Science to Practice

Top Ten Research Findings of 2015-2016

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Brody School of Medicine

VIDANT HEALTH

Science to Practice

Top Ten Research findings of 2015-2016

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 2015-2016 that have a direct bearing on the practice of clinical psychiatry.

*As identified by the methodology utilized for this presentation.

Disclosure

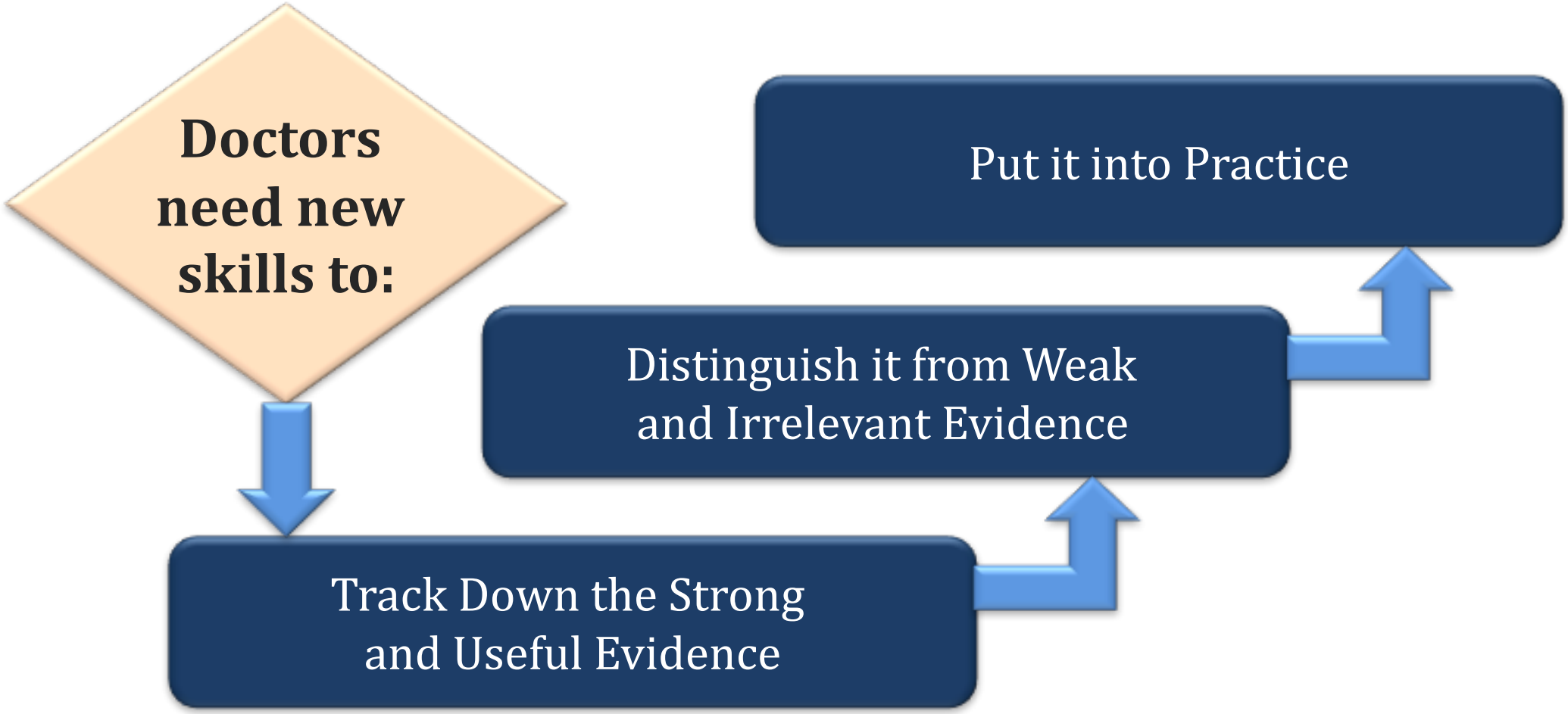
Neither I nor any member of my immediate family have any relevant financial relationship with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

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

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

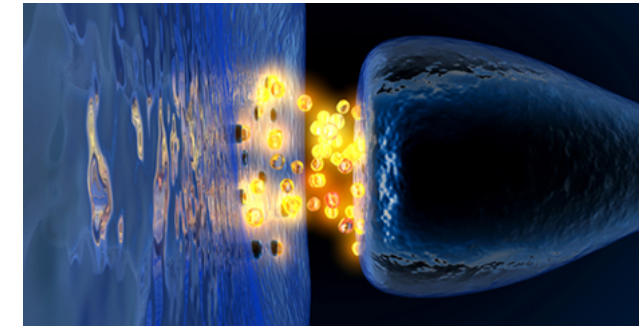
David Shenk. Data Smog: Surviving the Information Glut. San Francisco: Harper, 1998: 30.

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



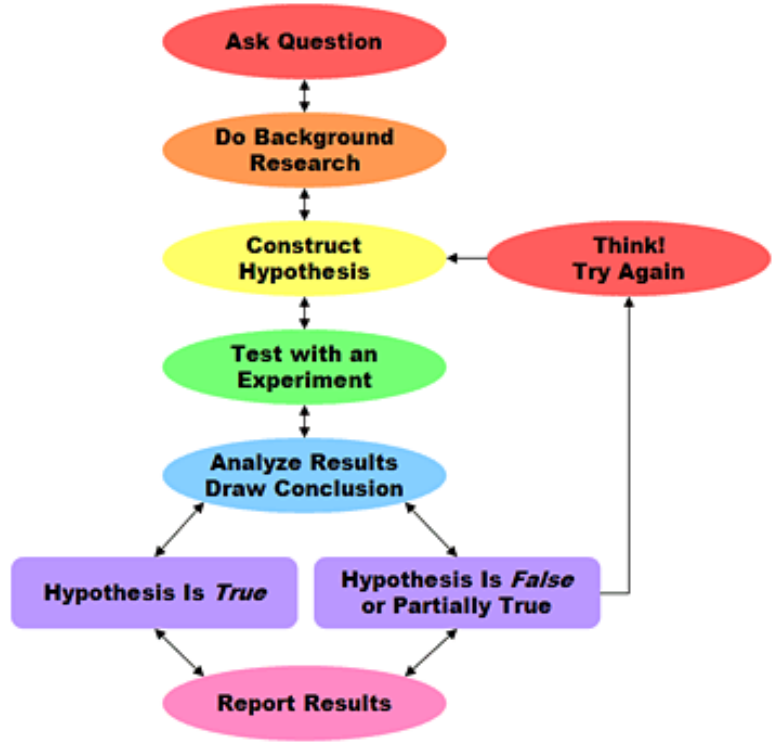
Signal-to-Noise Ratio [SNR]

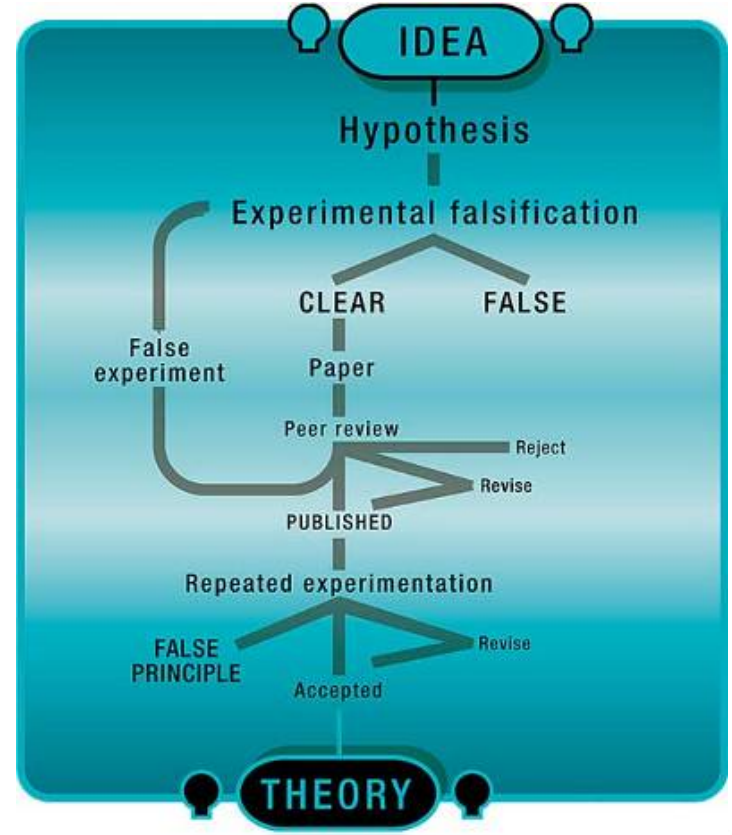
- A qualitative measure of value received relative to the garbage one must sift to get that value.
  - How should we do the sifting?
  - Can someone do the sifting for us? Who? [books, journals, CME presenters, drug reps, etc.]



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

YOU MUST ALWAYS OFFER EVIDENCE TO SUPPORT YOUR STATEMENTS.





All scientific truths are provisional!

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.

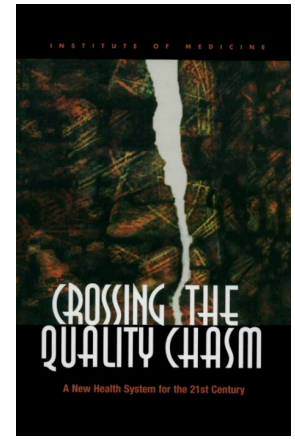
*** Institute of Medicine. *Crossing the quality chasm: a new health system for the 21st century.* Washington, DC: National Academy Press, 2001.

