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Pharmacological and psychological interventions for generalized anxiety disorder in adults: A network meta-analysis

Ting-Ren Chen[a,b,c], Hui-Chuan Huang[d], Jer-Hwa Hsu[e], Wen-Chen Ouyang[f,g], Kuan-Chia Lin[a,h,*]

[a] Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan
[b] Department of Psychiatry, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan
[c] Department of Psychiatry, School of Medicine, Tzu Chi University, Hualien, Taiwan
[d] School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan
[e] Chia-Yi Hospital, Ministry of Health and Welfare, Chiayi, Taiwan
[f] Department of Geriatric Psychiatry, Jianan Psychiatric Center, Ministry of Health and Welfare, Tainan, Taiwan
[g] Department of Psychiatry, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[h] Community Medicine Research Center, Preventive Medicine Research Center, National Yang-Ming University, Taipei, Taiwan

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ABSTRACT

Generalized anxiety disorder (GAD) is a significant and common mental illness with a lifetime prevalence of 3.7%. Regardless of the complexity of treatment decisions for GAD, few studies have conducted systematic comparisons of the efficacies of varying interventions. Thus, this study performed a valid network meta-analysis (NMA) of randomized controlled trials (RCTs) to synthesize direct and indirect evidence for alternative interventions for GAD. We searched four major bibliographic databases, the Cochrane Central Register of Controlled Trials, Embase, PsycINFO, and PubMed, for published RCTs of adult patients with a diagnosis of GAD and allowed for all comorbidities. A total of 91 articles (14,812 participants) were identified in the final NMA. The results showed that all pharmacological treatments except for serotonin modulators and second-generation antipsychotics had greater effects than placebo: norepinephrine–dopamine reuptake inhibitors (standardized mean difference (SMD) −1.84, 95% credible interval −3.05 to −0.62), noradrenergic and specific serotonergic antidepressants (−0.91, −1.62 to −0.20), melatonergic receptor agonists (−0.68, −1.15 to −0.21), selective serotonin reuptake inhibitors (SSRIs; −0.67, −0.90 to −0.43), azapirones (−0.58, −1.00 to −0.17), anticonvulsants (−0.56, −0.85 to −0.28), serotonin–norepinephrine reuptake inhibitors (SNRIs; −0.54, −0.79 to −0.30), and benzodiazepines (BZDs; −0.40, −0.65 to −0.15). Most psychological and self-help interventions exerted greater effects than the waitlist group. However, no psychological interventions had greater effects compared with the psychological placebo. Overall, most pharmacological interventions had larger effect sizes than psychological interventions, and most psychological interventions showed larger effect sizes than self-help interventions.

1. Introduction

Generalized anxiety disorder (GAD) constitutes one of the most common groups of mental illnesses in adults. Global cross-sectional general population surveys were conducted in 26 countries; people with GAD, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (American Psychiatric Association, 2013), had a lifetime prevalence of 3.7%; GAD was higher and more debilitating in high-income countries (Ruscio et al., 2017), which is consistent with previous reports (Kessler and Wang, 2008; Lieb et al., 2005; Yu et al., 2018). The core features of GAD are excessive and persistent worrying. Its associated symptoms include irritability, restlessness, fatigue, problems with sleep, difficulty concentrating, and somatic symptoms such as muscle tension (American Psychiatric Association, 2013). Patients with GAD usually worry about social, occupational, and other crucial concepts of daily life, and such behavior is associated with substantial impairments and a considerable effect on quality of life caused by both physical and emotional problems (Antunes et al., 2018; Hendriks et al., 2016; Hoffman et al., 2008; Lieb et al., 2005; Revicki et al., 2012; Yu et al., 2018). In addition to missed work days for individuals, high

* Corresponding author. Institute of Hospital and Health Care Administration, National Yang-Ming University, Community Medicine Research Center, Preventive Medicine Research Center, National Yang-Ming University, No.155, Sec.2, Linong Street, Taipei, 112, Taiwan.
E-mail address: kuanchia@ym.edu.tw (K.-C. Lin).

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health care resource utilization of patients with GAD in terms of the use of family doctors and medical specialists also leads to elevated social costs (Hoffman et al., 2008; Lieb et al., 2005; Revicki et al., 2012). Finally, GAD has also been demonstrated to be a strong risk factor for suicide, because the suicide rate is higher in patients with GAD compared with those without anxiety (Chartrand et al., 2012; Kanwar et al., 2013).

Many treatments have proven effective for GAD in comparison with placebo, such as pharmacological interventions including benzodiazepines (BZDs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), second-generation antipsychotics (SGAs), buspirone, and pregabalin; psychological interventions including cognitive behavioral therapy (CBT) and psychodynamic therapy; and self-help interventions (Baldwin et al., 2014; Reinhold and Rickels, 2015). However, apart from first-line pharmacotherapies for GAD, generally including SSRIs, SNRIs, and CBT, which are widely applied as a psychotherapy for GAD, there is no consensus on the roles of a number of other drugs or psychotherapies (Baldwin et al., 2014; National Institute for Health and Care Excellence, 2014; Reinhold and Rickels, 2015; Stein and Sareen, 2015). To the best of our knowledge, no comprehensive systematic comparison and analysis of the efficacies of various pharmacological interventions for GAD is available in the literature. Previous reviews have only evaluated the efficacy of individual drugs in comparison with placebo, and thus are unable to be compared with each other (Baldwin et al., 2014; Reinhold and Rickels, 2015; Stein and Sareen, 2015), or compared only a few medications (Baldwin et al., 2011). Furthermore, comparison of the psychological interventions was inconclusive, because the sample size was too small (Cuijpers et al., 2014). Some newly marketed antidepressants such as agomelatine, vilazodone, and vortioxetine have been demonstrated to be effective for treating GAD compared with placebo by double-blind randomized controlled trials (RCTs); however, these studies also lack comparative studies with other medications (Buoli et al., 2017; Pae et al., 2015; Zareifopoulos and Dylja, 2017). Considering the absence of a direct comparison of the therapeutic effects of all available interventions for GAD, our study employed a network meta-analysis (NMA) to compare all available treatments and provided a comprehensive review.

