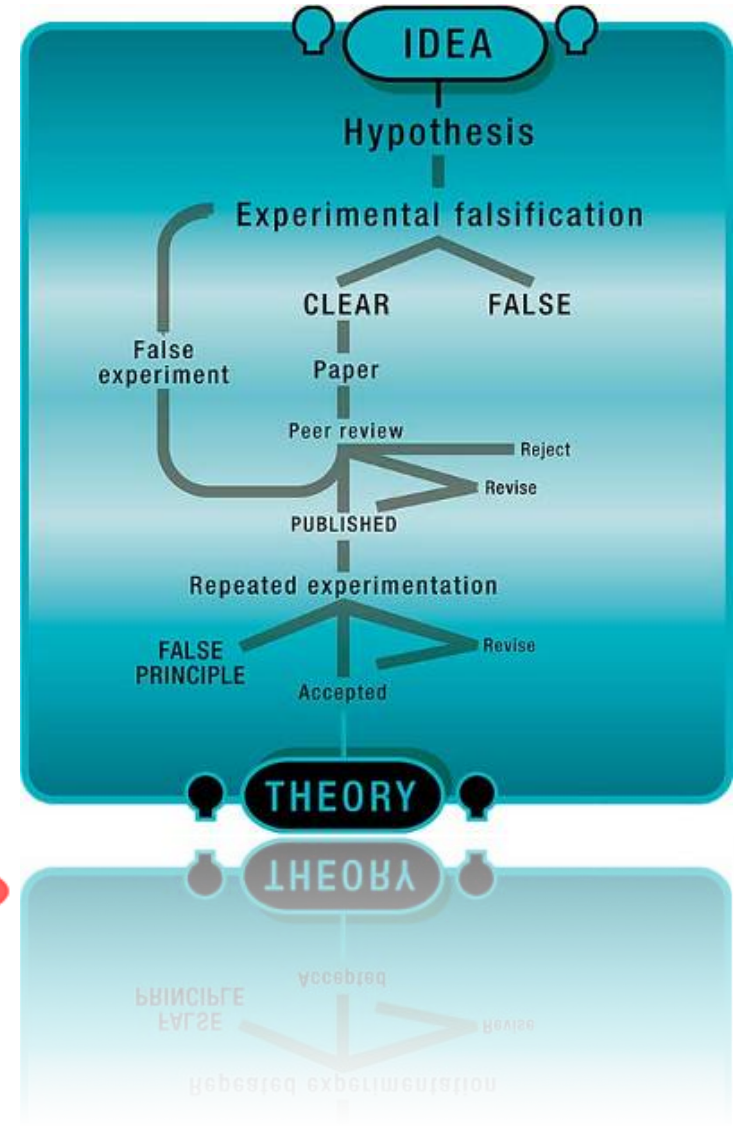
- A qualitative measure of value received relative to the garbage one must sift to get that value.
  - How should we do the sifting?
  - Can someone do the sifting for us? Who? [books, journals, CME presenters, drug reps, etc.]



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

YOU MUST ALWAYS OFFER EVIDENCE TO SUPPORT YOUR STATEMENTS.





All scientific truths are provisional!

Gap between what we know and what we practice

- A large gulf remains between what we know and what we practice*.
- Large gaps also exist between best evidence and practice in the implementation of guidelines*.
- Failure to follow best evidence highlights issues of underuse, overuse, and misuse of drugs** and has led to widespread interest in the safety of patients***.

* Eisenberg MJ, Garzon P. *Am J Cardiol* 1997;79: 867-72.

** Chassin MR, Galvin RW. *JAMA* 1998;280: 1000-5.

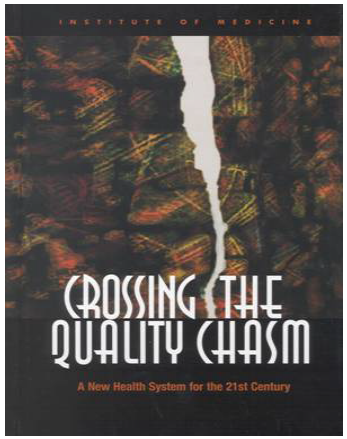
*** Institute of Medicine. *Crossing the quality chasm: a new health system for the 21st century.* Washington, DC: National Academy Press, 2001.

Quality of Health Care Delivered to Adults in the United States

- Only 55% chance of getting appropriate care
  - little difference among the proportion of recommended:
    - Preventive care (54.9 %)
    - Acute care (53.5 %)
    - Care for chronic conditions (56.1%)

McGlynn et al, 2003

The NEW ENGLAND JOURNAL of MEDICINE



"Between the health care we have and the care we could have lies not just a gap, but a chasm."

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

2001

Six Imperative Challenges in Redesigning Health Care

1. Redesign care processes
2. Effective use of information technologies
3. Knowledge and skills management
4. Development of effective teams
5. Coordination of care across patient conditions, services, and settings over time
6. Use of performance and outcome measures for CQI & accountability

Institute of Medicine. *Crossing the Quality Chasm*, 2001

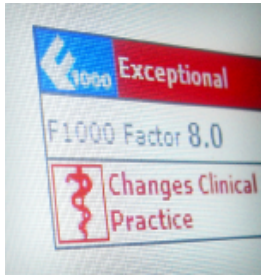
Methodology

- Primary Literature Search
- **Survey** [Question: *Amongst the papers published in the period July 1, 2014 to June 30, 2015, which ones in your opinion have [or likely to have or should have] impacted/ changed the clinical practice of psychiatry?*].
  - AACDP
  - AADPRT
  - AACP
  - AAPA
  - NCPA
  - GAP
  - Other Colleagues
- Secondary Literature, e.g. Faculty of 1000 Factor, Cochrane, NEJM Journal Watch, etc.

Disclaimers

- Selection of an article
  - Clinical relevance/applicability
- Order in which the articles appear in the list 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
STEM CELL ADVANCES
BJPsych
PSYCHOSOMATICS
nature medicine
BMJ
SUBCLINICAL vCJD: How common is it?
Science
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
BRITISH JOURNAL OF PSYCHIATRY
Psychological Bulletin
Behavioral Neuroscience
Journal of Consulting and Clinical Psychology
PERSONALITY DISORDERS
Theory, Research, and Treatment
Psychotherapy
Theory, Research, Practice, Training
Journal of the American Academy of CHILD & ADOLESCENT PSYCHIATRY
Behavioural Pharmacology
Psychiatry Research
Psychiatric Quarterly
PSYCHIATRIC SERVICES
International Clinical Psychopharmacology



MEDICINE REPORTS
NEW from Faculty of 1000
Fast reports on hot topics

NEJM Journal Watch

FACULTY OF 1000 MEDICINE
GLOBAL LEADERS. EXPERT KNOWLEDGE.

Bandolier
"Evidence based thinking about health care"

THE COCHRANE COLLABORATION®

F1000 | FACULTY of 1000
POST-PUBLICATION PEER REVIEW

EvidenceUPDATES
FROM THE BMJ EVIDENCE CENTRE

CEBM
CENTRE FOR EVIDENCE BASED MEDICINE
UNIVERSITY OF OXFORD

ESSENTIAL EVIDENCE PLUS

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

Science to Practice

Top Ten Research Findings of 2014-2015

The Risk of Switch to Mania in Patients With Bipolar Disorder During Treatment With an Antidepressant Alone and in Combination With a Mood Stabilizer

Alexander Viktorin, M.Sc.

Paul Lichtenstein, Ph.D.

Michael E. Thase, M.D.

Henrik Larsson, Ph.D.

Cecilia Lundholm, M.Sc.

Patrik K.E. Magnusson, Ph.D.

Mikael Landén, M.D., Ph.D.

Objective: This study examined the risk of antidepressant-induced manic switch in patients with bipolar disorder treated either with antidepressant monotherapy or with an antidepressant in conjunction with a mood stabilizer.

Method: Using Swedish national registries, the authors identified 3,240 patients with bipolar disorder who started treatment with an antidepressant and had no antidepressant treatment during the previous year. Patients were categorized into those receiving antidepressant monotherapy and those receiving an antidepressant plus a mood stabilizer. A within-individual design was used to control for confounding by disorder severity, genetic makeup, and early environmental factors. Cox regression analyses conditioned on individual were used to compare the rate of mania 0–3 months and 3–9 months after the start of antidepressant treatment with a preceding non-treatment period.

Results: Nearly 35% of the patients were treated with antidepressant monotherapy. The increased risk of treatment-emergent mania was confined to patients on antidepressant monotherapy (hazard ratio=2.83, 95% CI=1.12, 7.19). Among patients treated with a concurrent mood stabilizer, no acute change in risk of mania was observed during the 3 months after the start of antidepressant treatment (hazard ratio=0.79, 95% CI=0.54, 1.15), and a decreased risk was observed during the period 3–9 months after treatment initiation (hazard ratio=0.63, 95% CI=0.42, 0.93).

Conclusions: In this national registry study, antidepressant monotherapy was associated with an increased risk of mania. However, no risk of mania was seen in patients receiving an antidepressant while treated with a mood stabilizer. The results highlight the importance of avoiding antidepressant monotherapy in the treatment of bipolar disorder.

(Am J Psychiatry 2014; 171:1067–1073)

Specific Antidepressants Dispensed to Patients With Bipolar Disorder in a National Registry Study[a]

	Full Sample (N=3,240)		Antidepressant and Mood Stabilizer (N=1,641)		Antidepressant Monotherapy (N=1,117)	
Antidepressant	N	%	N	%	N	%
Citalopram	519	18.8	275	16.8	244	21.8
Sertraline	456	16.5	272	16.6	184	16.5
Mirtazapine	444	16.1	245	14.9	199	17.8
Escitalopram	358	13.0	254	15.5	104	9.3
Venlafaxine	189	6.9	113	6.9	76	6.8
Duloxetine	176	6.4	107	6.5	69	6.2
Fluoxetine	158	5.7	99	6.0	59	5.3
Amitriptyline	140	5.1	75	4.6	65	5.8
Bupropion	140	5.1	97	5.9	43	3.9
Paroxetine	66	2.4	35	2.1	31	2.8
Mianserin	50	1.8	38	2.3	12	1.1
Clomipramine	46	1.7	26	1.6	20	1.8
Nortriptyline	7	0.3	3	0.2	4	0.4
Maprotiline	4	0.2	0	0.0	4	0.4
Imipramine	2	0.1	2	0.1	0	0.0
Trimipramine	2	0.1	0	0.0	2	0.2
Fluvoxamine	1	0.05	0	0.0	1	0.1

[a] The antidepressants and numbers listed here are those that were dispensed at the start of the treatment period. Because we applied strict inclusion criteria to classify patients as being on a concurrent mood stabilizer or not, 482 patients from the full sample with ambiguous mood stabilizer use were not classified as either receiving monotherapy or receiving concurrent mood stabilizer treatment. Therefore, the sum of the individuals in the antidepressant monotherapy group and mood stabilizer group do not add up to the full sample.

- The study results clearly indicate that the risk of antidepressant-induced mania can be reduced by the prescription of an adjunctive mood stabilizer (lithium, valproate, or lamotrigine).
- The study does not, however, resolve the question of the efficacy of antidepressants in bipolar depression, which is, at best, arguable.
- While clinicians, and perhaps patients as well, tend to believe that antidepressants are effective in the treatment of bipolar depression—and even beyond, judging from the high rate of prescriptions in this and other studies—the evidence base is very weak.
- The other question that is not resolved in the Viktorin et al. study is the risk of switch in bipolar II disorder, given that data on hypomania were not captured. Thus, we are still left with the precise recommendation of not using antidepressant monotherapy in bipolar I disorder only.

EDUARD VIETA, M.D.
Editorial
Am J Psychiatry 171:10, October 2014

- Even though current practice guidelines suggest treatment with antidepressants only in combination with mood stabilizers in bipolar patients, and the effectiveness of antidepressants in treating bipolar depression is disputed, the clinical practice looks different.

- In this study, almost 35% of the patients were on antidepressant monotherapy, and 70%of all bipolar patients had at least one dispensation of an antidepressant over a 5-year period.

- Thus, these results are important for future guidelines, but probably even more important for reminding clinicians of the importance of these guidelines.

Autism Occurrence by MMR Vaccine Status Among US Children With Older Siblings With and Without Autism

Anjali Jain, MD; Jaclyn Marshall, MS; Ami Buikema, MPH; Tim Bancroft, PhD; Jonathan P. Kelly, MPP; Craig J. Newschaffer, PhD

JAMA April 21, 2015 Volume 313, Number 15

IMPORTANCE Despite research showing no link between the measles-mumps-rubella (MMR) vaccine and autism spectrum disorders (ASD), beliefs that the vaccine causes autism persist, leading to lower vaccination levels. Parents who already have a child with ASD may be especially wary of vaccinations.

OBJECTIVE To report ASD occurrence by MMR vaccine status in a large sample of US children who have older siblings with and without ASD.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study using an administrative claims database associated with a large commercial health plan. Participants included children continuously enrolled in the health plan from birth to at least 5 years of age during 2001-2012 who also had an older sibling continuously enrolled for at least 6 months between 1997 and 2012.

EXPOSURES MMR vaccine receipt (0, 1, 2 doses) between birth and 5 years of age.

Autism Occurrence by MMR Vaccine Status Among US Children With Older Siblings With and Without Autism

Anjali Jain, MD; Jaclyn Marshall, MS; Ami Buikema, MPH; Tim Bancroft, PhD; Jonathan P. Kelly, MPP; Craig J. Newschaffer, PhD

JAMA April 21, 2015 Volume 313, Number 15

MAIN OUTCOMES AND MEASURES ASD status defined as 2 claims with a diagnosis code in any position for autistic disorder or other specified pervasive developmental disorder (PDD) including Asperger syndrome, or unspecified PDD (*International Classification of Diseases, Ninth Revision, Clinical Modification* 299.0x, 299.8x, 299.9x).

RESULTS Of 95 727 children with older siblings, 994 (1.04%) were diagnosed with ASD and 1929 (2.01%) had an older sibling with ASD. Of those with older siblings with ASD, 134 (6.9%) had ASD, vs 860 (0.9%) children with unaffected siblings ($P < .001$). MMR vaccination rates (≥1 dose) were 84% (n = 78 564) at age 2 years and 92% (n = 86 063) at age 5 years for children with unaffected older siblings, vs 73% (n = 1409) at age 2 years and 86% (n = 1660) at age 5 years for children with affected siblings. MMR vaccine receipt was not associated with an increased risk of ASD at any age. For children with older siblings with ASD, at age 2, the adjusted relative risk (RR) of ASD for 1 dose of MMR vaccine vs no vaccine was 0.76 (95% CI, 0.49-1.18; $P = .22$), and at age 5, the RR of ASD for 2 doses compared with no vaccine was 0.56 (95% CI, 0.31-1.01; $P = .052$). For children whose older siblings did not have ASD, at age 2, the adjusted RR of ASD for 1 dose was 0.91 (95% CI, 0.67-1.20; $P = .50$) and at age 5, the RR of ASD for 2 doses was 1.12 (95% CI, 0.78-1.59; $P = .55$).

Autism Occurrence by MMR Vaccine Status Among US Children With Older Siblings With and Without Autism

Anjali Jain, MD; Jaclyn Marshall, MS; Ami Buikema, MPH; Tim Bancroft, PhD; Jonathan P. Kelly, MPP; Craig J. Newschaffer, PhD

CONCLUSIONS AND RELEVANCE In this large sample of privately insured children with older siblings, receipt of the MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD. These findings indicate no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD.

Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis

Taylor DM, Cornelius V, Smith L, Young AH. *Acta Psychiatr Scand 2014: 130: 452–469*

Objective: Treatment of bipolar depression is complicated by variable response and risk of switch to mania. Guidance is informed by the strength of evidence rather than by comparative data.