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

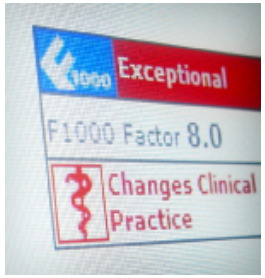
2001

Methodology

- Primary Literature Search
- **Survey** [Question: *Amongst the papers published in the period July 1, 2015 to June 30, 2016, which ones in your opinion have [or likely to have or should have] impacted/changed the clinical practice of psychiatry?*].
  - AACDP
  - AADPRT
  - AACP
  - AAPA
  - NCPA
  - GAP
  - Other Colleagues
- Secondary Literature, e.g. Faculty of 1000 Factor, Cochrane, NEJM Journal Watch, etc.

Disclaimers

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



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NEJM Journal Watch

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

Science to Practice

Top Ten Research Findings of 2015-2016

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

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

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

nature COMMUNICATIONS

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Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders

A Randomized, Placebo-Controlled Trial

G. Paul Amminger, MD; Miriam R. Schäfer, MD; Konstantinos Papageorgiou, MD; Claudia M. Klier, MD; Sue M. Cotton, PhD; Susan M. Harrigan, MSc; Andrew Mackinnon, PhD; Patrick D. McGorry, MD, PhD; Gregor E. Berger, MD

Context: The use of antipsychotic medication for the prevention of psychotic disorders is controversial. Long-chain ω-3 (omega-3) polyunsaturated fatty acids (PUFAs) may be beneficial in a range of psychiatric conditions, including schizophrenia. Given that ω-3 PUFAs are generally beneficial to health and without clinically relevant adverse effects, their preventive use in psychosis merits investigation.

Objective: To determine whether ω-3 PUFAs reduce the rate of progression to first-episode psychotic disorder in adolescents and young adults aged 13 to 25 years with subthreshold psychosis.

Design: Randomized, double-blind, placebo-controlled trial conducted between 2004 and 2007.

Setting: Psychosis detection unit of a large public hospital in Vienna, Austria.

Participants: Eighty-one individuals at ultra-high risk of psychotic disorder.

Interventions: A 12-week intervention period of 1.2-g/d ω-3 PUFA or placebo was followed by a 40-week monitoring period; the total study period was 12 months.

Arch Gen Psychiatry. 2010;67(2):146-154

Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders

Main Outcome Measures: The primary outcome measure was transition to psychotic disorder. Secondary outcomes included symptomatic and functional changes. The ratio of ω-6 to ω-3 fatty acids in erythrocytes was used to index pretreatment vs posttreatment fatty acid composition.

Results: Seventy-six of 81 participants (93.8%) completed the intervention. By study's end (12 months), 2 of 41 individuals (4.9%) in the ω-3 group and 11 of 40 (27.5%) in the placebo group had transitioned to psychotic disorder ($P=.007$). The difference between the groups in the cumulative risk of progression to full-threshold psychosis was 22.6% (95% confidence interval, 4.8-40.4). ω-3 Polyunsaturated fatty acids also significantly reduced positive symptoms ($P=.01$), negative symptoms ($P=.02$), and general symptoms ($P=.01$) and improved functioning ($P=.002$) compared with placebo. The incidence of adverse effects did not differ between the treatment groups.

Conclusions: Long-chain ω-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and efficacious strategy for indicated prevention in young people with subthreshold psychotic states.

Arch Gen Psychiatry. 2010;67(2):146-154

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

Study design.
A randomized, double-blind, placebo-controlled trial consisting of:

(1) a 12-week intervention period with 1.2 g per day omega-3 PUFAs or placebo;

(2) a 40-week period of all participants receiving state-of-the-art clinical care; and

(3) a longer-term follow-up assessment.

Patient eligibility criteria and exclusion criteria.
Individuals were eligible for participation if they were aged 13–25 years and met criteria for at least one of three operationally defined groups of specific state and/or trait risk factors for psychosis:

(1) attenuated positive psychotic symptoms;

(2) brief, limited intermittent psychotic symptoms (transient psychosis); and

(3) trait plus state risk factors (that is, genetic risk plus a decrease in functioning).

The rationale and validation for these ultrahigh risk groups has been previously described.

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Both treatment arms were comparable with respect to baseline characteristics, which included age, sex, body mass index, study entry criteria, illicit drug use, psychiatric symptoms and functioning, and erythrocyte fatty acid levels11.

After randomization, participants received weekly assessments for 4 weeks, and then at 8 and 12 weeks (end of intervention), and subsequent follow-up at 6, 12 months and 7 years after baseline.

The Positive and Negative Syndrome Scale (PANSS)13 and the Montgomery–Asberg Depression Rating Scale (MADRS)14 were used to examine psychiatric symptoms. The Global Assessment of Functioning (GAF) score was used as measure of functioning.

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At a mean follow-up of 6.7 years:

- 88% of participants received comprehensive assessments via interviews or hospital records.
- Conversion to psychosis occurred in 10% of omega-3 recipients versus 40% of controls, and analyses assuming that drop-outs developed psychosis produced similar findings.
- Participants who received active treatment also showed significantly better psychosocial and psychopathology outcomes, and significantly fewer received antipsychotics (29% vs. 54% of controls).

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

NEJM Journal Watch

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

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

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Bottom Line

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

Assumptions

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

Pharmacotherapy Relapse Prevention in Body Dysmorphic Disorder: A Double-Blind, Placebo-Controlled Trial

Katharine A. Phillips, M.D., Aparna Keshaviah, Sc.M., Darin D. Dougherty, M.D., Robert L. Stout, Ph.D., William Menard, B.A., Sabine Wilhelm, Ph.D.

Objective: Body dysmorphic disorder is common, distressing, and often severely impairing. Serotonin reuptake inhibitors appear efficacious, but the few existing pharmacotherapy studies were short term (≤4 months), and no relapse prevention studies or continuation phase studies have been conducted to the authors' knowledge. The authors report results from the first relapse prevention study in body dysmorphic disorder.

Method: Adults (N=100) with DSM-IV body dysmorphic disorder received open-label escitalopram for 14 weeks (phase 1); 58 responders were then randomized to double-blind continuation treatment with escitalopram versus switch to placebo for 6 months (phase 2). Reliable and valid outcome measures were utilized.

ajp in Advance

Published online: April 08, 2016

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Results: In phase 1, 67.0% of treated subjects and 81.1% of subjects who completed phase 1 responded to escitalopram. Body dysmorphic disorder severity (in both the intent-to-treat and the completer groups) and insight, depressive symptoms, psychosocial functioning, and quality of life significantly improved from baseline to end of phase 1. In phase 2, time to relapse was significantly longer with escitalopram than with placebo treatment (hazard ratio=2.72, 95% CI=1.01–8.57). Phase 2 relapse proportions were 18% for escitalopram and 40% for placebo. Among escitalopram-treated subjects, body dysmorphic disorder severity significantly decreased over time during the continuation phase, with 35.7% of subjects showing further improvement. There were no significant group differences in body dysmorphic disorder severity or insight, depressive symptoms, psychosocial functioning, or quality of life.

Conclusions: Continuation-phase escitalopram delayed time to relapse, and fewer escitalopram-treated subjects relapsed than did placebo-treated subjects. Body dysmorphic disorder severity significantly improved during 6 additional months of escitalopram treatment following acute response; more than one-third of escitalopram-treated subjects experienced further improvement.

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Published online: April 08, 2016

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Bottom Line

- Open label escitalopram for 14 weeks in 100 patients with BDD followed by random assignment of 58 responders to 6 month continuation versus placebo. Relapse was greater in placebo group showing that 6 month continuation after treatment response reduced relapse risk.

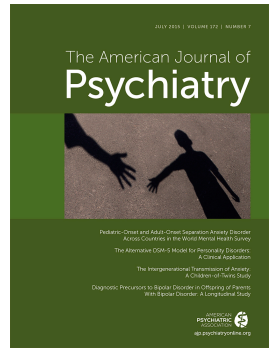
Assumptions

- While it is possible that change from escitalopram to placebo was detectable by the patients and therefore reduced the blinding, must assume that it is no more detectable than discontinuation of treatment after improvement in clinical care.

ajp in Advance
Published online: April 08, 2016

Early Improvement As a Predictor of Later Response to Antipsychotics in Schizophrenia: A Diagnostic Test Review

Myrto T. Samara, M.D., Claudia Leucht, M.D., Mariska M. Leeflang, Ph.D., Ion-George Anghelescu, M.D., Young-Chul Chung, Ph.D., M.D., Benedicto Crespo-Facorro, Ph.D., M.D., Helio Elkis, Ph.D., M.D., Kotaro Hatta, Ph.D., M.D., Ina Giegling, Ph.D., John M. Kane, M.D., Monica Kayo, M.D., Martin Lambert, M.D., Ching-Hua Lin, Ph.D., M.D., Hans-Jürgen Möller, Ph.D., M.D., José María Pelayo-Terán, Ph.D., M.D., Michael Riedel, M.D., Dan Rujescu, Ph.D., M.D., Benno G. Schimmelmann, M.D., Alessandro Serretti, Ph.D., M.D., Christoph U. Correll, M.D., Stefan Leucht, M.D.



Am J Psychiatry 172:7, July 2015

Objective: How long clinicians should wait before considering an antipsychotic ineffective and changing treatment in schizophrenia is an unresolved clinical question. Guidelines differ substantially in this regard. The authors conducted a diagnostic test meta-analysis using mostly individual patient data to assess whether lack of improvement at week 2 predicts later nonresponse.