2. Materials and methods

2.1. Search strategy and selection criteria

We conducted a search on four major bibliographic databases, the Cochrane Central Register of Controlled Trials, Embase, PsycINFO, and PubMed, by using the term “generalized anxiety disorder” for published studies on GAD, with a filter for RCT or clinical trial and with no language restrictions. Our latest search was conducted on Sept 30, 2017. We only included reports on RCTs of adult patients with a diagnosis of GAD and allowed for all comorbidities. We excluded studies focusing on adjunctive therapies for treatment-refractory patients or patients with a history of inadequate treatment response.

The eligible interventions for GAD were oral drugs, psychological interventions, and self-help interventions. We did not include combined interventions of the drugs or therapies because our study was intended to compare the efficacy of monotherapies. We included all antidepressants—TCAs, SSRIs, SNRIs, norepinephrine–dopamine reuptake inhibitors (NDRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), agomelatine, vilazodone, and vortioxetine. The other pharmacological interventions were included mainly based on guidelines and evidence (Baldwin et al., 2011; Baldwin et al., 2014; National Institute for Health and Care Excellence, 2014; Reinhold and Rickels, 2015; Stein and Sareen, 2015), but they were not necessarily licensed for GAD. Studies conducted on drugs that are no longer marketed were excluded.

No evidence indicates which drug or psychotherapy is the most effective among those of similar types. Therefore, we assumed that drugs with similar pharmacological mechanisms or psychotherapies of similar models have similar efficacies, and we thus grouped the current available interventions into several classes and compared them. If the intervention in one trial was grouped in the same class as another, it was not included in the analysis.

Two review authors (JHH and TRC) independently assessed the inclusion and exclusion criteria. When the reviewers had disagreements, they provided their justifications and reached a consensus eventually.

2.2. Data extraction

Structured Excel spreadsheets were used to extract data from published studies. We extracted general details of the studies (including country, length of follow-up, age range, sex, and study interventions), details of outcome assessment (such as number of patients randomized, dropouts, patients at the end of study and baseline, end of treatment, change from baseline rating scores with standard deviations). Methodological appraisal of each eligible study followed the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Outcome measured using validated instruments including Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), Generalized Anxiety Disorder 7 (GAD-7) (Spitzer et al., 2006), Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990). Although the HAM-A was used in all pharmacological trials, psychological trials and self-help trials did not adopt this. Thus, we calculated treatment effects for each study as a standardized mean difference (SMD). Data extraction was conducted independently by two reviewers (JHH and TRC) and validated by one reviewer (TRC).

2.3. Statistical analysis

Statistical analysis was conducted using STATA version 15.0 (StataCorp, College Station, TX, USA). The integrated analyses were conducted in a frequentist framework (Rucker and Schwarzer, 2015), and the Bayesian framework was applied to calculate ranks and surfaces under the cumulative ranking curve (SUCRAs) for calculating cumulative ranking for identifying superiority among interventions (Dias et al., 2013). An intervention resulting in a larger SUCRA was considered to be the more effective treatment. We used treatment effects to estimate changes in continuous measures for each intervention with 95% credible interval (CrI). The treatment effect of each intervention was compared with that of placebo, which was selected as the reference treatment. In term of examining the assumption of inconsistency, three methods were conducted to examine inconsistency of these included studies including node-splitting method, design inconsistency, and loop inconsistency (Higgins et al., 2012). Insignificant results ($p > 0.05$) indicated direct and indirect comparisons were consistent, showing no significant heterogeneity among these treatment comparisons. Random-effects network meta-analysis was then conducted to estimate the comparative effectiveness among various interventions.

Publication bias was examined using funnel plot and Egger's test. An Asymmetry funnel plot and Egger's test with statistical significance ($p < 0.05$) indicated detection of a publication bias (Sedgwick and Marston, 2015).

3. Results

We identified 2951 articles from a systematic search between 1981 and 2017 (Fig. 1) and assessed 269 full-text articles for eligibility. We excluded 175 articles and included 94 articles in the qualitative review. From the 94 articles eligible for inclusion in the network meta-analysis, we excluded 3 articles: two articles of TCAs were not suitable for being grouped into the same class, respectively, imipramine (Rocca et al., 1997) and opipramol (Möller et al., 2001), and one was not connected

