and Genomics, University Hospital, Ludwig Maximilian University, Munich, Germany (Papiol); Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilian University, Munich, Germany (Papiol).

Corresponding Author: Sabine Bahn, MD, PhD, Department of Chemical Engineering and Biotechnology, University of Cambridge, Philippa Fawcett Drive, Cambridge CB3 OAS, England (sb209@cam.ac.uk).

Accepted for Publication: January 6, 2019.

Published Online: April 3, 2019. doi:10.1001/jamapsychiatry.2019.0304

Author Contributions: Dr Tomasik had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Crespo-Facorro and Bahn contributed equally to this work.
Study concept and design: Tomasik, Lago, Crespo-Facorro, Bahn.
Acquisition, analysis, or interpretation of data: All authors.
Drafting the manuscript: Tomasik, Lago, Bahn.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Tomasik.
Administrative, technical, or material support: Crespo-Facorro, Bahn.
Study supervision: Crespo-Facorro, Bahn.

Conflict of Interest Disclosures: Dr Tomasik was a consultant for Psynova Neurotech, Ltd, until April 2016. Dr Lago was part funded by Psynova Neurotech Ltd until October 2015. Dr Bahn is a director of Psynova Neurotech Ltd and Psyomics Ltd. No other disclosures were reported.

Funding/Support: This work was supported by grants from the Stanley Medical Research Institute (Dr Bahn).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We are grateful to the individuals who participated in the study for sample donation and the technical and clinical support staff at the affiliated institutions for collection of samples, clinical data, and technical support. Participants were not compensated by the funding sponsor for their contribution.

1. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. *JAMA Psychiatry*. 2017;74(3):261-269. doi:10.1001/jamapsychiatry.2016.3803

2. Chouinard VA, Henderson DC, Dalla Man C, et al. Impaired insulin signaling in unaffected siblings and patients with first-episode psychosis. *Mol Psychiatry*. 2018. doi:10.1038/s41380-018-0045-1

3. Lago SG, Tomasik J, van Rees GF, et al. Exploring the neuropsychiatric spectrum using high-content functional analysis of single-cell signaling networks. *Mol Psychiatry*. 2018. doi:10.1038/s41380-018-0123-4

4. Ripke S, Neale BM, Corvin A, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-427. doi:10.1038/nature13595

5. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care*. 1998;21(12):2191-2192. doi:10.2337/diacare.21.12.2191

6. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia, PA: Elsevier Saunders; 2011.

Combining Pharmacological and Nonpharmacological Interventions in Network Meta-analysis in Psychiatry

Network meta-analyses (NMAs) assess the comparative associations of 2 or more interventions even if they have not been compared in a randomized clinical trial.[1] The validity of NMAs is founded on the assumption of transitivity (ie, that effect modifiers do not substantially differ across the included trials).[1] The popularity of NMAs on pharmacological or nonpharmacological interventions is increasing in psychiatry.[2] Recent NMAs have combined pharmacological and nonpharmacologic interventions in the same network. Although this may be informative for developing guidelines, it is methodologically challenging and could compromise the validity of NMAs. We aimed to evaluate NMAs that combined pharmacological and nonpharmacological interventions and provide guidance on how to conduct them.

Supplemental content

Methods | We searched PubMed, PsycINFO, Embase, OVID MEDLINE, biological abstracts, BIOSIS, and Web of Science from inception until August 31, 2018. We appraised NMAs of randomized clinical trials based on the approach proposed by Cope et al,[3] focusing on (1) how the control node (or neutral comparator) was defined in the network geometry, (2) differences between pharmacological and nonpharmacological studies with respect to patient characteristics, and (3) the distribution of risk of bias (RoB) in the network. According to the approach of Cope et al,[3] we checked if the association of these issues with the results was explored in the retained NMAs (eMethods in the Supplement).

Results | We retrieved 12 NMAs (eMethods in the Supplement). Eight were published between 2017 and 2018: 6 focused on adults, 5 on children/adolescents, and 1 on both. These NMAs covered several psychiatric conditions, including major depressive disorder, anxiety disorders, attention-deficit/hyperactivity disorder, obsessive compulsive disorder, bulimia nervosa, at-risk mental state, and poststroke depression (eMethods in the Supplement).

Five NMAs pooled different types of control conditions (eg, a placebo pill, psychological placebo, or sham intervention) into the same node of the network, assuming that these comparators have similar associations (eMethods in the Supplement). However, this hypothesis should be empirically tested via a meta-regression (when feasible) or subgroup/sensitivity analysis. Only 2 NMAs did so (eMethods in the Supplement).

The existing differences between pharmacological and nonpharmacological studies in patient characteristics for baseline disease severity or previous exposure to treatment were reported in only 3 NMAs and only 1 assessed its association with the results (eMethods in the Supplement). The heterogeneity of patient characteristics was unclear or had not been retrieved from primary studies in most of the NMAs.

We found 3 NMAs in which the risk of performance or detection bias was not distributed evenly across pharmacological and nonpharmacological studies (eMethods in the Supplement). Compared with pharmacological trials, those with nonpharmacological interventions were less likely to have participants, caregivers, and outcome assessors masked, which is often an unavoidable limitation as some nonpharmacological treatments cannot always be masked. Four NMAs performed a sensitivity analysis to assess the association of high RoB for lack of masking with the treatment effects, but most of the NMA data were too sparse to draw any conclusion (eMethods in the Supplement).