Method: The search included EMBASE, MEDLINE, BIOSIS, PsycINFO, Cochrane Library, CINAHL, and reference lists of relevant articles, supplemented by requests to authors of all relevant studies. The main outcome was prediction of nonresponse, defined as <50% reduction in total score on either the Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) (corresponding to at least much improved) from baseline to endpoint (4–12 weeks), by <20% PANSS or BPRS improvement (corresponding to less than minimally improved) at week 2. Secondary outcomes were absent cross-sectional symptomatic remission and <20% PANSS or BPRS reduction at endpoint. Potential moderator variables were examined by meta-regression.

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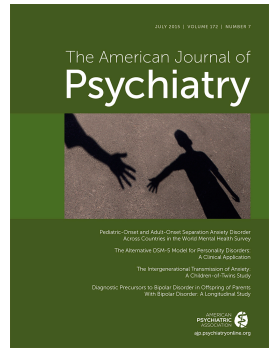
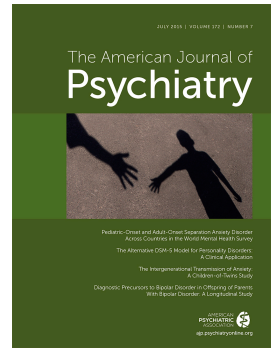


Results: In 34 studies (N=9,460) a <20% PANSS or BPRS reduction at week 2 predicted nonresponse at endpoint with a specificity of 86% and a positive predictive value (PPV) of 90%. Using data for observed cases (specificity=86%, PPV=85%) or lack of remission (specificity=77%, PPV=88%) yielded similar results. Conversely, using the definition of <20% reduction at endpoint yielded worse results (specificity=70%, PPV=55%). The test specificity was significantly moderated by a trial duration of <6 weeks, higher baseline illness severity, and shorter illness duration.

Conclusions: Patients not even minimally improved by week 2 of antipsychotic treatment are unlikely to respond later and may benefit from a treatment change.

Am J Psychiatry 172:7, July 2015

Early Improvement As a Predictor of Later Response to Antipsychotics in Schizophrenia: A Diagnostic Test Review



Bottom Line

- A less than 50% improvement on the PANSS or BPRS after 4-12 weeks of treatment was predicted by less than 20% change after 2 weeks, suggesting treatment change could be considered after a poor initial 2 weeks response.

Assumptions

- Must assume that changing meds after only two weeks does not increase risk of non-response

Am J Psychiatry 172:7, July 2015

Measurement-Based Care Versus Standard Care for Major Depression: A Randomized Controlled Trial With Blind Raters

Tong Guo, M.D., Yu-Tao Xiang, M.D., Ph.D., Le Xiao, M.D., Chang-Qing Hu, M.D., Helen F.K. Chiu, F.R.C.Psych., Gabor S. Ungvari, M.D., Ph.D., Christoph U. Correll, M.D., Kelly Y.C. Lai, M.R.C.Psych., Lei Feng, M.D., Ph.D., Ying Geng, M.D., M.Phil., Yuan Feng, M.D., Gang Wang, M.D., Ph.D.

Objective: The authors compared measurement-based care with standard treatment in major depression.

Methods: Outpatients with moderate to severe major depression were consecutively randomized to 24 weeks of either measurement-based care (guideline- and rating scale-based decisions; N=61), or standard treatment (clinicians' choice decisions; N=59). Pharmacotherapy was restricted to paroxetine (20–60 mg/day) or mirtazapine (15–45 mg/day) in both groups. Depressive symptoms were measured with the Hamilton Depression Rating Scale (HAM-D) and the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR). Time to response (a decrease of at least 50% in HAM-D score) and remission (a HAM-D score of 7 or less) were the primary endpoints. Outcomes were evaluated by raters blind to study protocol and treatment.

Am J Psychiatry 172:10, October 2015

Measurement-Based Care Versus Standard Care for Major Depression: A Randomized Controlled Trial With Blind Raters

Am J Psychiatry 172:10, October 2015

Results: Significantly more patients in the measurement-based care group than in the standard treatment group achieved response (86.9% compared with 62.7%) and remission (73.8% compared with 28.8%). Similarly, time to response and remission were significantly shorter with measurement-based care (for response, 5.6 weeks compared with 11.6 weeks, and for remission, 10.2 weeks compared with 19.2 weeks). HAM-D scores decreased significantly in both groups, but the reduction was significantly larger for the measurement-based care group (−17.8 compared with −13.6). The measurement-based care group had significantly more treatment adjustments (44 compared with 23) and higher antidepressant dosages from week 2 to week 24. Rates of study discontinuation, adverse effects, and concomitant medications did not differ between groups.

Conclusions: The results demonstrate the feasibility and effectiveness of measurement-based care for outpatients with moderate to severe major depression, suggesting that this approach can be incorporated in the clinical care of patients with major depression.

Measurement-Based Care Versus Standard Care for Major Depression: A Randomized Controlled Trial With Blind Raters

Bottom Line

- 120 moderate to severely depressed patients randomly assigned to paroxetine or mirtazapine titration decision based on guidelines and HAM D and QIDS-SR versus physician made decisions. MBC led to higher response rates and particularly higher remission rates in half the time, and led to more adjustments and higher doses.

Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program

John M. Kane, M.D., Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Kim T. Mueser, Ph.D., David L. Penn, Ph.D., Robert A. Rosenheck, M.D., Jean Addington, Ph.D., Mary F. Brunette, M.D., Christoph U. Correll, M.D., Sue E. Estroff, Ph.D., Patricia Marcy, B.S.N., James Robinson, M.Ed., Piper S. Meyer-Kalos, Ph.D., L.P., Jennifer D. Gottlieb, Ph.D., Shirley M. Glynn, Ph.D., David W. Lynde, M.S.W., Ronny Pipes, M.A., L.P.C.-S., Benji T. Kurian, M.D., M.P.H., Alexander L. Miller, M.D., Susan T. Azrin, Ph.D., Amy B. Goldstein, Ph.D., Joanne B. Severe, M.S., Haiqun Lin, M.D., Ph.D., Kyaw J. Sint, M.P.H., Majnu John, Ph.D., Robert K. Heinssen, Ph.D., A.B.P.P.

Objective: The primary aim of this study was to compare the impact of NAVIGATE, a comprehensive, multidisciplinary, team-based treatment approach for first-episode psychosis designed for implementation in the U.S. health care system, with community care on quality of life.

Method: Thirty-four clinics in 21 states were randomly assigned to NAVIGATE or community care. Diagnosis, duration of untreated psychosis, and clinical outcomes were assessed via live, two-way video by remote, centralized raters masked to study design and treatment. Participants (mean age, 23) with schizophrenia and related disorders and ≤6 months of antipsychotic treatment (N=404) were enrolled and followed for ≥2 years. The primary outcome was the total score of the Heinrichs-Carpenter Quality of Life Scale, a measure that includes sense of purpose, motivation, emotional and social interactions, role functioning, and engagement in regular activities.

Am J Psychiatry 173:4, April 2016

Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program

Results: The 223 recipients of NAVIGATE remained in treatment longer, experienced greater improvement in quality of life and psychopathology, and experienced greater involvement in work and school compared with 181 participants in community care. The median duration of untreated psychosis was 74 weeks. NAVIGATE participants with duration of untreated psychosis of <74 weeks had greater improvement in quality of life and psychopathology compared with those with longer duration of untreated psychosis and those in community care. Rates of hospitalization were relatively low compared with other first-episode psychosis clinical trials and did not differ between groups.

Conclusions: Comprehensive care for first-episode psychosis can be implemented in U.S. community clinics and improves functional and clinical outcomes. Effects are more pronounced for those with shorter duration of untreated psychosis.

Am J Psychiatry 173:4, April 2016

Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program

- Compared with the control group, NAVIGATE patients received more key services and remained in treatment significantly longer (median, 23 vs. 17 months).
- Overall, NAVIGATE patients showed significantly greater clinically meaningful improvements in quality of life (QOL), interpersonal relationships, intrapsychic foundations (sense of purpose, motivation, curiosity, emotional engagement), and work and school attendance.
- Hospitalization rates during the 2-year follow-up did not differ between groups (NAVIGATE, 34%; community care, 37%). Patients initially untreated for <74 weeks showed greater improvements in QOL and PANSS scores than those untreated for ≥74 weeks (effect sizes, 0.54 vs. 0.07 for QOL; 0.42 vs. 0.13 for PANSS).

RAISE-ing Our Expectations for First-Episode Psychosis

Thomas R. Insel, M.D.

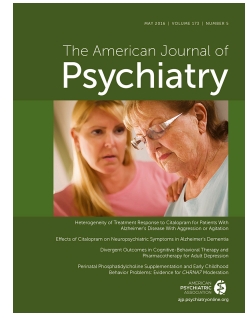
"If our experience with acute lymphoblastic leukemia is predictive of what can happen for young people with schizophrenia, RAISE should sound a hopeful note. While there is every reason to seek new and better treatments for schizophrenia, RAISE reminds us that we can achieve better outcomes by adapting the medical and psychosocial treatments we have today. As with acute lymphoblastic leukemia, the path to better outcomes depends on better organization of care and a commitment to continuous quality improvement. In the case of first-episode psychosis, that path includes early detection, training providers in comprehensive team-based approaches, combining several modalities of treatment and support, and orienting care around shared decision-making and patient preference. Sadly, this approach does not (yet) lead to a cure rate of 80%—schizophrenia may be a much tougher target than acute lymphoblastic leukemia. Of course, the transformation of acute lymphoblastic leukemia care began in 1970.We are still comparatively early in the process of transforming care for young people with schizophrenia. RAISE represents just the beginning of the change of our expectations for recovery after a first episode of psychosis."