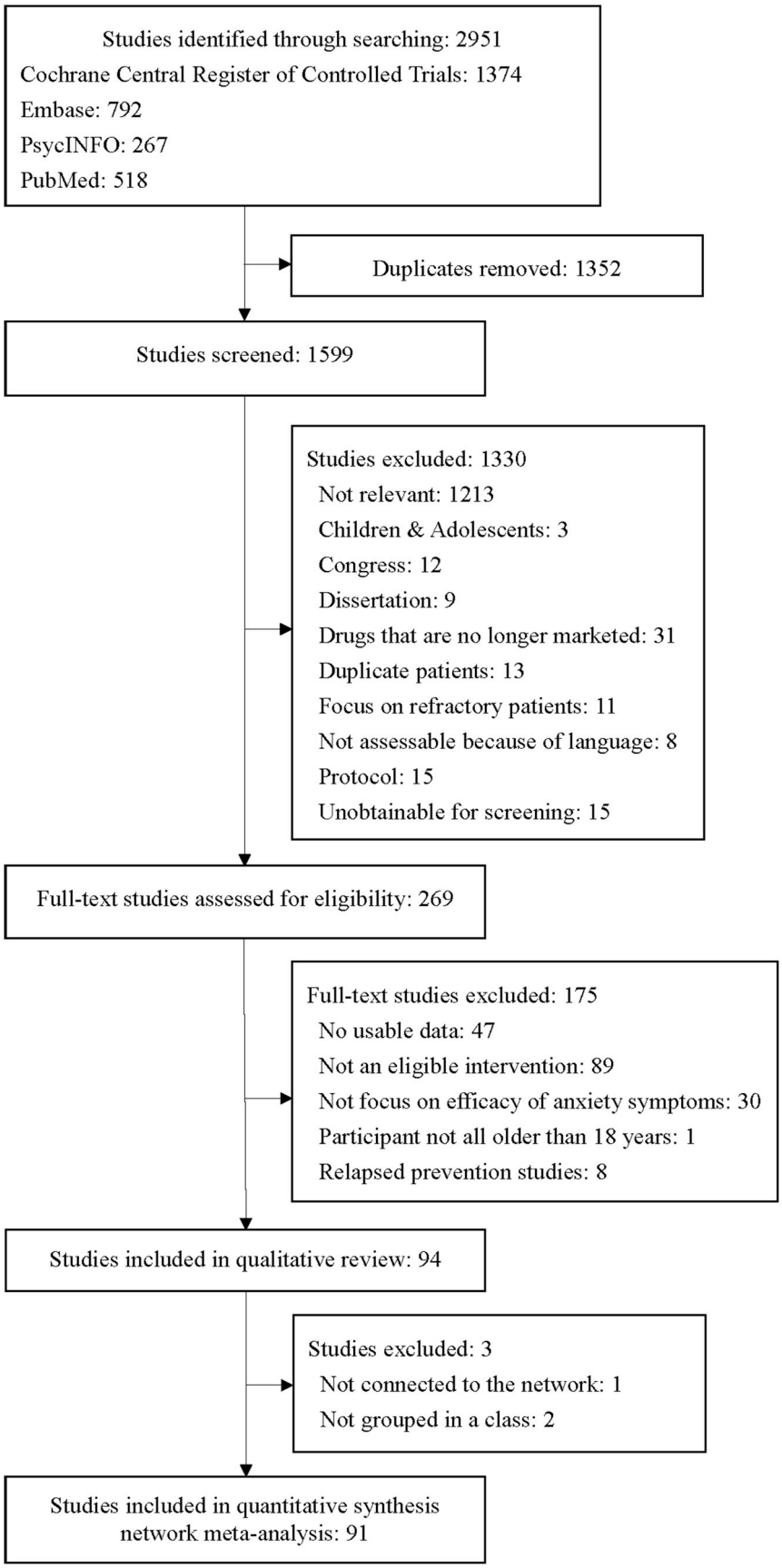

Fig. 1. PRISMA flowchart. PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

to the network (Supplementary References 1–178). Despite structural similarity to imipramine, opipramol does not act as a TCA for it does not impede the neuronal uptake of noradrenaline or serotonin (Holoubek and Müller, 2003; Möller et al., 2001). Nevertheless, considering the difference in the effects of these two drugs, it is not suitable for being grouped into the same class and added to the NMA. Therefore, we made a detailed supplementary explanation for the TCAs in the discussion section. A detailed list of the excluded studies is in the supplement (Supplementary Table 1). After selection, 91 articles (Alaka et al., 2014; Aliyev and Aliyev, 2008; Allgulander et al., 2004; Andersson et al., 2012; Avdagic et al., 2014; Baldwin et al., 2006; Bidzan et al., 2012; Borkovec and Costello, 1993; Brawman-Mintzer et al., 2006; Brenes et al., 2015; Brown et al., 2015; Butler et al., 1991; Bystritsky et al., 2008; Casacchia et al., 1990; Chen, 2006; Christensen et al., 2014; Conrad et al., 2008; Dahlin et al., 2016; Davidson et al., 2004; Davidson et al., 1999; Dimitriou et al., 1992; Dugas et al., 2003; Dugas et al., 2010; Durgam et al., 2016; Durham et al., 1994; Feltner et al., 2003; Gao et al., 2017; Gommoll et al., 2015a; Gommoll et al., 2015b; Hartford et al., 2007; Hayes-Skelton et al., 2013; Heiden et al., 2012; Hoge et al., 2013; Hoyer et al., 2009; Huang et al., 2006; Ji et al., 2004; Jiang et al., 2010; Kasper et al., 2009; Kasper et al., 2014; Ladouceur et al., 2000; Leichsenring et al., 2009; Lenze et al., 2009; Li et al., 2016; Li et al., 2005a; Li et al., 2005b; Li and Zeng, 2004; Linden et al., 2005; Liu et al., 2005; Mahableshwarkar et al., 2014a; Mahableshwarkar et al., 2014b; Mokhber et al., 2010; Montgomery et al., 2008; Montgomery et al., 2006; Nicolini et al., 2009; Nimatoudis et al., 2004; Niu et al., 2004; Ost and Breitholtz, 2000; Paxling et al., 2011; Peng et al., 2006; Pohl et al., 2005; Ramchandran et al., 1990; Richards et al., 2016; Rickels et al., 2005; Rickels et al., 2003; Robinson et al., 2010; Roemer et al., 2008; Rosenthal, 2003; Ross and Matas, 1987; Rothschild et al., 2012; Shen and Zhong, 1999; Shi et al., 2004; Stanley et al., 1996; Stanley et al., 2003a; Stanley et al., 2003b; Stanley et al., 2009; Stein et al., 2017; Stein et al., 2014; Stein et al., 2008; Titov et al., 2009; Wang et al., 2004; Wang and Ren, 2003; Weizhen et al., 2004; Wells et al., 2010; Wetherell et al., 2011; Wetherell et al., 2003; Wu et al., 2011; Yin and Xie, 2005; Zargar et al., 2012; Zeng et al., 2003; Zinbarg et al., 2007; Zullino et al., 2015) were included in the NMA (Table 1), comprising 57 RCTs for pharmacological interventions, 26 psychotherapeutic interventions, 6 self-help interventions, and 2 studies comparing pharmacological versus psychotherapeutic interventions and pharmacological versus self-help interventions. In all 91 RCTs, GAD diagnosis was confirmed through a diagnostic interview. In total, 15,596 participants were randomly assigned in the trials, and 14,812 were included in the analysis; 63.5% of the participants specified in the articles were female (9527/14997). The median of mean age was 40.13 years. The median and mean duration of treatment were 8 and 9.6 weeks (range, 4–44.8 weeks), respectively. A large number of the trials with drug groups (36 of 59 trials) were sponsored by pharmaceutical companies. There were 20 studies with the inclusion of participants receiving pharmacological treatments with a stable dose of drug among 26 psychological studies; but the prescription of medications did not describe clearly among the 20 studies. Excluding medication treatment may be impossible in studies of psychological interventions in the patients with GAD. Besides, performing a sensitivity analysis that exclude these psychological studies with medication treatment was difficult to demonstrate identical network diagram and reexamine the therapeutic effects of all available interventions for GAD.