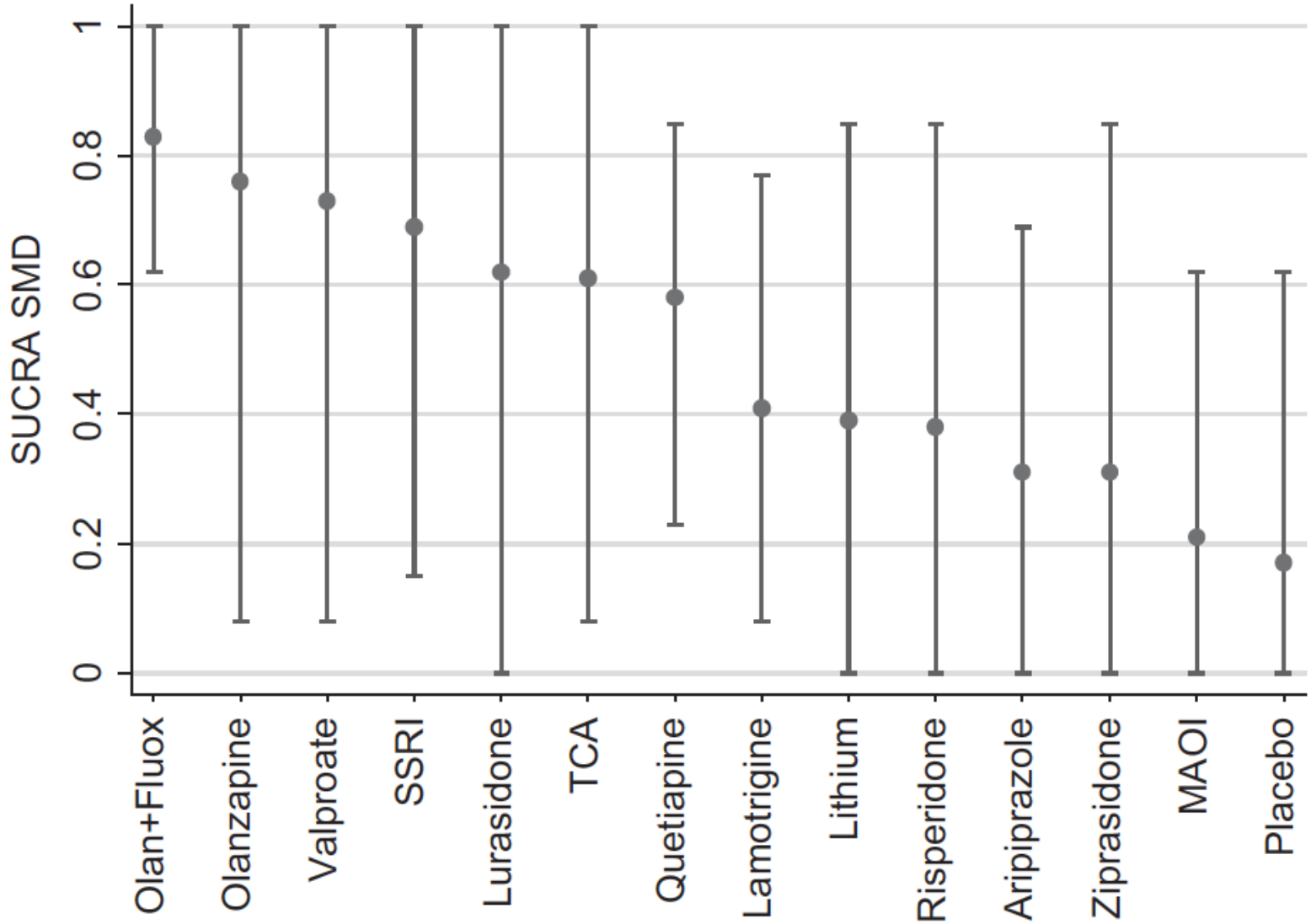
Method: We performed a multiple-treatments meta-analysis of randomised, double-blind, controlled comparisons of 4–16 weeks in adults in bipolar depression. The primary efficacy outcome was effect size. The primary acceptability outcome was 'switch to mania'. Secondary outcomes were likelihood of response and withdrawals from trials.

Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis

Taylor DM, Cornelius V, Smith L, Young AH. *Acta Psychiatr Scand 2014: 130: 452–469*

Results: Twenty-nine studies were included (8331 participants). Olanzapine + fluoxetine and olanzapine performed best on primary outcome measure being ranked highest for effect size. Switch to mania was least likely with ziprasidone and then quetiapine. Olanzapine + fluoxetine was also ranked the highest for response with lurasidone second, but olanzapine + fluoxetine and olanzapine had the optimal effect on response and withdrawal from treatment when the two parameters were considered together. Several treatments [monoamine oxidase inhibitors (MAOIs), ziprasidone, aripiprazole and risperidone] have limited or no therapeutic activity in bipolar depression.

Conclusion: Olanzapine + fluoxetine should be first-line treatment. Olanzapine, quetiapine, lurasidone, valproate and selective serotonin re-uptake inhibitors are also recommended. Tricyclic antidepressants and lithium are worthy of consideration but lamotrigine (high risk of switching, less robust efficacy) and MAOIs, ziprasidone, aripiprazole and risperidone (no evidence of efficacy) should not be used.



SUCRA and 95% CIs for efficacy (SMD) in rank order.
SUCRA: Surface under the cumulative ranking curve, higher value is favorable.

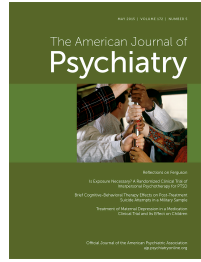
Acta Psychiatr Scand 2014: 130: 452–469

Summary of rankings

Symptom score change (effect size – highest first)	Response (highest likelihood first)	Switch to mania (lowest risk first)	Withdrawal (lowest risk first)
Olanzapine + fluoxetine	Olanzapine + fluoxetine	Ziprasidone	Olanzapine + fluoxetine
Olanzapine	Lurasidone	Quetiapine	Risperidone
Valproate	Valproate	TCA	Ziprasidone
SSRI	Quetiapine	SSRI	Olanzapine
Lurasidone	Lamotrigine	MAOI	Valproate

Acta Psychiatr Scand 2014: 130: 452–469

Brief Cognitive-Behavioral Therapy Effects on Post-Treatment Suicide Attempts in a Military Sample: Results of a Randomized Clinical Trial With 2-Year Follow-Up



M. David Rudd, Ph.D., A.B.P.P., Craig J. Bryan, Psy.D., A.B.P.P., Evelyn G. Wertenberger, Ph.D., L.C.S.W., Alan L. Peterson, Ph.D., A.B.P.P., Stacey Young-McCaughan, R.N., Ph.D., Jim Mintz, Ph.D., Sean R. Williams, L.C.S.W., Kimberly A. Arne, L.C.S.W., Jill Breitbach, Psy.D., A.B.P.P., Kenneth Delano, Ph.D., Erin Wilkinson, Psy.D., Travis O. Bruce, M.D.

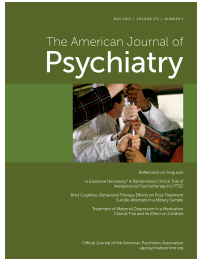
Objective: The authors evaluated the effectiveness of brief cognitive-behavioral therapy (CBT) for the prevention of suicide attempts in military personnel.

Method: In a randomized controlled trial, active-duty Army soldiers at Fort Carson, Colo., who either attempted suicide or experienced suicidal ideation with intent, were randomly assigned to treatment as usual (N=76) or treatment as usual plus brief CBT (N=76). Assessment of incidence of suicide attempts during the follow-up period was conducted with the Suicide Attempt Self-Injury Interview. Inclusion criteria were the presence of suicidal ideation with intent to die during the past week and/or a suicide attempt within the past month. Soldiers were excluded if they had a medical or psychiatric condition that would prevent informed consent or participation in outpatient treatment, such as active psychosis or mania. To determine treatment efficacy with regard to incidence and time to suicide attempt, survival curve analyses were conducted. Differences in psychiatric symptoms were evaluated using longitudinal random-effects models.

Results: From baseline to the 24-month follow-up assessment, eight participants in brief CBT (13.8%) and 18 participants in treatment as usual (40.2%) made at least one suicide attempt (hazard ratio=0.38, 95% CI=0.16–0.87, number needed to treat=3.88), suggesting that soldiers in brief CBT were approximately 60% less likely to make a suicide attempt during follow-up than soldiers in treatment as usual. There were no between-group differences in severity of psychiatric symptoms.

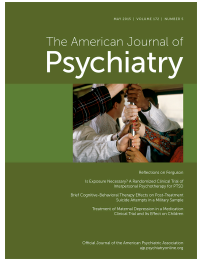
Conclusions: Brief CBT was effective in preventing follow-up suicide attempts among active-duty military service members with current suicidal ideation and/or a recent suicide attempt.

Am J Psychiatry 2015; 172:441–449; doi: 10.1176/appi.ajp.2014.14070843



- Randomly assigned 152 active-duty Army soldiers at high risk for suicide to treatment as usual or to treatment as usual plus brief CBT.
- Participating soldiers were recruited from inpatient and emergency department clinical settings; all of them had either a suicide attempt in the past month or suicidal ideation with intent to die in the past week.
- Treatment as usual could consist of psychotherapy, psychiatric medication, substance abuse treatment, or other support groups.

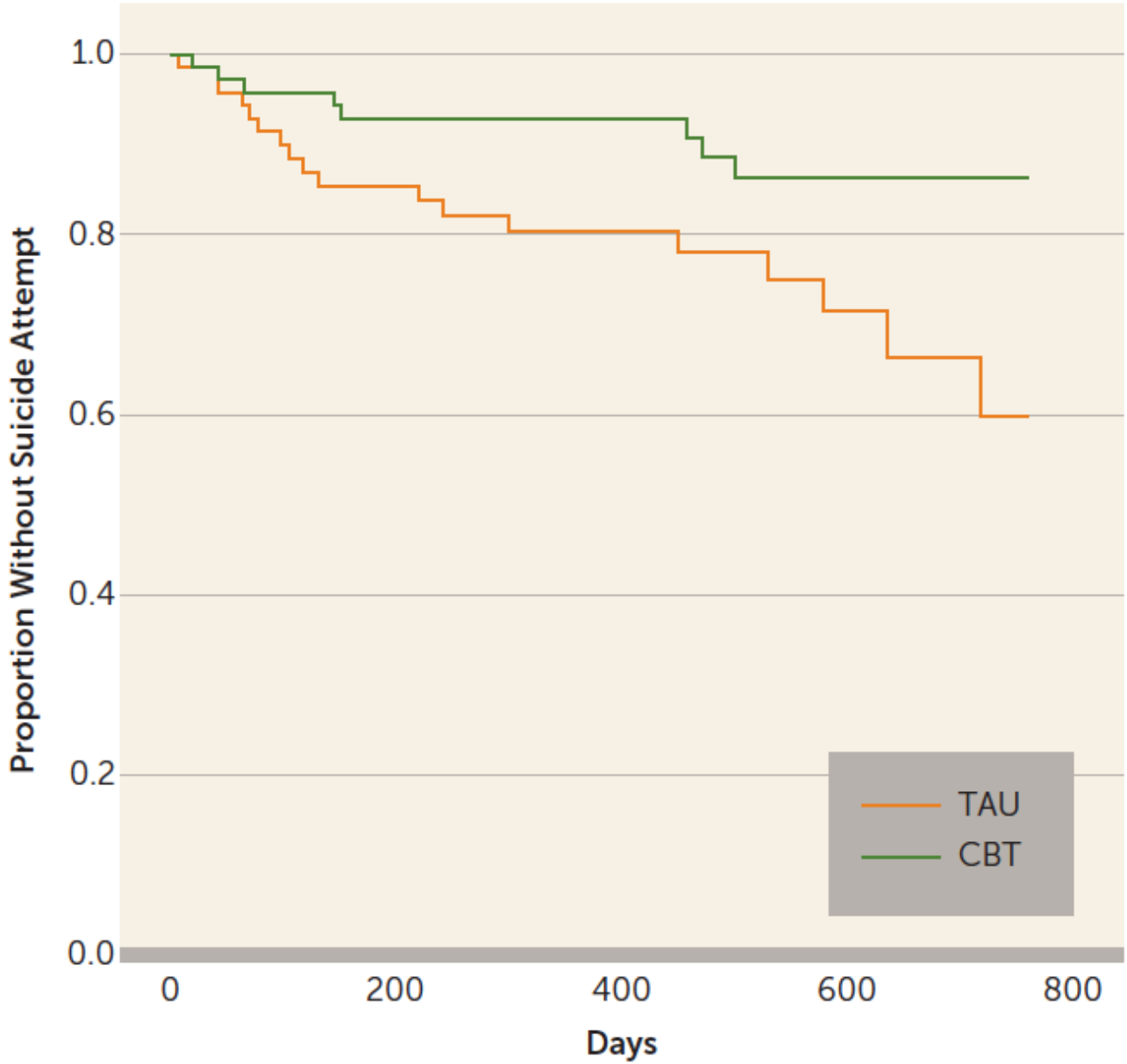
Am J Psychiatry 172:5, May 2015



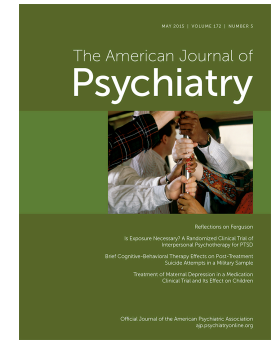
- Brief CBT consisted of 12 planned sessions on a weekly or biweekly basis, although there was flexibility in the actual duration of treatment depending on how well the participants mastered the skills that were covered.
- Assessments were conducted at baseline, and then at 3, 6, 12, 18, and 24 months after baseline, with the primary outcome consisting of the occurrence of suicide attempts over this 2-year period.

Am J Psychiatry 172:5, May 2015

FIGURE 2. Survival Curves for Time to First Suicide Attempt[a]



[a] CBT=cognitive-behavioral therapy; TAU=treatment as usual (log-rank χ^2=5.28, df=1, p=0.02).



Am J Psychiatry 172:5, May 2015

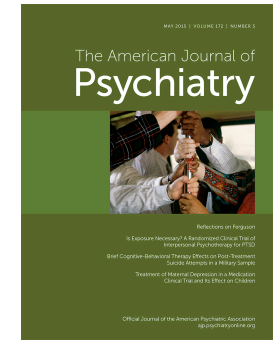


TABLE 2. Estimated Suicide Attempt-Free Probabilities

	Brief Cognitive-Behavioral Therapy		Treatment as Usual	
Assessment Period	Attempt-Free Probability	95% CI	Attempt-Free Probability	95% CI
3 Months	0.96	0.94–0.98	0.91	0.88–0.95
6 Months	0.96	0.94–0.98	0.85	0.81–0.88
12 Months	0.93	0.90–0.96	0.80	0.75–0.85
18 Months	0.86	0.81–0.91	0.75	0.69–0.81
24 Months	0.86	0.81–0.91	0.64	0.55–0.73

Results suggest that a brief, time-limited outpatient treatment that specifically focuses on skills training can be effectively implemented in a military setting and can reduce suicide attempts among military personnel who have made a suicide attempt or are currently experiencing suicidal thoughts with intent to die.

Am J Psychiatry 172:5, May 2015

Prescription Practices in the Treatment of First-Episode Schizophrenia Spectrum Disorders: Data From the National RAISE-ETP Study

Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Majnu John, Ph.D., Christoph U. Correll, M.D., Patricia Marcy, B.S.N., Jean Addington, Ph.D., Mary F. Brunette, M.D., Sue E. Estroff, Ph.D., Kim T. Mueser, Ph.D., David Penn, Ph.D., James Robinson, M.Ed., Robert A. Rosenheck, M.D., Joanne Severe, M.S., Amy Goldstein, Ph.D., Susan Azrin, Ph.D., Robert Heinssen, Ph.D., John M. Kane, M.D.

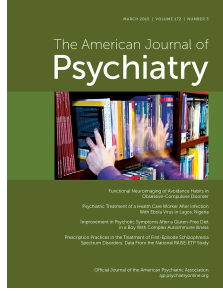
Objective: Treatment guidelines suggest distinctive medication strategies for first-episode and multiepisode patients with schizophrenia. To assess the extent to which community clinicians adjust their usual treatment regimens for first-episode patients, the authors examined prescription patterns and factors associated with prescription choice in a national cohort of early-phase patients.

Method: Prescription data at study entry were obtained from 404 participants in the Recovery After an Initial Schizophrenia Episode Project's Early Treatment Program (RAISE-ETP), a nationwide multisite effectiveness study for patients with first-episode schizophrenia spectrum disorders. Treatment with antipsychotics did not exceed 6 months at study entry.

