

## HIGHLIGHTS

- We examined moderators of interventions for the prevention of anxiety.
- Fourteen moderator studies nested within 13 randomized control trials were included.
- Potential moderators related to individual and intervention characteristics were evaluated.
- There was no consistent evidence for any moderators.
- The need for future moderator quality studies was identified.

## **Moderators of psychological and psychoeducational interventions for the prevention of anxiety: A systematic review.**

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## **ABSTRACT**

The aim of this study was to assess the available evidence on potential moderators of psychological and psychoeducational interventions for the prevention of anxiety. A systematic review using PubMed, PsycINFO, Web of Science, Embase, OpenGrey, and CENTRAL was performed up to October 2019. Two independent researchers assessed the fulfillment of eligibility criteria, extracted the data and performed a quality assessment of the included studies. Outcomes were moderators of the reduction of anxious symptoms or the incidence of anxiety disorders. Fourteen studies reporting results on moderator analyses performed in 13 randomized controlled trials were included. Twenty-seven potential moderators were organized into six categories: sociodemographic, clinical characteristics, cognitive variables, life events, interpersonal functioning and intervention characteristics. The most frequently examined variables were gender, age and baseline anxiety. We found insufficient evidence for all moderator categories studied. In children and adolescents, we found some studies with significant results for the low family support variable and higher levels of anxiety symptoms at baseline, which were both associated with higher effectiveness. Limited conclusions can be drawn about for whom and under what conditions interventions work in the prevention of anxiety. A strong need to improve the methodological quality and the number of moderator studies was identified.

**KEYWORDS:** Moderator; Anxiety; Prevention; Systematic Review

## INTRODUCTION

A total of 264 million individuals worldwide suffered from anxiety disorders in 2015, which is 14.9% more than the 2005 figures (WHO, 2017). The global disease burden attributable to anxiety disorders, measured in years lived with disability (YLD), ranked eighth and thirteenth for women and men respectively, which implies a 12.4% and 13.6% relative increase in YLD between 2007 and 2017 for women and men, respectively (GBD, 2018). Evidence shows that anxiety increases mortality by 43% (relative increase), regardless of whether patients suffer from any other concomitant diseases (Walker et al., 2015). The suicide relative risk in these patients is increased up to 117% compared to the general population (Whiteford et al., 2013).

To reduce the burden attributable to anxiety disorders, two main approaches can be described. The first consists of treating the illness once it affects the patients' health. This is known to be effective (Acarturk et al., 2009; Cuijpers et al., 2014), although not every patient has access to early and adequate treatments (Fernández et al., 2007). The second strategy, prevention, has emerged as a complementary strategy to treatment. Different types of prevention have been identified according to their target population. Universal prevention addresses the entire population; selective prevention focuses on high-risk groups; and indicated prevention is directed to people with prodromal symptoms that do yet not fulfil the criteria for a full blown disorder (Mrazek and Haggerty, 1994).

Preventive intervention can be either psychological or psychoeducational. Psychological interventions aim to assist people in modifying behaviors, cognitions, emotional states or feelings that cause discomfort/distress (Campbell et al., 2013; Norcross, 1990), while psychoeducational interventions provide informative materials about anxiety such as lectures, leaflets, emails or information websites. It is assumed that these two modalities share similar working mechanisms of action. The effectiveness of these interventions in preventing anxiety disorders has been **demonstrated** in a recent meta-analysis (Moreno-Peral et al., 2017). However, the effectiveness of preventive interventions varied across individuals, and their effect sizes ranged from small to moderate (Fisak et al., 2011; Moreno-Peral et al., 2017; Teubert and Pinguart, 2011; Werner-Seidler et al., 2017; Zalta, 2011). **Meta-analyses conducted in varied populations showed effect sizes between small and moderate (Moreno-Peral et al., 2017; Zalta, 2011). However, those performed in children and adolescents obtained lower effect sizes (Fisak et al., 2011; Teubert and Pinguart, 2011; Werner-Seidler et al., 2017). Specifically, one of these last meta-analyses found that studies targeted to samples**

with higher anxiety symptoms or at risk of anxiety disorders showed larger effect sizes; in addition, studies conducted in samples with higher percentages of girls obtained lower effect sizes (Teubert and Pinquart, 2011). In overall terms and according to the most recent data, preventive interventions reduced the incidence of anxiety disorders by 43% compared to control conditions (Moreno-Peral et al., 2017), and approximately 60% of patients did not experience significant improvements. Therefore, there is significant room for improvement in the field of psychological and psychoeducational interventions for anxiety.