In total, the trials assessed 57 interventions or control conditions, which were grouped into 21 classes (Supplementary Table 2). Of the 210 unique pairwise comparisons between the 21 interventions, 47 (22.38%) were studied head to head in the included studies (Fig. 2). Most psychological and self-help interventions were compared with waitlist. However, in addition to comparison with placebo, many drugs were compared with SSRIs or SNRIs.

To assess inconsistency, we conducted three tests; the side-splitting approach showed that *P* values for all 47 direct comparisons were > 0.05. Although some minor design and loop inconsistencies were observed, the overall *P* values were 0.96 and 0.40, respectively (both > 0.05), and thus were not statistically significant. Overall, we identified no evidence of inconsistency.

Table 1
General characteristics of eligible studies included in the NMA.

	Trials in analysis (n = 91)
Patients randomized	15596
Age (years)	40.13[a]
Female	9527[b]
Male	5470[b]
Patients included in the analysis	14812
Duration (weeks)	9.6
Type of intervention	
Pharmacotherapy only	57
Psychotherapy only	26
Self-help only	6
Mixed	2
Measures	
HAM-A	71
GAD-7	6
PSWQ	14
Number of arms	
Two	61
Three	20
Four	6
Five	4
Year of publication	
1987–1990	3
1991–2000	9
2001–2010	51
2011–2017	28
Continent	
North America	38
Asia	21
Europe	18
Oceania	4
Multiple	10
Pharmaceutical industry sponsorship	
Yes	36
No	6
Unclear	17

[a] Median of mean.
[b] Some articles did not specify the gender of patients recruited in their studies, so the number of male and female do not add up to the total number.

All pharmacological interventions had greater effects on outcomes compared with placebo (Figs. 3 and 4), except serotonin modulators (SMDs −0.23, 95% CrI −0.53 to 0.06) and SGAs (−0.06, −0.63 to 0.51). When compared with placebo, the drugs with largest effects were NDRIs (−1.84, −3.05 to −0.62) and NaSSAs (−0.91, −1.62 to −0.20); however, the effects of both were assessed in small sample sizes. The next largest effects were found for melatonergic receptor agonists (−0.68, −1.15 to −0.21) and SSRIs (−0.67, −0.90 to −0.43), followed by azapirones (−0.58, −1.00 to −0.17), anticonvulsants (−0.56, −0.85 to −0.28), and SNRIs (−0.54, −0.79 to −0.30), which had similar effect sizes; the least effective were BZDs (−0.40, −0.65 to −0.15).

In our NMA, analysis-based psychotherapy was the only psychotherapy that did not have a greater effect than waitlist (−0.39, −0.99 to 0.20). All the remaining psychological interventions and self-help interventions had greater effects on outcomes compared with waitlist (Figs. 3 and 4). Compared with waitlist, the intervention with largest effects was mindfulness-based psychotherapy (−1.16, −1.66 to −0.67), followed by individual CBT (−1.11, −1.43 to −0.80), other psychological intervention (−1.11, −1.57 to −0.66), applied relaxation (−0.98, −1.39 to −0.57), group CBT (−0.82, −1.30 to −0.34), and self-help with support (−0.81, −1.18 to −0.44). However, compared with psychological placebo, no psychological interventions had greater effects. In fact, psychological placebo itself had a greater effect

