Network meta-analysis: science or alchemy? - What works best in generalized anxiety disorder

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Summary

Recently Papola et al. (2023) recently published a network meta-analysis (NMA) on psychotherapy of generalized anxiety disorder (GAD) and concluded that cognitive-behavioral therapy (CBT) should be considered the first-line treatment for GAD. However, there are several concerns with regard to the procedures and the conclusions of this NMA and of NMA in general. We show that these concerns question the conclusions by Papola et al. Furthermore, we place concerns about this NMA in a broader context and question whether existing evidence is consistent with the notion that one form of psychotherapy can be regarded as the gold standard for mental disorders and for all patients and therapists.

Key words: Network meta-analysis, generalized anxiety disorder, gold standard psychotherapy

Zusammenfassung

Kürzlich haben Papola et al. (2023) eine Netzwerk Meta-Analyse zur Psychotherapie von generalisierter Angststörung publiziert, die ausschließlich kognitive Verhaltenstherapie als first-line Behandlung empfiehlt. Es gibt jedoch verschiedene Bedenken im Hinblick auf die Prozeduren und die Schlussfolgerung dieser Netzwerk Meta-Analyse und von Netzwerk Meta-Analysen im Allgemeinen. Wir zeigen, dass diese Bedenken die Schlussfolgerung der Autoren in Frage stellen. Weiterhin diskutieren wir die Prozeduren und Ergebnisse dieser Netzwerk Metaanalyse in einem breiteren Kontext und stellen in Frage, ob eine Form der Psychotherapie als Goldstandard für alle Störungen und für alle Patienten und Therapeuten angesehen werden kann.

Schlüsselwörter: Netzwerk-Meta-Analyse, Generalisierte Angststörung, Goldstandard-Psychotherapie

Background

Anxiety disorders are among the most common mental disorders (Kessler et al., 2005). They may be treated by psychotherapy or pharmacotherapy (Leichsenring et al., 2022). However, whether pharmacotherapy is as efficacious as psychotherapy in the long-run, has not yet been demonstrated (Leichsenring & Hoyer, 2019). With regard to psychotherapy, cognitive-behavioral therapy (CBT) is often recommended as the gold standard treatment (Szuhany & Simon, 2022). However, the rates of remission and response achieved by CBT in anxiety disorders are limited (Loerinc et al., 2015; Springer et al., 2018). In addition, CBT has not proved to be superior to other forms of psychotherapy in anxiety disorders such as psychodynamic therapy (Keefe et al., 2014; Leichsenring et al., 2023).

A network meta- analysis on generalized anxiety disorder

Recently, a network meta- analysis (NMA) was published which found CBT to be the only active treatment that was superior to treatment-as-usual (TAU) both at treatment termination and at follow-up in generalized anxiety disorder (GAD, Papola et al., 2023). This led the authors to conclude that CBT may represent the first-line treatment of GAD. However, we have several concerns with regard to the procedures followed and the conclusions drawn from this NMA, as well as regarding NMA in general.

(1) Transitivity and Consistency

NMA has the advantage of incorporating both direct and indirect evidence. If, for example, CBT and treatment X have never been compared directly in randomized controlled trials (RCTs), but CBT was compared to TAU in RCTs with an effect size (standardized mean difference, SMD) of 0.70, for instance, and X was compared to TAU in RCTs with an effect size of 0.40, an indirect comparison of CBT and X can be obtained by subtracting these

effect sizes (Cipriani et al., 2013). Thus, in this example, CBT would be superior to X by an effect size of 0.30. However, complex assumptions need to be fulfilled to be able to draw such conclusions: (1) Transitivity assumes that study characteristics relevant to outcome are balanced between studies, including important features such as treatment duration, patient features, or type of comparator (Cipriani et al., 2013; Faltinsen et al., 2018). The transitivity assumption, however, can only be tested for known effect modifiers. In contrast, randomization controls for all possible effect modifiers. As the treatments being compared in indirect comparisons have not been randomized directly within the individual trials NMA provides evidence of only an observational nature (Cipriani et al., 2013). (2) Analogously, differences between direct and indirect effect sizes (i.e. consistency assumption), can only be tested where direct evidence is available. In sum, the level of evidence provided by NMA is a matter of debate (Cipriani et al., 2013; Faltinsen et al., 2018). The Canadian Agency for Drugs and Technologies in Health, for example, allows indirect and mixed comparisons only as a sensitivity or supportive analysis to supplement the direct evidence (Wells et al., 2009). Papola et al. (2023), however, used the NMA as the primary method of analysis.

