Science to Practice

Top Ten Research Findings of 2012-2013

Sy Saeed, MD, MS, FAC*Psych*
Professor and Chairman
Department of Psychiatric Medicine
The Brody School of Medicine
East Carolina University
and
Chief of Psychiatry
Vidant Medical Center, Greenville, NC

Science to Practice

Top Ten Research findings of 2012-2013

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 2012-2013 that have a direct bearing on the practice of clinical psychiatry.

*As identified by the methodology utilized for this presentation.

Disclosure

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

VIDANT™ Medical Center

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Knowledge is growing faster than ever! There is a deluge of information that must be sorted, evaluated, and applied.

When confronted by such an overload of information, most of us today tend to take the first or most easily accessed information—often without any concern for the quality of that information.

As a result, use of such poor information costs billions of dollars annually in medical errors, accidents, and problems associated with underuse, overuse, and misuse.

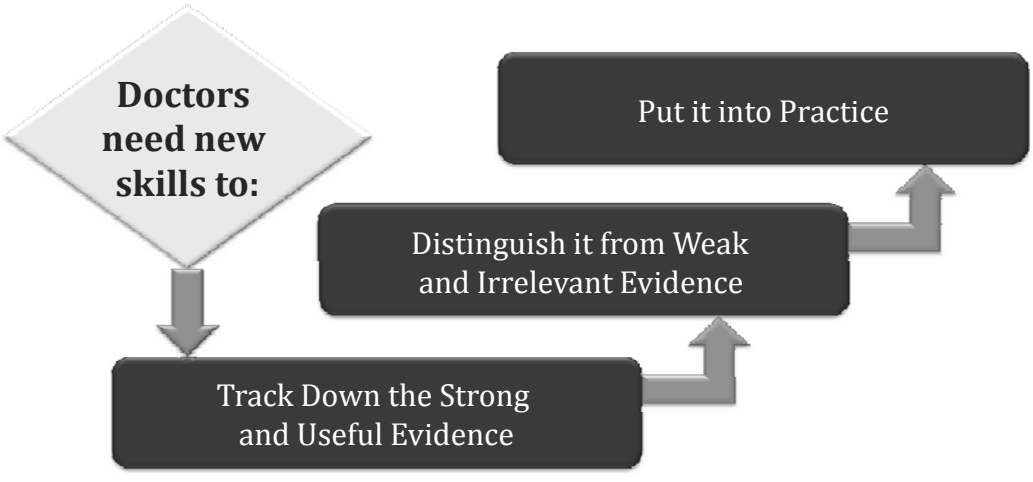
For today's and tomorrow's physicians, the workplace is going through cataclysmic changes that very few will be prepared to participate in successfully and productively unless they are information literate.

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

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

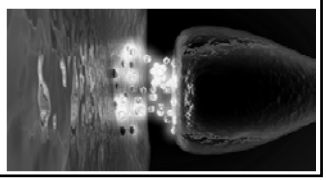
David Shenk. Data Smog: Surviving the Information Glut. San Francisco: Harper, 1998: 30.

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



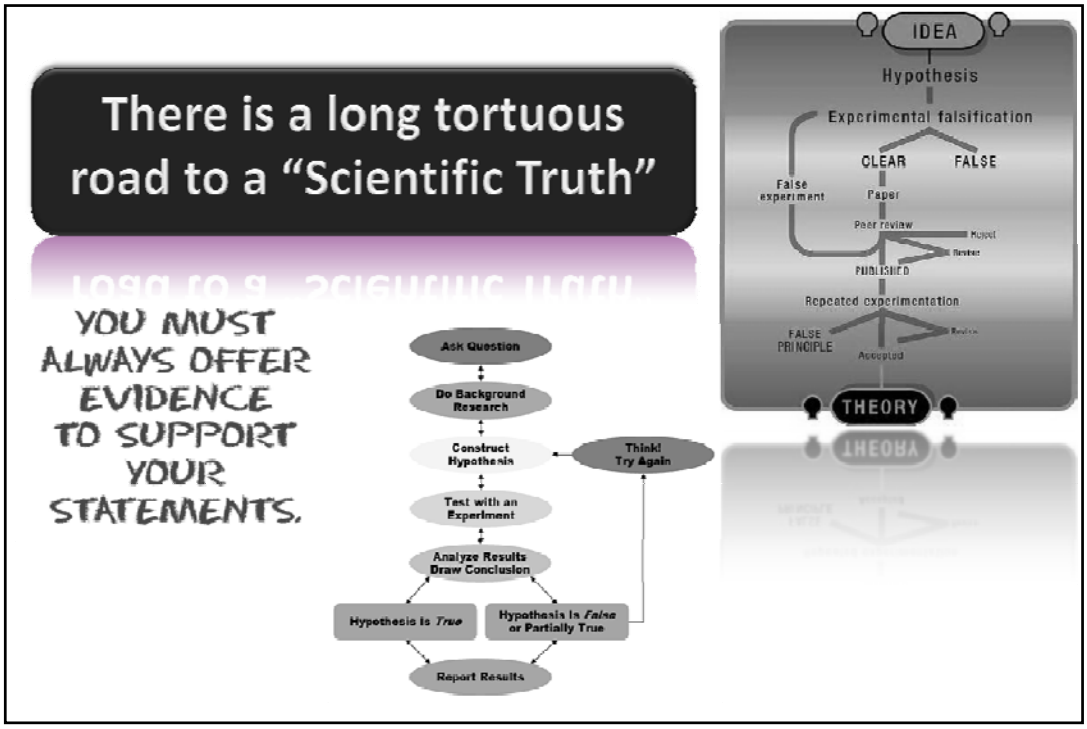
Signal-to-Noise Ratio [SNR]

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



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

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



Methodology

- Literature Search
- **Survey** [Question: *Amongst the papers published in the period July 1, 2012 to June 30, 2013, which ones in your opinion have [or likely to have or should have] impacted/changed the clinical practice of psychiatry?*].
  - ❖ AACDP
  - ❖ AADPRT
  - ❖ AACP
  - ❖ AAPA
  - ❖ NCPA
  - ❖ GAP
  - ❖ Other Colleagues
- Faculty of 1000 Factor

Disclaimers

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

Science to Practice

Top Ten Research Findings of 2012-2013

- Folic-acid and related deficiencies have been associated with depression.
- A promising strategy for treatment-resistant depression is to target the one-carbon cycle involving homocysteine's conversion to methionine, where l -methylfolate, facilitated by vitamin B12 , acts as a methyl donor; methionine next combines with ATP to form S -adenosylmethionine, a methyl donor facilitating dopamine, norepinephrine, and serotonin synthesis.

