

frailty, may still exist.⁴ Some covariates (eg, categories of liver diseases) can act as a proxy for laboratory tests. Frailty is difficult to measure and quantify clinically. Self-controlled design, as advised by Li and colleagues, may be needed to ascertain its influence. Specific drug characteristics, for example thrombocytopenia associated with rifampin,⁴ may change bleeding risk beyond the influence of altered NOAC levels. Drug-disease interactions also make the risk estimation of adverse drug reactions more difficult.⁵ Wang and colleagues comment that the increased risk associated with phenytoin may be a bystander of intracranial hemorrhage and related seizure. Li and colleagues describe the healthy user effect to explain the reduction in bleeding risk with atorvastatin use.

We respond to other comments briefly:

1. The weight to estimate the average treatment effect was 1 for NOAC users with a concurrent medication whereas those who received a NOAC alone received a weight based on propensity score. Therefore, the number of patients should remain unchanged in the reference group.⁶
2. The hypothesis for each drug combination was tested independently, considering multiple testing using the Bonferroni method. To address the effect of multiple concurrent medications, each of the medication combinations would need to be modeled, which we will perform in the future.
3. NOACs are new in Taiwan; patients receiving a NOAC were often taking aspirin or warfarin before being replaced by a NOAC.
4. The inconsistent pattern shown in sensitivity tests, such as the risk of fractures as well as differential bleeding risks at different sites, may represent unmeasured confounding and frailty, as previously discussed.
5. Antifungal agents such as ketoconazole were grouped in the analysis because of the low frequency of combination with NOACs.

Data from routinely collected clinical information are the best source available at present to study the complex issue of drug-drug interactions. The key messages are that NOAC users often had comorbidities and took multiple concomitant medications; the combination of NOACs with specific medications changed both the absolute and relative risks of major bleeding; and mechanistic background for drug-drug interactions could not fully explain or predict dangerous drug combinations.

Shang-Hung Chang, MD, PhD
Ming-Shien Wen, MD
Chang-Fu Kuo, MD, PhD

Author Affiliations: Cardiovascular Department, Chang Gung Memorial Hospital, Taoyuan, Taiwan (Chang, Wen); Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan (Kuo).

Corresponding Author: Chang-Fu Kuo, MD, PhD, Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, No. 5, Fuxing St, Guishan District, Taoyuan City 333, Taiwan (zandis@gmail.com).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Parasrampur DA, Mendell J, Shi M, Matsushima N, Zahir H, Truitt K. Edoxaban drug-drug interactions with ketoconazole, erythromycin, and cyclosporine. *Br J Clin Pharmacol*. 2016;82(6):1591-1600.
2. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Eur Heart J*. 2017;38(27):2137-2149.
3. Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A. Association between use of warfarin with common sulfonylureas and serious hypoglycemic events. *BMJ*. 2015;351:h6223.
4. Grosset J, Leventis S. Adverse effects of rifampin. *Rev Infect Dis*. 1983;5(suppl 3):S440-S450.
5. Dumbreck S, Flynn A, Nairn M, et al. Drug-disease and drug-drug interactions. *BMJ*. 2015;350:h949.
6. Austin PC. The use of propensity score methods with survival or time-to-event outcomes. *Stat Med*. 2014;33(7):1242-1258.

The Evidence for Cognitive Behavioral Therapy

To the Editor Drs Leichsenring and Steinert argued that cognitive behavioral therapies (CBTs) should not be the gold standard treatment for mental disorders.¹ They acknowledged that CBTs have been more widely studied than other forms of therapy but suggested that other treatments should be considered equivalent to CBTs unless evidence emerges to suggest otherwise. In doing so, they shifted the burden of evidence about the efficacy of other treatments away from those treatments and onto the evidence base for CBTs. In other areas of medicine, treatments with a broader positive evidence base are not considered equal to less widely studied treatments.