Results: The authors identified 159 patients (39.4% of the sample) who might benefit from changes in their psychotropic prescriptions. Of these, 8.8% received prescriptions for recommended antipsychotics at higher than recommended dosages; 32.1% received prescriptions for olanzapine (often at high dosages), 23.3% for more than one antipsychotic, 36.5% for an antipsychotic and also an antidepressant without a clear indication, 10.1% for psychotropic medications without an antipsychotic, and 1.2% for stimulants. Multivariate analysis showed evidence for sex, age, and insurance status effects on prescription practices. Racial and ethnic effects consistent with effects reported in previous studies of multiepisode patients were found in univariate analyses. Despite some regional variations in prescription practices, no region consistently had different practices from the others. Diagnosis had limited and inconsistent effects.

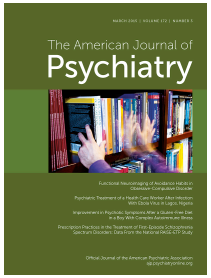
Conclusions: Besides prescriber education, policy makers may need to consider not only patient factors but also service delivery factors in efforts to improve prescription practices for first-episode schizophrenia patients.

Am J Psychiatry 2015; 172:237–248; doi: 10.1176/appi.ajp.2014.13101355



- Early treatment for individuals experiencing schizophrenia has the potential to alter the course of illness and improve outcomes.
- Because of differential responses to medications in first-episode and multiepisode schizophrenia, prominent guidelines suggest different treatment practices for these patient groups.
  - For example, the 2010 Schizophrenia Patient Outcomes Research Team (PORT) underlines the importance of using low dosages of medication and specifies that olanzapine and clozapine should not be first-line treatments because of their risks of adverse effects.
- Because medication experiences for individuals at the beginning of treatment may have a lasting impact on their attitudes toward medication and course of illness, this is a critical time to optimize prescribing.

Am J Psychiatry 172:3, March 2015



- The Recovery After an Initial Schizophrenia Episode project's Early Treatment Program (RAISE-ETP) study is a nationwide comparative effectiveness trial that enrolled 404 individuals with a schizophrenia spectrum diagnosis at 34 community sites throughout the country.
- Study participants had received less than 6 months of antipsychotic treatment at enrollment.
- The relatively large sample and geographic breadth of the study provided the first opportunity to characterize typical community treatment of early-phase schizophrenia patients in the United States.
- While the article focuses on potential prescribing problems, it is first worth noting that the prescribing for more than 60% of the sample appeared to follow existing guidelines.

Am J Psychiatry 172:3, March 2015

- Data from 34 sites in 21 states to examine prescribing patterns in 404 patients experiencing first-episode schizophrenia or schizophrenia spectrum disorder (mean age, 24; 72% male; 78% with psychiatric-hospitalization histories).
- No patients had received antipsychotic medications for >6 months at study entry (mean cumulative antipsychotic treatment, 47 days).
- Allowed diagnoses included schizoaffective disorder, psychosis NOS, and brief psychotic disorder;
- Patients with bipolar disorder, psychotic depression, substance-induced psychotic disorder, or psychosis due to a general medical condition were excluded.
- At study entry, 353 patients were taking psychotropic medications;
    - 337 were taking antipsychotics (typical antipsychotics, 12%; long-acting injectables, 9%).
    - Antipsychotic monotherapy (risperidone, 36%; olanzapine, 17%) was supplied to 300 patients (89%).
- Overall, 28% also received antidepressant medication, only half of whom had documented diagnoses to support such medication.

Am J Psychiatry 172:3, March 2015

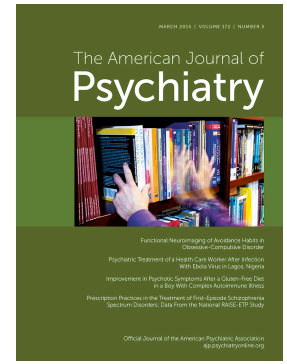


TABLE 2. Frequency of Prescription of Major Medication Classes for Patients Assessed in a Study of Prescription Practices in First-Episode Schizophrenia Spectrum Disorders (N=404)[a]

Medication Class	N	%
No medication	48	11.9
Only medications for general medical conditions	3	0.7
Antipsychotics	337	83.4
Antidepressants	129	31.9
Mood stabilizers	37	9.2
Antianxiety agents	42	10.4
Sedative-hypnotics	20	5.0
Opioid analgesics	7	1.7
Opioid replacement addiction medications	2	0.5
Stimulants	5	1.2
Non-stimulant ADHD medication	1	0.2
α_2-Adrenergic agonist	3	0.7

[a] Patients could receive prescriptions for more than one agent in a class. ADHD=attention deficit hyperactivity disorder.

TABLE 3. Patients Who Received Prescriptions for a Single Antipsychotic Agent in a Study of Prescription Practices in First-Episode Schizophrenia Spectrum Disorders (N=300)

Medication	Prescriptions[a]		Prescriptions for Only Oral or Only Long-Acting Formulations (N)	Dosage[b] (mg/day or mg/month)				Dosage Exceeding 2009 PORT Recommendations[c] for:	
	N	%		Median	Mean	SD	Range	Multiepisode Patients (N)	First-Episode Patients (N)
Risperidone	109	36.3							
			Oral[d]: 107	3	2.9	1.5	0.25–7.0	0	8
			Long-acting: 1	75	75			N/A	N/A
Olanzapine	51	17.0	Oral[e]: 51	15	16.5	7.8	2.5–40	8	22
Aripiprazole	35	11.7	Oral[f]: 35	10	10.0	4.8	2–20	0	N/A
Paliperidone	30	10.0							
			Oral: 17	6	5.8	2.2	3–9	0	N/A
			Long-acting[f]: 13	136.5	149.5	43.5	117–234	N/A	N/A
Quetiapine	28	9.2	Oral[f]: 28	300	309.7	192.7	20–800	1	N/A
Haloperidol	21	7							
			Oral[f]: 12	10	11.3	7.3	3–30	3[g]	N/A
			Long-acting: 4	75	81.2	37.5	50–125	N/A	N/A
Ziprasidone	12	4.0	Oral[h]: 12	80	102.2	57.8	40–200	1	N/A
Lurasidone	4	1.3	Oral[f]: 4	40	66.7	46.2	40–120	N/A	N/A
Asenapine	2	0.7	Oral: 2	10	10		10	N/A	N/A
Clozapine	2	0.7	Oral: 2	250	250	70.7	200–300	0	N/A
Thiothixene	2	0.7	Oral: 2	5	5		5	0	N/A
Chlorpromazine	1	0.3	Oral: 1						N/A
Fluphenazine	1	0.3	Oral: 1	15	15			1[g]	N/A
Loxapine	1	0.3	Oral: 1	40	40			0	N/A
Perphenazine	1	0.3	Oral: 1	4	4			0	N/A

- The investigators found evidence of potentially problematic prescribing for 159 individuals (39.4% of the sample).
- The most common issues were use of an antidepressant along with an antipsychotic without a clear indication; prescription of olanzapine; and use of more than one antipsychotic.
- A small subgroup also had psychotropic medications prescribed without antipsychotics.
- Patients with private insurance had strikingly lower rates of prescription of two or more antipsychotics than patients with public insurance or no insurance.

Am J Psychiatry 172:3, March 2015

Is Exposure Necessary? A Randomized Clinical Trial of Interpersonal Psychotherapy for PTSD

John C. Markowitz, M.D., Eva Petkova, Ph.D., Yuval Neria, Ph.D., Page E. Van Meter, Ph.D., Yihong Zhao, Ph.D., Elizabeth Hembree, Ph.D., Karina Lovell, Ph.D., Tatyana Biyanova, Ph.D., Randall D. Marshall, M.D.

Objective: Exposure to trauma reminders has been considered imperative in psychotherapy for posttraumatic stress disorder (PTSD). The authors tested interpersonal psychotherapy (IPT), which has demonstrated antidepressant efficacy and shown promise in pilot PTSD research as a non-exposure-based non-cognitive-behavioral PTSD treatment.

Method: The authors conducted a randomized 14-week trial comparing IPT, prolonged exposure (an exposure-based exemplar), and relaxation therapy (an active control psychotherapy) in 110 unmedicated patients who had chronic PTSD and a score >50 on the Clinician-Administered PTSD Scale (CAPS). Randomization stratified for comorbid major depression. The authors hypothesized that IPT would be no more than minimally inferior (a difference <12.5 points in CAPS score) to prolonged exposure.

Results: All therapies had large within-group effect sizes (d values, 1.32–1.88). Rates of response, defined as an improvement of >30% in CAPS score, were 63% for IPT, 47% for prolonged exposure, and 38% for relaxation therapy (not significantly different between groups). CAPS outcomes for IPT and prolonged exposure differed by 5.5 points (not significant), and the null hypothesis of more than minimal IPT inferiority was rejected (p=0.035). Patients with comorbid major depression were nine times more likely than non-depressed patients to drop out of prolonged exposure therapy. IPT and prolonged exposure improved quality of life and social functioning more than relaxation therapy.

Conclusions: This study demonstrated noninferiority of individual IPT for PTSD compared with the gold-standard treatment. IPT had (nonsignificantly) lower attrition and higher response rates than prolonged exposure. Contrary to widespread clinical belief, PTSD treatment may not require cognitive-behavioral exposure to trauma reminders. Moreover, patients with comorbid major depression may fare better with IPT than with prolonged exposure.

Am J Psychiatry 2015; 172:430–440; doi: 10.1176/appi.ajp.2014.14070908

Is Exposure Necessary? A Randomized Clinical Trial of Interpersonal Psychotherapy for PTSD

John C. Markowitz, M.D., Eva Petkova, Ph.D., Yuval Neria, Ph.D., Page E. Van Meter, Ph.D., Yihong Zhao, Ph.D., Elizabeth Hembree, Ph.D., Karina Lovell, Ph.D., Tatyana Biyanova, Ph.D., Randall D. Marshall, M.D.

Am J Psychiatry 172:5, May 2015

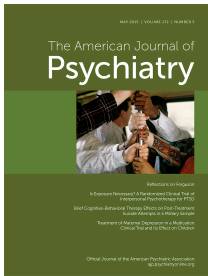
- Although prolonged exposure to traumatic events features prominently among evidence-based treatments for post-traumatic stress disorder (PTSD), other psychotherapies may also be helpful.
- Researchers examined the effectiveness of interpersonal psychotherapy (IPT).
- The investigators randomized 110 un-medicated patients with long-term PTSD of at least moderate severity (mean age, 40; female, 70%; married or cohabitating, 16%) to 14 weeks of IPT, prolonged exposure therapy (imaginal and in vivo exposures), or relaxation therapy (active control).
- Exclusions included active psychosis; substance abuse; suicidality; antisocial, schizotypal, or schizoid personality disorders; and concurrent psychiatric treatment.

Is Exposure Necessary? A Randomized Clinical Trial of Interpersonal Psychotherapy for PTSD

John C. Markowitz, M.D., Eva Petkova, Ph.D., Yuval Neria, Ph.D., Page E. Van Meter, Ph.D., Yihong Zhao, Ph.D., Elizabeth Hembree, Ph.D., Karina Lovell, Ph.D., Tatyana Biyanova, Ph.D., Randall D. Marshall, M.D.

Conclusions: This study demonstrated noninferiority of individual IPT for PTSD compared with the gold-standard treatment. IPT had (nonsignificantly) lower attrition and higher response rates than prolonged exposure. Contrary to widespread clinical belief, PTSD treatment may not require cognitive behavioral exposure to trauma reminders. Moreover, patients with comorbid major depression may fare better with IPT than with prolonged exposure.

Am J Psychiatry 172:5, May 2015



Is Exposure Necessary? A Randomized Clinical Trial of Interpersonal Psychotherapy for PTSD

John C. Markowitz, M.D., Eva Petkova, Ph.D., Yuval Neria, Ph.D., Page E. Van Meter, Ph.D., Yihong Zhao, Ph.D., Elizabeth Hembree, Ph.D., Karina Lovell, Ph.D., Tatyana Biyanova, Ph.D., Randall D. Marshall, M.D.

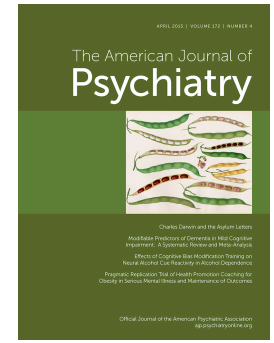
Am J Psychiatry 172:5, May 2015

- Although the study population was too small to permit important sub analyses, these findings suggest that IPT is useful, particularly for PTSD patients incapable of directly facing their traumas. Other non-exposure-based psychotherapies might also benefit these patients.
- Future studies should delineate common factors in PTSD psychotherapies contributing to their effectiveness, patient characteristics predicting differential response to specific psychotherapies, and the possible benefits of combining medications with psychotherapies.
- Overall, the current findings offer new alternatives for treating PTSD.

NEJM Journal Watch Yager, Joel. NEJM Journal Watch. Psychiatry (Feb 20, 2015).

Pragmatic Replication Trial of Health Promotion Coaching for Obesity in Serious Mental Illness and Maintenance of Outcomes

Stephen J. Bartels, M.D., M.S., Sarah I. Pratt, Ph.D., Kelly A. Aschbrenner, Ph.D., Laura K. Barre, M.D., John A. Naslund, M.P.H., Rosemarie Wolfe, M.S., Haiyi Xie, Ph.D., Gregory J. McHugo, Ph.D., Daniel E. Jimenez, Ph.D., Ken Jue, M.S.S.A., James Feldman, M.D., M.P.H., Bruce L. Bird, Ph.D.



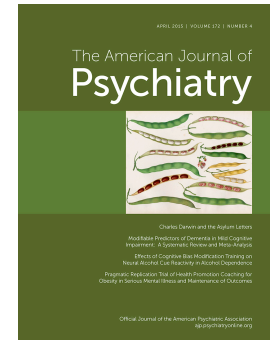
Objective: Few studies targeting obesity in serious mental illness have reported clinically significant risk reduction, and none have been replicated in community settings or demonstrated sustained outcomes after intervention withdrawal. The authors sought to replicate positive health outcomes demonstrated in a previous randomized effectiveness study of the In SHAPE program across urban community mental health organizations serving an ethnically diverse population.

Method: Persons with serious mental illness and a body mass index (BMI) >25 receiving services in three community mental health organizations were recruited and randomly assigned either to the 12-month In SHAPE program, which included membership in a public fitness club and weekly meetings with a health promotion coach, or to fitness club membership alone. The primary outcome measures were weight and cardiorespiratory fitness (as measured with the 6-minute walk test), assessed at baseline and at 3, 6, 9, 12, and 18 months.

Am J Psychiatry 172:4, April 2015

Pragmatic Replication Trial of Health Promotion Coaching for Obesity in Serious Mental Illness and Maintenance of Outcomes

Stephen J. Bartels, M.D., M.S., Sarah I. Pratt, Ph.D., Kelly A. Aschbrenner, Ph.D., Laura K. Barre, M.D., John A. Naslund, M.P.H., Rosemarie Wolfe, M.S., Haiyi Xie, Ph.D., Gregory J. McHugo, Ph.D., Daniel E. Jimenez, Ph.D., Ken Jue, M.S.S.A., James Feldman, M.D., M.P.H., Bruce L. Bird, Ph.D.