L-Methylfolate as Adjunctive Therapy for SSRI-Resistant Major Depression: Results of Two Randomized, Double-Blind, Parallel-Sequential Trials

Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M:

Am J Psychiatry 169:12, December 2012

Objective: The authors conducted two multicenter sequential parallel comparison design trials to investigate the effect of L-methylfolate augmentation in the treatment of major depressive disorder in patients who had a partial response or no response to selective serotonin reuptake inhibitors (SSRIs).

Method: In the first trial, 148 outpatients with SSRI-resistant major depressive disorder were enrolled in a 60-day study divided into two 30-day periods. Patients were randomly assigned, in a 2:3:3 ratio, to receive L-methylfolate for 60 days (7.5 mg/day for 30 days followed by 15 mg/day for 30 days), placebo for 30 days followed by L-methylfolate (7.5 mg/day) for 30 days, or placebo for 60 days. SSRI dosages were kept constant throughout the study. In the second trial, with 75 patients, the design was identical to the first, except that the L-methylfolate dosage was 15 mg/day during both 30-day periods.

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Results: In the first trial, no significant difference was observed in outcomes between the treatment groups. In the second trial, adjunctive L-methylfolate at 15 mg/day showed significantly greater efficacy compared with continued SSRI therapy plus placebo on both primary outcome measures (response rate and degree of change in depression symptom score) and two secondary outcome measures of symptom severity. The number needed to treat for response was approximately six in favor of adjunctive L-methylfolate at 15 mg/day. L-Methylfolate was well tolerated, with rates of adverse events no different from those reported with placebo.

Conclusions: Adjunctive L-methylfolate at 15 mg/day may constitute an effective, safe, and relatively well tolerated treatment strategy for patients with major depressive disorder who have a partial response or no response to SSRIs.

(Am J Psychiatry 2012; 169:1267–1274)

The Papakostas et al. study suggests that L-methylfolate is a useful
treatment for depression that has proved to be resistant to a course of SSRI treatment. Previous studies of folic acid, folinic acid, and L-methylfolate support this contention. L-methylfolate was well tolerated and may be preferred by patients for that reason. It may be particularly helpful in patients with the TT genetic variant. The efficacy of L-methylfolate in resistant depression has not been compared with that of other adjunctive agents, nor has long-term use of the agent been reported in major depression. The potential value of long-term administration of L-methylfolate in individuals with recurrent depression and the genetic enzyme deficiency is particularly intriguing.

Editorial

The Evolving Story of Folate in Depression and the Therapeutic Potential of L-Methylfolate

J. CRAIG NELSON, M.D.

Am J Psychiatry 169:12, December 2012

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Folate metabolism genes, dietary folate and response to antidepressant medications in late-life depression

Brenda D. Jamerson[1,2,3], Martha E. Payne[2,4], Melanie E. Garrett[5], Allison E. Ashley-Koch[5], Marcy C. Speer[5,1] and David C. Steffens[2]

Objective: The primary aims of this study were to (i) determine whether folate metabolism genetic polymorphisms predict age of onset and occurrence of late life depression; and (ii) determine whether folate metabolism genetic polymorphisms predict response to antidepressant medications in late-life depression.

Methods: This study used the Conte Center for the Neuroscience of Depression and the Neurocognitive Outcomes of Depression in the Elderly Study database, which includes individuals aged ≥60. The folate nutrition assessment was determined by the Block Food Frequency Questionnaire. Genotype was evaluated for 15 single nucleotide polymorphisms from 10 folate metabolism genes. Logistic regression models were used to examine genetic polymorphisms and folate estimates with association with depression age of onset and remission status.

RESEARCH ARTICLE

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Results: There were 304 Caucasians in the database, 106 of these were not depressed and 198 had a diagnosis of depression. There were no significant differences between remitters and non-remitters in age, sex or estimated folate intakes. There were no folate estimates or folate metabolism gene single nucleotide polymorphisms that significantly predicted age of onset of depression or occurrence of depression. Methionine synthase reductase (MTRR) A66G (rs1801394) was significantly associated with remission status ($p = 0.0077$) such that those with the AA genotype were 3.2 times as likely as those with the GG genotype to be in remission ($p = 0.0020$). Methylenetetrahydrofolate reductase A1298C (rs1801131) achieved a borderline significance for association with remission status ($p = 0.0313$).

Conclusion: The major finding from this study is that the MTRR A66G genotype predicts response to selective serotonin reuptake inhibitor antidepressants in late life depression.

Randomized Multicenter Investigation of Folate Plus Vitamin B_{12} Supplementation in Schizophrenia

Joshua L. Roffman, MD, MMSc; J. Steven Lamberti, MD; Eric Achtyes, MD, MS; Eric A. Macklin, PhD; Gail C. Galendez, BS; Lisa H. Raeke, MA; Noah J. Silverstein, BA; Jordan W. Smoller, MD, ScD; Michele Hill, MD; Donald C. Goff, MD

Importance: More effective treatments are needed for negative symptoms of schizophrenia, which are typically chronic, disabling, and costly. Negative symptoms have previously been associated with reduced blood folate levels, especially among patients with low-functioning variants in genes that regulate folate metabolism, suggesting the potential utility of folate supplementation.

Objectives: To determine whether folic acid plus vitamin B_{12} supplementation reduces negative symptoms of schizophrenia and whether functional variants in folate-related genes influence treatment response.

Design: Parallel-group, randomized, double-blind, placebo-controlled clinical trial of 16 weeks of treatment with 2 mg of folic acid and 400 μg of vitamin B_{12}.

Setting: Three community mental health centers affiliated with academic medical centers in the United States.

Participants: Outpatients with chronic schizophrenia who were psychiatrically stable but displayed persistent symptoms despite antipsychotic treatment. Eligible patients were 18 to 68 years old, were treated with an antipsychotic agent for 6 months or more at a stable dose for 6 weeks or more, and scored 60 or more on the Positive and Negative Syndrome Scale.

Intervention: One hundred forty subjects were randomized to receive daily oral folic acid plus vitamin B_{12} or placebo.

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doi:10.1001/jamapsychiatry.2013.900

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Results: Folate plus vitamin B_{12} improved negative symptoms significantly compared with placebo (group difference, −0.33 change in SANS score per week; 95% CI, −0.62 to −0.05) when genotype was taken into account but not when genotype was excluded. An interaction of the 484C>T variant of *FOLH1* (rs202676) with treatment was observed ($P=.02$), where only patients homozygous for the 484T allele demonstrated significantly greater benefit with active treatment (−0.59 change in SANS score per week; 95% CI, −0.99 to −0.18). In parallel, we observed an inverse relationship between red blood cell folate concentration at baseline and 484C allele load ($P=.03$), which persisted until 8 weeks of treatment. Change in positive and total symptoms did not differ between treatment groups.