The authors pointed out that few studies are deemed high quality, the effects of CBTs relative to active controls tend to be small, and that a full account of the mechanisms of change is not present. These statements are probably as true of other forms of psychotherapy as they are of CBTs. Indeed, considering those limitations would make the evidence base of other treatments appear even weaker. For example, if only treatment studies that included either a pill placebo control were considered valid, the list of empirically supported treatments for depression would be composed chiefly of CBTs.² Criticism of CBTs is important because of, not despite, the fact that they are so widely studied. However, the presence and validity of criticisms do not undermine the wealth of evidence supporting the efficacy of CBTs. For some disorders, including obsessive-compulsive disorder and sleep disorders, CBTs are virtually the only treatments that have been studied. For bulimia, a form of CBT appears to be more effective than psychoanalysis³ and appears to work faster than interpersonal therapy.⁴

The term *gold standard* is not meant to describe a treatment or assessment that is known to be far superior to all possible known alternatives and for all time.⁵ Instead, it applies to a practice that appears to be best supported by the currently available evidence. With this context, it is appropriate to consider CBTs the gold standard psychotherapy.

Lorenzo Lorenzo-Luaces, PhD

Author Affiliation: Indiana University, Bloomington.

Corresponding Author: Lorenzo Lorenzo-Luaces, PhD, Indiana University, 1101 E 10th St, Room 158, Bloomington, IN 47405 (lolorenz@indiana.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported receiving training in cognitive behavioral therapies (CBTs) and having published work relevant to understanding treatment outcomes and processes in CBTs.

1. Leichsenring F, Steinert C. Is cognitive behavioral therapy the gold standard for psychotherapy? the need for plurality in treatment and research. *JAMA*. 2017;318(14):1323-1324.
2. Cuijpers P, Turner EH, Mohr DC, et al. Comparison of psychotherapies for adult depression to pill placebo control groups: a meta-analysis. *Psychol Med*. 2014;44(4):685-695.
3. Poulsen S, Lunn S, Daniel SI, et al. A randomized controlled trial of psychoanalytic psychotherapy or cognitive-behavioral therapy for bulimia nervosa. *Am J Psychiatry*. 2014;171(1):109-116.
4. Fairburn CG, Bailey-Straebl S, Basden S, et al. A transdiagnostic comparison of enhanced cognitive behaviour therapy (CBT-E) and interpersonal psychotherapy in the treatment of eating disorders. *Behav Res Ther*. 2015;70:64-71.
5. Versi E. "Gold standard" is an appropriate term. *BMJ*. 1992;305(6846):187.

To the Editor In their Viewpoint, Drs Leichsenring and Steinert¹ questioned the status of CBT as the gold standard for psychotherapy and called for "plurality in treatment and research" because of several limitations of current treatment outcome research in CBT. Although we agree that outcome research may have limitations and must be appropriately interpreted, the authors' arguments are unconvincing for at least 4 reasons.

First, present-day CBT is an umbrella term that includes a range of different empirically supported interventions, techniques, and modalities. Similarly, the many CBT associations, journals, and conferences include a diverse range of approaches, many of which fall outside the CBT that was developed in the 1970s and 1980s. Examples may include schema-focused therapy, metacognitive therapy, and acceptance or mindfulness-based approaches. Plurality is thus a characteristic of modern CBT.

Second, the authors based their conclusions in large part on an overly negative interpretation of a meta-analysis of CBT in major depression and anxiety disorders.² Even when taking into account publication bias, low quality of trials, and the nocebo effects of waiting list control groups, the meta-analysis still concluded that CBT had positive effects in major depression, generalized anxiety disorder, panic disorder, and social anxiety disorder. Also, it did not compare CBT with other psychotherapies and therefore cannot inform such comparisons.

Third, the methodological issues mentioned by the authors are in no way inherent or limited to CBT research. It remains to be seen how other approaches perform in the so-called "weak empirical tests" that CBT has been subjected to so far.

Fourth, although the evidence base of CBT in general is large,³ some approaches possess a larger, stronger, and wider evidence base than others. As more has been learned about the nature of a particular psychopathology, CBT strategies have become more targeted and more effective. This is by no means a weakness but instead scientific progress.

So far, CBT is the most effective treatment approach, based on solid yet ever-evolving scientific models and methods. However, the field would advance with clearly articulated and testable theories that result in concrete and empirically supported treatment approaches.

Arnold A. P. van Emmerik, PhD
Kim de Jong, PhD
Stefan G. Hofmann, PhD

Author Affiliations: Department of Clinical Psychology, University of Amsterdam, Amsterdam, the Netherlands (van Emmerik); Institute of Psychology, Leiden University, Leiden, the Netherlands (de Jong); Department of Psychological and Brain Sciences, Boston University, Boston, Massachusetts (Hofmann).