Am J Psychiatry 173:4, April 2016

NAVIGATING the Management of First-Episode Psychosis

- Bundling medication plus psychosocial treatments produced significantly greater benefits than usual treatment.
- Although the NAVIGATE program's overall aim — to achieve full recovery through evidence-based treatments — may be more aspirational than fully realistic using contemporary interventions, its achievements are impressive. An editorialist describes the NIMH Early Psychosis Intervention Network (EPINET), launched to help disseminate these methods and expand the results.
- Communities should get on board.

Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program



Bottom Line

- Clinics randomized to multidisciplinary teams for treatment of 1st episode psychosis showed better quality of life and psychopathology scores than usual community care. Effects greater for earlier intervention.

Assumptions

- Must assume that benefits outweigh the costs of implementing and monitoring a potentially more expensive/intensive treatment approach

Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia: Evidence From the CitAD Study

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Objective: Citalopram has been shown to improve agitation in patients with Alzheimer's disease. The authors evaluated whether other neuropsychiatric symptoms improve with citalopram treatment compared with placebo.

Method: In this planned secondary analysis of the Citalopram for Agitation in Alzheimer's Disease study, the authors evaluated the effect of citalopram on the 12 neuropsychiatric symptom domains assessed by the Neuropsychiatric Inventory (NPI). They compared caregiver-reported NPI scores at week 9 in patients receiving citalopram (30 mg/day) or placebo with regard to both the presence or absence of individual neuropsychiatric symptoms and individual domain scores (reflecting severity) in participants who had symptoms at week 9.

Results: At week 9, participants treated with citalopram were significantly less likely to be reported as showing delusions (odds ratio=0.40), anxiety (odds ratio=0.43), and irritability/lability (odds ratio=0.38). A comparison of median scores of participants with symptoms present at week 9 showed significant differences favoring citalopram for hallucinations and favoring placebo for sleep/nighttime behavior disorders.

Conclusions: While dosage constraints must be considered because of citalopram's adverse effect profile, this agent's overall therapeutic effects in patients with Alzheimer's disease and agitation, in addition to efficacy for agitation/aggression, included reductions in the frequency of irritability, anxiety, and delusions; among patients who had these symptoms at week 9, they included a reduction in the severity of hallucinations but an increase in the severity of sleep/nighttime behavior disorders.

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Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia: Evidence From the CitAD Study

Bottom Line

- This is a secondary analysis of a previous study. 12 domains of the NPI caregiver reporting on symptoms at week 9 of treatment with either citalopram or placebo. Citalopram lowered levels of reported delusions, anxiety, irritability…while placebo lowered sleep and night time behavior disorders.

Assumptions

- Must assume that caregiver reports are reliable and valid.

Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis

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Summary

Background Major depressive disorder is one of the most common mental disorders in children and adolescents. However, whether to use pharmacological interventions in this population and which drug should be preferred are still matters of controversy. Consequently, we aimed to compare and rank antidepressants and placebo for major depressive disorder in young people.

Methods We did a network meta-analysis to identify both direct and indirect evidence from relevant trials. We searched PubMed, the Cochrane Library, Web of Science, Embase, CINAHL, PsycINFO, LiLACS, regulatory agencies' websites, and international registers for published and unpublished, double-blind randomised controlled trials up to May 31, 2015, for the acute treatment of major depressive disorder in children and adolescents. We included trials of amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine. Trials recruiting participants with treatment-resistant depression, treatment duration of less than 4 weeks, or an overall sample size of less than ten patients were excluded. We extracted the relevant information from the published reports with a predefined data extraction sheet, and assessed the risk of bias with the Cochrane risk of bias tool. The primary outcomes were efficacy (change in depressive symptoms) and tolerability (discontinuations due to adverse events). We did pair-wise meta-analyses using the random-effects model and then did a random-effects network meta-analysis within a Bayesian framework. We assessed the quality of evidence contributing to each network estimate using the GRADE framework. This study is registered with PROSPERO, number CRD42015016023.

Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis

Findings We deemed 34 trials eligible, including 5260 participants and 14 antidepressant treatments. The quality of evidence was rated as very low in most comparisons. For efficacy, only fluoxetine was statistically significantly more effective than placebo (standardised mean difference –0·51, 95% credible interval [CrI] –0·99 to –0·03). In terms of tolerability, fluoxetine was also better than duloxetine (odds ratio [OR] 0·31, 95% CrI 0·13 to 0·95) and imipramine (0·23, 0·04 to 0·78). Patients given imipramine, venlafaxine, and duloxetine had more discontinuations due to adverse events than did those given placebo (5·49, 1·96 to 20·86; 3·19, 1·01 to 18·70; and 2·80, 1·20 to 9·42, respectively). In terms of heterogeneity, the global I^2 values were 33·21% for efficacy and 0% for tolerability.

Interpretation When considering the risk–benefit profile of antidepressants in the acute treatment of major depressive disorder, these drugs do not seem to offer a clear advantage for children and adolescents. Fluoxetine is probably the best option to consider when a pharmacological treatment is indicated.

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Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis

Bottom Line

- Compared different 14 different antidepressants for MDD in adolescents using 34 trials w/5260 total participants which is low N for each drug. Only fluoxetine was statistically different from placebo.

Assumptions

- Probable that fluoxetine was the most often tested and therefore had the largest N.

Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses

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Objective: There is burgeoning interest in augmentation strategies for improving inadequate response to antidepressants. The adjunctive use of standardized pharmaceutical-grade nutrients, known as nutraceuticals, has the potential to modulate several neurochemical pathways implicated in depression. While many studies have been conducted in this area, to date no specialized systematic review (or meta-analysis) has been conducted.

Method: A systematic search of PubMed, CINAHL, Cochrane Library, and Web of Science was conducted up to December 2015 for clinical trials using adjunctive nutrients for depression. Where sufficient data were available, a random-effects model analyzed the standard mean difference between treatment and placebo in the change from baseline to endpoint, combining the effect size data. Funnel plot and heterogeneity analyses were also performed.

Results: Primarily positive results were found for replicated studies testing *S*-adenosylmethionine (SAMe), methylfolate, omega-3 (primarily EPA or ethyl-EPA), and vitamin D, with positive isolated studies for creatine, folinic acid, and an amino acid combination. Mixed results were found for zinc, folic acid, vitamin C, and tryptophan, with nonsignificant results for inositol. No major adverse effects were noted in the studies (aside from minor digestive disturbance). A meta-analysis of adjunctive omega-3 versus placebo revealed a significant and moderate to strong effect in favor of omega-3. Conversely, a meta-analysis of folic acid revealed a nonsignificant difference from placebo. Marked study heterogeneity was found in a Higgins test for both omega-3 and folic acid studies; funnel plots also revealed asymmetry (reflecting potential study bias).

Conclusions: Current evidence supports adjunctive use of SAMe, methylfolate, omega-3, and vitamin D with antidepressants to reduce depressive symptoms.

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Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses

Bottom Line

- SAMe, omegea-3s, methylfolate, and Vitamin D found to produce positive effects on depression when used as adjunctive treatment.

Assumptions

- Doses, durations, and treatments being complimented are unclear and probably quite variable. Statistical impact demonstrated but unclear if remission rate or time to remission, or time to relapse affected.

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Mary Ann Forciea, MD; Molly Cooke, MD; and Thomas D. Denberg, MD, PhD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the management of chronic insomnia disorder in adults.

Methods: This guideline is based on a systematic review of randomized, controlled trials published in English from 2004 through September 2015. Evaluated outcomes included global outcomes assessed by questionnaires, patient-reported sleep outcomes, and harms. The target audience for this guideline includes all clinicians, and the target patient population includes adults with chronic insomnia disorder. This guideline grades the evidence and recommendations by using the ACP grading system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

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Recommendation 1: *ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)*

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

Bottom Line

- Based on review of literature by consensus panel, guideline recommends CBT for chronic insomnia. This is recognition that current practice has limited efficacy with side effect burdens, which is second recommendation.

Assumptions

- No data presented on guideline implementation effects. It has long been known that behavioral elements important so sleep hygiene training has been used. Not surprising recommendation but often not available within physician practices with questionable reimbursement.

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Comparative Effectiveness of Clozapine and Standard Antipsychotic Treatment in Adults With Schizophrenia

T. Scott Stroup, M.D., M.P.H., Tobias Gerhard, Ph.D., Stephen Crystal, Ph.D., Cecilia Huang, Ph.D., Mark Olfson, M.D., M.P.H.

Objective: The authors compared the effectiveness of initiating treatment with either clozapine or a standard antipsychotic among adults with evidence of treatment-resistant schizophrenia in routine clinical practice.

Method: U.S. national Medicaid data from 2001 to 2009 were used to examine treatment outcomes in a cohort of patients with schizophrenia and evidence of treatment resistance that initiated clozapine (N=3,123) and in a propensity score-matched cohort that initiated a standard antipsychotic (N=3,123). Interventions were new initiation of clozapine or a standard antipsychotic medication, defined as no exposure to the new medication in the prior 365 days. The primary outcome was hospital admission for a mental disorder. Secondary outcomes included discontinuation of the index antipsychotic, use of an additional antipsychotic, incidence of serious medical conditions, and mortality.