Main Outcome Measures: Change in negative symptoms (Scale for the Assessment of Negative Symptoms [SANS]), as well as positive and total symptoms (Positive and Negative Syndrome Scale).

Conclusions: Folate plus vitamin B_{12} supplementation can improve negative symptoms of schizophrenia, but treatment response is influenced by genetic variation in folate absorption. These findings support a personalized medicine approach for the treatment of negative symptoms.

JAMA Psychiatry. 2013;70(5):481-489.
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Relapse Duration, Treatment Intensity, and Brain Tissue Loss in Schizophrenia: A Prospective Longitudinal MRI Study

Nancy C. Andreasen, M.D., Ph.D.

Dawei Liu, Ph.D.

Steven Ziebell, B.A.

Anvi Vora, M.D.

Beng-Choon Ho, M.D.

Objective: Longitudinal structural MRI studies have shown that patients with schizophrenia have progressive brain tissue loss after onset. Recurrent relapses are believed to play a role in this loss, but the relationship between relapse and structural MRI measures has not been rigorously assessed. The authors analyzed longitudinal data to examine this question.

Methods: The authors studied data from 202 patients drawn from the Iowa Longitudinal Study of first-episode schizophrenia for whom adequate structural MRI data were available (N=659 scans) from scans obtained at regular intervals over an average of 7 years. Because clinical follow-up data were obtained at 6-month intervals, the authors were able to compute measures of relapse number and duration and relate them to structural MRI measures. Because higher treatment intensity has been associated with smaller brain tissue volumes, the authors also examined this countereffect in terms of dose-years.

Results: Relapse duration was related to significant decreases in both general (e.g., total cerebral volume) and regional (e.g., frontal) brain measures. Number of relapses was unrelated to brain measures. Significant effects were also observed for treatment intensity.

Conclusions: Extended periods of relapse may have a negative effect on brain integrity in schizophrenia, suggesting the importance of implementing proactive measures that may prevent relapse and improve treatment adherence. By examining the relative balance of effects, that is, relapse duration versus antipsychotic treatment intensity, this study sheds light on a troublesome dilemma that clinicians face. Relapse prevention is important, but it should be sustained using the lowest possible medication dosages that will control symptoms.

(Am J Psychiatry 2013; 170:609–615)

Metformin for Treatment of Antipsychotic-Induced Amenorrhea and Weight Gain in Women With First-Episode Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Study

Ren-Rong Wu, M.D., Ph.D.

Hua Jin, M.D.

Keming Gao, M.D., Ph.D.

Elizabeth W. Twamley, Ph.D.

Jian-Jun Ou, M.D.

Ping Shao, M.D.

Juan Wang, M.D.

Xiao-Feng Guo, M.D., Ph.D.

John M. Davis, M.D.

Philip K. Chan, M.S.

Jing-Ping Zhao, M.D., Ph.D.

Objective: Data on the treatment of antipsychotic-induced amenorrhea, particularly when occurring with weight gain, are limited. The authors investigated the efficacy and safety of metformin in the treatment of antipsychotic-induced amenorrhea and weight gain in women with first-episode schizophrenia.

Method: Eighty-four women (ages 18–40 years) with first-episode schizophrenia who suffered from amenorrhea during antipsychotic treatment were randomly assigned, in a double-blind study design, to receive 1000 mg/day of metformin or placebo in addition to their antipsychotic treatment for 6 months. The primary outcome measures were restoration of menstruation and change in body weight and body mass index (BMI). Secondary outcome measures were changes in levels of prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and testosterone; in fasting levels of insulin and glucose; in LH/FSH ratio; and in insulin resistance index. Repeated mixed models with repeated-measures regression analyses and binary logistic regression were used in the analysis.

Results: A total of 76 patients completed the 6-month trial. Significantly more patients in the metformin group (N=28, 66.7%) than in placebo group (N=2, 4.8%) resumed their menstruation. Among patients treated with metformin, BMI decreased by a mean of 0.93 and the insulin resistance index by 2.04. In contrast, patients who received placebo had a mean increase in BMI of 0.85. The prolactin, LH, and testosterone levels and LH/FSH ratio decreased significantly in the metformin group at months 2, 4, and 6, but these levels did not change in the placebo group.

Conclusions: Metformin was effective in reversing antipsychotic-induced adverse events, including restoration of menstruation, promotion of weight loss, and improvement in insulin resistance in female patients with schizophrenia.

(Am J Psychiatry 2012; 169:813–821)

- Examines effects of metformin in 84 physically healthy, non-substance-abusing outpatients experiencing amenorrhea in their first year of treatment for first-episode schizophrenia.
- Weight gain of greater than 10%, measured from initiation of antipsychotic treatment to study entry, occurred in 70% of patients.
- Antipsychotics were clozapine, olanzapine, risperidone, or sulpiride; doses were relatively stable for the preceding 6 months.
- In a randomized, double-blind protocol, patients received metformin (1000 mg/day) or placebo plus their antipsychotic medications for up to 6 months.
  - Menstruation resumed in 66.7% of metformin recipients (within 3 months of starting metformin) and in 4.8% of placebo recipients -- a significant difference.
  - Significantly more metformin recipients than placebo recipients lost more than 10% of their baseline weight (28.6% vs. 2.4%) by 6 months.
  - Mean insulin resistance index and levels of insulin, prolactin, and luteinizing hormone also decreased significantly with metformin compared with placebo.
- Normalization of weight, insulin resistance, and levels of prolactin and luteinizing hormone contributed to the increased probability of return of menses.

Toward Clinically Useful Neuroimaging in Depression Treatment

Prognostic Utility of Subgenual Cingulate Activity for Determining Depression Outcome in Cognitive Therapy Across Studies, Scanners, and Patient Characteristics

Greg J. Siegle, PhD; Wesley K. Thompson, PhD; Amanda Collier, BS; Susan R. Berman, MEd; Joshua Feldmiller, BA; Michael E. Thase, MD; Edward S. Friedman, MD

Context: Among depressed individuals not receiving medication in controlled trials, 40% to 60% respond to cognitive therapy (CT). Multiple previous studies suggest that activity in the subgenual anterior cingulate cortex (sgACC; Brodmann area 25) predicts outcome in CT for depression, but these results have not been prospectively replicated.

Objective: To examine whether sgACC activity is a reliable and robust prognostic outcome marker of CT for depression and whether sgACC activity changes in treatment.

Design: Two inception cohorts underwent assessment with functional magnetic resonance imaging using different scanners on a task sensitive to sustained emotional information processing before and after 16 to 20 sessions of CT, along with a sample of control participants who underwent testing at comparable intervals.