Corresponding Author: Arnold A. P. van Emmerik, PhD, Department of Clinical Psychology, University of Amsterdam, PO Box 15933, 1001 NK, Amsterdam, the Netherlands (a.a.p.vanemmerik@uva.nl).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr van Emmerik reported being the president and Dr de Jong reported being a board member of the Dutch Association for Behavioral and Cognitive Therapies. Dr Hofmann reported a grant to his institution from the National Institute of Mental Health; being a consultant to Schering-Plough; and receiving royalties from books.

1. Leichsenring F, Steinert C. Is cognitive behavioral therapy the gold standard for psychotherapy? the need for plurality in treatment and research. *JAMA*. 2017;318(14):1323-1324.
2. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? a meta-analytic update of the evidence. *World Psychiatry*. 2016;15(3):245-258.
3. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. *Cognit Ther Res*. 2012;36(5):427-440.

In Reply Dr Lorenzo-Luaces and Dr van Emmerik and colleagues take issue with our discussion of the evidence base for CBT and other psychotherapies. We acknowledge that CBT, an umbrella concept for different interventions, is an effective treatment for many patients with more studies than for other approaches.

Nevertheless, quantity does not imply quality. If study quality is considered, the evidence base for CBT shrinks to a modest number of studies; for example, in anxiety or depressive disorders, it goes down to only 17% of 144 studies.¹ If publication bias, study quality, comparisons with waiting list, and researcher allegiance are additionally taken into account, the effect sizes of CBT also decrease.¹ Cuijpers et al¹ concluded that the effects of CBT are "uncertain and should be considered with caution." Thus, this description was not an "overly negative interpretation" by us as suggested by van Emmerik and colleagues.

It is true that the biases mentioned by us and Cuijpers et al¹ are not limited to CBT, but other approaches do not claim to be the gold standard. As noted in our Viewpoint, fewer studies exist for other psychotherapies, and applying the same criteria would reduce the number of high-quality studies for these approaches as well. It is not clear, however, whether these high-quality studies would yield substantial differences in outcome between different approaches.

A gold standard treatment usually is clearly superior to other treatments. As we discussed in the Viewpoint, no clear evidence exists that CBT is superior to other approaches. According to van Emmerik and colleagues' claim, CBT has become "more targeted and more effective." Instead, effect sizes for CBT in anxiety and depressive disorders seem to have stagnated or even decreased over recent decades.²⁻⁴ We agree, however, with Lorenzo-Luaces that for obsessive-

compulsive disorder and sleep disorders, CBT is virtually the only treatment that has been studied in randomized clinical trials. This does not necessarily imply that other treatments are not efficacious or less efficacious than CBT. With regard to bulimia, most studies do not show that CBT is superior to, for example, psychodynamic therapy.⁵

With response rates of about 50% or less and even lower remission rates, CBT cannot claim to be a panacea. Patients who do not benefit sufficiently from CBT may benefit from other psychotherapies. In pharmacotherapy, for example, a patient who does not sufficiently respond to a specific selective serotonin reuptake inhibitor may be offered an alternative medication. Thus, a plurality of approaches not only including the variants of CBT mentioned by van Emmerik and colleagues but also the variants of other evidence-based approaches is needed to offer all patients helpful treatment. A plurality of different approaches allows better care for patients and possible further treatment improvements.⁴ No form of psychotherapy may presently claim to be the best for all patients.

Thus, we agree with DeRubeis and Lorenzo-Luaces⁶ who stated: “If the question at hand is whether research is far enough along to support the view that only CBTs should be investigated, taught in training programs, and offered to individuals with mental health problems, then the answer is clearly ‘no’.”

Falk Leichsenring, DSc
Christiane Steinert, PhD

Author Affiliations: Department of Psychosomatics and Psychotherapy, University of Giessen, Giessen, Germany (Leichsenring); Department of Psychology, MSB Medical School Berlin, Berlin, Germany (Steinert).

