See article by Zhou et al

Improving the Care of Patients Who Have Treatment-Resistant Depression: The Promise of the PCORnet Mood Network

Andrew A. Nierenberg, MD; Louisa Sylvia, PhD; Allen Doederlein, BA; Susan Edgman-Levitan, PA; Alies Muskin, MA; Lucinda Jewell, EdM; Muffy Walker, MBA; Dan Goodman, MBA; Massoud Farahbakhsh, MBA; Casey Hearing, BA; Roberta Tovey, PhD; and Thilo Deckersbach, PhD

In this issue of *JCP*, Zhou and colleagues[1] review and integrate placebo-controlled efficacy trials of medications for treatment-resistant depression (TRD) to compare efficacy in a meta-analysis. They conclude that, among 11 augmentation options for TRD, aripiprazole and quetiapine have the most robust evidence for efficacy, with the caveats that these treatments carry substantial risks of adverse events and no long-term data are available. In the absence of direct comparisons, this exercise highlights the formidable challenges that clinicians face when making decisions. While Zhou and colleagues[1] provide an excellent analysis of the available data, we will argue that these findings are of limited use for most people receiving and providing care for TRD. As stated by Tricoci and colleagues in commenting on guidelines in cardiology, "the current system generating research is inadequate to satisfy the information needs of caregivers and patients in determining benefits and risks of drugs, devices, and procedures."[2(p837)] It is not just in psychiatry that we lack evidence for most clinical decisions. We need a new research paradigm beyond meta-analyses of efficacy studies. The audacious initiative from the Patient-Centered Outcomes Research Institute (PCORI) was developed to form a network of networks: PCORnet, the National Patient-Centered Clinical Research Network (www.PCORnet.org). This network includes a Mood Patient-Powered Research Network that can provide a national infrastructure to address clinical questions of most importance to people who have mood disorders as they partner with their clinicians.

Unanswered Questions

Which treatment for which TRD patient? When should it be given? For how long? What is the best dose? What sort of combinations of medications and psychotherapy would be best? How long should a treatment be given until it is clear that it will not work and should be abandoned? If it is going to work, when should it start working? What is the comparative *effectiveness* (not efficacy) among the options? What is the treatment of choice for TRD patients with suicidal behaviors and risk? What about comorbid disorders, psychiatric and medical? What is the effect of taking other medications, eg, birth control or chemotherapy? If a treatment works in the short term, how long should it be continued? What are the long-term risks and adverse effects? Which of these risks are unacceptable to patients such that they would no longer be willing to take the treatment, even if it worked? None of these questions are addressed by Zhou and colleagues[1] because the extant data available for meta-analyses omit the answers. But people who have mood disorders and their clinicians face these questions every day. Montgomery[3] argues that the way clinicians approach questions without clear answers is through practical reasoning (phronesis). But clinicians' practical reasoning would benefit from evidence that is more *clinically relevant*.

Challenges for Researchers

The data used by Zhou and colleagues[1] arise from carefully controlled efficacy studies that address the question, Does the intervention have an effect on the outcome of interest?[4] By design, these studies had extensive inclusion and exclusion criteria that limit the generalizability of the results[5,6]; the patients who participated in the studies represent a small fraction of the patients treated by clinicians. These patients have a limited scope of comorbid psychiatric and medical conditions and limited (if any) risk of suicidal behavior. Clinicians perceive that efficacy studies include patients who differ substantially from those that present for clinical care. *Effectiveness* studies, in contrast to efficacy studies, address the question, How does the intervention function in the clinic?[4,7] In the clinic, we don't want to know if the intervention is better than placebo; we want to know how well it works for our patients. If done well, and if powered sufficiently (with enough participants to provide statistically powered confidence in positive and negative findings), effectiveness studies can also allow for moderator analyses (What patient characteristics or biomarkers will predict response or nonresponse?).[8,9] In comparative effectiveness studies, moderator analyses can also address the questions, Who should get treatment A and not treatment B? Who should get treatment B and not treatment A? Who can get either treatment, or who should get neither treatment? The major challenge is that comparative effectiveness studies tend to be complex and expensive. How then can we obtain data that will inform clinical decisions for TRD and other complex, real-life presentations of mood disorders? Additionally, can we build a biobank to explore how biomarkers and genes can help inform treatment outcomes and decisions?

Submitted: *October 6, 2014; accepted October 7, 2014.*

Corresponding author: *Andrew A. Nierenberg, MD, Department of Psychiatry, Massachusetts General Hospital, 50 Stanford St, 5th Floor, Boston, MA 02114 (anierenberg@partners.org).*

J Clin Psychiatry 2015;76(4):e528–e530 (doi:10.4088/JCP.14com09570).