Setting: A hospital outpatient clinic.

Patients: Forty-nine unmedicated depressed adults and 35 healthy controls.

Arch Gen Psychiatry. 2012;69(9):913-924

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Greg J. Siegle, PhD; Wesley K. Thompson, PhD; Amanda Collier, BS; Susan R. Berman, MEd; Joshua Feldmiller, BA; Michael E. Thase, MD; Edward S. Friedman, MD

Main Outcome Measures: Pretreatment sgACC activity in an a priori region in response to negative words was correlated with residual severity and used to classify response and remission.

Results: As expected, in both samples, participants with the lowest pretreatment sustained sgACC reactivity in response to negative words displayed the most improvement after CT (R^2=0.29, >75% correct classification of response, >70% correct classification of remission). Other a priori regions explained additional variance. Response/remission in cohort 2 was predicted based on thresholds from cohort 1. Subgenual anterior cingulate activity remained low for patients in remission after treatment.

Conclusions: Neuroimaging provides a quick, valid, and clinically applicable way of assessing neural systems associated with treatment response/remission. Subgenual anterior cingulate activity, in particular, may reflect processes that interfere with treatment (eg, emotion generation) in addition to its putative regulatory role; alternately, its absence may facilitate treatment response.

Arch Gen Psychiatry. 2012;69(9):913-924

Early Intervention May Prevent the Development of Posttraumatic Stress Disorder: A Randomized Pilot Civilian Study with Modified Prolonged Exposure

Barbara Olasov Rothbaum, Megan C. Kearns, Matthew Price, Emily Malcoun, Michael Davis, Kerry J. Ressler, Delia Lang, and Debra Houry

Background: Posttraumatic stress disorder (PTSD) is a major public health concern with long-term sequelae. There are no accepted interventions delivered in the immediate aftermath of trauma. This study tested an early intervention aimed at modifying the memory to prevent the development of PTSD before memory consolidation.

Methods: Patients (n = 137) were randomly assigned to receive three sessions of an early intervention beginning in the emergency department compared with an assessment only control group. Posttraumatic stress reactions (PTSR) were assessed at 4 and 12 weeks postinjury and depression at baseline and week 4. The intervention consisted of modified prolonged exposure including imaginal exposure to the trauma memory, processing of traumatic material, and in vivo and imaginal exposure homework.

Results: Patients were assessed an average of 11.79 hours posttrauma. Intervention participants reported significantly lower PTSR than the assessment group at 4 weeks postinjury, $p < .01$, and at 12 weeks postinjury, $p < .05$, and significantly lower depressive symptoms at week 4 than the assessment group, $p < .05$. In a subgroup analysis, the intervention was the most effective at reducing PTSD in rape victims at week 4 ($p = .004$) and week 12 ($p = .05$).

Conclusions: These findings suggest that the modified prolonged exposure intervention initiated within hours of the trauma in the emergency department is successful at reducing PTSR and depression symptoms 1 and 3 months after trauma exposure and is safe and feasible. This is the first behavioral intervention delivered immediately posttrauma that has been shown to be effective at reducing PTSR.

BIOL PSYCHIATRY 2012;72:957–963

Psychotherapy to prevent PTSD

Treatment and prevention of PTSD may involve extinguishing fear, averting the consolidation of an association between a traumatic stimulus and a fear response, or replacing that association with another. Thus, researchers hypothesized that PE to stimuli associated with a trauma very soon after the event would prevent PTSD.

- The 137 participants were screened in a level 1 trauma center after rape, other assaults, motor vehicle accidents, or other traumas (mean age, 31; 48 men).
- They were assigned within 12 hours to three weekly 1-hour individual sessions of PE (imaginal and in vivo exposure, cognitive restructuring, relaxation training, self-care, and homework) or assessment only.
- Compared with the control group, the PE group had significantly lower PTSD symptoms, measured at 1 and 3 months, and fewer depressive symptoms, measured at 1 month.
- The effect size for PTSD symptoms was greatest for rape victims. The intervention was specific for the trauma and did not affect PTSD related to previous traumas, experienced by more than 40% of participants.

Clinical and Functional Outcome of Childhood Attention-Deficit/Hyperactivity Disorder 33 Years Later

Rachel G. Klein, PhD; Salvatore Mannuzza, PhD; María A. Ramos Olazagasti, PhD; Erica Roizen, MS; Jesse A. Hutchison, BA; Erin C. Lashua, MA; F. Xavier Castellanos, MD

Context: Prospective studies of childhood attention-deficit/hyperactivity disorder (ADHD) have not extended beyond early adulthood.

Objective: To examine whether children diagnosed as having ADHD at a mean age of 8 years (probands) have worse educational, occupational, economic, social, and marital outcomes and higher rates of ongoing ADHD, antisocial personality disorder (ASPD), substance use disorders (SUDs), adult-onset psychiatric disorders, psychiatric hospitalizations, and incarcerations than non-ADHD comparison participants at a mean age of 41 years.

Design: Prospective, 33-year follow-up study, with masked clinical assessments.

Setting: Research clinic.

Participants: A total of 135 white men with ADHD in childhood, free of conduct disorder, and 136 men without childhood ADHD (65.2% and 76.4% of original cohort, respectively).

Main Outcome Measures: Occupational, economic, and educational attainment; marital history; occupational and social functioning; ongoing and lifetime psychiatric disorders; psychiatric hospitalizations; and incarcerations.

Results: Probands had significantly worse educational, occupational, economic, and social outcomes; more divorces; and higher rates of ongoing ADHD (22.2% vs 5.1%, $P<.001$), ASPD (16.3% vs 0%, $P<.001$), and SUDs (14.1% vs 5.1%, $P=.01$) but not more mood or anxiety disorders ($P=.36$ and .33) than did comparison participants. Ongoing ADHD was weakly related to ongoing SUDs ($\varphi=0.19$, $P=.04$), as well as ASPD with SUDs ($\varphi=0.20$, $P=.04$). During their lifetime, probands had significantly more ASPD and SUDs but not mood or anxiety disorders and more psychiatric hospitalizations and incarcerations than comparison participants. Relative to comparisons, psychiatric disorders with onsets at 21 years or older were not significantly elevated in probands. Probands without ongoing psychiatric disorders had worse social, but not occupational, functioning.

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Conclusions: The multiple disadvantages predicted by childhood ADHD well into adulthood began in adolescence, without increased onsets of new disorders after 20 years of age. Findings highlight the importance of extended monitoring and treatment of children with ADHD.

Arch Gen Psychiatry. 2012;69(12):1295-1303.
Published online October 15, 2012.