Moderators identify on whom and under what circumstances a treatment (or any type of interventions, including preventive interventions) has different effects (Kraemer et al., 2002). ~~The moderator must be a baseline or prerandomization characteristic that can be shown to have an interactive effect with treatment on the outcome. An interactive effect means that the effect of treatment on individual subjects depends on their value of the moderator.~~ The moderator helps to explain individual differences in the effect of treatment. If the moderator is a characteristic of the individual (e.g., sex, age, initial severity, comorbidity), then the moderator indicates on whom the treatment may have the most clinically significant effects. Moderators can also indicate under what treatment delivery forms the intervention may have the most clinically significant effects (e.g., inpatients vs outpatients) (Kraemer et al., 2002). Identifying the most effective treatments and understanding of for whom treatments work and do not work depends on efforts to identify moderators of treatment outcome (Frazier et al., 2004; Kraemer et al., 2002). This information could guide treatment decision-making, allowing clinicians and researchers to identify the subgroups of patients who benefit the most from each intervention in given circumstances (Kraemer et al., 2002) and subsequently may allow to deliver more effective tailored preventive approaches.

The identification of moderators in psychological and psychoeducational interventions is crucial. In fact, the National Institute of Mental Health (NIMH) includes the study of these variables among its objectives. Randomized controlled trials (RCTs) are valuable in revealing moderators of therapeutic change, and it has been suggested that RCTs routinely include and report a moderating effect analysis (Kraemer et al., 2002). As the field moves towards personalized medicine, it is crucial to know the specific effects of specific kinds of interventions in patients with certain characteristics to select the best possible treatment for an individual patient (Ebert et al., 2018).

Many subgroup analyses have been conducted within RCTs to assess a wide range of potential moderators in therapeutic interventions for the treatment of anxiety. Different systematic reviews, meta-analyses and individual patient data meta-analyses (IPD) have been conducted to collect such evidence (Bennet et al., 2013; Nilsen et al., 2013; Schneider et al., 2015). In the field of prevention, although efforts have also been made to understand whom and under what circumstances preventive interventions obtain better results in the reduction of new episodes of anxiety disorders or the reduction of anxious symptoms, no systematic review has been performed to date to identify potential moderators of psychological and psychoeducational intervention effects in the prevention of anxiety.

To guide the development of evidence-based personalized interventions for the prevention of anxiety, and as a result, allow us to offer more effective interventions according to the characteristics of people or circumstances, we aimed to perform a systematic review of potential moderators of psychological and psychoeducational interventions for the prevention of anxiety in all types of populations.

## **METHODS**

The protocol of this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018118248) according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

### **Search strategies**

The electronic PubMed, PsycINFO, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), Web of Science (WOS) and OpenGrey (system for information on grey literature in Europe) databases were searched from inception to October 30<sup>th</sup>, 2019. In addition, we conducted a manual search of the reference lists of the included articles and other relevant reviews on this topic, and experts in the field were contacted to identify additional relevant articles missing from our search.

MeSH terms and words related to the terms “anxiety disorder”, “prevention”, “psychological intervention”, “psychoeducational intervention”, and “randomized controlled trial” were combined in the electronic database searches. The term “moderator” was not included in the search strategy, since this term could not be indexed or included in keywords or abstracts. The description of the search strategy for each database consulted provided in

Appendix A. The search strategy was developed for PubMed first, and it was then adapted for use in the rest of the electronic databases. No restrictions based on language, date or setting were considered.

### **Selection of the studies: Eligibility criteria**

The studies were included according to the following criteria:

#### ***Participants***

Studies that only included participants that do not fulfill the criteria for any anxiety disorder at baseline, as determined by standardized interviews (e.g., Structured Clinical Interview for DSM Disorders), validated self-reports with standard cutoff points (e.g., Beck Anxiety Inventory) or diagnosis by a mental health professional, were eligible. Studies with a subset of participants with a history of anxiety disorders were included, but studies that were focused only on subjects with a previous diagnosis of anxiety (prevention of recurrence or relapse) were excluded. **There were no other restrictions on the characteristics of the participants (such as age range, gender, education level, or any other clinical characteristic).**

#### ***Interventions***

Studies were eligible when focused on psychological and psychoeducational **preventive** interventions, since they share common mechanisms of action that induce changes in attitudes and behaviors, and in real practice, psychological and psychoeducational interventions usually overlap. Any type of format was valid (including face-to-face (individual and group) and internet-based (guided, unguided, psychoeducational websites)).

#### ***Comparisons***

The comparators allowed were “only assessments” or “no intervention”, “usual care”, “waiting list”, or “attention control” (active control or placebo). Other types of comparators were excluded.

#### ***Outcomes***

**Any moderator variables of the effectiveness of psychological or psychoeducational preventive interventions** were included. Effectiveness was defined through the reduction of symptoms or incidence of anxiety **disorders**, as assessed by validated scales or standardized structured

interviews. An interaction test was required as an analysis measure of the moderating effect (Kraemer et al., 2002). Studies that reported solely on predictors of outcome were excluded.