Results: Initiation of clozapine was associated with a significantly decreased rate of psychiatric hospital admission (hazard ratio=0.78, 95% CI=0.69–0.88), index antipsychotic discontinuation (hazard ratio=0.60, 95% CI=0.55–0.65), and use of an additional antipsychotic (hazard ratio=0.76, 95% CI=0.70–0.82). Clozapine was associated with significantly increased incidence of diabetes mellitus (2.8% for clozapine vs. 1.4% for standard antipsychotic; hazard ratio=1.63, 95% CI=0.98–2.70), hyperlipidemia (12.9% for clozapine vs. 8.5% for standard antipsychotic; hazard ratio=1.40, 95%CI=1.09–1.78), and intestinal obstruction (0.9% for clozapine vs. 0.3% for standard antipsychotic; hazard ratio=2.50, 95% CI=0.97–6.44).

Conclusions: In adults with schizophrenia and evidence of treatment resistance, initiating clozapine compared with initiating a standard antipsychotic was associated with greater effectiveness on several important outcomes. Increasing the judicious use of clozapine is warranted together with vigilance to prevent and detect serious medical adverse effects.

Am J Psychiatry 2016; 173:166–173; doi: 10.1176/appi.ajp.2015.15030332

Comparative Effectiveness of Clozapine and Standard Antipsychotic Treatment in Adults With Schizophrenia

Bottom Line

- In normal outpatient clinical practice indexed by the Medicaid database, treatment resistant schizophrenia showed fewer hospitalizations, fewer medication discontinuations or changes, and greater side effects when treated with clozapine than other standard antipsychotics.

Assumptions

- Must assume that clozapine prescribed to all patients instead of selected patients would show the same patterns of outcome and that side effect burden is more than offset by improvements.

Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression

A Systematic Review and Meta-analysis

Alexander Jarde, PhD; Michelle Morais, MD; Dawn Kingston, PhD; Rebecca Giallo, PhD; Glenda M. MacQueen, MD; Lucy Giglia, MD; Joseph Beyene, PhD; Yi Wang, BHSc; Sarah D. McDonald, MD

IMPORTANCE Despite the prevalence of antenatal depression and the fact that only one-third of pregnant women with depression consider it acceptable to take antidepressants, the effect of untreated depression on neonatal outcomes remains to be addressed thoroughly.

OBJECTIVE To undertake a systematic review and meta-analysis to understand the effect of untreated depression on neonatal outcomes.

DATA SOURCES We executed our search strategy, with emphasis on its exhaustiveness, in MEDLINE, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials, and Web of Science. The search was conducted in July, 2015.

STUDY SELECTION We included randomized and nonrandomized studies that examined neonatal outcomes in women with depression receiving neither pharmacological nor nonpharmacological treatment compared with women without depression.

JAMA Psychiatry Published online June 8, 2016

Key Points

Question Do women with untreated antenatal depression have worse neonatal outcomes than women without depression?

Findings In this meta-analysis, pregnant women not receiving any treatment for their depression were associated with significantly increased risks of preterm birth and low birth weight when compared with women without depression, with a trend towards higher risks for exposure to more severe depression. Studies reporting conflicts of interest reported significantly higher odds of preterm birth.

Meaning Untreated depression during pregnancy is associated with adverse effects not only for the mother but also for the fetus through worse neonatal outcomes.

Neonatal Outcomes in Women With Untreated Antenatal Depression

JAMA Psychiatry Published online June 8, 2016

DATA EXTRACTION AND SYNTHESIS Two reviewers independently screened titles and abstracts, assessed full-text articles, extracted data, and assessed their quality using a modified version of the Newcastle-Ottawa Scale. We pooled data using random-effects meta-analyses, quantified heterogeneity using the I^2 statistic, and explored it with subgroup analyses by type of assessment of depression, severity, reported conflicts of interest, and study quality.

MAIN OUTCOMES AND MEASURES Primary outcomes were preterm birth before 37 weeks and before 32 weeks, small and large for gestational age, low birth weight, and neonatal intensive care unit admission.

Neonatal Outcomes in Women With Untreated Antenatal Depression

RESULTS Of the 6646 titles initially identified, 23 studies met inclusion criteria, all observational, with a total of 25 663 women. Untreated depression was associated with significantly increased risks of preterm birth (odds ratio [OR], 1.56; 95% CI, 1.25-1.94; 14 studies; I^2, 39%) and low birth weight (OR, 1.96; 95% CI, 1.24-3.10; 8 studies; I^2, 48%), with a trend toward higher risks for exposure to more severe depression. While the odds of preterm birth more than doubled in studies reporting conflicts of interest (OR, 2.50; 95% CI, 1.70-3.67; 5 studies; I^2, 0%), studies not reporting such conflicts showed more moderate results (OR, 1.34; 95% CI, 1.08-1.66; 9 studies; I^2, 30%).

CONCLUSIONS AND RELEVANCE Our results contrast with what is, to our knowledge, the only previous systematic review that examined the question of untreated depression because we found significant risks of 2 key perinatal outcomes, preterm birth and low birth weight. These are important results for pregnant women and clinicians to take into account in the decision-making process around depression treatment.

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Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression

A Systematic Review and Meta-analysis

Bottom Line

- Birthweight and pregnancy length worse in women with untreated depression during pregnancy compared to non-depressed women.

Assumptions

- Must assume that treatment of depression in this group would normalize birthweight and pregnancy length.

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Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data

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Background

Transcranial direct current stimulation (tDCS) is a non-pharmacological intervention for depression. It has mixed results, possibly caused by study heterogeneity.

Aims

To assess tDCS efficacy and to explore individual response predictors.

Method

Systematic review and individual patient data meta-analysis.

BJPsych | The British Journal of Psychiatry (2016) 208, 522–531. doi: 10.1192/bjp.bp.115.164715

Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data

Results

Data were gathered from six randomised sham-controlled trials, enrolling 289 patients. Active tDCS was significantly superior to sham for response (34% *v.* 19% respectively, odds ratio (OR) = 2.44, 95% CI 1.38–4.32, number needed to treat (NNT) = 7), remission (23.1% *v.* 12.7% respectively, OR = 2.38, 95% CI 1.22–4.64, NNT = 9) and depression improvement (*B* coefficient 0.35, 95% CI 0.12–0.57). Mixed-effects models showed that, after adjustment for other predictors and confounders, treatment-resistant depression and higher tDCS 'doses' were, respectively, negatively and positively associated with tDCS efficacy.

Conclusions

The effect size of tDCS treatment was comparable with those reported for repetitive transcranial magnetic stimulation and antidepressant drug treatment in primary care. The most important parameters for optimisation in future trials are depression refractoriness and tDCS dose.

BJPsych | The British Journal of Psychiatry (2016) 208, 522–531. doi: 10.1192/bjp.bp.115.164715

Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data

Bottom Line

- Combined data from 6 RCTs w/ sham controls. Showed transcranial DC stimulation better than placebo, and not as effective with treatment resistant patients..

Assumptions

- Must assume it is at least comparable to more available repetitive transcranial stimulation and usual pharmacotherapies.

BJPsych | The British Journal of Psychiatry (2016) 208, 522–531. doi: 10.1192/bjp.bp.115.164715

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence

A Randomized Clinical Trial

JAMA April 28, 2015 Volume 313, Number 16

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IMPORTANCE Opioid-dependent patients often use the emergency department (ED) for medical care.

OBJECTIVE To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.

INTERVENTIONS After screening, 104 patients were randomized to the referral group, 111 to the brief intervention group, and 114 to the buprenorphine treatment group.

MAIN OUTCOMES AND MEASURES Enrollment in and receiving addiction treatment 30 days after randomization was the primary outcome. Self-reported days of illicit opioid use, urine testing for illicit opioids, human immunodeficiency virus (HIV) risk, and use of addiction treatment services were the secondary outcomes.

RESULTS Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95% CI, 70%-85%]) vs 37% in the referral group (38 of 102 [95% CI, 28%-47%]) and 45% in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization ($P < .001$). The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) vs a reduction from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group ($P < .001$ for both time and intervention effects; $P = .02$ for the interaction effect). The rates of urine samples that tested negative for opioids did not differ statistically across groups, with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group ($P = .17$). There were no statistically significant differences in HIV risk across groups ($P = .66$). Eleven percent of patients in the buprenorphine group (95% CI, 6%-19%) used inpatient addiction treatment services, whereas 37% in the referral group (95% CI, 27%-48%) and 35% in the brief intervention group (95% CI, 25%-37%) used inpatient addiction treatment services ($P < .001$).

CONCLUSIONS AND RELEVANCE Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence

Bottom Line

- The probability of receiving addiction treatment in 30 days increased if buprenorphine/naloxone treatment was administered in the ED. Also self reported use decreased although urine levels and HIV risk was not affected.

Assumptions

- Must assume that increased access to addiction treatment in 30 days has better outcomes. Must assume that urine levels less important that self reported use.

Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression*

Brian Hallahan, Timothy Ryan, Joseph R. Hibbeln, Ivan T. Murray, Shauna Glynn, Christopher E. Ramsden, John Paul SanGiovanni and John M. Davis

Background

Trials evaluating efficacy of omega-3 highly unsaturated fatty acids (HUFAs) in major depressive disorder report discrepant findings.

Aims

To establish the reasons underlying inconsistent findings among randomised controlled trials (RCTs) of omega-3 HUFAs for depression and to assess implications for further trials.

Method

A systematic bibliographic search of double-blind RCTs was conducted between January 1980 and July 2014 and an exploratory hypothesis-testing meta-analysis performed in 35 RCTs including 6665 participants receiving omega-3 HUFAs and 4373 participants receiving placebo.