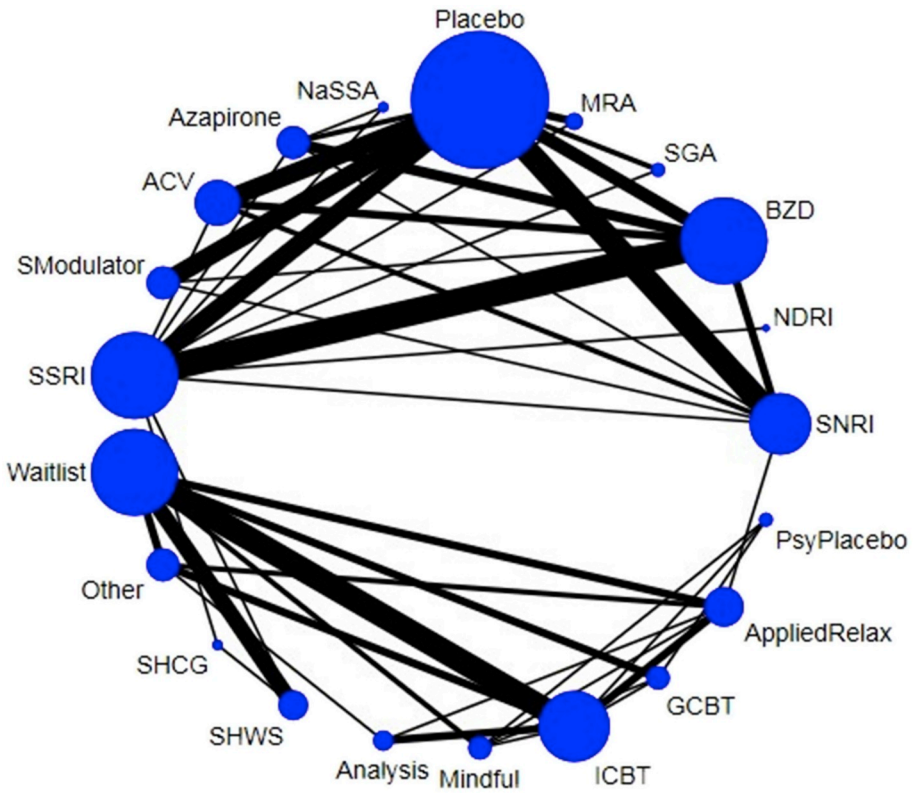

Fig. 2. Network diagram for efficacy analysis representing direct comparisons among classes. The size of each circle is proportional to the number of randomly allocated participants who received each treatment. The width of each line is proportional to the number of trials in which each direct comparison is made. ACV = anticonvulsant, BZD = benzodiazepine, MRA = melatonergic receptor agonist, NDRI = norepinephrine–dopamine reuptake inhibitor, NaSSA = noradrenergic and specific serotonergic antidepressant, SGA = second generation antipsychotic, SModulator = serotonin modulator, SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, Analysis = analysis-based psychotherapy, AppliedRelax = applied relaxation, GCBT = group cognitive behavioral therapy, ICBT = individual cognitive behavioral therapy, Mindful = mindfulness-based psychotherapy, Other = other psychological intervention, PsyPlacebo = psychological placebo, SHWS = self-help with support, SHCG = self-help control group.

than waitlist (−1.02, −1.64 to −0.39), similarly to applied relaxation. By contrast, only one study used the self-help control group, a control website with the content of which was not related to anxiety reduction, did not have a greater effect (0.56, −0.79 to 1.90) than waitlist.

Overall, compared with placebo, most pharmacological interventions had larger effect sizes than psychological interventions; most psychological interventions showed larger effect sizes than self-help intervention (Fig. 3, Table 2, and Supplementary Fig. 1).

We assessed all included trials for risk of bias (Supplementary Table 3), results showed that 30 studies fulfilled the criteria of random sequence generation, but only 11 studies clearly reported how they had achieved allocation concealment. Additionally, 41 studies achieved a low risk of blinding participants or personnel and 22 studies included a blinded assessor who performed the outcome assessment. Thirty six studies clearly addressed how they managed incomplete outcome data. Only 3 studies had no reporting bias because the protocols had previously been published. To examine publication biases, we constructed a funnel plot and conducted Egger's test (Supplementary Fig. 2). The funnel plot was largely symmetrical, and the *P* value of Egger's test was 0.075 (> 0.05), indicating no publication bias in our NMA.

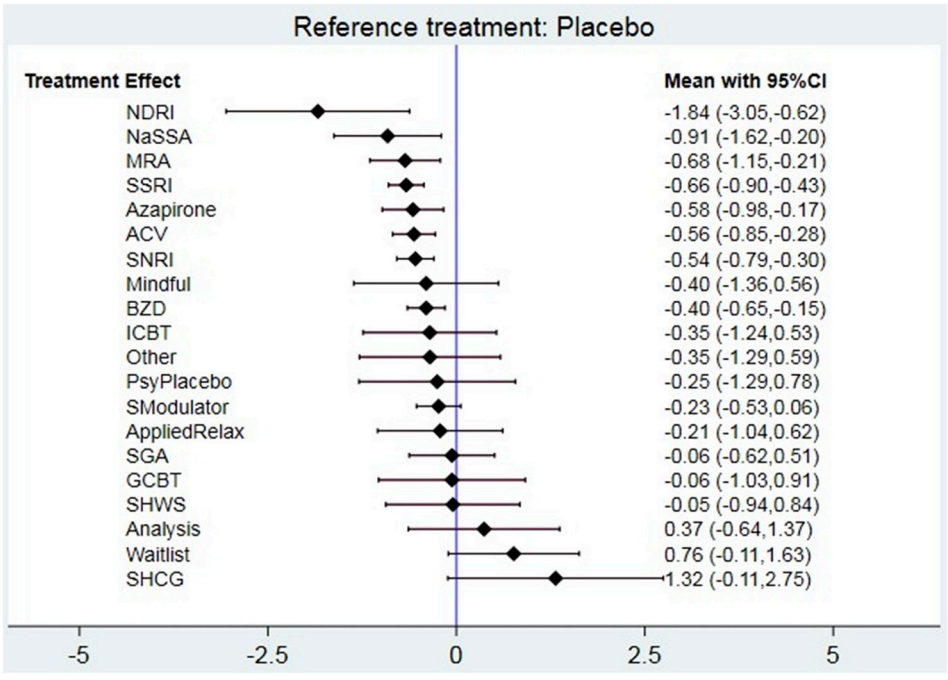

Fig. 3. Interval plot of treatment effects of classes of interventions compared with placebo. Data are SMDs and 95% credible intervals compared with placebo as a reference. ACV = anticonvulsant, BZD = benzodiazepine, MRA = melatonergic receptor agonist, NDRI = norepinephrine–dopamine reuptake inhibitor, NaSSA = noradrenergic and specific serotonergic antidepressant, SGA = second generation antipsychotic, SModulator = serotonin modulator, SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, Analysis = analysis-based psychotherapy, AppliedRelax = applied relaxation, GCBT = group cognitive behavioral therapy, ICBT = individual cognitive behavioral therapy, Mindful = mindfulness-based psychotherapy, Other = other psychological intervention, PsyPlacebo = psychological placebo, SHWS = self-help with support, SHCG = self-help control group.