(2) Comparing effect sizes without testing of significance

The conclusions by Papola et al concerning CBT as a first-line treatment are based on the comparisons of active therapies with TAU provided by NMA: "after removing studies with high risk of bias, only CBT … remained superior to treatment as usual…. " (Papola et al., 2023, Key Points). However, assuming differences between treatments if one treatment shows descriptively larger effect sizes compared to a control condition than others, without comparing the differences in effect sizes statistically between the treatments, should be avoided (Makin & Orban de Xivry, 2019).

(3) No significant differences between active treatments

The former issue is all the more important since the Papola et al. NMA did not find any

significant differences between active treatments in the treatment-vs.-TAU- effect sizes (Papola et al., 2023, Figure 2). This is true also for acceptance. Papola et al did not take these results of their own NMA into account when drawing conclusions about first-line treatments.

(4) Risk of Bias

Some of the differences between active treatments correspond to medium effect sizes ≥-0.50. However, these differences may be reduced when controlling for risk of bias. The difference between CBT and psychodynamic therapy, for example, is reduced from -0.46 to -0.23 when controlling for risk of bias (Papola et al., 2023, eAppendix N) which is below the cut-off score for an clinically meaningful effect (SMD ≥ -0.40) defined by Papola et al. (2023, supplement, p. 54) themselves.

(5) Is the CBT effect size clinically meaningful ?

T5he 95% CI of the effect size of CBT vs TAU (SMD=-0.64) is wide (95% CI -1.05 to -0.32), with the lower bond being below -0.40, defined by Papola et al. (2023, supplement, p. 54) as a clinically meaningful effect. Thus, further studies are needed to confirm that the effect of CB5T is clinically meaningful, truly lying above -0.40.

(6) Rates for remission and response

For anxiety disorders the remission rates of CBT show that less than half of the patients were free of clinically relevant symptoms post-therapy (47.9%, Springer et al., 2018). As a limitation, Papola et al. (2023) did not assess the clinical significance of the CBT effects in GAD in terms of remission or response.

(7) Certainty of evidence

Certainty of evidence was only moderate due to within-study risk of bias and heterogeneity (Papola et al., 2023).

(8) Heterogeneity of TAU

A recent meta-analysis reported that the intensity of TAU control conditions varied markedly in psychotherapy trials, and that TAU intensity is related to outcome in RCTs of depression (Munder et al., 2022). It cannot be ruled out that this applies to the TAU conditions of (Papola et al., 2023), too. In any case, the confidence interval of the SMD (-0.37) for the comparison of TAU with waiting list is wide (-0.78 to 0.04), suggesting considerable variance in estimates. Differences in the quality of TAU (Munder et al., 2022) are not detectable by the tests for transitivity applied by Papola et al. (2023) who tested for differences in age, sex, baseline symptomatology and number of therapy sessions. Yet, there may also have been important differences between conditions in terms of whether TAU was an evidence-based treatment or in accordance with treatment guidelines, or whether treatments were provided by mental health professionals with access to training or supervision (Munder et al., 2022).

Conclusions

As described above, NMA results and the derived inferences require extra caution (Mills et al., 2013). In particular, NMA can only provide evidence of an observational nature. The recommendation by Papola et al. to recommend CBT over other psychotherapies without clearly showing that CBT is superior to other evidence-based treatments in GAD is questionable. Furthermore, taking the limited response and remission rates of CBT into account, it seems indicated to continue to offer patients a variety of evidence-based treatments. This does not only apply to anxiety disorders, but to other mental disorders such as depression as well (Cuijpers et al., 2021). More generally, evidence suggests that it is at this point questionable to assume that one form of psychotherapy can be considered to be the "gold standard" treatment for any mental disorder or for all patients (Leichsenring et al., 2018; Leichsenring & Steinert, 2017). The evidence for such an assumption is simply lacking.

Furthermore, attempts to unify the different psychotherapeutic approaches such as CBT, psychodynamic therapy, systemic therapy or interpersonal therapy under the umbrella of a one-fits-all-therapy as suggested by some authors (Hayes et al., 2022; Herpertz & Herpertz, 2013), risks to ignore important differences between the basic assumptions and approaches of these different types of psychotherapy as well as individual differences between patients and therapists (Leichsenring et al., 2019). The implied (atheoretical) tool box model of techniques and change processes is not applicable to a complex human treatment such as psychotherapy (Leichsenring et al., 2019). Therapists and patients need a firm conceptual orientation, not only a tool box out of which therapists can choose. In addition, the tool box model of psychotherapy currently lacks any evidence for efficacy (Leichsenring et al., 2019).

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