Corresponding Author: Falk Leichsenring, DSc, Department of Psychosomatics and Psychotherapy, University of Giessen, Ludwigstr 76, 35392 Giessen, Germany (falk.leichsenring@psycho.med.uni-giessen.de).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? a meta-analytic update of the evidence. *World Psychiatry*. 2016;15(3):245-258.
2. Johnsen TJ, Friberg O. The effects of cognitive behavioral therapy as an anti-depressive treatment is falling: a meta-analysis. *Psychol Bull*. 2015;141(4):747-768.
3. Öst L-G. Cognitive behavior therapy for anxiety disorders: 40 years of progress. *Nord J Psychiatry*. 2008;62(suppl 47):5-10.
4. Roy-Byrne P. Transdiagnostic cognitive behavioral therapy and the return of the repressed. *JAMA Psychiatry*. 2017;74(9):867-868.
5. Stefani A, Salzer S, Reich G, et al. Cognitive-behavioral and psychodynamic therapy in female adolescents with bulimia nervosa: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2017;56(4):329-335.
6. DeRubeis RJ, Lorenzo-Luaces L. Recognizing that truth is unattainable and attending to the most informative research evidence. *Psychother Res*. 2017;27(1):33-35.

CORRECTION

Omitted Disclosure of Potential Conflicts of Interest: In the Viewpoint titled “The Iatrogenic Potential of the Physician’s Words”¹ published in the December 26, 2017, issue of *JAMA*, the author omitted disclosure of potential conflicts of interest. The disclosure statement should include the following: “Dr Barsky reported having served as an expert witness in cases that involved providing opinions on the relationship between somatic symptoms and underlying disease processes.” This article was corrected online.

1. Barsky AJ. The iatrogenic potential of the physician’s words. *JAMA*. 2017;318(24):2425-2426.

Errors in Text and Supplement: In the Original Investigation entitled “Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation”¹ published in the October 3, 2017, issue of *JAMA*, the incorrect mechanism of action for 2 drugs, rifampin and phenytoin, was reported in the text and Supplement. In the Methods, the final sentence under Follow-up Time and Person-Quarters should read: “These medications were selected because they were P-glycoprotein competitors (digoxin, verapamil, diltiazem, amiodarone, and cyclosporine), CYP3A4 inhibitors (fluconazole and ketoconazole, itraconazole, voriconazole, or posaconazole), or both (atorvastatin, erythromycin or clarithromycin, dronedarone) or CYP3A4 inducer (rifampin and phenytoin), which may have a potential drug-drug interaction with NOACs.” In the Results, the first sentence in the final paragraph under Sensitivity and Additional Analyses should read: “In the third additional analysis, 12 concurrent medications were categorized into 2 metabolic pathway groups: P-glycoprotein competitors group (digoxin, verapamil, diltiazem, amiodarone, and cyclosporine) and both P-glycoprotein competitors and CYP3A4 inhibitors group (atorvastatin, fluconazole, ketoconazole, itraconazole, voriconazole, or posaconazole; erythromycin or clarithromycin; and dronedarone).” Additionally, the footnote in eTable 7 of the Supplement should read: “P, C: Atorvastatin, Fluconazole, Ketoconazole, Itraconazole, Voriconazole, Posaconazole, Clarithromycin, Erythromycin, Dronedarone, P: Digoxin, Verapamil, Diltiazem, Amiodarone, Cyclosporin.” This article was corrected online.

1. Chang SH, Chou JJ, Yeh YH, et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA*. 2017;318(13):1250-1259.

Missing Corresponding Author Information and Error in Supplement Note: In the Original Contribution entitled “Association of Insulin Pump Therapy vs Insulin Injection Therapy With Severe Hypoglycemia, Ketoacidosis, and Glycemic Control Among Children, Adolescents, and Young Adults With Type 1 Diabetes”¹ published in the October 10, 2017, issue of *JAMA*, contact information for the corresponding author was missing and there was an error in a note in the Supplement. On the first page of the article, the corresponding author’s contact information should have appeared below the affiliations information. In the online Supplement, the information after the asterisk in the eFigure 1 legend should have read “denotes *P* values <.05 and ≥.001.” This article was corrected online.

1. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA*. 2017;318(14):1358-1366.

Incorrect Unit in Laboratory Value: In the US Preventive Services Task Force Recommendation Statement entitled “Screening for Preeclampsia: US Preventive Services Task Force Recommendation Statement”¹ published in the April 25, 2017, issue of *JAMA*, a unit reported with a laboratory value was incorrect. Near the end of the “Screening Tests” subsection of the “Clinical Considerations” section, “protein to creatinine ratio of ≥0.3 mg/mmol” should have read “protein to creatinine ratio of ≥0.3 [each measured as mg/dL].” This article was corrected online.

1. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. US Preventive Services Task Force. Screening for preeclampsia: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;317(16):1661-1667.