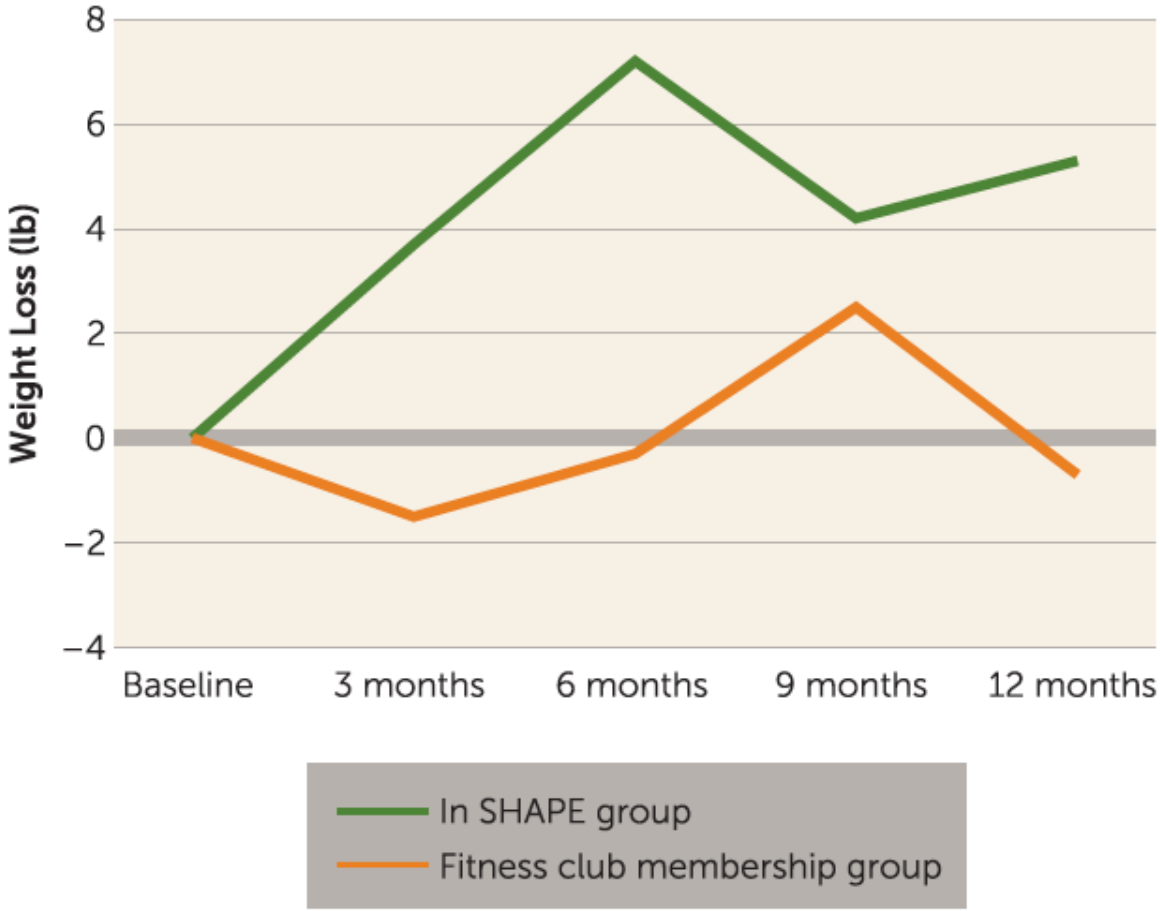


Results: Participants (N=210) were ethnically diverse (46% were nonwhite), with a mean baseline BMI of 36.8 (SD=8.2). At 12 months, the In SHAPE group (N=104) had greater reduction in weight and improved fitness compared with the fitness club membership only group (N=106). Primary outcomes were maintained at 18 months. Approximately half of the In SHAPE group (51% at 12 months and 46% at 18 months) achieved clinically significant cardiovascular risk reduction (a weight loss ≥5% or an increase of >50 meters on the 6-minute walk test).

Conclusions: This is the first replication study confirming the effectiveness of a health coaching intervention in achieving and sustaining clinically significant reductions in cardiovascular risk for overweight and obese persons with serious mental illness.

Am J Psychiatry 172:4, April 2015

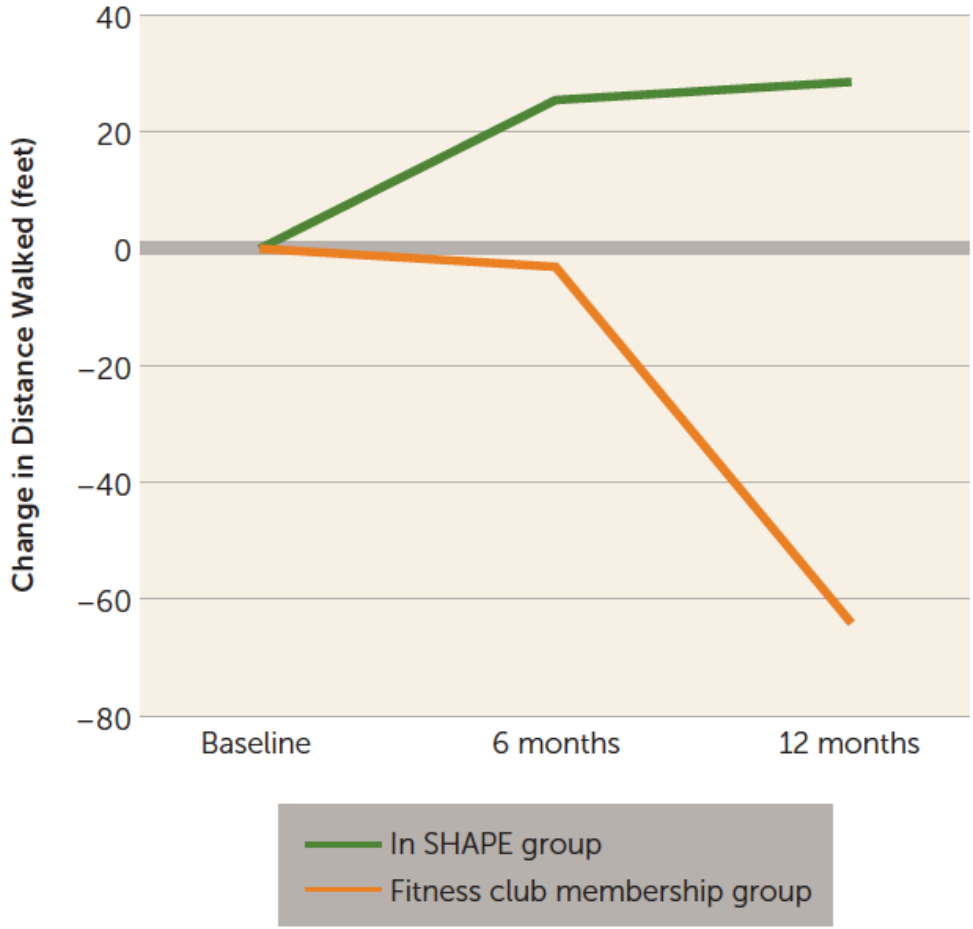
Weight Loss in the In SHAPE Intervention Group and the Fitness Club Membership Only Group[a]



[a] Each data point represents the mean weight loss for all participants examined at baseline and at 3, 6, 9, and 12 months. At 12 months, the In SHAPE group had lost significantly more weight compared with the fitness club membership only group (F=4.9, df=1, 185, p=0.029).

Am J Psychiatry 172:4, April 2015

Change in Fitness as Assessed by the 6-Minute Walk Test in the In SHAPE Group and the Fitness Club Membership Only Group[a]



[a] Each data point represents the mean change in distance walked in the 6-minute walk test for all participants examined at baseline and at 6 and 12 months. At 12 months, the In SHAPE group showed significantly greater improvement in fitness compared with the fitness club membership only group ($F=4.4$, $df=1, 170$, $p=0.037$).

Am J Psychiatry 172:4, April 2015

- These findings demonstrate the success of a health-behavior improvement program in a real-world setting.
- Similar studies have shown the effectiveness of lifestyle interventions embedded in psychiatric rehabilitation day programs and of interventions combining dietary group counseling with moderate physical activity.
- Clinicians' efforts to encourage, support, and sustain healthy behaviors seem well worth the effort.

Am J Psychiatry 172:4, April 2015

The STRIDE Weight Loss and Lifestyle Intervention for Individuals Taking Antipsychotic Medications: A Randomized Trial

Carla A. Green, Ph.D., M.P.H., Bobbi Jo H. Yarborough, Psy.D., Michael C. Leo, Ph.D., Micah T. Yarborough, M.A., Scott P. Stumbo, M.A., Shannon L. Janoff, M.P.H., Nancy A. Perrin, Ph.D., Greg A. Nichols, Ph.D., Victor J. Stevens, Ph.D.

Objectives: The STRIDE study assessed whether a lifestyle intervention, tailored for individuals with serious mental illnesses, reduced weight and diabetes risk. The authors hypothesized that the STRIDE intervention would be more effective than usual care in reducing weight and improving glucose metabolism.

Method: The study design was a multisite, parallel two-arm randomized controlled trial in community settings and an integrated health plan. Participants who met inclusion criteria were ≥18 years old, were taking antipsychotic agents for ≥30 days, and had a body mass index ≥27. Exclusions were significant cognitive impairment, pregnancy/breastfeeding, recent psychiatric hospitalization, bariatric surgery, cancer, heart attack, or stroke. The intervention emphasized moderate caloric reduction, the DASH (Dietary Approaches to Stop Hypertension) diet, and physical activity. Blinded staff collected data at baseline, 6 months, and 12 months.

Results: Participants (men, N=56; women, N=144; mean age=47.2 years [SD=10.6]) were randomly assigned to usual care (N=96) or a 6-month weekly group intervention plus six monthly maintenance sessions (N=104). A total of 181 participants (90.5%) completed 6-month assessments, and 170 (85%) completed 12-month assessments, without differential attrition. Participants attended 14.5 of 24 sessions over 6 months. Intent-to-treat analyses revealed that intervention participants lost 4.4 kg more than control participants from baseline to 6 months (95% CI=−6.96 kg to −1.78 kg) and 2.6 kg more than control participants from baseline to 12 months (95% CI=−5.14 kg to −0.07 kg). At 12 months, fasting glucose levels in the control group had increased from 106.0 mg/dL to 109.5 mg/dL and decreased in the intervention group from 106.3 mg/dL to 100.4 mg/dL. No serious adverse events were study-related; medical hospitalizations were reduced in the intervention group (6.7%) compared with the control group (18.8%).

Conclusions: Individuals taking antipsychotic medications can lose weight and improve fasting glucose levels. Increasing reach of the intervention is an important future step.

Am J Psychiatry 2015; 172:71–81; doi: 10.1176/appi.ajp.2014.14020173

- Adults with serious mental illness represent the single greatest and least recognized health disparity in the nation, reflected in a 13- to 30-year reduced life expectancy[1, 2].
- The primary cause of this epidemic of early mortality is cardiovascular disease associated with disproportionately high rates of obesity and tobacco use[1].
- Atypical antipsychotic medications increase risks for weight gain, insulin resistance, and diabetes.

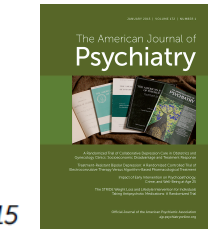
1. Colton CW, Manderscheid RW: Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis 2006; 3:A42
2. DE Hert M, Correll CU, Bobes J, et al: Physical illness in patients with severe mental disorders, I: prevalence, impact of medications and disparities in health care. World Psychiatry 2011; 10: 52–77

- In the 12-month study, researchers randomized 200 overweight patients taking antipsychotics to a group intervention or usual care. Patients were recruited from an integrated healthcare system and two community mental health centers.
- Patients (mean body-mass index, 38.3; mean age, 47) were predominantly low income (45% received disability income) and female (72%).
- Diagnoses were predominantly bipolar disorder/affective psychoses (69%) or schizophrenia spectrum (29%). Almost all patients (91%) received atypical antipsychotics; 75% of medications were known to cause weight gain, 64% severely so.
- The intervention (next slide) was followed by six monthly meetings emphasizing weight maintenance and motivational enhancement.
- Attendance during the first 6 months averaged 60%.

Am J Psychiatry 172:1, January 2015

TABLE 1. STRIDE Core Intervention Components

Increasing awareness through monitoring: diet, physical activity, and sleep
Creating personalized diet and physical activity plans
Reducing calories
Reducing portion sizes, identifying and choosing alternative foods, modifying meals
Increasing consumption of fruits, vegetables, fiber, and low-fat dairy products
Increasing physical activity
Developing action plans for high-risk eating situations
Graphing progress and making adjustments
Addressing mental health effects on lifestyle-change efforts



Am J Psychiatry 172:1, January 2015

FIGURE 2. Adjusted Mean Weights of Intervention and Control Groups From Baseline to 12 Months

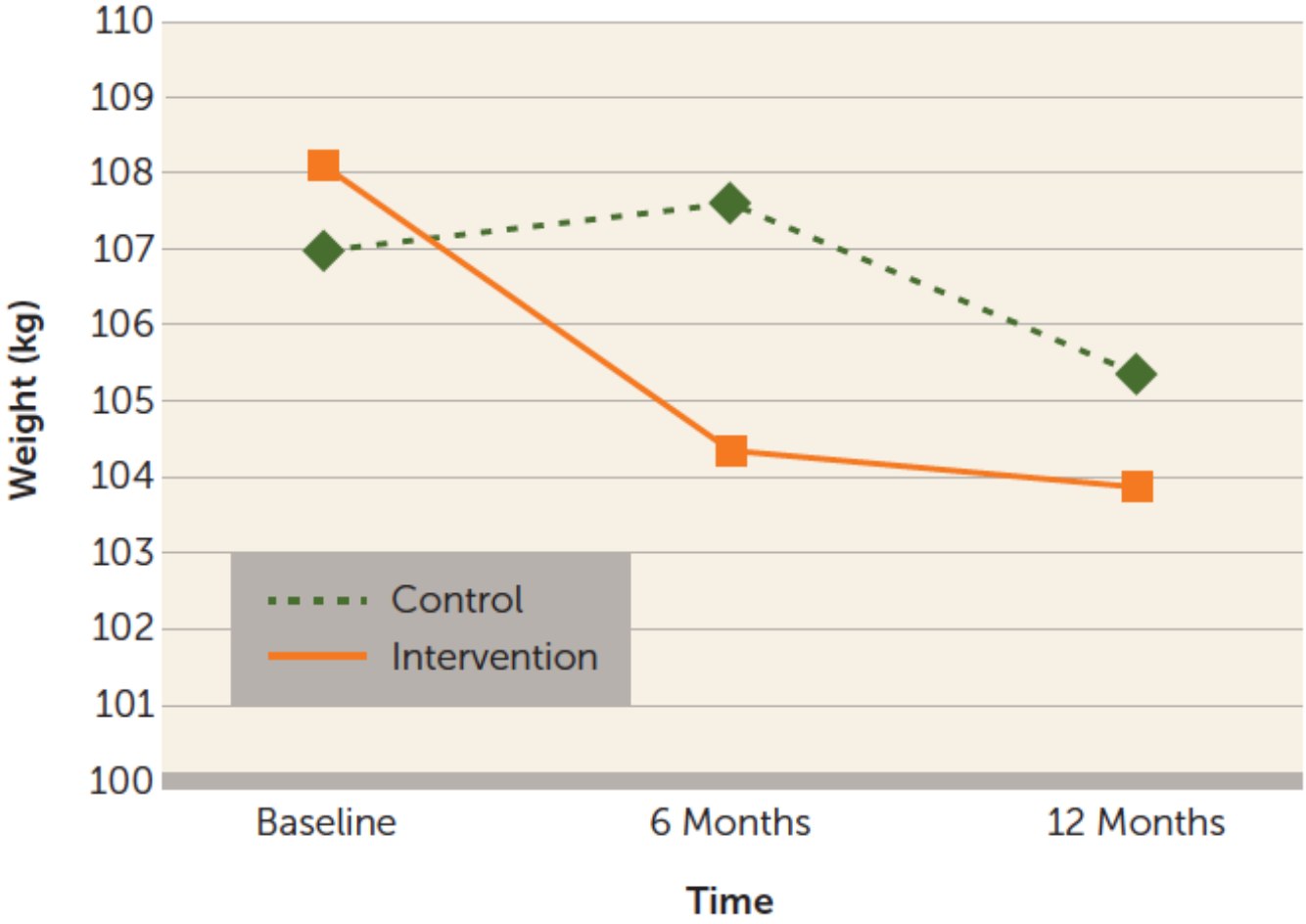
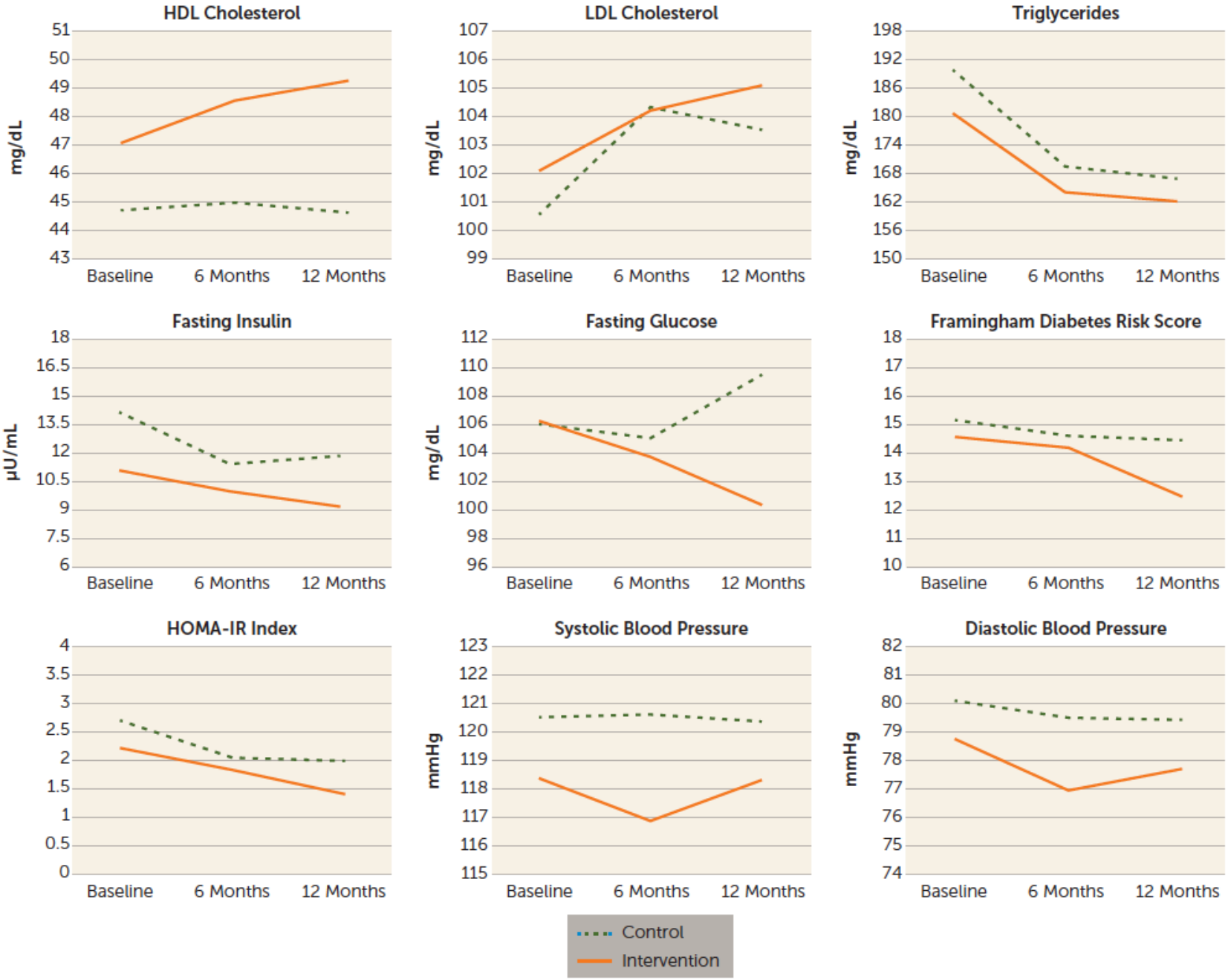