Psychotic Symptoms in Adolescence Index Risk for Suicidal Behavior

Findings From 2 Population-Based Case-Control Clinical Interview Studies

Ian Kelleher, PhD; Fionnuala Lynch, MD; Michelle Harley, MD; Charlene Molloy, MD; Sarah Roddy, PhD; Carol Fitzpatrick, MD; Mary Cannon, MD, PhD

Context: Recent evidence from both clinical and population research has pointed to psychotic symptoms as potentially important markers of risk for suicidal behavior. However, to our knowledge, there have been no epidemiological studies to date that have reported data on psychotic symptoms and suicidality in individuals who have been clinically assessed for suicidal behavior.

Objectives: To explore associations between psychotic symptoms in nonpsychotic adolescents and risk for suicidal behavior in (1) the general population, (2) adolescents with psychiatric disorder, and (3) adolescents with suicidal ideation.

Design: Two independently conducted case-control clinical interview studies.

Setting: Population-based studies in Ireland.

Participants: Study 1 included 212 adolescents aged 11 to 13 years. Study 2 included 211 adolescents aged 13 to 15 years. Participants were recruited from schools.

Main Outcome Measures: Suicidal behavior and psychotic symptoms, assessed by semi-structured diagnostic clinical interview.

Results: Psychotic symptoms were associated with a 10-fold increased odds of any suicidal behavior (ideation, plans, or acts) in both the early and middle adolescence studies (odds ratio [OR], 10.23; 95% CI, 3.25-32.26; $P<.001$ and OR, 10.5; 95% CI, 3.14-35.17; $P<.001$, respectively). Adolescents with depressive disorders who also experienced psychotic symptoms were at a nearly 14-fold increased odds of more severe suicidal behavior (suicide plans and suicide acts) compared with adolescents with depressive disorders who did not experience psychotic symptoms (OR, 13.7; 95% CI, 2.1-89.6). Among all adolescents with suicidal ideation, those who also reported psychotic symptoms had a nearly 20-fold increased odds of suicide plans and suicide acts compared with adolescents with suicidal ideation who did not report psychotic symptoms (OR, 19.6; 95% CI, 1.8-216.1).

Psychotic Symptoms in Adolescence Index Risk for Suicidal Behavior

Findings From 2 Population-Based Case-Control Clinical Interview Studies

Ian Kelleher, PhD; Fionnuala Lynch, MD; Michelle Harley, MD; Charlene Molloy, MD; Sarah Roddy, PhD; Carol Fitzpatrick, MD; Mary Cannon, MD, PhD

Conclusions: Psychotic symptoms are strongly associated with increased risk for suicidal behavior in the general adolescent population and in adolescents with (nonpsychotic) psychiatric disorder. In both studies, an absolute majority of adolescents with more severe suicidal behavior (suicidal plans and acts) reported psychotic symptoms when directly questioned about this as part of a psychiatric interview. Assessment of psychotic symptoms should form a key part of suicide risk assessment.

Arch Gen Psychiatry. 2012;69(12):1277-1283.
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THE LANCET

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

Summary

Background The question of which antipsychotic drug should be preferred for the treatment of schizophrenia is controversial, and conventional pairwise meta-analyses cannot provide a hierarchy based on the randomised evidence. We aimed to integrate the available evidence to create hierarchies of the comparative efficacy, risk of all-cause discontinuation, and major side-effects of antipsychotic drugs.

Methods We did a Bayesian-framework, multiple-treatments meta-analysis (which uses both direct and indirect comparisons) of randomised controlled trials to compare 15 antipsychotic drugs and placebo in the acute treatment of schizophrenia. We searched the Cochrane Schizophrenia Group's specialised register, Medline, Embase, the *Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for reports published up to Sept 1, 2012.* Search results were supplemented by reports from the US Food and Drug Administration website and by data requested from pharmaceutical companies. Blinded, randomised controlled trials of patients with schizophrenia or related disorders were eligible. We excluded trials done in patients with predominant negative symptoms, concomitant medical illness, or treatment resistance, and those done in stable patients. Data for seven outcomes were independently extracted by two reviewers. The primary outcome was efficacy, as measured by mean overall change in symptoms. We also examined all-cause discontinuation, weight gain, extrapyramidal side-effects, prolactin increase, QTc prolongation, and sedation.

www.thelancet.com **Published online June 27, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60733-3**

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

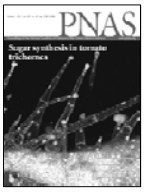
Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

Findings We identified 212 suitable trials, with data for 43 049 participants. All drugs were significantly more effective than placebo. The standardised mean differences with 95% credible intervals were: clozapine 0·88, 0·73–1·03; amisulpride 0·66, 0·53–0·78; olanzapine 0·59, 0·53–0·65; risperidone 0·56, 0·50–0·63; paliperidone 0·50, 0·39–0·60; zotepine 0·49, 0·31–0·66; haloperidol 0·45, 0·39–0·51; quetiapine 0·44, 0·35–0·52; aripiprazole 0·43, 0·34–0·52; sertindole 0·39, 0·26–0·52; ziprasidone 0·39, 0·30–0·49; chlorpromazine 0·38, 0·23–0·54; asenapine 0·38, 0·25–0·51; lurasidone 0·33, 0·21–0·45; and iloperidone 0·33, 0·22–0·43. Odds ratios compared with placebo for all-cause discontinuation ranged from 0·43 for the best drug (amisulpride) to 0·80 for the worst drug (haloperidol); for extrapyramidal side-effects 0·30 (clozapine) to 4·76 (haloperidol); and for sedation 1·42 (amisulpride) to 8·82 (clozapine). Standardised mean differences compared with placebo for weight gain varied from −0·09 for the best drug (haloperidol) to −0·74 for the worst drug (olanzapine), for prolactin increase 0·22 (aripiprazole) to −1·30 (paliperidone), and for QTc prolongation 0·10 (lurasidone) to −0·90 (sertindole). Efficacy outcomes did not change substantially after removal of placebo or haloperidol groups, or when dose, percentage of withdrawals, extent of blinding, pharmaceutical industry sponsorship, study duration, chronicity, and year of publication were accounted for in meta-regressions and sensitivity analyses.

Interpretation Antipsychotics differed substantially in side-effects, and small but robust differences were seen in efficacy. Our findings challenge the straightforward classification of antipsychotics into first-generation and second-generation groupings. Rather, hierarchies in the different domains should help clinicians to adapt the choice of antipsychotic drug to the needs of individual patients. These findings should be considered by mental health policy makers and in the revision of clinical practice guidelines.

Funding None.