Br J Psychiatry. 2016 Apr 21

Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression*

Brian Hallahan, Timothy Ryan, Joseph R. Hibbeln, Ivan T. Murray, Shauna Glynn, Christopher E. Ramsden, John Paul SanGiovanni and John M. Davis

Results

Among participants with diagnosed depression, eicosapentaenoic acid (EPA)-predominant formulations (>50% EPA) demonstrated clinical benefits compared with placebo (Hedge's $G=0.61$, $P<0.001$) whereas docosahexaenoic acid (DHA)-predominant formulations (>50% DHA) did not. EPA failed to prevent depressive symptoms among populations not diagnosed for depression.

Conclusions

Further RCTs should be conducted on study populations with diagnosed or clinically significant depression of adequate duration using EPA-predominant omega-3 HUFA formulations.

Br J Psychiatry. 2016 Apr 21

Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression*

Bottom Line

- Compared omega-3 formulations high in DHA versus high in EPA. EPA predominant formulations were more effective at reducing depression scores than placebo while DHA predominant formulations were not.

Assumptions

- Have to assume that findings would be consistent within populations diagnosed with MDD since not all studies used this population. Have to assume that EPA better than DHA in direct comparison.

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Interpersonal Psychotherapy for Mental Health Problems: A Comprehensive Meta-Analysis

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Objective: Interpersonal psychotherapy (IPT) has been developed for the treatment of depression but has been examined for several other mental disorders. A comprehensive meta-analysis of all randomized trials examining the effects of IPT for all mental health problems was conducted.

Method: Searches in PubMed, PsycInfo, Embase, and Cochrane were conducted to identify all trials examining IPT for any mental health problem.

Results: Ninety studies with 11,434 participants were included. IPT for acute-phase depression had moderate-to-large effects compared with control groups (g=0.60; 95% CI=0.45–0.75). No significant difference was found with other therapies (differential g=0.06) and pharmacotherapy (g=−0.13). Combined treatment was more effective than IPT alone (g=0.24). IPT in subthreshold depression significantly prevented the onset of major depression, and maintenance IPT significantly reduced relapse. IPT had significant effects on eating disorders, but the effects are probably slightly smaller than those of cognitive-behavioral therapy (CBT) in the acute phase of treatment. In anxiety disorders, IPT had large effects compared with control groups, and there is no evidence that IPT was less effective than CBT. There was risk of bias as defined by the Cochrane Collaboration in the majority of studies. There was little indication that the presence of bias influenced outcome.

Conclusions: IPT is effective in the acute treatment of depression and may be effective in the prevention of new depressive disorders and in preventing relapse. IPT may also be effective in the treatment of eating disorders and anxiety disorders and has shown promising effects in some other mental health disorders.

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Interpersonal Psychotherapy for Mental Health Problems: A Comprehensive Meta-Analysis

Bottom Line

- 90 studies using IPT with over 11,000 pts were combined to show that IPT was effective for the treatment of depression, anxiety, and eating disorders and was as effective for all disorders as CBT and pharmacotherapies.

Assumptions

- Must assume that unlike all other treatment modalities, is as good as the best in treating any individual disorder, which is highly counter intuitive. Probably takes advantage of heterogeneity in 90 studies to prove equivalence to everything.

Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports

Jennita Reefhuis,[1] Owen Devine,[1] Jan M Friedman,[2] Carol Louik,[3] Margaret A Honein[1]

OBJECTIVE

To follow up on previously reported associations between periconceptional use of selective serotonin reuptake inhibitors (SSRIs) and specific birth defects using an expanded dataset from the National Birth Defects Prevention Study.

DESIGN

Bayesian analysis combining results from independent published analyses with data from a multicenter population based case-control study of birth defects.

SETTING

10 centers in the United States.

PARTICIPANTS

17 952 mothers of infants with birth defects and 9857 mothers of infants without birth defects, identified through birth certificates or birth hospitals, with estimated dates of delivery between 1997 and 2009.

EXPOSURES

Citalopram, escitalopram, fluoxetine, paroxetine, or sertraline use in the month before through the third month of pregnancy. Posterior odds ratio estimates were adjusted to account for maternal race/ethnicity, education, smoking, and prepregnancy obesity.

MAIN OUTCOME MEASURE

14 birth defects categories that had associations with SSRIs reported in the literature.

Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports

RESULTS

Sertraline was the most commonly reported SSRI, but none of the five previously reported birth defects associations with sertraline was confirmed. For nine previously reported associations between maternal SSRI use and birth defect in infants, findings were consistent with no association. High posterior odds ratios excluding the null value were observed for five birth defects with paroxetine (anencephaly 3.2, 95% credible interval 1.6 to 6.2; atrial septal defects 1.8, 1.1 to 3.0; right ventricular outflow tract obstruction defects 2.4, 1.4 to 3.9; gastroschisis 2.5, 1.2 to 4.8; and omphalocele 3.5, 1.3 to 8.0) and for two defects with fluoxetine (right ventricular outflow tract obstruction defects 2.0, 1.4 to 3.1 and craniosynostosis 1.9, 1.1 to 3.0).

CONCLUSIONS

These data provide reassuring evidence for some SSRIs but suggest that some birth defects occur 2-3.5 times more frequently among the infants of women treated with paroxetine or fluoxetine early in pregnancy.

Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports

WHAT IS ALREADY KNOWN ON THIS TOPIC

Selective serotonin reuptake inhibitors (SSRIs) are increasingly used by women of reproductive age and during pregnancy

However, inconsistent reports on the association with birth defects have limited opportunities for clinicians to carefully evaluate the risk compared with benefit of specific SSRIs during pregnancy

WHAT THIS STUDY ADDS

This study combined summarized results from published literature with data from the National Birth Defects Prevention Study using bayesian analysis

It showed consistent results for 7 of 21 evaluated associations between specific SSRIs and birth defects

Which SSRIs Are Safest in Pregnancy?

NEJM Journal Watch

- Sertraline wasn't associated with any of five defects to which it had previously been linked (e.g., septal defects).
- Neither citalopram nor escitalopram was associated with defects, except for a “marginal” link between citalopram and neural tube defects.
- Fluoxetine was associated with ventricular septal defects, right ventricular outflow tract obstruction cardiac defects, and craniosynostosis.
- Paroxetine was associated with anencephaly, atrial septal defects, right ventricular outflow tract obstruction cardiac defects, gastroschisis, and omphalocele.

The authors note that if the associations observed are causal, the absolute risks are small. For example, for babies exposed to paroxetine, the absolute risk for anencephaly would increase from 2 to 7 per 10,000.

As always, these risks must be balanced against the risks of discontinuing or changing antidepressants, especially in women whose illnesses have been treatment refractory and have only responded to fluoxetine or paroxetine. However, the current findings suggest that in general sertraline should be the first-line agent in pregnant women needing an SSRI.

Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports

Bottom Line

- Use of SSRIs in early pregnancy compared in case-control design. Paroxetine and fluoxetine only SSRIs showing increased risk for birth defects.

Assumptions

- No causal relationship between paroxetine/fluoxetine use and birth defects in this study. Replicates multiple findings of increased risks for paroxetine use but failed to replicate previous associations with sertraline. Have to assume that choice of SSRIs are random and doses are comparable.

thebmj | *BMJ* 2015;350:h3190

Thirty-Day Mortality After Infection Among Persons With Severe Mental Illness: A Population-Based Cohort Study in Denmark

Anette Riisgaard Ribe, M.D., Mogens Vestergaard, M.D., Wayne Katon, M.D., Morten Charles, M.D., Michael Eriksen Benros, M.D., Erik Vanderlip, M.D., Merete Nordentoft, M.D., Thomas Munk Laursen, Ph.D.

Objective: Persons with severe mental illness die 15–20 years earlier on average than persons without severe mental illness. Although infection is one of the leading overall causes of death, no studies have evaluated whether persons with severe mental illness have a higher mortality after infection than those without.

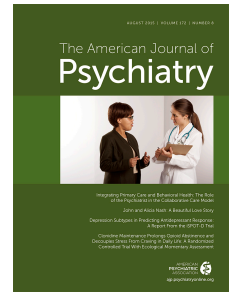
Method: The authors studied mortality rate ratios and cumulative mortality proportions after an admission for infection for persons with severe mental illness compared with persons without severe mental illness by linking data from Danish national registries.

Results: The cohort consisted of all persons hospitalized for infection during the period 1995–2011 in Denmark (N=806,835), of whom 11,343 persons had severe mental illness. Within 30 days after an infection, 1,052 (9.3%) persons with a history of severe mental illness and 58,683 (7.4%) persons without a history of severe mental illness died. Thirty-day mortality after any infection was 52% higher in persons with severe mental illness than in persons without (mortality rate ratio=1.52, 95% CI=1.43–1.61). Mortality was increased for all infections, and the mortality rate ratios ranged from 1.27 (95% CI=1.15–1.39) for persons hospitalized for sepsis to 2.61 (95% CI=1.69–4.02) for persons hospitalized for CNS infections. Depending on age, 1.7 (95% CI=1.2–2.2) to 2.9 (95% CI=2.0–3.7) more deaths were observed within 30 days after an infection per 100 persons with a history of severe mental illness compared with 100 persons without such a history.

Conclusions: Persons with severe mental illness have a markedly elevated 30-day mortality after infection. Some of these excess deaths may be prevented by offering individualized and targeted interventions.

Am J Psychiatry 2015; 172:776–783; doi: 10.1176/appi.ajp.2015.14091100

Thirty-Day Mortality After Infection Among Persons With Severe Mental Illness: A Population-Based Cohort Study in Denmark



Bottom Line

- Huge cohort over 16 years in Denmark of people hospitalized for infection. Those with severe mental illness history, and even more for those with current severe mental illness, showed higher mortality rates than those without mental illness. This was most true for CNS infections.