NDRI	-0.93 (-2.31 to 0.46)	-1.16 (-2.45 to 0.14)	-1.17 (-2.37 to 0.02)	-1.26 (-2.52 to 0.001)	-1.28 (-2.51 to-0.04)	-1.29 (-2.53 to -0.06)	-1.44 (-2.65 to -0.22)	-1.60 (-2.85 to -0.35)	-1.78 (-3.11 to -0.45)	-1.84 (-3.05 to -0.62)
Mindfulness-based	NaSSA	-0.23 (-1.08 to 0.61)	-0.25 (-0.94 to 0.45)	-0.34 (-1.03 to 0.36)	-0.35 (-1.10 to 0.40)	-0.37 (-1.10 to 0.37)	-0.51 (-1.22 to 0.20)	-0.68 (-1.44 to 0.09)	-0.85 (-1.75 to 0.04)	-0.91 (-1.62 to -0.20)
-0.05 (-0.56 to 0.47)	Individual CBT	MRA	-0.02 (-0.52 to 0.49)	-0.10 (-0.71 to 0.51)	-0.12 (-0.66 to 0.42)	-0.14 (-0.66 to 0.39)	-0.28 (-0.80 to 0.24)	-0.45 (-0.10 to 0.11)	-0.62 (-1.35 to 0.11)	-0.68 (-1.15 to -0.21)
-0.05 (-0.68 to 0.58)	-0.002 (-0.45 to 0.44)	Other Psychological	SSRI	-0.09 (-0.50 to 0.32)	-0.10 (-0.43 to 0.23)	-0.12 (-0.43 to 0.18)	-0.27 (-0.51 to -0.03)	-0.43 (-0.80 to -0.07)	-0.61 (-1.18 to -0.03)	-0.67 (-0.90 to -0.43)
-0.15 (-0.77 to 0.48)	-0.10 (-0.70 to 0.51)	-0.10 (-0.82 to 0.63)	Psychological Placebo	Azapirone	-0.01 (-0.48 to 0.45)	-0.03 (-0.47 to 0.40)	-0.18 (-0.57 to 0.22)	-0.34 (-0.83 to 0.15)	-0.52 (-1.20 to 0.16)	-0.58 (-1.0 to -0.17)
-0.19 (-0.74 to 0.36)	-0.14 (-0.55 to 0.27)	-0.14 (-0.64 to 0.37)	-0.04 (-0.72 to 0.64)	Applied Relaxation	Anticonvulsant	-0.02 (-0.36 to 0.32)	-0.16 (-0.48 to 0.16)	-0.33 (-0.73 to 0.07)	-0.50 (-1.13 to 0.12)	-0.56 (-0.85 to -0.28)
-0.34 (-0.92 to 0.24)	-0.29 (-0.81 to 0.23)	-0.29 (-0.92 to 0.34)	-0.20 (-0.85 to 0.46)	-0.16 (-0.75 to 0.43)	Group CBT	SNRI	-0.14 (-0.44 to 0.16)	-0.31 (-0.67 to 0.06)	-0.49 (-1.10 to 1.13)	-0.54 (-0.79 to -0.30)
-0.35 (-0.97 to 0.26)	-0.31 (-0.79 to 0.18)	-0.30 (-0.89 to 0.28)	-0.21 (-0.93 to 0.51)	-0.17 (-0.71 to 0.37)	-0.01 (-0.61 to 0.59)	Self-Help With Support	BZD	-0.17 (-0.53 to 0.20)	-0.34 (-0.94 to 0.26)	-0.40 (-0.65 to -0.15)
-0.77 (-1.49 to -0.05)	-0.72 (-1.25 to -0.19)	-0.72 (-1.35 to 0.09)	-0.62 (-1.42 to 0.17)	-0.58 (-1.20 to 0.04)	-0.43 (-1.15 to 0.30)	-0.41 (-1.11 to 0.28)	Analysis-based	Serotonin Modulator	-0.18 (-0.81 to 0.46)	-0.23 (-0.53 to 0.06)
-1.16 (-1.66 to -0.67)	-1.11 (-1.43 to -0.80)	-1.11 (-1.57 to -0.66)	-1.02 (-1.64 to -0.39)	-0.98 (-1.39 to -0.57)	-0.82 (-1.30 to -0.34)	-0.81 (-1.18 to -0.44)	-0.39 (-0.99 to 0.20)	Waitlist	SGA	-0.06 (-0.63 to 0.51)
-1.72 (-3.14 to -0.29)	-1.67 (-3.04 to -0.30)	-1.67 (-3.08 to -0.26)	-1.57 (-3.05 to -0.10)	-1.53 (-2.91 to -0.15)	-1.38 (-2.80 to 0.05)	-1.36 (-2.68 to -0.05)	-0.95 (-2.41 to 0.51)	-0.56 (-1.90 to 0.79)	Self-Help Control Group	Placebo

Fig. 4. Effect sizes of classes of treatments in pairwise comparisons. Classes of treatments are ordered according to efficacy ranking from largest mean effect (top, left) to smallest mean effect (bottom, right). The treatment classes highlighted in light gray are belonged to the pharmacological interventions; the treatment classes highlighted in dark gray are belonged to the psychological and self-help interventions. The values are shown as SMDs (95% credible interval). BZD = benzodiazepine, MRA = melatonergic receptor agonist, NDRI = norepinephrine–dopamine reuptake inhibitor, NaSSA = noradrenergic and specific serotonergic antidepressant, SGA = second generation antipsychotic, SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, Analysis-based = analysis-based psychotherapy, CBT = cognitive behavioral therapy, Mindfulness-based = mindfulness-based psychotherapy, Other Psychological = other psychological intervention.

Table 2
Ranking probability of the pharmacological and psychological interventions for GAD. Mean ranking is ordered from the best treatment to the least treatment effect. SUCRA: Surface under the cumulative ranking curve.