Discussion | Network meta-analyses that combine pharmacological and nonpharmacological interventions for psychiatric conditions may be prone to violating the transitivity assump-

tion, which may affect their validity. The definition and classification of the control node in the geometry of the network could affect the results of the NMA. A novel approach called *component NMA* could address this issue, as it explores the treatment effects of interventions with multiple components.[4] Furthermore, differences in baseline participants' characteristics, study RoB, and the level of masking may represent a limitation of NMA in combining pharmacological and nonpharmacological therapies.[5] An individual participant data NMA could overcome these limitations, as it allows exploring treatment-patient interactions to check RoB and obtain extra data from trialists.[6] Caution is needed when pharmacological and nonpharmacological interventions are combined in an NMA, and the specific potential limitations of this type of NMAs should always be systematically and transparently discussed.

Cinzia Del Giovane, PhD
Samuele Cortese, MD, PhD
Andrea Cipriani, MD, PhD

Author Affiliations: Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland (Del Giovane); Center for Innovation in Mental Health, Academic Unit of Psychology; Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southhampton, England (Cortese); Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, England (Cipriani); Oxford Health National Health Service Foundation Trust, Warneford Hospital, Oxford, England (Cipriani).

Corresponding Author: Cinzia Del Giovane, Institute of Primary Health Care (BIHAM), University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland (cinzia.delgiovane@biham.unibe.ch).

Published Online: April 17, 2019. doi:10.1001/jamapsychiatry.2019.0574

Author Contributions: Dr Del Giovane has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Del Giovane, Cortese, Cipriani.
Drafting of the manuscript: Del Giovane, Cortese.
Critical revision of the manuscript for important intellectual content: Cipriani.
Statistical analysis: Del Giovane.
Administrative, technical, or material support: All authors.
Supervision: Cipriani.

Conflict of Interest Disclosures: Dr Cortese declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) from lectures delivered for ACAMH and from Healthcare Convention for educational activity on attention-deficit/hyperactivity disorder. Dr Cipriani is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility, by an NIHR research professorship (grant RP-2017-08-ST2-006), and by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215-20005). No other disclosures are reported.

Funding/Support: This study was funded by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215-20005; Dr Cipriani).

Role of the Funder/Sponsor: The NIHR did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the UK Department of Health.

Additional Contributions: We thank Kali Tal, PhD, Institute of Primary Health Care (BIHAM), University of Bern, Switzerland, for her editorial suggestions. She was not compensated for her contributions.

1. Mavridis D, Giannatsi M, Cipriani A, Salanti G. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health*. 2015;18(2):40-46. doi:10.1136/eb-2015-102088

2. Cortese S, Tomlinson A, Cipriani A. Meta review: network meta-analyses in child and adolescent psychiatry. *J Am Acad Child Adolesc Psychiatry*. 2019;58(2):167-179. doi:10.1016/j.jaac.2018.07.891

3. Cope S, Zhang J, Saletan S, Smiechowski B, Jansen JP, Schmid P. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer. *BMC Med*. 2014;12:93. doi:10.1186/1741-7015-12-93

4. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol*. 2009;169(9):1158-1165. doi:10.1093/aje/kwp014

5. Streiner DL, Joffe R. The adequacy of reporting randomized, controlled trials in the evaluation of antidepressants. *Can J Psychiatry*. 1998;43(10):1026-1030. doi:10.1177/070674379804301008

6. Tierney JF, Vale C, Riley R, et al. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. *PLoS Med*. 2015;12(7):e1001855. doi:10.1371/journal.pmed.1001855

COMMENT & RESPONSE

Positive Predictive Values and Potential Success of Suicide Prediction Models

To the Editor We write to disagree with the pessimism of Belsher et al[1] regarding the potential utility of models predicting suicidal behavior. They argue that no existing models have positive predictive value high enough to guide prevention efforts.

Some existing models predicting suicide attempt have positive predictive values equal to or exceeding those of widely accepted risk prediction tools. Among mental health outpatient visits, we can accurately identify those with a 5% risk of suicide attempt over the following 90 days.[2] For comparison, the US Preventive Services Task Force recommends tamoxifen in women with a predicted risk of breast cancer exceeding 3% over 5 years[3] and recommends statins for people with predicted risk of cardiovascular event exceeding 10% over 10 years.[4]

Effective secondary or selective prevention requires accurate tools for identifying those at risk as well as effective, safe, and scalable interventions. For any identification tool, our threshold for acceptable positive predictive value depends on the balance of benefits and harms (including nonmedical harms) of any subsequent intervention.

We now lack clear evidence for effective and scalable intervention for secondary prevention of suicidal behavior. However, if or when such an intervention is identified, existing risk prediction tools would likely be adequate to guide its application, in the same way that existing risk prediction tools guide the use of interventions to prevent breast cancer or cardiovascular disease.

Gregory E. Simon, MD, MPH
Susan M. Shortreed, PhD
R. Yates Coley, PhD

Author Affiliations: Kaiser Permanente Washington Health Research Institute, Seattle, Washington.

Corresponding Author: Gregory E. Simon, MD, MPH, Kaiser Permanente Washington Health Research Institute, 1730 Minor Ave, Ste 1600, Seattle, WA 98101 (gregory.e.simon@kp.org).

Published Online: June 26, 2019. doi:10.1001/jamapsychiatry.2019.1516