Persistent cannabis users show neuropsychological decline from childhood to midlife



Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

[a]Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, [b]Department of Psychology and Neuroscience, and [c]Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; [d]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; [e]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and [f]Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

PNAS | **Published online August 27, 2012** |

Persistent adolescent-onset cannabis use, persistent cognitive decline

- Compared with adult-onset persistent users, adolescent-onset persistent users with at least three cannabis dependence diagnoses had an average 8-point decline in IQ by age 38.
- Regardless of dependence diagnoses, adolescent-onset users showed statistically significant impairments across multiple domains of cognitive functioning.
- Informants, who were chosen by the participants, reported decrements in attention and memory functioning at age 38 among those who began using cannabis in adolescence.
- Results remained significant when controlled for alcohol, tobacco, and hard drug intake; cannabis use at the time of testing; and schizophrenia diagnoses.
- Earlier and more-intensive use was associated with greater cognitive impairment. Among adolescent-onset users who had stopped use 1 year before testing, neuropsychological outcomes did not fully improve.

Replication of Ketamine's Antidepressant Efficacy in Bipolar Depression: A Randomized Controlled Add-On Trial

Carlos A. Zarate Jr., Nancy E. Brutsche, Lobna Ibrahim, Jose Franco-Chaves, Nancy Diazgranados, Anibal Cravchik, Jessica Selter, Craig A. Marquardt, Victoria Liberty, and David A. Luckenbaugh

Background: Currently, no pharmacological treatments for bipolar depression exist that exert rapid (within hours) antidepressant or antisuicidal effects. We previously reported that intravenous administration of the *N*-methyl-D-aspartate antagonist ketamine produced rapid antidepressant effects in patients with treatment-resistant bipolar depression. The present study sought to replicate this finding in an independent sample.

Methods: In this double-blind, randomized, crossover, placebo-controlled study, 15 subjects with DSM-IV bipolar I or II depression maintained on therapeutic levels of lithium or valproate received a single intravenous infusion of either ketamine hydrochloride (.5 mg/kg) or placebo on 2 test days 2 weeks apart. The primary outcome measure was the Montgomery-Asberg Depression Rating Scale, which was used to rate overall depressive symptoms at baseline; at 40, 80, 110, and 230 minutes postinfusion; and on days 1, 2, 3, 7, 10, and 14 postinfusion.

Results: Within 40 minutes, depressive symptoms, as well as suicidal ideation, significantly improved in subjects receiving ketamine compared with placebo (d = .89, 95% confidence interval = .61–1.16, and .98, 95% confidence interval = .64–1.33, respectively); this improvement remained significant through day 3. Seventy nine percent of subjects responded to ketamine and 0% responded to placebo at some point during the trial. The most common side effect was dissociative symptoms, which occurred only at the 40-minute time point.

Conclusions: This study replicated our previous finding that patients with bipolar depression who received a single ketamine infusion experienced a rapid and robust antidepressant response. In addition, we found that ketamine rapidly improved suicidal ideation in these patients.

Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis

Andrea Cipriani *lecturer in psychiatry*[1 2], Keith Hawton *professor of psychiatry*[2], Sarah Stockton *senior information scientist*[2], John R Geddes *professor of epidemiological psychiatry*[2]

Results 48 randomised controlled trials (6674 participants, 15 comparisons) were included. Lithium was more effective than placebo in reducing the number of suicides (odds ratio 0.13, 95% confidence interval 0.03 to 0.66) and deaths from any cause (0.38, 0.15 to 0.95). No clear benefits were observed for lithium compared with placebo in preventing deliberate self harm (0.60, 0.27 to 1.32). In unipolar depression, lithium was associated with a reduced risk of suicide (0.36, 0.13 to 0.98) and also the number of total deaths (0.13, 0.02 to 0.76) compared with placebo. When lithium was compared with each active individual treatment a statistically significant difference was found only with carbamazepine for deliberate self harm. Lithium tended to be generally better than the other active comparators, with small statistical variation between the results.

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Andrea Cipriani *lecturer in psychiatry*[1 2], Keith Hawton *professor of psychiatry*[2], Sarah Stockton *senior information scientist*[2], John R Geddes *professor of epidemiological psychiatry*[2]

Conclusions Lithium is an effective treatment for reducing the risk of suicide in people with mood disorders. Lithium may exert its antisuicidal effects by reducing relapse of mood disorder, but additional mechanisms should also be considered because there is some evidence that lithium decreases aggression and possibly impulsivity, which might be another mechanism mediating the antisuicidal effect.

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Evaluation of the FDA Warning Against Prescribing Citalopram at Doses Exceeding 40 mg

Kara Zivin, Ph.D.

Paul N. Pfeiffer, M.D.

Amy S.B. Bohnert, Ph.D.

Dara Ganoczy, M.P.H.

Frederic C. Blow, Ph.D.

Brahmajee K. Nallamothu, M.D.

Helen C. Kales, M.D.

Objective: A recent Food and Drug Administration (FDA) warning cautioned that citalopram dosages exceeding 40 mg/day may cause abnormal heart rhythms, including torsade de pointes. The authors assessed relationships between citalopram use and ventricular arrhythmias and mortality.

Method: A cohort study was conducted using Veterans Health Administration data between 2004 and 2009 from depressed patients who received a prescription for citalopram (N=618,450) or for sertraline (N=365,898), a comparison medication with no FDA warning. Cox regression models, adjusted for demographic and clinical characteristics, were used to examine associations of antidepressant dosing with ventricular arrhythmia and cardiac, noncardiac, and all-cause mortality.

Results: Citalopram daily doses >40 mg were associated with lower risks of ventricular arrhythmia (adjusted hazard ratio=0.68, 95% CI=0.61–0.76), all-cause mortality (adjusted hazard ratio=0.94, 95% CI=0.90–0.99), and noncardiac mortality (adjusted hazard ratio=0.90, 95% CI=0.86–0.96) compared with daily doses of 1–20 mg. No increased risks of cardiac mortality were found. Citalopram daily doses of 21–40 mg were associated with lower risks of ventricular arrhythmia (adjusted hazard ratio=0.80, 95% CI=0.74–0.86) compared with dosages of 1–20 mg/day but did not have significantly different risks of any cause of mortality. The sertraline cohort revealed similar findings, except there were no significant associations between daily dose and either all-cause or noncardiac mortality.

Conclusions: This large study found no elevated risks of ventricular arrhythmia or all-cause, cardiac, or noncardiac mortality associated with citalopram dosages >40 mg/day. Higher dosages were associated with fewer adverse outcomes, and similar findings were observed for a comparison medication, sertraline, not subject to the FDA warning. These results raise questions regarding the continued merit of the FDA warning.