FIGURE 3. Adjusted Mean Outcomes of Intervention and Control Groups From Baseline to 12 Months[a]



[a] Abbreviations: LDL=low-density lipoprotein; HDL=high-density lipoprotein; HOMA-IR=homeostasis model assessment-insulin resistance.

- Intervention recipients lost a mean of 4.4 kg more than controls (who gained a mean of 0.5 kg) at 6 months and 2.6 kg more at 12 months.
- Mean fasting glucose levels by 12 months fell in the intervention group (baseline, 106.3 mg/dL; 1 year, 100.4 mg/dL) and rose in controls (106.0 mg/dL to 109.5 mg/dL).
- During the year, 6.7% of intervention patients versus 18.8% of controls required medical hospitalization.

Am J Psychiatry 172:1, January 2015

- Intervention recipients lost a mean of 4.4 kg more than controls (who gained a mean of 0.5 kg) at 6 months and 2.6 kg more at 12 months. Mean fasting glucose levels by 12 months fell in the intervention group (baseline, 106.3 mg/dL; 1 year, 100.4 mg/dL) and rose in controls (106.0 mg/dL to 109.5 mg/dL). During the year, 6.7% of intervention patients versus 18.8% of controls required medical hospitalization.
- This 12-month, freestanding intervention improved weight and overall health in a diverse population taking weight-inducing antipsychotics. Alterations to the program might engage and retain more patients, and even-longer interventions might better sustain health benefits.
- Actively empowering patients in their own recovery and wellness clearly yields multiple benefits. Clinicians should consider prescribing these programs routinely.

Am J Psychiatry 172:1, January 2015

Long-Term Outcome of Psychodynamic Therapy and Cognitive-Behavioral Therapy in Social Anxiety Disorder

Falk Leichsenring, D.Sc., Simone Salzer, D.Sc., Manfred E. Beutel, M.D., Stephan Herpertz, M.D., Wolfgang Hiller, Ph.D., Juergen Hoyer, Ph.D., Johannes Huesing, Dr.Rer.Medic., Peter Joraschky, M.D., Bjoern Nolting, M.D., Karin Poehlmann, Ph.D., Viktoria Ritter, D.Phil.Nat., Ulrich Stangier, D.Sc., Bernhard Strauss, Ph.D., Susan Tefikow, Ph.D., Tobias Teismann, Ph.D., Ulrike Willutzki, Ph.D, Joerg Wiltink, M.D., Eric Leibing, D.Sc.

Objective: Relatively few studies have examined the long-term outcome of psychotherapy in social anxiety disorder. The authors previously reported findings of a clinical trial comparing cognitive behavioral therapy (CBT), psychodynamic therapy, and a wait-list control. The purpose of the present study was to follow the participants' status over the ensuing 24 months.

Method: Outpatients with social anxiety disorder who were treated with CBT (N=209) or psychodynamic therapy (N=207) in the previous trial were assessed 6, 12, and 24 months after the end of therapy. Primary outcome measures were rates of remission and response.

Am J Psychiatry 171:10, October 2014

Long-Term Outcome of Psychodynamic Therapy and Cognitive-Behavioral Therapy in Social Anxiety Disorder

Falk Leichsenring, D.Sc., Simone Salzer, D.Sc., Manfred E. Beutel, M.D., Stephan Herpertz, M.D., Wolfgang Hiller, Ph.D., Juergen Hoyer, Ph.D., Johannes Huesing, Dr.Rer.Medic., Peter Joraschky, M.D., Bjoern Nolting, M.D., Karin Poehlmann, Ph.D., Viktoria Ritter, D.Phil.Nat., Ulrich Stangier, D.Sc., Bernhard Strauss, Ph.D., Susan Tefikow, Ph.D., Tobias Teismann, Ph.D., Ulrike Willutzki, Ph.D, Joerg Wiltink, M.D., Eric Leibing, D.Sc.

Results: For both CBT and psychodynamic therapy, response rates were approximately 70% by the 2-year follow-up. Remission rates were nearly 40% for both treatment conditions. Rates of response and remission were stable or tended to increase for both treatments over the 24-month follow-up period, and no significant differences were found between the treatment conditions after 6 months.

Am J Psychiatry 171:10, October 2014

FIGURE 2. Response Rates for Cognitive-Behavioral Therapy (CBT) and Psychodynamic Therapy in Patients With Social Anxiety Disorder

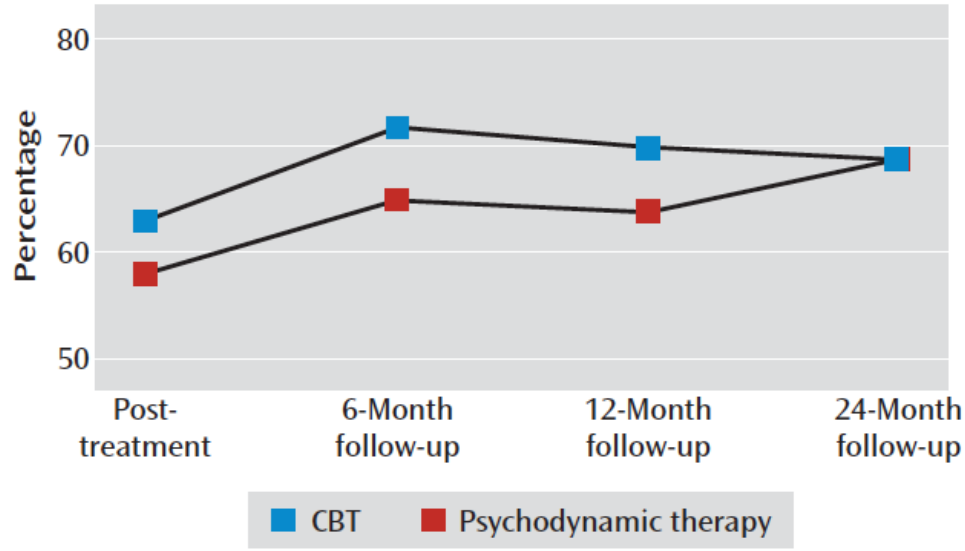
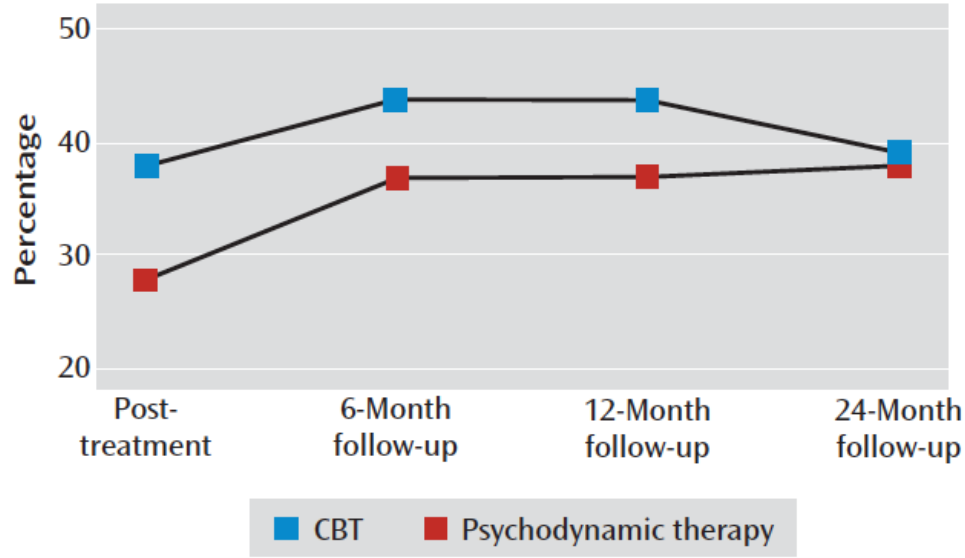


FIGURE 3. Remission Rates for Cognitive-Behavioral Therapy (CBT) and Psychodynamic Therapy in Patients With Social Anxiety Disorder



Long-Term Outcome of Psychodynamic Therapy and Cognitive-Behavioral Therapy in Social Anxiety Disorder

Falk Leichsenring, D.Sc., Simone Salzer, D.Sc., Manfred E. Beutel, M.D., Stephan Herpertz, M.D., Wolfgang Hiller, Ph.D., Juergen Hoyer, Ph.D., Johannes Huesing, Dr.Rer.Medic., Peter Joraschky, M.D., Bjoern Nolting, M.D., Karin Poehlmann, Ph.D., Viktoria Ritter, D.Phil.Nat., Ulrich Stangier, D.Sc., Bernhard Strauss, Ph.D., Susan Tefikow, Ph.D., Tobias Teismann, Ph.D., Ulrike Willutzki, Ph.D, Joerg Wiltink, M.D., Eric Leibing, D.Sc.

Conclusions:

- CBT and psychodynamic therapy were efficacious in treating social anxiety disorder, in both the short- and long-term, when patients showed continuous improvement.
- Although in the short-term, intention-to-treat analyses yielded some statistically significant but small differences in favor of CBT in several outcome measures, no differences in outcome were found in the long-term.

Am J Psychiatry 171:10, October 2014

Comparison of Low and Moderate Dosages of Extended-Release Quetiapine in Borderline Personality Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

Donald W. Black, M.D.

Mary C. Zanarini, Ed.D.

Ann Romine, R.N.

Martha Shaw, B.A.

Jeff Allen, Ph.D.

S. Charles Schulz, M.D.

Objective: The authors compared the efficacy and tolerability of low and moderate dosages of extended-release quetiapine in adults with borderline personality disorder.

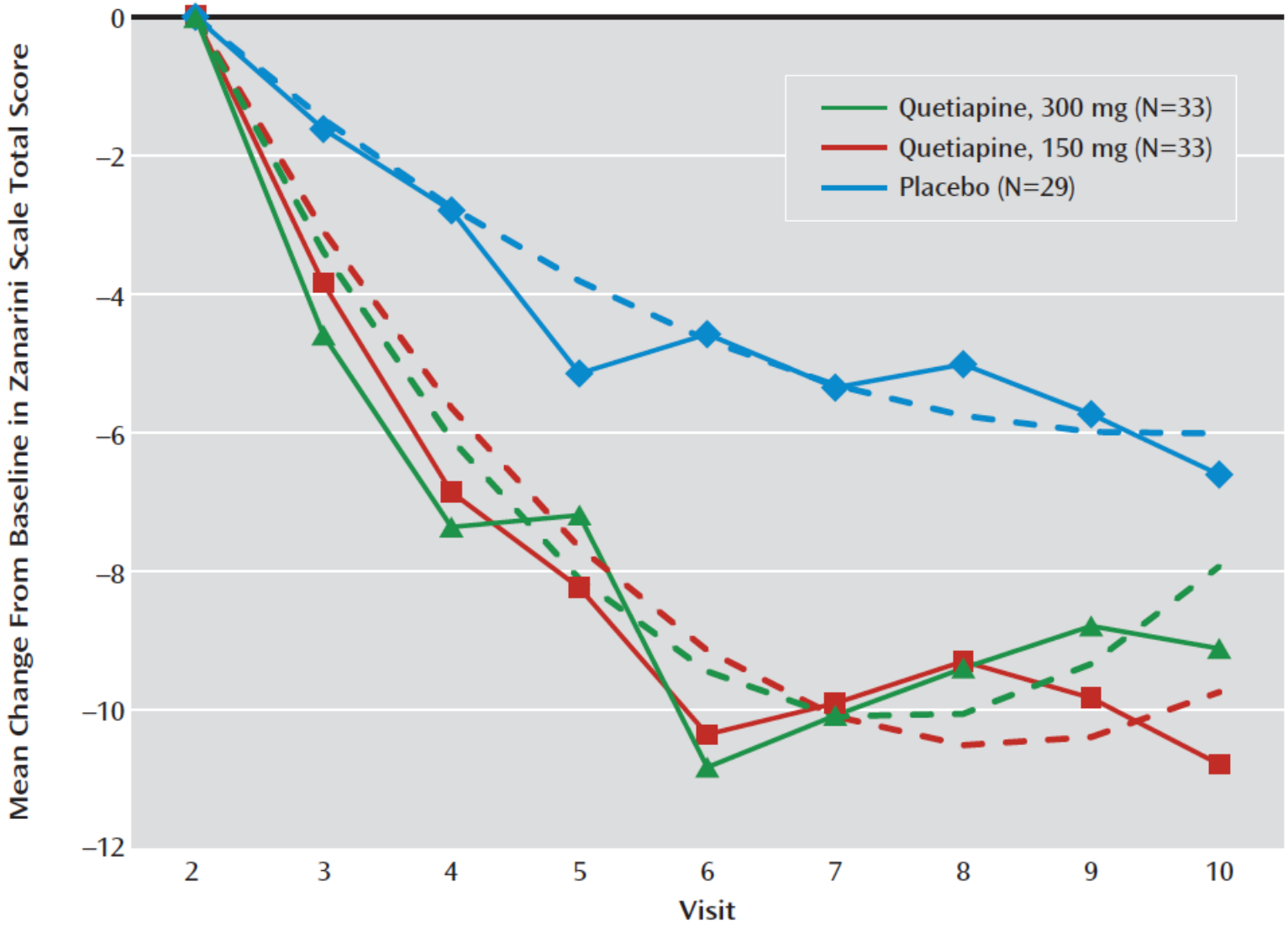
Method: Ninety-five participants with DSM-IV borderline personality disorder were randomly assigned to receive 150 mg/day of quetiapine (the low-dosage group; N=33), 300 mg/day of quetiapine (the moderate-dosage group; N=33), or placebo (N=29). Total score over time on the clinician-rated Zanarini Rating Scale for Borderline Personality Disorder ("Zanarini scale") was analyzed in a mixed-effects model accounting for informative dropout.