Treatment	Mean Rank	SUCRA
Norepinephrine–Dopamine Reuptake Inhibitor	1.4	97.9
Noradrenergic and Specific Serotonergic Antidepressant	4	85
Selective Serotonin Reuptake Inhibitor	5.6	77
Melatonergic Receptor Agonist	5.9	75.7
Anticonvulsant	7.3	68.6
Azapirone	7.4	67.9
Serotonin–Norepinephrine Reuptake Inhibitor	7.6	67
Mindfulness-Based Psychotherapy	9	60
Individual CBT	9.6	57.1
Other Psychological Intervention	9.8	56
Benzodiazepine	10.3	53.7
Psychological Placebo	11.3	48.7
Applied Relaxation	12.1	44.3
Serotonin Modulator	12.7	41.7
Group CBT	14	34.8
Second Generation Antipsychotic	14.5	32.6
Self-Help With Support	14.5	32.3
Placebo	15.7	26.3
Analysis-Based Psychotherapy	17.9	15.5
Waitlist	20	5
Self-Help Control Group	20.4	2.8

4. Discussion

In this NMA, we included 91 RCTs and 14,812 participants. The female-to-male ratio was 1.74, which is similar to a female-to-male ratio of 1.8–2 reported in previous epidemiology studies (Lieb et al., 2005; Ruscio et al., 2017). A higher proportion of studies from Asia were included in our study (21/91) because of the language familiarity of the authors. In this analysis, we found that most pharmacological and psychological interventions were indeed more efficacious than placebo and control conditions. However, the efficacies were inconsistent, which was in line with our assumption. We discuss different interventions in the following section.

4.1. Pharmacological interventions

4.1.1. NDRIs and NaSSAs

The NDRI and NaSSA classes each consist of one drug, bupropion and mirtazapine, respectively. Although they had the greatest effects in this NMA, there were only one and two reports on these two drugs with only 11 and 69 participants involved, respectively. Therefore, the results should be treated with caution, and conclusions should be drawn carefully. Despite the wide use of both bupropion and mirtazapine as antidepressants, studies on their efficacy in treating GAD and other anxiety disorders are lacking (Mayo-Wilson et al., 2014; Skapinakis et al., 2016).

4.1.2. SSRIs and SNRIs

SSRIs and SNRIs are currently widely used as first-line treatments for GAD. Studies on these drugs recruited 2142 and 1666 patients, respectively, and their efficacies were significant, as expected. In particular, the efficacy of SSRI only ranked next to NRDIs and NaSSAs. Compared with studies on NRDI and NaSSA, those on SSRIs and SNRIs comprised more patients and compared more treatments, thus providing a stronger evidence. No evidence of which SSRIs or SNRIs were particularly efficacious was found in the literature. SSRIs and SNRIs

were generally well tolerated. However, bleeding risk under SSRIs, which is relatively serious and has recently attracted scholars' attention, may also occur (Laporte et al., 2017; Roose and Rutherford, 2016). Besides, venlafaxine may lead to elevated blood pressure and we should pay attention to this issue at higher dosage especially (Feighner, 1995; Thase, 1998).

4.1.3. Melatonergic receptor agonists

Agomelatine, a new antidepressant, alone represents the class of melatonergic receptor agonists. It exhibited a greater effect than placebo in treatment, and its effect was similar to that of SSRIs. A total of 470 participants were involved in the RCTs of these drugs, which were three studies by the same author. In one study, a 25-mg agomelatine dose had a greater effect than a 10-mg dose, and both doses outperformed placebo. Although it was well tolerated, the higher rate of liver injury was worthy of noting clinically. (Freiesleben and Furczyk, 2015; Stein et al., 2017).

4.1.4. Anticonvulsants

The anticonvulsant class includes pregabalin, tiagabine, and valproate, among which pregabalin was the most common and constituted 1510 of 1566 participants in this class. Pregabalin is the recommended drug according to the guideline if a person does not tolerate SSRIs or SNRIs (National Institute for Health and Care Excellence, 2014). Its advantages include early onset of anxiolytic efficacy equivalent to high-potency benzodiazepines and minimal adverse effects, such as somnolence, dizziness, dry mouth, and weight gain. This class had a greater effect size on outcomes compared with placebo, similar to SNRIs. A pregabalin dosage of 300 mg/d was most effective among dosages of 300, 450, and 600 mg/d tested by a fixed-dose study in which the efficacy did not improve with increasing doses; it was well tolerated across a dosage range of 300–600 mg/d (Rickels et al., 2005).

4.1.5. Azapirones

Apart from the well-known drug, buspirone, this class includes another drug, tandospirone, which has been applied in China and Japan. However, only one study on tandospirone (Li et al., 2004) was available in our search result; however, because this drug was comparable to buspirone in the same class, the study was excluded from the analysis. All seven RCTs of azapirones included in this analysis studied buspirone with 221 participants. Buspirone is a non-BZD anxiolytic drug and a partial serotonin 5-HT1A receptor agonist. Although the onset of action for buspirone was slower, approximately 1–2 weeks, the treatment effect of buspirone was greater compared with placebo and similar to that of pregabalin and SNRIs. Furthermore, in comparison with BZDs, buspirone had fewer adverse effects, such as sedation or influence on psychomotor performance or cognition. Additionally, its potential for abuse and dependence tended to be minimal (Fulton and Brogden, 1997).

4.1.6. BZDs

This class has been one of the earliest applied for the treatment of GAD, and its benefit is the early onset of action. However, considering that long-term use of BZDs may cause dependence, the current guideline does not recommend it as a first-line treatment but as a short-term adjuvant treatment before SSRIs and SNRIs take effects (Baldwin et al., 2014; National Institute for Health and Care Excellence, 2014). Even if the potential risk of dependence is not considered, its effect size was smaller than that of other active medications, as shown in our NMA.

4.1.7. Serotonin modulators

This class includes three drugs, trazodone (30 participants) and two new antidepressants, vilazodone and vortioxetine (844 and 927 patients, respectively). Although previous review papers have commented that vilazodone and vortioxetine were effective in the treatment of GAD, their efficacies were not shown to be greater than placebo in our NMA.