(Am J Psychiatry 2013; 170:642–650)

Antidepressant Use and Risk of Out-of-Hospital Cardiac Arrest: A Nationwide Case–Time–Control Study

P Weeke[1,2], A Jensen[3], F Folke[1], GH Gislason[1], JB Olesen[1], C Andersson[1], EL Fosbøl[1,4], JK Larsen[5], FK Lippert[6], SL Nielsen[7], T Gerds[3], PK Andersen[3], JK Kanters[8], HE Poulsen[9], S Pehrson[10], L Køber[10] and C Torp-Pedersen[1]

Treatment with some types of antidepressants has been associated with sudden cardiac death. It is unknown whether the increased risk is due to a class effect or related to specific antidepressants within drug classes. All patients in Denmark with an out-of-hospital cardiac arrest (OHCA) were identified (2001–2007). Association between treatment with specific antidepressants and OHCA was examined by conditional logistic regression in case–time–control models. We identified 19,110 patients with an OHCA; 2,913 (15.2%) were receiving antidepressant treatment at the time of OHCA, with citalopram being the most frequently used type of antidepressant (50.8%). Tricyclic antidepressants (TCAs; odds ratio (OR) = 1.69, confidence interval (CI): 1.14–2.50) and selective serotonin reuptake inhibitors (SSRIs; OR = 1.21, CI: 1.00–1.47) were both associated with comparable increases in risk of OHCA, whereas no association was found for serotonin–norepinephrine reuptake inhibitors/noradrenergic and specific serotonergic antidepressants (SNRIs/NaSSAs; OR = 1.06, CI: 0.81–1.39). The increased risks were primarily driven by: citalopram (OR = 1.29, CI: 1.02–1.63) and nortriptyline (OR = 5.14, CI: 2.17–12.2). An association between cardiac arrest and antidepressant use could be documented in both the SSRI and TCA classes of drugs.

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 92 NUMBER 1 | JULY 2012

A recent FDA warning of QT prolongation at higher doses of citalopram has led to concerns about the risk for out-of-hospital cardiac arrest (OHCA) with this and other antidepressants.

Researchers used national medical databases to study all 19,110 individuals who had an OHCA in Denmark between 2001 and 2007.

15% were taking antidepressants at the time of the OHCA. In a study design using patients as their own controls during periods of drug exposure and non-exposure, risk for OHCA was associated with beginning to take an antidepressant in the preceding month (odds ratio, 1.23). Increased risk for OHCA was primarily attributable to citalopram (OR, 1.29) and nortriptyline (OR, 5.14), but not to other selective serotonin or norepinephrine reuptake inhibitors, mirtazapine, or mianserin (a relative of mirtazapine available outside the U.S.).

Comment:

The finding of an increased risk for out-of-hospital cardiac arrest with nortriptyline and citalopram warrants caution using these antidepressants in patients with cardiac disease.

Dubovsky, S. (2012). A cautionary note for cardiac patients taking antidepressants. Journal Watch. Psychiatry, doi:http://dx.doi.org/10.1056/JP201207230000004

Vitamin D deficiency and depression in adults: systematic review and meta-analysis

Rebecca E. S. Anglin, Zainab Samaan, Stephen D. Walter and Sarah D. McDonald

Background
There is conflicting evidence about the relationship between vitamin D deficiency and depression, and a systematic assessment of the literature has not been available.

Aims
To determine the relationship, if any, between vitamin D deficiency and depression.

Method
A systematic review and meta-analysis of observational studies and randomised controlled trials was conducted.

Results
One case–control study, ten cross-sectional studies and three cohort studies with a total of 31 424 participants were analysed. Lower vitamin D levels were found in people with depression compared with controls (SMD = 0.60, 95% CI 0.23–0.97) and there was an increased odds ratio of depression for the lowest *v.* highest vitamin D categories in the cross-sectional studies (OR = 1.31, 95% CI 1.0–1.71). The cohort studies showed a significantly increased hazard ratio of depression for the lowest *v.* highest vitamin D categories (HR = 2.21, 95% CI 1.40–3.49).

Conclusions
Our analyses are consistent with the hypothesis that low vitamin D concentration is associated with depression, and highlight the need for randomised controlled trials of vitamin D for the prevention and treatment of depression to determine whether this association is causal.

Declaration of interest
None.

Escitalopram for the Prevention of Peginterferon-α2a–Associated Depression in Hepatitis C Virus–Infected Patients Without Previous Psychiatric Disease

A Randomized Trial

Background: Depression is a major complication during treatment of chronic hepatitis C virus (HCV) infection with interferon-α (IFN-α). It is unclear whether antidepressants can prevent IFN-induced depression in patients without psychiatric risk factors.

Objective: To examine whether preemptive antidepressant treatment with escitalopram can decrease the incidence or severity of depression associated with pegylated IFN-α in HCV-infected patients without a history of psychiatric disorders.

Design: Randomized, multicenter, double-blind, prospective, placebo-controlled, parallel-group trial. (ClinicalTrials.gov registration number: NCT00136318)

Setting: 10 university and 11 academic hospitals in Germany.

Patients: 181 HCV-infected patients with no history of psychiatric disorders enrolled between August 2004 and December 2008.

Intervention: Escitalopram, 10 mg/d ($n = 90$), or placebo ($n = 91$) administered 2 weeks before and for 24 to 48 weeks during antiviral therapy.

Measurements: The primary end point was the incidence of depression, defined as a Montgomery–Asberg Depression Rating Scale (MADRS) score of 13 or higher. Secondary end points were time to depression, incidence of major depression according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, quality of life, sustained virologic response, tolerability, and safety.

Results: 32% (95% CI, 21% to 43%) of the patients in the escitalopram group developed a MADRS score of 13 or higher compared with 59% (CI, 48% to 69%) in the placebo group (absolute difference, 27 percentage points [CI, 12 to 42 percentage points]; $P < 0.001$). Major depression was diagnosed in 8% of the patients in the escitalopram group and 19% in the placebo group (absolute risk difference, 11 percentage points [CI, 5 to 15 percentage points]; $P = 0.031$). Tolerability and safety parameters did not differ between the groups. In the escitalopram group, 56% (CI, 46% to 66%) of patients achieved a sustained virologic response compared with 46% (CI, 37% to 57%) in the placebo group ($P = 0.21$).

Limitations: Results might not be generalizable to patients with previous psychiatric disease. Some patients withdrew or developed temporary elevated MADRS scores after randomization but before the study medication was started.

Primary Funding Source: Roche Pharma and Lundbeck.