Results: Participants in the low-dosage quetiapine group had significant improvement on the Zanarini scale compared with those in the placebo group. Time to response (defined as a reduction of 50% or more on the Zanarini scale total score) was significantly shorter for both the low-dosage quetiapine group (hazard ratio=2.54, p=0.007) and the moderate-dosage quetiapine group (hazard ratio=2.37, p=0.011) than for the placebo group. Among participants who completed the study, 82% in the low-dosage quetiapine group were rated as "responders," compared with 74% in the moderate-dosage group and 48% in the placebo group. Treatment-emergent adverse events included sedation, change in appetite, and dry mouth. The overall completion rate for the 8-week double-blind treatment phase was 67% (67% for the low-dosage quetiapine group, 58% for the moderate-dosage quetiapine group, and 79% for the placebo group). Participants who experienced sedation were more likely to drop out.

Conclusions: Participants treated with 150 mg/day of quetiapine had a significant reduction in the severity of borderline personality disorder symptoms compared with those who received placebo. Adverse events were more likely in participants taking 300 mg/day of quetiapine.

(Am J Psychiatry 2014; 171:1174–1182)

FIGURE 1. Changes in Mean Total Score on the Zanarini Rating Scale for Borderline Personality Disorder Among Study Participants Who Received Quetiapine or Placebo[a]



[a] Solid lines represent least-square mean estimates; dashed lines represent estimates from the shared parameter model with linear and quadratic effects. Results do not align completely because of differences in how group means are modeled and because the shared parameter model corrects for informative dropout.

- In an industry-funded, multisite, double-blind study, academic researchers randomized 95 patients with borderline personality disorder to 8 weeks of extended-release quetiapine at 150 mg/day, 300 mg/day, or placebo (mean age, 29; 29% male).
- Quetiapine dosing was started at 50 mg/day and gradually increased over several weeks.
- Response (≥50% reduction from baseline scores on a standardized scale) was achieved for total and some symptom scores in at least one post-baseline visit by 82% of patients on low-dose quetiapine, 67% on moderate-dose quetiapine, and 62% receiving placebo.
- At the last treatment visit, 82%, 74%, and 48%, respectively, were rated as responders; the number needed to treat for one patient to benefit was about three for low-dose and four for moderate-dose quetiapine.

Am J Psychiatry 171:11, November 2014

- A well-designed clinical trial that provides evidence that low-dosage quetiapine (150 mg) is effective in the short-term treatment of some of the core symptoms of borderline personality disorder. The estimated effect size (20.79) and number needed to treat for response (2.9) suggest a moderate to large effect on the primary outcome.
- A number of questions remain:
  - whether the response will be maintained over longer periods
  - long-term safety, especially in regard to metabolic syndrome

MAURICIO TOHEN, M.D., DR .P.H.
Am J Psychiatry 171:11, November 2014

Quetiapine for Borderline Personality Disorder?

Yager, Joel. NEJM Journal Watch. Psychiatry (Jul 21, 2014).

- Although improvement with low-dose quetiapine occurred, this 8-week study was too short to prove meaningful long-term value for the medication.
- Although this limited study demonstrated effectiveness across a range of symptoms (particularly for lower-dose quetiapine), placebo response and dropout rates were high.

NEJM Journal Watch

Multicenter Pilot Treatment Trial for Psychogenic Nonepileptic Seizures

A Randomized Clinical Trial

W. Curt LaFrance Jr, MD, MPH; Grayson L. Baird, MS; John J. Barry, MD; Andrew S. Blum, MD, PhD; Anne Frank Webb, MA; Gabor I. Keitner, MD; Jason T. Machan, PhD; Ivan Miller, PhD; Jerzy P. Szaflarski, MD, PhD; for the NES Treatment Trial (NEST-T) Consortium

IMPORTANCE There is a paucity of controlled treatment trials for the treatment of conversion disorder, seizures type, also known as psychogenic nonepileptic seizures (PNES). Psychogenic nonepileptic seizures, the most common conversion disorder, are as disabling as epilepsy and are not adequately addressed or treated by mental health clinicians.

OBJECTIVE To evaluate different PNES treatments compared with standard medical care (treatment as usual).

DESIGN, SETTING, AND PARTICIPANTS Pilot randomized clinical trial at 3 academic medical centers with mental health clinicians trained to administer psychotherapy or psychopharmacology to outpatients with PNES. Thirty-eight participants were randomized in a blocked schedule among 3 sites to 1 of 4 treatment arms and were followed up for 16 weeks between September 2008 and February 2012; 34 were included in the analysis.

Multicenter Pilot Treatment Trial for Psychogenic Nonepileptic Seizures

INTERVENTIONS Medication (flexible-dose sertraline hydrochloride) only, cognitive behavioral therapy informed psychotherapy (CBT-ip) only, CBT-ip with medication (sertraline), or treatment as usual.

MAIN OUTCOMES AND MEASURES Seizure frequency was the primary outcome; psychosocial and functioning measures, including psychiatric symptoms, social interactions, quality of life, and global functioning, were secondary outcomes. Data were collected prospectively, weekly, and with baseline, week 2, midpoint (week 8), and exit (week 16) batteries. Within-group analyses for each arm were performed on primary (seizure frequency) and secondary outcomes from treatment-blinded raters using an intention-to-treat analysis.

Multicenter Pilot Treatment Trial for Psychogenic Nonepileptic Seizures

RESULTS The psychotherapy (CBT-ip) arm showed a 51.4% seizure reduction ($P = .01$) and significant improvement from baseline in secondary measures including depression, anxiety, quality of life, and global functioning ($P < .001$). The combined arm (CBT-ip with sertraline) showed 59.3% seizure reduction ($P = .008$) and significant improvements in some secondary measures, including global functioning ($P = .007$). The sertraline-only arm did not show a reduction in seizures ($P = .08$). The treatment as usual group showed no significant seizure reduction or improvement in secondary outcome measures ($P = .19$).

CONCLUSIONS AND RELEVANCE This pilot randomized clinical trial for PNES revealed significant seizure reduction and improved comorbid symptoms and global functioning with CBT-ip for PNES without and with sertraline. There were no improvements in the sertraline-only or treatment-as-usual arms. This study supports the use of manualized psychotherapy for PNES and successful training of mental health clinicians in the treatment. Future studies could assess larger-scale intervention dissemination.

Psychotherapy for Conversion Symptoms?

Dubovsky, Steven. NEJM Journal Watch. Psychiatry (Aug 31 2009).

NEJM Journal Watch

- The most that can be concluded from this pilot study is that patients who are willing to accept the psychogenic nature of their conversion symptoms -- typically, a minority of these patients -- may be able to substitute more-mature solutions to cognitive, intrapsychic, and interpersonal problems.
- Eclectic psychotherapy for somatization has promise for patients who can mobilize some insight into the mind-body connection.

Long-Term Effectiveness of Supported Employment: 5-Year Follow-Up of a Randomized Controlled Trial

Holger Hoffmann, M.D.

Dorothea Jäckel, M.A.

Sybille Glauser, M.A.

Kim T. Mueser, Ph.D.

Zeno Kupper, Ph.D.

Objective: The individual placement and support model of supported employment has been shown to be more effective than other vocational approaches in improving competitive work over 1–2 years in persons with severe mental illness. The authors evaluated the longer-term effects of the model compared with traditional vocational rehabilitation over 5 years.

Method: A randomized controlled trial compared supported employment to traditional vocational rehabilitation in 100 unemployed persons with severe mental illness. Competitive work and hospital admissions were tracked for 5 years, and interviews were conducted at 2 and 5 years to assess recovery attitudes and quality of life. A cost-benefit analysis compared program and total treatment costs to earnings from competitive employment.

Am J Psychiatry 171:11, November 2014

Long-Term Effectiveness of Supported Employment: 5-Year Follow-Up of a Randomized Controlled Trial

- Participants had persistent impairments in role, social or independent living, and self-care; no recent substance disorder or disabling physical conditions; and significant underemployment at baseline (65% men, mean age, 34; mean hospitalizations, 1.7; moderate-serious symptoms on a standardized scale assessing function).
- Supported employment included individual placement and job coaching, biweekly coach contact, and monthly coach contact with work supervisors, treatment team, and others. Traditional vocational rehabilitation included prevocational training in sheltered workshops (6-12 months); employable participants then received training in competitive jobs (3-6 months).

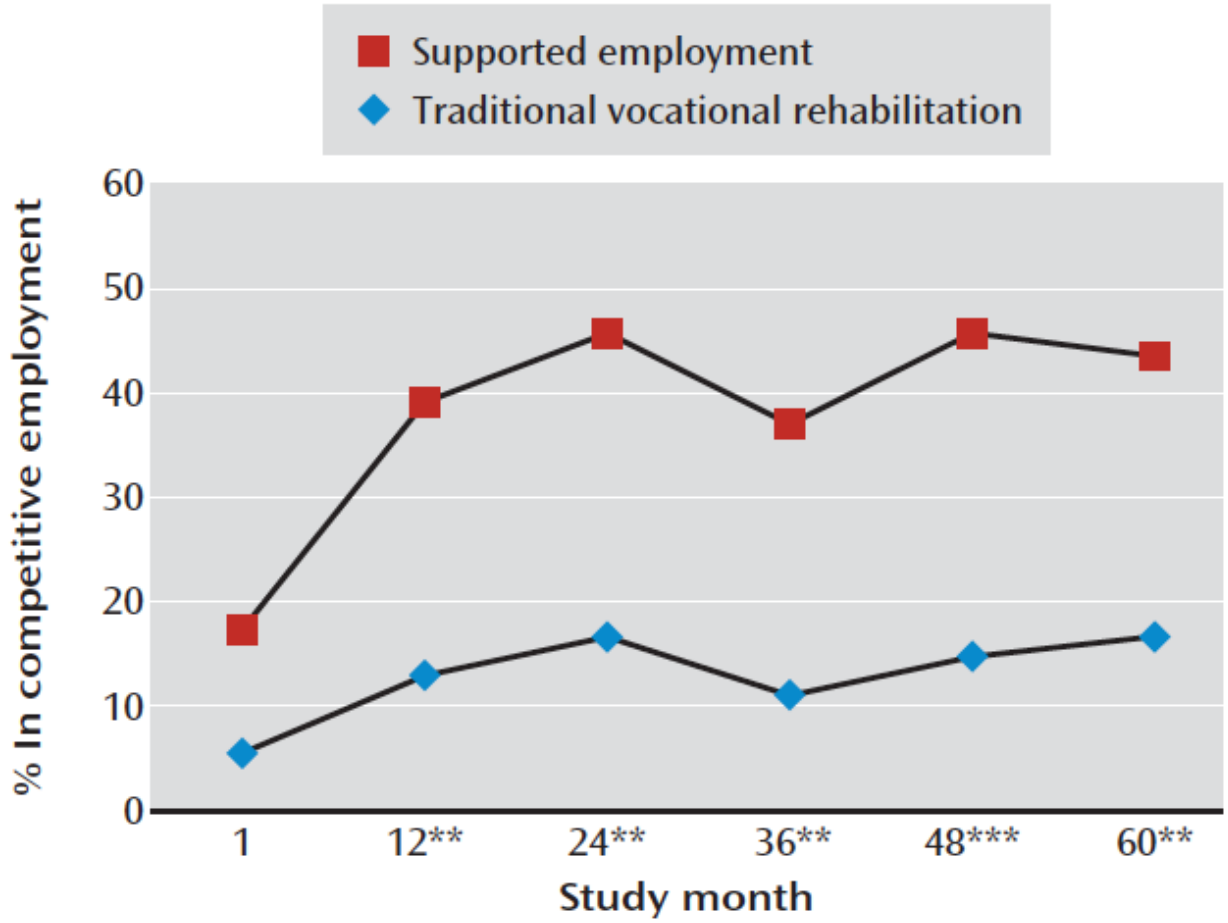
Am J Psychiatry 171:11, November 2014

Long-Term Effectiveness of Supported Employment: 5-Year Follow-Up of a Randomized Controlled Trial

Results: The beneficial effects of supported employment on work at 2 years were sustained over the 5-year follow-up period. Participants in supported employment were more likely to obtain competitive work than those in traditional vocational rehabilitation (65% compared with 33%), worked more hours and weeks, earned more wages, and had longer job tenures. Reliance on supported employment services for retaining competitive work decreased from 2 years to 5 years for participants in supported employment. Participants were also significantly less likely to be hospitalized, had fewer psychiatric hospital admissions, and spent fewer days in the hospital. The social return on investment was higher for supported employment participants, whether calculated as the ratio of work earnings to vocational program costs or of work earnings to total vocational program and mental health treatment costs.

Am J Psychiatry 171:11, November 2014

FIGURE 2. Year-by-Year Rates of Competitive Employment Among Participants in Supported Employment and Traditional Vocational Rehabilitation Programs



**p<0.01. ***p<0.001.

Long-Term Effectiveness of Supported Employment: 5-Year Follow-Up of a Randomized Controlled Trial

Holger Hoffmann, M.D.

Dorothea Jäckel, M.A.

Sybille Glauser, M.A.

Kim T. Mueser, Ph.D.

Zeno Kupper, Ph.D.

Conclusions: The results demonstrate that the greater effectiveness of supported employment in improving competitive work outcomes is sustained beyond 2 years and suggest that supported employment programs contribute to reduced hospitalizations and produce a higher social return on investment.

Am J Psychiatry 171:11, November 2014

Supported Employment Reaps Clinical and Social Benefits

Yager, Joel. NEJM Journal Watch. Psychiatry (Aug 26, 2014).

- Helping psychiatrically impaired patients achieve and maintain competitive employment can assist meaningful recovery and individual self-worth and reduce disability costs and psychiatric treatment expenses.
- These largely encouraging results are consistent with studies in the U.S. and elsewhere showing sustained and significant benefits for supported employment programs. Helping patients with serious mental illness gain access to supported employment programs should be both a clinical and a social policy priority.

Emergency Department Visits by Adults for Psychiatric Medication Adverse Events

Lee M. Hampton, MD, MSc; Matthew Daubresse, MHS; Hsien-Yen Chang, PhD; G. Caleb Alexander, MD, MS; Daniel S. Budnitz, MD, MPH

IMPORTANCE In 2011, an estimated 26.8 million US adults used prescription medications for mental illness.

OBJECTIVE To estimate the numbers and rates of adverse drug event (ADE) emergency department (ED) visits involving psychiatric medications among US adults between January 1, 2009, and December 31, 2011.

DESIGN AND SETTING Descriptive analyses of active, nationally representative surveillance of ADE ED visits using the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance system and of drug prescribing during outpatient visits using the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.

PARTICIPANTS Medical records from national probability samples of ED and outpatient visits by adults 19 years or older were reviewed and analyzed.

Emergency Department Visits by Adults for Psychiatric Medication Adverse Events

- Of 89,094 ED visits for psychiatric ADRs (about 10% of all ADR visits to EDs), almost 20% resulted in hospitalization.
- The highest rate of ED visits relative to the number of outpatient presumed prescriptions was found for antipsychotics (especially, typical antipsychotics), primarily for severe extrapyramidal effects, and lithium, with the most common problems being "abnormal drug level," altered mental status, and movement disorder.
- In an examination of individual drugs, zolpidem led to more ED visits than any other psychiatric medication, especially in older patients.
- The analyses did not include anticonvulsants.

Emergency Department Visits by Adults for Psychiatric Medication Adverse Events

EXPOSURES Antidepressants, antipsychotics, lithium salts, sedatives and anxiolytics, and stimulants.

MAIN OUTCOMES AND MEASURES National estimates of ADE ED visits resulting from therapeutic psychiatric medication use and of psychiatric medication ADE ED visits per 10 000 outpatient visits at which psychiatric medications were prescribed.

RESULTS From 2009 through 2011, there were an estimated 89 094 (95% CI, 68 641-109 548) psychiatric medication ADE ED visits annually, with 19.3% (95% CI, 16.3%-22.2%) resulting in hospitalization and 49.4% (95% CI, 46.5%-52.4%) involving patients aged 19 to 44 years. Sedatives and anxiolytics, antidepressants, antipsychotics, lithium salts, and stimulants were implicated in an estimated 30 707 (95% CI, 23 406-38 008), 25 377 (95% CI, 19 051-31 704), 21 578 (95% CI, 16 599-26 557), 3620 (95% CI, 2311-4928), and 2779 (95% CI, 1764-3794) respective ADE ED visits annually. Antipsychotics and lithium salts were implicated in 11.7 (95% CI, 10.1-13.2) and 16.4 (95% CI, 13.0-19.9) ADE ED visits per 10 000 outpatient prescription visits, respectively, compared with 3.6 (95% CI, 3.2-4.1) for sedatives and anxiolytics, 2.9 (95% CI, 2.3-3.5) for stimulants, and 2.4 (95% CI, 2.1-2.7) for antidepressants. The commonly used sedative zolpidem tartrate was implicated in 11.5% (95% CI, 9.5%-13.4%) of all adult psychiatric medication ADE ED visits and in 21.0% (95% CI, 16.3%-25.7%) of visits involving adults 65 years or older, in both cases significantly more than any other psychiatric medication.