4.1.8. SGAs

Although many studies have investigated the treatment effects of SGAs for GAD, most studies used SGAs as the adjunctive therapy for refractory patients with GAD and were thus excluded. Only three monotherapy SGA studies that tested quetiapine were included in this analysis. However, the treatment effects were not superior to that of placebo. Additionally, considering the side effects such as metabolic syndrome (Allison et al., 1999; Correll et al., 2011) SGA monotherapy is not recommended until sufficient evidence demonstrates its efficacy.

4.1.9. TCAs

A total of 2 RCTs are in line with our study inclusion criteria, respectively, imipramine (Rocca et al., 1997) and opipramol (Möller et al., 2001). In the study about imipramine, imipramine was effective for the treatment of GAD and the effect for imipramine was similar to paroxetine. This supports imipramine played one important role in the treatment of GAD in a previous study, whose results provided evidence that imipramine have efficacy in the treatment of GAD, somewhat better than trazodone and diazepam (Rickels et al., 1993). Opipramol is an atypical TCA, it links with high affinity towards sigma1 and slightly lower affinity towards sigma2 sites. The results indicated opipramol has superior efficacy over placebo in GAD and similar effects as alprazolam in the study about opipramol (Möller et al., 2001). However, we should note the side effects of TCAs which was associated with elevated risk of cardiovascular disease (Hamer et al., 2011; Taylor, 2008).

4.2. Psychological and self-help interventions

Although pharmacological and psychological treatments were reported to have broadly similar efficacies in acute treatment of GAD (Bandelow et al., 2007), our result did not evidence this. This may be because few studies in our NMA directly compared pharmacological and psychological treatments, and the results of those may have been biased. Furthermore, most studies applied waitlists instead of psychological placebos, which were defined as control conditions that was regarded as inactive by the researchers but was to be perceived as active by the participants, as controls to evaluate the therapeutic effects of psychotherapies; this may have overestimated efficacies because waitlists may be a nocebo (Baldwin et al., 2014; Cuijpers et al., 2016; Furukawa et al., 2014). Our result was consistent with this; compared with waitlist, all active psychological interventions except analysis-based psychotherapy, including self-help intervention, had greater effects. In particular, mindfulness-based psychotherapy, individual CBT, and other psychological interventions had larger effect sizes than psychological placebo. However, compared with psychological placebo, no psychological interventions showed greater effects (Fig. 4). Even psychological placebo had a greater effect than waitlist. Moreover, placebo had a greater effect size than waitlist; however, the difference was not significant (-0.76, -1.63 to 0.11; Fig. 3).

Although analysis-based psychotherapy is not new, unlike CBT, it is not widely recommended for the treatment of GAD. Previous meta-analysis suggests that psychodynamic therapy, an analysis-based psychotherapy, was as effective at treating anxiety disorders as other psychotherapies tested in RCTs. However, for GAD, conclusions were inconsistent (Keefe et al., 2014). Our NMA demonstrated a similar result, but only three RCTs with 75 participants were involved in analysis-based psychotherapy.

All psychotherapies had larger effect sizes than self-help intervention, except analysis-based psychotherapy, compared with waitlist; when compared directly with self-help intervention, none showed significant differences (Fig. 4). Although the effect size of self-help intervention was not as large as that of pharmacological or psychological interventions, self-help intervention has the advantages of convenience and lack of side effects from medication. Pharmacological interventions have substantial and rapid effects. However, they also cause side effects, and the maintained therapeutic effect after patients stop taking

the provided medication was not sufficient proofed. By contrast, psychological interventions do not result in side effects, and the therapeutic effects can be maintained (Stanley et al., 1996; Ladouceur et al., 2000; Ost and Breitholtz, 2000; Dugas et al., 2003), but they are time consuming.

4.3. Combined therapy

Many experts have recommended combined treatment, even lack of insufficient evidence that combined therapy was more effective than monotherapy for the treatment of GAD (Black, 2006). Although our study focused on monotherapy, we included what we have found in our literature. That is, studies on combined therapy for patients with GAD have been scarce, with only one RCT being found. In this study, the efficacy of CBT plus venlafaxine XR was compared with that of venlafaxine XR alone; however, the treatment outcomes were not superior (Crits-Christoph et al., 2011).

4.4. Limitations

First, the NMA included only one paper each comparing pharmacotherapy versus psychological intervention and comparing pharmacotherapy versus self-help intervention, and neither compared the therapies with placebo. Therefore, there was insufficient evidence to support the superiority of overall efficacy of pharmacotherapy to that of psychological and self-help interventions. Second, the sample sizes of some treatment strategies in the included studies were too small after classification because of their uniqueness, for example, the studies on NDRIs, NaSSAs, and self-help control groups. Thus, results of studies including a small number of participants should be treated with caution. Additionally, because of the lack of similarities among some psychological interventions, some were classified as “other psychological intervention.” However, because of this lack of homogeneity, the efficacy could not represent all the treatment outcomes of this class. Finally, although all the included studies were RCTs, the quality of the studies varied. In the future, additional RCTs with a high quality are required to confirm efficacy of existing treatments or newer treatments, such as repetitive transcranial magnetic stimulation (Diefenbach et al., 2016; Dilkov et al., 2017).

5. Conclusions

All pharmacological treatments except for serotonin modulators and second-generation antipsychotics had greater effects than placebo. SSRIs, SNRIs, buspirone, pregabalin, and BZDs were more likely to be effective than others. Agomelatine is a potentially effective medication for treatment of GAD. Most psychotherapies and self-help interventions exerted greater effects than waitlist. However, no psychological interventions had greater effects compared with psychological placebo. These effects might overestimate their therapeutic effects because waitlist can be a nocebo. Although the effect size of self-help intervention was less than that of pharmacological or psychological interventions, self-help intervention presented the advantages of convenience and lack of side effects from medication. Overall, most pharmacological interventions had larger effect sizes than psychological interventions, and most psychological interventions showed larger effect sizes than self-help interventions.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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