Answers for Clinicians

One path to address key clinical questions is through randomized comparative effectiveness studies that include a broad range of individuals who are representative of those seen in typical care settings. In mood disorders, STAR*D,[10] CoMed,[11] STEP-BD,[12] LiTMUS[13] and Bipolar CHOICE[14] provided data that in many ways highlighted (1) the difficult course for people with depression or bipolar disorder despite guideline-based care and (2) the challenge in finding differences between competing treatments. The STAR*D and STEP-BD built large infrastructures (coordinating centers, data management centers, electronic data capture, clinical researchers, clinics, and participants) that were then discontinued when the National Institute of Mental Health shifted its priorities. Now, PCORI has provided funding to build a comparative effectiveness infrastructure for the field to conduct studies through the Mood Network.

The ultimate goal of the Mood Network is to improve the lives of people with mood disorders through prospective comparative effectiveness trials embedded within routine care[15] and through patient-reported outcomes as well as outcome data from electronic medical records,[16] when available. The main aim of the Mood Network is to bring together at least 50,000 participants who have or have had mood disorder diagnoses and who are willing and able to consider participating in prospective comparative effectiveness studies. The main strategy to achieve this extraordinary aim is to collaborate with multiple mental health advocacy groups with their broad reach through their membership and Web sites to provide opportunities for appropriate individuals to volunteer. From the start, people with diagnoses have been true partners in this initiative and are instrumental in determining priorities and the scope of patient-reported outcome measures to be collected. Key members of the team include Allen Doederlein, President of the Depression Bipolar Support Alliance; Alies Muskin, Executive Director of the Anxiety Depression Association of America; Muffy Walker, President of the International Bipolar Foundation; Ken Duckworth, Medical Director of the National Alliance on Mental Illness; and, most importantly, the constituencies of these advocacy groups alongside individuals who receive care from a wide network of clinicians.

As the Mood Network evolves, it should do so in response to the needs, questions, and priorities of people receiving care. But it should also include the perspective of clinicians, not only to disseminate and implement findings from comparative effectiveness studies but also to address the questions that clinicians have and to provide them with better data so that they can help patients make decisions that are right for them, informed by the best evidence. The paradigm shift must educate researchers to truly partner with audiences that are not educated in research methodology in order to provide scientifically informed treatment options that will improve patient outcomes.

Returning to the Zhou et al article,[1] while envisioning the future of the Mood Network, the authors' unanswered questions could be addressed in the Mood Network: How do aripiprazole and quetiapine compare in a randomized head-to-head study? What are the problems with akathisia, tardive dyskinesia, and metabolic syndrome after 6 months? If someone responds to these (or any other effective intervention), when, if ever, can treatment be discontinued? Can these treatments prevent relapses or recurrences? If some new promising treatment arises in the next few years, how will that compare to these more established treatments? Can we determine who should choose aripiprazole and who should opt for quetiapine? Can we determine who is at risk of adverse effects and how best to manage those adverse effects? What is the role of psychotherapy?

The Mood Network will provide a unique opportunity for people with major depressive disorder or bipolar disorder to join a group of fellow citizen-scientists to collaborate together with clinicians and researchers to understand these disorders and improve outcomes. As the Mood Network Web site (www.moodnetwork.org) is under construction at the time of this writing, those interested in learning more about how we can all collectively learn together are urged to contact us at the following email address: moodnetwork@partners.org.

Author affiliations: Department of Psychiatry (Drs Nierenberg, Sylvia, Deckersbach, and Ms Hearing), John D. Stoeckle Center for Primary Care Innovation (Ms Edgman-Levitan), and MoodNetwork (Messrs Goodman and Farahbakhsh and Ms Tovey), Massachusetts General Hospital; Department of Psychiatry, Harvard Medical School (Drs Nierenberg, Sylvia, and Deckersbach), Boston, Massachusetts; Depression and Bipolar Support Alliance, Chicago, Illinois (Mr Doederlein and Ms Jewell); Anxiety and Depression Association of America, Silver Spring, Maryland (Ms Muskin); and International Bipolar Foundation, San Diego, California (Ms Walker).
Potential conflicts of interest: Dr. Nierenberg has been a consultant to Abbott, American Psychiatric Association, Appliance Computing (Mindsite), Basliea, Brain Cells, Brandeis University, Bristol-Myers Squibb, Clintara, Corcept, Dey, Dainippon Sumitomo (now Sunovion), Eli Lilly, EpiQ, LP/Mylan, Forest, Genaissance, Genentech, GlaxoSmithKline, Healthcare Global Village, Hoffman LaRoche, Infomedic, Lundbeck, Janssen, Jazz, Medavante, Merck, Methylation Sciences, Naurex, Novartis, PamLab, Parexel, Pfizer, PGx Health, Ridge Diagnostics Shire, Schering-Plough, Somerset, Sunovion, Takeda, Targacept, and Teva; consulted through the Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI) for AstraZeneca, Brain Cells, Dainippon Sumitomo/Sepracor, Johnson & Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Targacept and Takeda/Lundbeck; has received grant/research support from American Foundation for Suicide Prevention, Agency for Healthcare Research and Quality (AHRQ), Brain and Behavior Research Foundation, Bristol-Myers Squibb, Cederroth, Cephalon, Cyberonics, Elan, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Lichtwer Pharma, Marriott Foundation, Mylan, National Intstitute of Mental Health (NIMH), PamLab, PCORI, Pfizer, Shire, Stanley Foundation, Takeda, and Wyeth-Ayerst; has received honoraria from Belvoir Publishing, University of Texas Southwestern Dallas, Brandeis University, Bristol-Myers Squibb, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Baystate Medical Center, Columbia University, CRICO, Dartmouth Medical School, Health New England, Harold Grinspoon Charitable Foundation, Imedex, International Society for Bipolar Disorder, Israel Society for Biological Psychiatry, Johns Hopkins University, MJ Consulting, New York State, Medscape, MBL Publishing, MGH Psychiatry Academy, National Association of Continuing Education, Physicians Postgraduate Press, SUNY Buffalo, University of Wisconsin, University of Pisa, University of Michigan, University of Miami, University of Wisconsin at Madison, American Professional Society of ADHD and Related Disorders, SciMed, Slack Publishing and Wolters Klower Publishing, American Society of Clinical Psychopharmacology, New Clinical Drug Evaluation Unit, Rush Medical College, Yale University School of Medicine, National Network of Depression Centers, Nova Southeastern University, National Alliance on