Assumptions

- The highest mortality rate for CNS infections among severely mentally ill suggests a possible confound, that the symptoms of CNS infections and symptoms of severe mental illness overlap and hinder identification of infection. If true, this would lead to later admission and treatment initiation which could inflate mortality. Must assume that symptoms of severe mental illness does not induce greater severity of infection upon admission.

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

Tabea Schoeler, Anna Monk, Musa B Sami, Ewa Klamerus, Enrico Foglia, Ruth Brown, Giulia Camuri, A Carlo Altamura, Robin Murray, Sagnik Bhattacharyya

Summary

Background Although the link between cannabis use and development of psychosis is well established, less is known about the effect of continued versus discontinued cannabis use after the onset of psychosis. We aimed to summarise available evidence focusing on the relationship between continued and discontinued cannabis use after onset of psychosis and its relapse.

Methods In this systematic review and meta-analysis, we searched MEDLINE for articles published in any language from the database inception date up until April 21, 2015 that included a sample of patients with a pre-existing psychotic disorder with a follow-up duration of at least 6 months. We used a combination of search terms for describing cannabis, the outcome of interest (relapse of psychosis), and the study population. We excluded studies if continued cannabis use or discontinued cannabis use could not be established. We compared relapse outcomes between those who continued (CC) or discontinued (DC) cannabis use or were non-users (NC). We used summary data (individual patient data were not sought out) to estimate Cohen's d, which was entered into random effects models (REM) to compare CC with NC, CC with DC, and DC with NC. Meta-regression and sensitivity analyses were used to address the issue of heterogeneity.

Lancet Psychiatry 2016; 3: 215–25

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

Findings Of 1903 citations identified, 24 studies (16 565 participants) met the inclusion criteria. Independent of the stage of illness, continued cannabis users had a greater increase in relapse of psychosis than did both non-users (d_{CC-NC}=0·36, 95% CI 0·22–0·50, p<0·0001) and discontinued users (d_{CC-DC}=0·28, 0·12–0·44, p=0·0005), as well as longer hospital admissions than non-users (d_{CC-NC}=0·36, 0·13 to 0·58, p=0·02). By contrast, cannabis discontinuation was not associated with relapse (d_{DC-NC}=0·02, –0·12 to 0·15; p=0·82). Meta-regression suggested greater effects of continued cannabis use than discontinued use on relapse (d_{CC-NC}=0·36 *vs* d_{DC-NC}=0·02, p=0·04), positive symptoms (d_{CC-NC}=0·15 *vs* d_{DC-NC}=–0·30, p=0·05) and level of functioning (d_{CC-NC}=0·04 *vs* d_{DC-NC}=–0·49, p=0·008) but not on negative symptoms (d_{CC-NC}=-0·09 *vs* d_{DC-NC}=–0·31, p=0·41).

Interpretation Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.

Lancet Psychiatry 2016;
3: 215–25

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

Bottom Line

- In cannabis users who develop psychotic disorders, some continue to use while some stop use. Those who stop have fewer relapses, fewer positive symptoms, better level of functioning, and shorter hospitalization duration.

Assumptions

- Must assume that those that continue to use were not more severely psychotic, did not have more positive symptoms before hospitalization, did not have a worse level of functioning. Possible confounds a plenty. Must assumes that focusing more attention of stopping cannabis use will be effective and will have similar affects of hospital course.

Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study

Jari Tiihonen, M.D., Ph.D., Ellenor Mittendorfer-Rutz, Ph.D., Minna Torniainen, Ph.D., Kristina Alexanderson, Ph.D., Antti Tanskanen, Ph.Lic.

Objective: Although mortality related to psychotropic medications has received much attention in recent years, little is known about the relationship between risk of death and cumulative antipsychotic load, and even less about the relationship between mortality and cumulative exposure to antidepressants or benzodiazepines. The authors examined these relationships using nationwide databases.

Method: The authors used prospectively collected nationwide databases to identify all individuals 16–65 years of age with a schizophrenia diagnosis (N=21,492) in Sweden. All-cause and cause-specific mortality rates were calculated as a function of cumulative low, moderate, and high exposure to antipsychotics, antidepressants, and benzodiazepines from 2006 through 2010.

Results: Compared with no exposure, both moderate (adjusted hazard ratio=0.59, 95% CI=0.49–0.70) and high (adjusted hazard ratio=0.75, 95% CI=0.63–0.89) antipsychotic exposures were associated with substantially lower overall mortality. Moderate antidepressant exposure was associated with a lower mortality (adjusted hazard ratio=0.85, 95% CI=0.73–0.98), and high exposure, even lower (adjusted hazard ratio=0.71, 95% CI=0.59–0.86). Exposure to benzodiazepines showed a dose-response relationship with mortality (hazard ratios up to 1.74 [95% CI=1.50–2.03]).

Conclusions: Moderate and high-dose antipsychotic and antidepressant use were associated with 15%–40% lower overall mortality, whereas chronic high-dose use of benzodiazepines was associated with up to a 70% higher risk of death compared with no exposure. Since patients with anxiety and depressive symptoms may have a higher intrinsic risk of death, the finding for benzodiazepines may be attributable to some extent to residual confounding.

Am J Psychiatry 2016; 173:600–606; doi: 10.1176/appi.ajp.2015.15050618

Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study

Bottom Line

- This Swedish study found that moderate and high exposure to antipsychotics and antidepressants from 2006-10 were associated with lower mortality compared to no exposure, while benzodiazepines were related to higher mortality.

Assumptions

- Must assume that no exposure is treated in the same environments, i.e. hospital, as moderate and high antipsychotic exposures. If not then confounded.

Systematic Review and Meta-Analysis: Dose-Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disorder

Ewgeni Jakubovski, M.A., Anjali L. Varigonda, M.D., Nicholas Freemantle, Ph.D., Matthew J. Taylor, Ph.D., Michael H. Bloch, M.D., M.S.

Objective: Previous studies suggested that the treatment response to selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder follows a flat response curve within the therapeutic dose range. The present study was designed to clarify the relationship between dosage and treatment response in major depressive disorder.

Method: The authors searched PubMed for randomized placebo-controlled trials examining the efficacy of SSRIs for treating adults with major depressive disorder. Trials were also required to assess improvement in depression severity at multiple time points. Additional data were collected on treatment response and all-cause and side effect-related discontinuation. All medication doses were transformed into imipramine-equivalent doses. The longitudinal data were analyzed with a mixed-regression model. Endpoint and tolerability analyses were analyzed using meta-regression and stratified subgroup analysis by predefined SSRI dose categories in order to assess the effect of SSRI dosing on the efficacy and tolerability of SSRIs for major depressive disorder.

Results: Forty studies involving 10,039 participants were included. Longitudinal modeling (dose-by-time interaction=0.0007, 95% CI=0.0001–0.0013) and endpoint analysis (meta-regression: β=0.00053, 95% CI=0.00018–0.00088, z=2.98) demonstrated a small but statistically significant positive association between SSRI dose and efficacy. Higher doses of SSRIs were associated with an increased likelihood of dropouts due to side effects (meta-regression: β=0.00207, 95% CI=0.00071–0.00342, z=2.98) and decreased likelihood of all-cause dropout (meta-regression: β=−0.00093, 95% CI=−0.00165 to −0.00021, z=−2.54).

Conclusions: Higher doses of SSRIs appear slightly more effective in major depressive disorder. This benefit appears to plateau at around 250 mg of imipramine equivalents (50 mg of fluoxetine). The slightly increased benefits of SSRIs at higher doses are somewhat offset by decreased tolerability at high doses.

Am J Psychiatry 2016; 173:174–183; doi: 10.1176/appi.ajp.2015.15030331

Systematic Review and Meta-Analysis: Dose-Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disorder

Bottom Line

- With an N>10K slight relationship between higher SSRI doses and treatment efficacy and increased likelihood of dropout due to side effects.

Assumptions

- Must assume that an extremely small statistical effect is clinically meaningful and that small effect isn't offset by dropout.

Prospective Longitudinal Evaluation of the Effect of Deployment-Acquired Traumatic Brain Injury on Posttraumatic Stress and Related Disorders: Results From the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)

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Objective: Traumatic brain injury (TBI) is increasingly recognized as a risk factor for deleterious mental health and functional outcomes. The purpose of this study was to examine the strength and specificity of the association between deployment-acquired TBI and subsequent posttraumatic stress and related disorders among U.S. Army personnel.

Method: A prospective, longitudinal survey of soldiers in three Brigade Combat Teams was conducted 1–2 months prior to an average 10-month deployment to Afghanistan (T0), upon redeployment to the United States (T1), approximately 3 months later (T2), and approximately 9 months later (T3). Outcomes of interest were 30-day prevalence postdeployment of posttraumatic stress disorder (PTSD), major depressive episode, generalized anxiety disorder, and suicidality, as well as presence and severity of postdeployment PTSD symptoms.

Results: Complete information was available for 4,645 soldiers. Approximately one in five soldiers reported exposure to mild (18.0%) or more-than-mild (1.2%) TBI(s) during the index deployment. Even after adjusting for other risk factors (e.g., predeployment mental health status, severity of deployment stress, prior TBI history), deployment-acquired TBI was associated with elevated adjusted odds of PTSD and generalized anxiety disorder at T2 and T3 and of major depressive episode at T2. Suicidality risk at T2 appeared similarly elevated, but this association did not reach statistical significance.

