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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 (i.e., 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 nonpharmacological 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.

Methods | We searched PubMed, PsyicINFO, 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 assum-
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. 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. 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. 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.

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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 al1 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 years3 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.

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