Emergency Department Visits by Adults for Psychiatric Medication Adverse Events

Lee M. Hampton, MD, MSc; Matthew Daubresse, MHS; Hsien-Yen Chang, PhD; G. Caleb Alexander, MD, MS; Daniel S. Budnitz, MD, MPH

CONCLUSIONS AND RELEVANCE Psychiatric medications are implicated in many ADEs treated in US EDs. Efforts to reduce ADEs should include adults of all ages but might prioritize medications causing high numbers and rates of ED visits.

How Risky Are Psychiatric Medications?

Dubovsky, Steven View Profile. NEJM Journal Watch. Psychiatry (Aug 1, 2014).

- Prescribers should be mindful of the risks for adverse reactions with psychiatric drugs, especially antipsychotics, lithium, and zolpidem.
- A diverse group of providers are prescribing escalating amounts of antipsychotics, zolpidem, and other psychiatric medications, but they may not be aware that these medications carry significant risks.
- All prescribers should be mindful of a growing number of reports of amnesia, falls, and other ADRs with zolpidem, particularly in older patients, despite its initial reputation as being safer than benzodiazepines.

Antipsychotics and Associated Risk of Out-of-Hospital Cardiac Arrest

P Weeke[1], A Jensen[2], F Folke[1], GH Gislason[1,3], JB Olesen[1], EL Fosbøl[4], M Wissenberg[1], FK Lippert[5], EF Christensen[5], SL Nielsen[4], E Holm[6], JK Kanters[7], HE Poulsen[8], L Køber[4] and C Torp-Pedersen[9]

Antipsychotic drugs have been associated with sudden cardiac death, but differences in the risk of out-of-hospital cardiac arrest (OHCA) associated with different antipsychotic drug classes are not clear. We identified all OHCAs in Denmark (2001–2010). The risk of OHCA associated with antipsychotic drug use was evaluated by conditional logistic regression analysis in case–time–control models. In total, 2,205 (7.6%) of 28,947 OHCA patients received treatment with an antipsychotic drug at the time of the event. Overall, treatment with any antipsychotic drug was associated with OHCA (odds ratio (OR) = 1.53, 95% confidence interval (CI): 1.23–1.89), as was use with typical antipsychotics (OR = 1.66, CI: 1.27–2.17). By contrast, overall, atypical antipsychotic drug use was not (OR = 1.29, CI: 0.90–1.85). Two individual typical antipsychotic drugs, haloperidol (OR = 2.43, CI: 1.20–4.93) and levomepromazine (OR = 2.05, CI: 1.18–3.56), were associated with OHCA, as was one atypical antipsychotic drug, quetiapine (OR = 3.64, CI: 1.59–8.30).

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Although antipsychotic drugs have previously been associated with SCD, it is unclear whether there are differences in the risk of a cardiac arrest in an out-of-hospital setting that are associated with the type of antipsychotic drug being used.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study evaluated the possible association between antipsychotic drug use and OHCA in a nationwide cohort of Danish OHCA patients (2001–2010) using conditional logistic regression analysis in case–time–control models.

Antipsychotics and Associated Risk of Out-of-Hospital Cardiac Arrest

- To address concerns about adverse effects of antipsychotic drugs, these researchers correlated 10 years of Danish registry data on all out-of-hospital cardiac arrests (OHCAs), all prescriptions, and inpatient and outpatient treatment.
- In 28,947 people with OHCA, 2205 were taking at least one antipsychotic drug (median age, 66). The risk for OHCA was significantly increased with any antipsychotic (odds ratio, 1.53). Typical antipsychotics as a class were associated with an increased OHCA risk (OR, 1.66), but atypical antipsychotics were not.
- In analyses of 11 individual medications, greater OHCA risk was associated with the atypical quetiapine (OR, 3.64) and the neuroleptics haloperidol (OR, 2.43) and levomepromazine, a low-potency phenothiazine not available in the U.S. (OR, 2.05).
- The results were not explained by typical risk factors, substance abuse, hospitalization 2 months before OHCA, or above-median doses.
- Only 47% of OHCA patients taking an antipsychotic drug appeared to have a psychiatric illness. Numbers were too small to assess the effect of dosage or treatment duration, and the risk of other, less frequently prescribed antipsychotics was not explored.
- No data were available on whether OHCA was caused by torsades de pointes.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ This study found that overall, antipsychotic drug use is associated with OHCA. Moreover, overall use of typical antipsychotic drugs was associated with OHCA, whereas atypical antipsychotic drug use was not. Significant associations between OHCA and specific antipsychotic drugs were identified for haloperidol, levomepromazine, and quetiapine.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ This study adds to the existing body of literature on the associations between psychotropic drugs and risk of cardiac arrest and SCD and may help clinicians decide which antipsychotic drugs to prescribe.

Antipsychotic Drugs and Cardiac Arrest in Outpatients

Dubovsky, Steven. NEJM Journal Watch. Psychiatry (Sep 16, 2014).

Despite the lack of data on QT interval or arrhythmias preceding OHCA, some antipsychotic drugs may have contributed to alterations in cardiac conduction. It is not clear whether the risk is higher in non-psychiatric patients taking antipsychotics (usually for agitation), but the results clearly indicate a need for caution when using antipsychotics -- the benefits must clearly outweigh the growing list of risks.

Electroconvulsive Therapy Augmentation in Clozapine-Resistant Schizophrenia: A Prospective, Randomized Study

Georgios Petrides, M.D., Chitra Malur, M.D., Raphael J. Braga, M.D., Samuel H. Bailine, M.D., Nina R. Schooler, Ph.D., Anil K. Malhotra, M.D., John M. Kane, M.D., Sohag Sanghani, M.D., Terry E. Goldberg, Ph.D., Majnu John, Ph.D., Alan Mendelowitz, M.D.

Objective: Up to 70% of patients with treatment-resistant schizophrenia do not respond to clozapine. Pharmacological augmentation to clozapine has been studied with unimpressive results. The authors examined the use of ECT as an augmentation to clozapine for treatment-refractory schizophrenia.

Method: In a randomized single-blind 8-week study, patients with clozapine-resistant schizophrenia were assigned to treatment as usual (clozapine group) or a course of bilateral ECT plus clozapine (ECT plus clozapine group). Nonresponders from the clozapine group received an 8-week open trial of ECT (crossover phase). ECT was performed three times per week for the first 4 weeks and twice weekly for the last 4 weeks. Clozapine dosages remained constant. Response was defined as ≥40% reduction in symptoms based on the psychotic symptom subscale of the Brief Psychiatric Rating Scale, a Clinical Global Impressions (CGI)-severity rating <3, and a CGI-improvement rating ≤2.

Am J Psychiatry 172:1, January 2015

Electroconvulsive Therapy Augmentation in Clozapine-Resistant Schizophrenia: A Prospective, Randomized Study

Am J Psychiatry 172:1, January 2015

Results: The intent-to-treat sample included 39 participants (ECT plus clozapine group, N=20; clozapine group, N=19). All 19 patients from the clozapine group received ECT in the crossover phase. Fifty percent of the ECT plus clozapine patients met the response criterion. None of the patients in the clozapine group met the criterion. In the crossover phase, response was 47%. There were no discernible differences between groups on global cognition. Two patients required the postponement of an ECT session because of mild confusion.

Conclusions: The augmentation of clozapine with ECT is a safe and effective treatment option. Further research is required to determine the persistence of the improvement and the potential need for maintenance treatments.

Electroconvulsive Therapy Augmentation in Clozapine-Resistant Schizophrenia: A Prospective, Randomized Study

Am J Psychiatry 172:1, January 2015

- Controlled trial enrolling 39 inpatients with schizophrenia who showed persistent psychotic symptoms at moderate or more-severe levels after at least 12 weeks of clozapine with plasma levels ≥350 ng/ml.
- Patients continued clozapine and either were treated or were not treated with bilateral electroconvulsive therapy (ECT) for 8 weeks (72% men; 54% white; mean age: clozapine-only group, 43; combination-treatment group, 36).
- Raters blinded to group assignment performed weekly assessments. At the end of treatment (mean, 16 treatments), 50% of patients treated with ECT met responder criteria (≥40% reduction in psychotic symptoms) versus 0% of those without ECT treatment.
- All nonresponders in the clozapine-only arm eventually received ECT; 47% met response criteria.
- No impact was seen on negative symptoms. Adverse reactions were few and minor.

When Clozapine Is Insufficient for Schizophrenia, Then What?
Yager, Joel. NEJM Journal Watch. Psychiatry (Sep 8, 2014).

Because this study examined outcomes only at the end of treatment, extensions are necessary to ascertain whether the observed clinical improvement is sustained. If a sizable fall-off in improvement occurs after 20 treatments, maintenance ECT might help, but studies assessing this possibility should be conducted. The potential benefits for transcranial magnetic stimulation also deserve study in clozapine nonresponders. Given the reluctance of many patients and families to accept ECT, clinicians should be prepared to provide considerable education about the procedure and a full informed consent process. For patients with persistent, disturbing, and impairing symptoms of schizophrenia that fail to improve with clozapine, these results offer new treatment directions.

NEJM Journal Watch

Antipsychotic Treatment and Mortality in Schizophrenia

- Life expectancy in patients with schizophrenia is 10 to 20 years shorter than in people without schizophrenia and of similar age and sex.
- Some studies suggest that this is partly attributable to the adverse cardiovascular effects of antipsychotic medications, but detailed understanding is lacking.
- Studying Swedish national registries from 2006 through 2010, investigators examined cumulative antipsychotic exposure in relation to all-cause and disease-specific mortality in two cohorts of patients with schizophrenia (age range, 17-65)
  - 21,492 patients diagnosed before 2006 ("chronic"), and
  - 1230 patients initially diagnosed between 2006 and 2010 ("first-episode").
- Data on 214,670 and 12,110 matched general-population controls, respectively, were also examined.

Schizophrenia Bulletin Advance Access published November 24, 2014

Antipsychotic Treatment and Mortality in Schizophrenia

Minna Torniainen[1], Ellenor Mittendorfer-Rutz[2], Antti Tanskanen[2], Charlotte Björkenstam[2], Jaana Suvisaari[1], Kristina Alexanderson[2], and Jari Tiihonen*[,1–3]

[1]Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland; [2]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [3]Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland

Background: It is generally believed that long-term use of antipsychotics increases mortality and, especially, the risk of cardiovascular death. However, there are no solid data to substantiate this view.

Methods: We identified all individuals in Sweden with schizophrenia diagnoses before year 2006 (N = 21 492), aged 17–65 years, and persons with first-episode schizophrenia during the follow-up 2006–2010 (N = 1230). Patient information was prospectively collected through nationwide registers. Total and cause-specific mortalities were calculated as a function of cumulative antipsychotic exposure from January 2006 to December 2010.

Schizophrenia Bulletin Advance Access published November 24, 2014

Antipsychotic Treatment and Mortality in Schizophrenia

Minna Torniainen[1], Ellenor Mittendorfer-Rutz[2], Antti Tanskanen[2], Charlotte Björkenstam[2], Jaana Suvisaari[1], Kristina Alexanderson[2], and Jari Tiihonen*[,1–3]

[1]Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland; [2]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [3]Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland

- During the 5-year follow-up, 1591 of chronic patients (7.4%), 3438 of their controls (1.6%), and 45 of first-episode patients (3.7%) died.
- In both patient groups, antipsychotic exposure had U-shaped associations with mortality from cardiovascular disease and cancer: No exposure and highest exposure were linked to higher mortality than low and moderate exposure.
- For respiratory diseases, mortality increased with antipsychotic exposure; for suicide, mortality decreased with greater exposure. Cardiovascular- and cancer-specific death rates were the highest (chronic patients, 2.4% and 1.2%, respectively).
- Among high-exposure patients, mortality was higher in women than in men.
- Overall, mortality was highest for first-episode patients having no antipsychotic exposure (hazard ratio, 9.9) and for unexposed chronic patients who had been hospitalized in the year before follow-up (HR, 6.3). However, mortality was not elevated among unexposed patients who had never been hospitalized.

Schizophrenia Bulletin Advance Access published November 24, 2014

Antipsychotic Treatment and Mortality in Schizophrenia

Minna Torniainen[1], Ellenor Mittendorfer-Rutz[2], Antti Tanskanen[2], Charlotte Björkenstam[2], Jaana Suvisaari[1], Kristina Alexanderson[2], and Jari Tiihonen*[,1–3]

[1]Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland; [2]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [3]Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland

Results: Compared with age- and gender-matched controls from the general population (*N* = 214 920), the highest overall mortality was observed among patients with no antipsychotic exposure (hazard ratio [HR] = 6.3, 95% CI: 5.5–7.3), i.e., 0.0 defined daily dose (DDD)/day, followed by high exposure (>1.5 DDD/day) group (HR = 5.7, 5.2–6.2), low exposure (<0.5 DDD/day) group (HR = 4.1, 3.6–4.6), and moderate exposure (0.5–1.5 DDD/day) group (HR = 4.0, 3.7– 4.4). High exposure (HR = 8.5, 7.3–9.8) and no exposure (HR = 7.6, 5.8–9.9) were associated with higher cardiovascular mortality than either low exposure (HR = 4.7, 3.7–6.0) or moderate exposure (HR = 5.6, 4.8–6.6). The highest excess overall mortality was observed among first- episode patients with no antipsychotic use (HR = 9.9, 5.9–16.6).

Conclusions: Among patients with schizophrenia, the cumulative antipsychotic exposure displays a U-shaped curve for overall mortality, revealing the highest risk of death among those patients with no antipsychotic use. These results indicate that both excess overall and cardiovascular mortality in schizophrenia is attributable to other factors than antipsychotic treatment when used in adequate dosages.

Schizophrenia Bulletin Advance Access published November 24, 2014

Schizophrenia Bulletin Advance Access published November 24, 2014

- These associations between antipsychotic exposure and specific causes of death are complex.
- General health monitoring is essential for patients with high antipsychotic exposure.
- Even though this observational study cannot prove causality, the notably higher mortality among patients with no antipsychotic exposure suggests that adherence-increasing interventions, including use of long-acting injectable medications, might reduce risk for death.

NEJM Journal Watch

Joel Yager, MD - NEJM Journal Watch- Psychiatry

Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia

Number Needed to Harm *

JAMA Psychiatry May 2015 Volume 72, Number 5

Donovan T. Maust, MD, MS; Hyungjin Myra Kim, ScD; Lisa S. Seyfried, MD, MS; Claire Chiang, PhD; Janet Kavanagh, MS; Lon S. Schneider, MD, MS; Helen C. Kales, MD

IMPORTANCE Antipsychotic medications are associated with increased mortality in older adults with dementia, yet their absolute effect on risk relative to no treatment or an alternative psychotropic is unclear.

OBJECTIVE To determine the absolute mortality risk increase and number needed to harm (NNH) (ie, number of patients who receive treatment that would be associated with 1 death) of antipsychotic, valproic acid and its derivatives, and antidepressant use in patients with dementia relative to either no treatment or antidepressant treatment.

DESIGN, SETTING, AND PARTICIPANTS A retrospective case-control study was conducted in the Veterans Health Administration from October 1, 1998, through September 30, 2009. Participants included 90 786 patients 65 years or older with a diagnosis of dementia. Final analyses were conducted in August 2014.

*number needed to harm = number of patients receiving the drug to produce one excess death

Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia - Number Needed to Harm

EXPOSURES A new prescription for an antipsychotic (haloperidol, olanzapine, quetiapine, and risperidone), valproic acid and its derivatives, or an antidepressant (46 008 medication users).

MAIN OUTCOMES AND MEASURES Absolute change in mortality risk and NNH over 180 days of follow-up in medication users compared with nonmedication users matched on several risk factors. Among patients in whom a treatment with medication was initiated, mortality risk associated with each agent was also compared using the antidepressant group as the reference, adjusting for age, sex, years with dementia, presence of delirium, and other clinical and demographic characteristics. Secondary analyses compared dose-adjusted absolute change in mortality risk for olanzapine, quetiapine, and risperidone.

Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia - Number Needed to Harm

RESULTS Compared with respective matched nonusers, individuals receiving haloperidol had an increased mortality risk of 3.8% (95% CI, 1.0%-6.6%; $P < .01$) with an NNH of 26 (95% CI, 15-99); followed by risperidone, 3.7% (95% CI, 2.2%-5.3%; $P < .01$) with an NNH of 27 (95% CI, 19-46); olanzapine, 2.5% (95% CI, 0.3%-4.7%; $P = .02$) with an NNH of 40 (95% CI, 21-312); and quetiapine, 2.0% (95% CI, 0.7%-3.3%; $P < .01$) with an NNH of 50 (95% CI, 30-150). Compared with antidepressant users, mortality risk ranged from 12.3% (95% CI, 8.6%-16.0%; $P < .01$) with an NNH of 8 (95% CI, 6-12) for haloperidol users to 3.2% (95% CI, 1.6%-4.9%; $P < .01$) with an NNH of 31 (95% CI, 21-62) for quetiapine users. As a group, the atypical antipsychotics (olanzapine, quetiapine, and risperidone) showed a dose-response increase in mortality risk, with 3.5% greater mortality (95% CI, 0.5%-6.5%; $P = .02$) in the high-dose subgroup relative to the low-dose group. When compared directly with quetiapine, dose-adjusted mortality risk was increased with both risperidone (1.7%; 95% CI, 0.6%-2.8%; $P = .003$) and olanzapine (1.5%; 95% CI, 0.02%-3.0%; $P = .047$).

CONCLUSIONS AND RELEVANCE The absolute effect of antipsychotics on mortality in elderly patients with dementia may be higher than previously reported and increases with dose.

- The 45,393 participants with dementia aged >65 received monotherapy with haloperidol, risperidone, olanzapine, quetiapine, valproate or one of its derivatives, or an antidepressant other than a tricyclic or monoamine oxidase inhibitor.
- They were matched to dementia patients of similar ages not taking any study medications.
- In analyses controlling for relevant risk factors, mortality increased significantly over the 180 days after prescription of a study medication, compared with no study medication, as follows:
  - Haloperidol, 3.8% NNH= 26
  - Risperidone, 3.7% NNH= 27
  - Olanzapine, 2.5% NNH= 40
  - Quetiapine, 2.0% NNH= 50
- Mortality risk increased only slightly with antidepressants and not at all with valproate.
- In analyses of atypical antipsychotics, higher doses (haloperidol-equivalent dose, ≥3 mg) were associated with higher mortality risks.

JAMA Psychiatry May 2015 Volume 72, Number 5

- The elevated mortality risk with haloperidol is consistent with findings elsewhere.
- In this study, however, haloperidol patients compared with other treated patients had greater comorbidity and more institutional treatment and were more likely to be delirious, all severity factors that could increase mortality.
- Quetiapine seems safer than other atypical antipsychotics but still poses an elevated risk for death and may be less effective for agitation and psychosis.
- Substantial caution and close monitoring are necessary when prescribing antipsychotics to older demented patients.
- Atypical antipsychotics may be preferable to haloperidol, and the lowest possible dose of any drug should be used.

Sustained and "Sleeper" Effects of Group Metacognitive Training for Schizophrenia
A Randomized Clinical Trial

Steffen Moritz, PhD; Ruth Veckenstedt, PhD; Christina Andreou, MD, PhD; Francesca Bohn, MSc; Birgit Hottenrott, Dipl-Psych; Lucy Leighton, MSc; Ulf Köther, Dipl-Psych; Todd S. Woodward, PhD; András Treszl, MD; Mahesh Menon, PhD; Brooke C. Schneider, PhD; Ute Pfueller, PhD; Daniela Roesch-Ely, MD

IMPORTANCE Cognitive interventions increasingly complement psychopharmacological treatment to enhance symptomatic and functional outcome in schizophrenia. Metacognitive training (MCT) is targeted at cognitive biases involved in the pathogenesis of delusions.

OBJECTIVE To examine the long-term efficacy of group MCT for schizophrenia in order to explore whether previously established effects were sustained.

DESIGN, SETTING, AND PARTICIPANTS A 2-center, randomized, controlled, assessor-blind, parallel group trial was conducted. A total of 150 inpatients or outpatients with *DSM-IV* diagnoses of schizophrenia spectrum disorders were enrolled. All patients were prescribed antipsychotic medication. The second follow-up assessment took place 3 years later after the intervention phase was terminated.

Metacognitive Training (MCT) for Psychosis

- Metacognitive training (MCT), is a manual-based group treatment addressing attributional style, jumping to conclusions, flexible beliefs, theory of mind/social cognition, avoiding overconfidence in false memories, and mood/self-esteem.
- The primary aims of MCT are to transfer knowledge about basic research on cognitive distortions to patients and to raise awareness about the dysfunctionality of these biases.
- The exercises pursue the goal of providing corrective experiences and teaching patients alternative information-processing strategies in an entertaining manner.
- Finally, normalization, an element of CBT highlighting that cognitive biases are normal to some degree, is an essential part of each module.

- Researchers randomized 150 patients with schizophrenia spectrum diagnoses (mean age, 35) who were taking antipsychotics to one of two 16-session therapies:
  - Metacognitive training (MCT)
  - The control treatment, COGPACK, is an individualized, computer-based program, conducted in a group setting, to improve memory.
- Assessors were blinded as to treatment group.
- Overall, 86% of patients stayed in the study for 6 months, and 61% stayed for 3 years of planned follow-up.
- Positive symptoms, especially delusions, decreased significantly more with MCT than with COGPACK at 6 months' follow-up, and this difference was maintained at 3 years.
- In addition, self-esteem and quality of life were significantly more improved in the MCT group at 3 years although not earlier.
- Attention improved more in the COGPACK group. Jumping to conclusions improved in both groups.

JAMA Psychiatry October 2014 Volume 71, Number 10

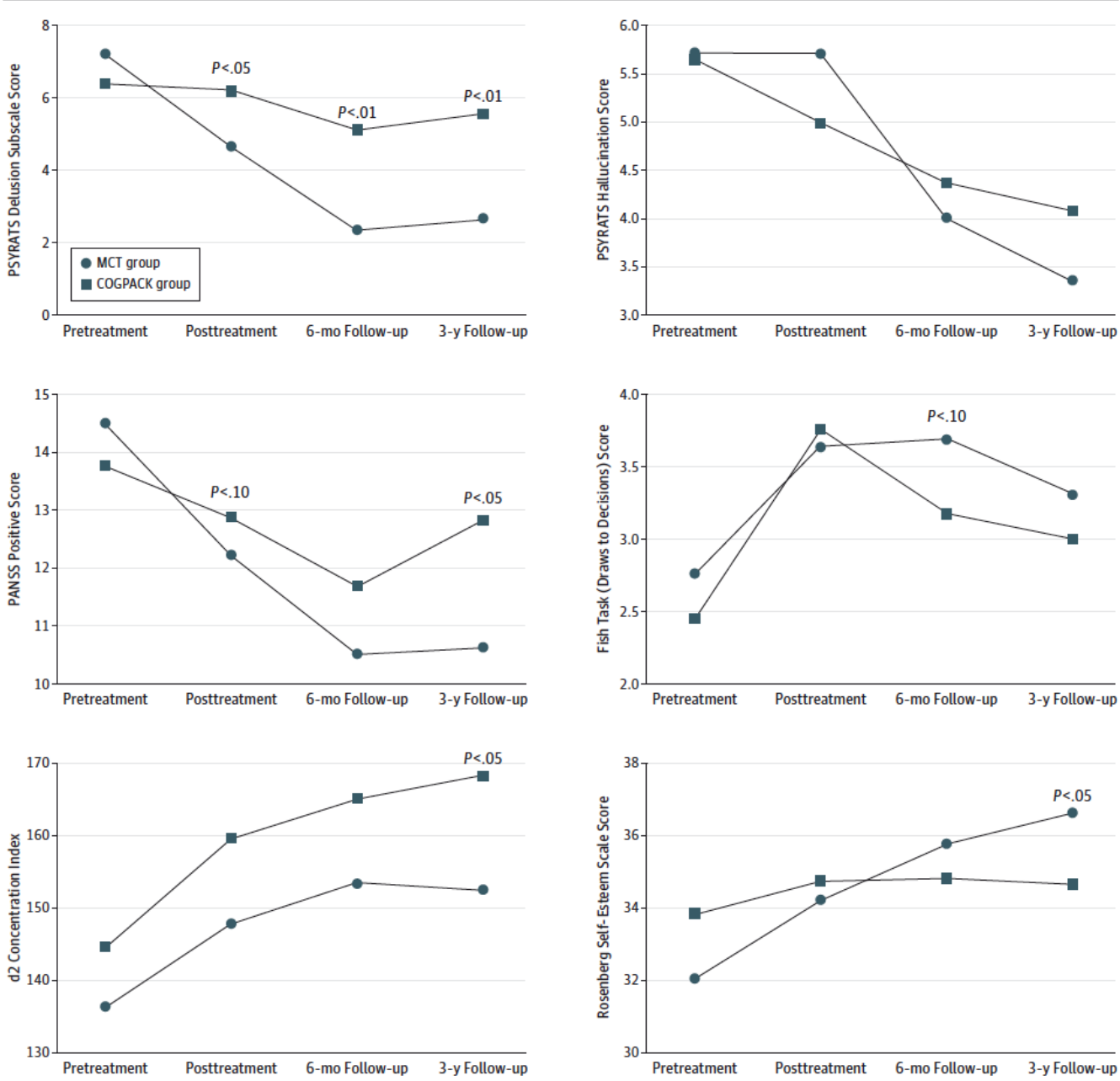
Sustained and "Sleeper" Effects of Group Metacognitive Training for Schizophrenia

INTERVENTIONS Group MCT targeting cognitive biases vs neuropsychological training (COGPACK). Patients received a maximum of 16 sessions.

MAIN OUTCOMES AND MEASURES The primary outcome measure was a delusion score derived from the Positive and Negative Syndrome Scale (PANSS). The PANSS positive syndrome and total scores, the Psychotic Symptom Rating Scales, the jumping to conclusions bias, self-esteem, and quality of life served as secondary outcome measures.

RESULTS The intention-to-treat analyses demonstrated that patients in the MCT group had significantly greater reductions in the core PANSS delusion score, after 3 years compared with the control group ($\eta^2_{partial}$ = .037; *P* = .05). Among the secondary outcomes, the intention-to-treat analyses also demonstrated that patients in the MCT group had significantly greater reductions in the PANSS positive syndrome score ($\eta^2_{partial}$ = .055; *P* = .02) and the Psychotic Symptom Rating Scales delusion score ($\eta^2_{partial}$ = .109; *P* = .001). Significant group differences at the 3-year follow-up were also found on measures of self-esteem and quality of life, which did not distinguish groups at earlier assessment points. Attention was improved in the neuropsychological training group relative to the MCT group. The completion rate was 61.3% after 3 years.

Figure 2. Group Differences Across Time (Per-Protocol Analyses)



Unless otherwise noted, group differences were $P > .10$. MCT indicates metacognitive training; PANSS, Positive and Negative Syndrome Scale; and PSYRATS, Psychotic Symptom Rating Scales.

Sustained and "Sleeper" Effects of Group Metacognitive Training for Schizophrenia

CONCLUSIONS AND RELEVANCE Metacognitive training demonstrated sustained effects in the reduction of delusions, which were over and above the effects of antipsychotic medication. Moreover, there were some unanticipated ("sleeper") effects as both self-esteem and quality of life were improved after 3 years. Effects on self-esteem and well-being were found even in the absence of an improvement on the jumping to conclusions bias.

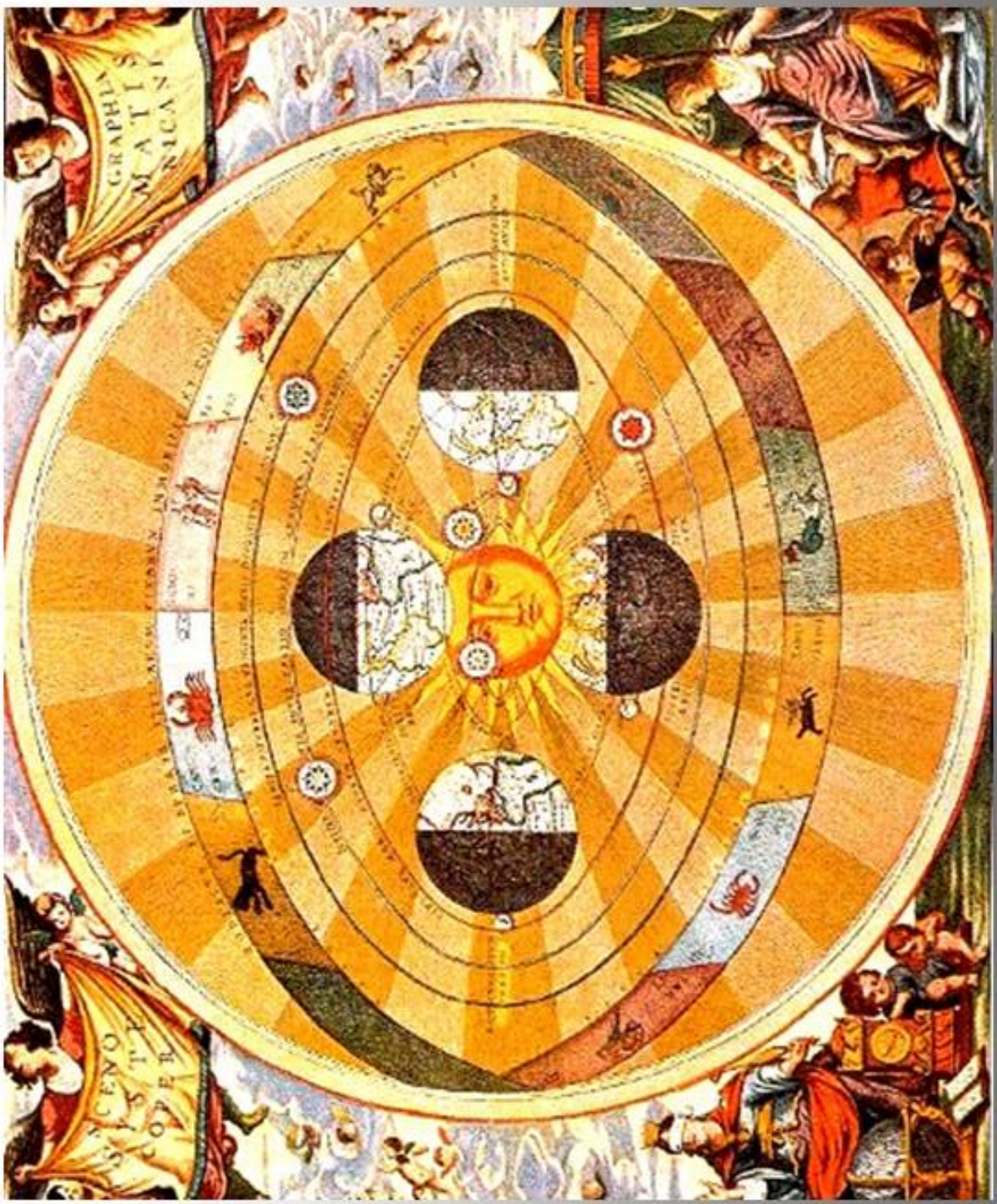
Psychotherapy for Disordered Thinking in Schizophrenia

- The benefit of a time-limited, structured approach to addressing disturbances in logic and interpretation of social and other cues lasted long after the conclusion of the intervention.
- Adherence rates were far better than those in long-term, pure pharmacological trials.
- Insofar as no antipsychotic drug has been shown to cure schizophrenia, cognitive and other behavioral approaches should always be considered for patients with this disorder.
- Not only does metacognitive training yield immediate benefits, but others emerge only after time.

Dubovsky, Steven. NEJM Journal Watch. Psychiatry (Oct 31, 2014).

NEJM Journal Watch

Thanks



Science to Practice

Top Ten Research Findings of 2014-2015

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

Q and A

NORTH CAROLINA
Psychiatric
Association

Winston-Salem, NC | Twin City Quarter
October 1-4, 2015