Mental Illness, Institute of Medicine, CME Institute, and International Society for CNS Trials and Methodology; owns stock in Appliance Computing (MindSite), Brain Cells, and Medavante; and holds copyright for Clinical Positive Affect Scale and the MGH Structured Clinical Interview for the Montgomery Asberg Depression Scale exclusively licensed to the MGH CTNI. **Dr Sylvia** has been a consultant to Clintara and Bracket; has received grant/research support from NIMH, Takeda and American Foundation for Suicide Prevention; and has received honoraria from the MGH Psychiatry Academy. **Dr Deckersbach** has received research funding from NIMH, NARSAD, Tourette Syndrome Association, International OCD Foundation, Tufts University, and Depressive and Bipolar Disorder Alternative Treatment Foundation; has received honoraria, consultation fees, or royalties from MGH Psychiatry Academy, BrainCells, Clintara, Systems Research and Applications, Boston University, Catalan Agency for Health Technology Assessment and Research, National Association of Social Workers Massachusetts, Massachusetts Medical Society, Tufts University, National Institute on Drug Abuse, NIMH, and Oxford University Press; and has participated in research funded by National Institutes of Health, National Institute on Aging, AHRQ, PCORI, Janssen, Forest Research Institute, Shire Development, Medtronic, Cyberonics, Northstar, and Takeda. **Messrs Doederlein**, **Goodman**, and **Farahbakhsh** and **Mss Edgman-Levitan**, **Muskin**, **Jewell**, **Walker**, **Hearing**, and **Tovey** have no conflicts of interest to report.

Funding/support: Support for this commentary was received from PCORI PPRN-1306-04925.

Role of the sponsor: The sponsor had no role in the preparation, review, or approval of the commentary.

REFERENCES

1. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *J Clin Psychiatry*. 2015;76(4):e487–e498.
2. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301(8):831–841.
3. Montgomery K. *How Doctors Think: Clinical Judgment and the Practice of Medicine*. New York, NY: Oxford University Press; 2005.
4. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol*. 2009;62(5):464–475.
5. Wisniewski SR, Rush AJ, Nierenberg AA, et al. Can phase III trial results of antidepressant medications be generalized to clinical practice? a STAR*D report. *Am J Psychiatry*. 2009;166(5):599–607.
6. Friedman ES, Calabrese JR, Ketter TA, et al. Using comparative effectiveness design to improve the generalizability of bipolar treatment trials data: contrasting LiTMUS baseline data with pre-existing placebo controlled trials. *J Affect Disord*. 2014;152–154:97–104.
7. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol*. 2009;62(5):499–505.
8. Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002;59(10):877–883.
9. Kraemer HC, Schultz SK, Arndt S. Biomarkers in psychiatry: methodological issues. *Am J Geriatr Psychiatry*. 2002;10(6):653–659.
10. Rush AJ, Fava M, Wisniewski SR, et al; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25(1):119–142.
11. Rush AJ, Trivedi MH, Stewart JW, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry*. 2011;168(7):689–701.
12. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry*. 2003;53(11):1028–1042.
13. Nierenberg AA, Sylvia LG, Leon AC, et al; Litmus Study Group. Lithium treatment—moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. *Clin Trials*. 2009;6(6):637–648.
14. Nierenberg AA, Sylvia LG, Leon AC, et al; Bipolar CHOICE Study Group. Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE): a pragmatic trial of complex treatment for a complex disorder. *Clin Trials*. 2014;11(1):114–127.
15. Wang PS, Ulbricht CM, Schoenbaum M. Improving mental health treatments through comparative effectiveness research. *Health Aff (Millwood)*. 2009;28(3):783–791.
16. McMurry AJ, Murphy SN, MacFadden D, et al. SHRINE: enabling nationally scalable multi-site disease studies. *PLoS ONE*. 2013;8(3):e55811.