Ann Intern Med. 2012;157:94-103. www.annals.org

ORIGINAL RESEARCH | Annals of Internal Medicine

Escitalopram for the Prevention of Peginterferon-α2a–Associated Depression in Hepatitis C Virus–Infected Patients Without Previous Psychiatric Disease

A Randomized Trial

Martin Schaefer, MD; Rahul Sarkar, MD; Viola Knop, MD; Susanne Effenberger, MSc; Astrid Friebe, MD; Loni Heinze, MD; Ulrich Spengler, MD; Thomas Schlaepfer, MD; Jens Reimer, MD; Peter Buggisch, MD; Johann Ockenga, MD; Ralph Link, MD; Michael Rentrop, MD; Hans Weidenbach, MD; Gwendolyn Fromm, MD; Klaus Lieb, MD; Thomas F. Baumert, MD; Andreas Heinz, MD; Thomas Discher, MD; Konrad Neumann, PhD; Stefan Zeuzem, MD; and Thomas Berg, MD

Conclusion: Prophylactic antidepressant treatment with escitalopram was effective in reducing the incidence and severity of IFN-associated depression in HCV-infected patients without previous psychiatric disease.

Ann Intern Med. 2012;157:94-103.

Pharmacological interventions for smoking cessation: an overview and network meta-analysis

Kate Cahill, Sarah Stevens, Rafael Perera, Tim Lancaster

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Authors' Conclusions

- NRT, bupropion, varenicline and cytisine have been shown to improve the chances of quitting.
- Combination NRT and varenicline are equally effective.
- Nortriptyline also improves the chances of quitting.
- On current evidence, none of the treatments appear to have an incidence of adverse events that would mitigate their use.
- Further research is warranted into the safety of varenicline and into cytisine's potential as an effective and affordable treatment, but not into the efficacy and safety of NRT.

- 12 Cochrane reviews of different treatments.
- The treatments include nicotine replacement therapy (NRT); antidepressants (bupropion and nortriptyline); nicotine receptor partial agonists (varenicline and cytisine); anxiolytics; selective type 1 cannabinoid receptor antagonists (rimonabant); clonidine; lobeline; dianicline; mecamylamine; Nicobrevin; opioid antagonists; nicotine vaccines; and silver acetate.
- The reviews were conducted between 2008 and 2012, and analysed 267 trials, covering more than 101,000 smokers.
- All the reviews used randomised controlled trials, and compared the active treatment with a placebo, and sometimes with other treatments.
- The outcomes were measured at least six months from the start of treatment, and the results were usually checked by testing breath, blood or urine. We also assessed the risk of harms from each treatment. We then compared NRT, bupropion and varenicline with each other, using a network meta-analysis.

Medication for attention deficit-hyperactivity disorder and criminality.

Lichtenstein P, Halldner L, Zetterqvist J, Sjölander A, Serlachius E, Fazel S, Långström N, Larsson H
N Engl J Med. 2012 Nov 22; 367(21):2006-14

BACKGROUND
Attention deficit–hyperactivity disorder (ADHD) is a common disorder that has been associated with criminal behavior in some studies. Pharmacologic treatment is available for ADHD and may reduce the risk of criminality.

METHODS
Using Swedish national registers, we gathered information on 25,656 patients with a diagnosis of ADHD, their pharmacologic treatment, and subsequent criminal convictions in Sweden from 2006 through 2009. We used stratified Cox regression analyses to compare the rate of criminality while the patients were receiving ADHD medication, as compared with the rate for the same patients while not receiving medication.

RESULTS
As compared with nonmedication periods, among patients receiving ADHD medication, there was a significant reduction of 32% in the criminality rate for men (adjusted hazard ratio, 0.68; 95% confidence interval [CI], 0.63 to 0.73) and 41% for women (hazard ratio, 0.59; 95% CI, 0.50 to 0.70). The rate reduction remained between 17% and 46% in sensitivity analyses among men, with factors that included different types of drugs (e.g., stimulant vs. nonstimulant) and outcomes (e.g., type of crime).

CONCLUSIONS
Among patients with ADHD, rates of criminality were lower during periods when they were receiving ADHD medication. These findings raise the possibility that the use of medication reduces the risk of criminality among patients with ADHD. (Funded by the Swedish Research Council and others.)

Strategies for managing sexual dysfunction induced by antidepressant medication.

Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K
Cochrane Database Syst Rev. 2013; 5:CD003382

OBJECTIVES:

1. To determine the effectiveness of management strategies for sexual dysfunction caused by antidepressants.
2. To determine the adverse effects and acceptability of the different management strategies.

SEARCH METHODS: We searched the Cochrane Depression, Anxiety and Neurosis Group's Specialized Register (CCDANCTR, to 1 January 2013), which includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years), EMBASE (1974 to date), MEDLINE (1950 to date) and PsycINFO (1967 to date). Additional searches were carried out by the author team on the same biomedical databases (using terms for 'sexual dysfunction' only) together with CINAHL (1982 to Jan 2012). The reference lists of reports of all included studies were screened.
SELECTION CRITERIA: We included randomised controlled trials that compared management strategies for antidepressant-induced sexual dysfunction versus placebo or any alternative strategy.
DATA COLLECTION AND ANALYSIS: Two authors independently extracted data and assessed trial quality. Study authors were contacted for additional information.

Strategies for managing sexual dysfunction induced by antidepressant medication

Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K

- 23 randomized studies, with a total of 1886 participants who had developed their sexual problems while taking antidepressant medication.
- 22 of these studies looked at the addition of further medication to the ongoing treatment for depression.

CONCLUSIONS: The evidence currently available is rather limited.

- For men with antidepressant-induced erectile dysfunction, the addition of sildenafil or tadalafil appears to be an effective strategy.
- For women with antidepressant-induced sexual dysfunction the addition of bupropion at higher doses appears to be the most promising approach studied so far.

Cochrane Database Syst Rev. 2013; 5:CD003382

Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside

A Randomized, Double-blind, Placebo-Controlled Trial

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

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

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

SETTING University teaching hospital in São Paulo, Brazil.

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

INTERVENTION Sodium nitroprusside administration.

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

Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside

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

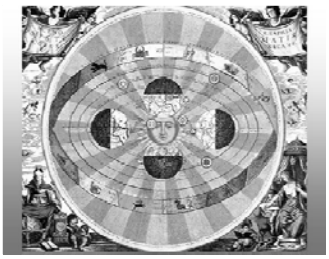
CONCLUSIONS The results clearly show a therapeutic effect of sodium nitroprusside. If this drug is approved for routine clinical use in patients with schizophrenia, this discovery will be an important advance in the pharmacologic treatment of this devastating disorder.

JAMA Psychiatry July 2013 Volume 70, Number 7

Science to Practice

Top Ten Research Findings of 2012-2013

Qs and As



Sy Saeed, MD, MS, FAC*Psych*
Professor and Chairman
Department of Psychiatric Medicine
The Brody School of Medicine
East Carolina University
and
Chief of Psychiatry
Vidant Medical Center, Greenville, NC