Conclusions: The findings highlight the importance of surveillance efforts to identify soldiers who have sustained TBIs and are therefore at risk for an array of postdeployment adverse mental health outcomes, including but not limited to PTSD. The mechanism(s) accounting for these associations need to be elucidated to inform development of effective preventive and early intervention programs.

Am J Psychiatry 2015; 172:1101–1111; doi: 10.1176/appi.ajp.2015.14121572

Prospective Longitudinal Evaluation of the Effect of Deployment-Acquired Traumatic Brain Injury on Posttraumatic Stress and Related Disorders:

Bottom Line

- Study showed that TBI experienced during army deployment was associated with higher rates of depression, GAD and PTSD.

Assumptions

- No clear treatment implications but suggest studies needed to identify field or early interventions that focus on TBI patients to reduce possibly related mental health sequelae.

Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study

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Objective: Despite a prevailing assumption that adult ADHD is a childhood-onset neurodevelopmental disorder, no prospective longitudinal study has described the childhoods of the adult ADHD population. The authors report follow-back analyses of ADHD cases diagnosed in adulthood, alongside follow-forward analyses of ADHD cases diagnosed in childhood, in one cohort.

Method: Participants belonged to a representative birth cohort of 1,037 individuals born in Dunedin, New Zealand, in 1972 and 1973 and followed to age 38, with 95% retention. Symptoms of ADHD, associated clinical features, comorbid disorders, neuropsychological deficits, genome-wide association study-derived polygenic risk, and life impairment indicators were assessed. Data sources were participants, parents, teachers, informants, neuropsychological test results, and administrative records. Adult ADHD diagnoses used DSM-5 criteria, apart from onset age and cross-setting corroboration, which were study outcome measures.

Results: As expected, childhood ADHD had a prevalence of 6% (predominantly male) and was associated with childhood comorbid disorders, neurocognitive deficits, polygenic risk, and residual adult life impairment. Also as expected, adult ADHD had a prevalence of 3% (gender balanced) and was associated with adult substance dependence, adult life impairment, and treatment contact. Unexpectedly, the childhood ADHD and adult ADHD groups comprised virtually nonoverlapping sets; 90% of adult ADHD cases lacked a history of childhood ADHD. Also unexpectedly, the adult ADHD group did not show tested neuropsychological deficits in childhood or adulthood, nor did they show polygenic risk for childhood ADHD.

Conclusions: The findings raise the possibility that adults presenting with the ADHD symptom picture may not have a childhood-onset neurodevelopmental disorder. If this finding is replicated, then the disorder's place in the classification system must be reconsidered, and research must investigate the etiology of adult ADHD.

Am J Psychiatry 2015; 172:967–977; doi: 10.1176/appi.ajp.2015.14101266

How Related Are Adult and Childhood ADHD?

- In this four-decade-long study, almost no individuals had attention-deficit/hyperactivity disorder diagnosed in both childhood and adulthood.
- These findings suggest that frequently, childhood and adult ADHD are not the same disorder. Attentional problems associated with adult ADHD might instead be nonspecifically related to substance dependence and other comorbidities.
- Regardless, high impairment rates in adults with ADHD underscore the need for better understanding and treatment studies.

NEJM Journal Watch

Joel Yager, MD reviewing Moffitt TE et al. Am J Psychiatry 2015 May 22.

Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study

Bottom Line

- New Zealand cohort of adult ADHD with 90% having no record of childhood ADHD. Suggests different populations.

Assumptions

- Record keeping 40 years ago would be expected to be questionable. Must assume record keeping standards constant and that there are treatment implications.

Clonidine Maintenance Prolongs Opioid Abstinence and Decouples Stress From Craving in Daily Life: A Randomized Controlled Trial With Ecological Momentary Assessment

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Objective: The authors tested whether clonidine blocks stress-induced seeking of heroin and cocaine. The study was also intended to confirm translational findings from a rat model of drug relapse by using ecological momentary assessment of patients' stress to test hypotheses about clonidine's behavioral mechanism of action.

Method: The authors conducted a randomized double-blind placebo-controlled clinical trial with 208 opioid-dependent patients at an outpatient buprenorphine clinic. The 118 participants (57%) who maintained abstinence during weeks 5–6 were continued on buprenorphine and randomly assigned to receive clonidine (N=61) or placebo (N=57) for 14 weeks. Urine was tested thrice weekly. Lapse was defined as any opioid-positive or missed urine test, and relapse as two or more consecutive lapses. Time to lapse and relapse were examined with Cox regressions; longest period of abstinence was examined with a t test, and ecological momentary assessment data were examined with generalized linear mixed models.

Results: In an intent-to-treat analysis, clonidine produced the longest duration (in consecutive days) of abstinence from opioids during the intervention phase (34.8 days [SD=3.7] compared with 25.5 days [SD=2.7]; Cohen's d=0.38). There was no group difference in time to relapse, but the clonidine group took longer to lapse (hazard ratio=0.67, 95% CI=0.45–1.00). Ecological momentary assessment showed that daily-life stress was partly decoupled from opioid craving in the clonidine group, supporting the authors' hypothesized mechanism for clonidine's benefits.

Conclusions: Clonidine, a readily available medication, is useful in opioid dependence not just for reduction of withdrawal signs, but also as an adjunctive maintenance treatment that increases duration of abstinence. Even in the absence of physical withdrawal, it decouples stress from craving in everyday life.

Am J Psychiatry 2015; 172:760–767; doi: 10.1176/appi.ajp.2014.14081014

Clonidine Maintenance Prolongs Opioid Abstinence and Decouples Stress From Craving in Daily Life:

Bottom Line

- 208 opioid addicted patients were treated for 5-6 weeks with buprenorphine with 108 abstinent at the end of interval…randomized to continued treatment plus clonidine or placebo. Clonidine supplementation increased #days to 1 day relapse but not to #days to 2 day relapse.

Assumptions

- Must assume that equalization of time to relapse for 2 days is less relevant that difference in days to 1 day relapse. Without this questionable assumption, there was no effect of adding clonidine.

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

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

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

Results: In total, 67 (45 women) of 68 randomized patients received treatment. In the twice-weekly dosing groups, the mean change in MADRS score at day 15 was −18.4 (SD=12.0) for ketamine and −5.7 (SD=10.2) for placebo; in the thrice-weekly groups, it was −17.7 (SD=7.3) for ketamine and −3.1 (SD=5.7) for placebo. Similar observations were noted for ketamine during the open-label phase (twice-weekly, −12.2 [SD=12.8] on day 4; thrice-weekly, −14.0 [SD=12.5] on day 5). Both regimens were generally well tolerated. Headache, anxiety, dissociation, nausea, and dizziness were the most common (≥20%) treatment-emergent adverse events. Dissociative symptoms occurred transiently and attenuated with repeated dosing.

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

AJP in Advance (doi: 10.1176/appi.ajp.2016.16010037)

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

Bottom Line

- Intravenous Ketamine 2-3 times per week for patients with treatment resistant depression maintained ketamine's antidepressant effects for over 15 days. Mental side effects tended to decrease over time.

Assumptions

- Must assume that this is more than experimental effort to extend ketamine's effects but offers some clinical advantages.

Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression

D. Jeffrey Newport, M.D., M.S., M.Div., Linda L. Carpenter, M.D., William M. McDonald, M.D., James B. Potash, M.D., M.P.H., Mauricio Tohen, M.D., Dr.P.H., M.B.A., Charles B. Nemeroff, M.D., Ph.D., The APA Council of Research Task Force on Novel Biomarkers and Treatments

Objective: The authors conducted a systematic review and meta-analysis of ketamine and other *N*-methyl-D-aspartate (NMDA) receptor antagonists in the treatment of major depression.

Method: Searches of MEDLINE, PsycINFO, and other databases were conducted for placebo-controlled, double-blind, randomized clinical trials of NMDA antagonists in the treatment of depression. Primary outcomes were rates of treatment response and transient remission of symptoms. Secondary outcomes included change in depression symptom severity and the frequency and severity of dissociative and psychotomimetic effects. Results for each NMDA antagonist were combined in meta-analyses, reporting odds ratios for dichotomous outcomes and standardized mean differences for continuous outcomes.

Results: Ketamine (seven trials encompassing 147 ketamine-treated participants) produced a rapid, yet transient, antidepressant effect, with odds ratios for response and transient remission of symptoms at 24 hours equaling 9.87 (4.37–22.29) and 14.47 (2.67–78.49), respectively, accompanied by brief psychotomimetic and dissociative effects. Ketamine augmentation of ECT (five trials encompassing 89 ketamine-treated participants) significantly reduced depressive symptoms following an initial treatment (Hedges' g=0.933) but not at the conclusion of the ECT course. Other NMDA antagonists failed to consistently demonstrate efficacy; however, two partial agonists at the NMDA coagonist site, D-cycloserine and rapastinel, significantly reduced depressive symptoms without psychotomimetic or dissociative effects.

Conclusions: The antidepressant efficacy of ketamine, and perhaps D-cycloserine and rapastinel, holds promise for future glutamate-modulating strategies; however, the ineffectiveness of other NMDA antagonists suggests that any forthcoming advances will depend on improving our understanding of ketamine's mechanism of action. The fleeting nature of ketamine's therapeutic benefit, coupled with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants caution.

Am J Psychiatry 2015; 172:950–966; doi: 10.1176/appi.ajp.2015.15040465

Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression

Bottom Line

- Ketamine NMDA antagonist) and D-cycloserine and raspatinel (NMDA partial agonists) had quick and brief affects on greatly lowered depression, while other NMDA antagonists had no effect. Affects do not last.

Assumptions

- No assumptions relevant since this is examination of mechanisms that could explain ketamine effect.

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
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