### ***Design***

Studies were eligible when they were based on RCTs. We selected RCTs because they are a reference standard for clinical trials since they provide more evidence on causality (Piantadosi, 2005).

### **Selection of the studies**

Once duplicate articles were removed, the titles and abstracts of the retrieved studies were independently screened against the inclusion criteria by at least two members of the review team. The full-text versions of the remaining studies were examined further by at least two reviewers for final inclusion. In cases of insufficient information, authors were contacted to clarify the eligibility of studies. Differences regarding study selection were resolved by discussion among the reviewers.

### **Data extraction**

A data extraction sheet adapted for this systematic review was used to extract relevant information from each article including the following: authors, year of publication, country, target population, study setting, type of prevention (universal, selected or indicated), baseline exclusion criteria, inclusion criteria, sample size (control and intervention groups), experimental conditions, orientation and intervention type, provider (who implemented the intervention), outcomes, follow-up time, potential moderators assessed and results of the moderation effect analyses. The data extraction was independently conducted by at least two reviewers. The two reviewers discussed any discrepancies, and, if necessary, consulted a third team member to reach a final decision. Authors were contacted for clarification, where appropriate.

Due to our inclusion criteria were quite wide and we expected to obtain high heterogeneity across studies, a meta-analytical approach was not feasible and we performed a narrative review of the studies instead.

### **Methodological quality**

The methodological quality of the studies was evaluated by two reviewers (SCC and PMP); the evaluation was based on the quality of both the RCTs and the moderation analyses to obtain a combined quality score. The differences between the two reviewers were resolved by discussion until a consensus was reached.

### ***Risk of bias of the RCTs***

The methodological quality of the RCTs was assessed using the Cochrane Risk of Bias tool (version 1) (Higgins and Green, 2011). This tool uses six criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of evaluators of outcomes, incomplete outcome data and other sources of bias (availability of the trial protocol or registration). Each criterion was classified as 'high', 'unclear', or 'low', and 2 points, 1 point and 0 points were assigned, respectively, to account for the risk of bias of each RCT. Therefore, a study was considered to have a low risk of bias if the total score was  $\leq 4$ , a moderate risk of bias if the total score was 5 or 6, and a high risk of bias if the total score was  $\geq 7$ .

### ***Quality of moderator analysis***

To evaluate the quality of the moderating effect analysis, we used the Pincus et al. (2011) criteria. This checklist addresses the following domains: 1) use of an *a priori* hypothesis (when a moderating effect analysis was reported to have been planned *a priori*); 2) a theoretical or evidence-based selection of moderators (when a description of the theoretical background or evidence leading to the hypothesis was provided); 3) assessment of the moderator prior to randomization (when baseline measurements were reported to have been performed prior to randomization); and 4) adequate quality of baseline measurements (when there is published evidence to support good measurement properties of the assessment or instrument used for the target population). All these items had a yes/no response format. We did not evaluate the quality of tests for assessing interaction between a moderator and the intervention because it was one of our inclusion criteria; therefore, all the RCTs included in this systematic review had to meet this criterion. According to the results of these 4 factors, the strength of evidence was classified into three groups: confirmatory evidence (complying with the four criteria), exploratory evidence (complying with criteria number three and four), and insufficient evidence (all other combinations).

### ***Combined quality***

An overall measure of study quality was obtained according to the risk of bias of the RCTs and the quality of the moderating effect analyses (Moreno-Peral et al., 2020). A study was classified as 'good quality' when the total score for risk of bias was low and the evidence of the moderating effect analysis was confirmatory. 'Satisfactory quality' combined quality was considered when the studies had either a low/moderate risk of bias and provided exploratory evidence, or a high/moderate risk of bias and provided confirmatory evidence. Studies that did not comply with these criteria were classified as 'unsatisfactory quality' (Table 1).

\*\*\*Insert Table 1\*\*\*

### **Level of global scientific evidence**

We pooled the combined quality and number of studies reporting statistically significant results to obtain the global evidence of the moderators studied (Moreno-Peral et al., 2020). The global evidence was considered to be 'strong' when at least 75% of the potential moderators (in at least three independent studies) were statistically significant in studies with good combined quality. 'Moderate' global evidence was obtained when at least 65% of the potential moderators (in at least two independent studies) were statistically significant in studies with satisfactory combined quality. Finally, the global evidence was considered 'insufficient' when less than 65% of the potential moderators were statistically significant or more than 65% of the potential moderators were statistically significant, but the combined quality of the studies was unsatisfactory or the effects of the potential moderator had only been assessed in one study (Figure 1).

\*\*\*Figure 1\*\*\*

## **RESULTS**

### **Study selection**

As Figure 2 shows, our search strategy yielded 7010 articles. After removing duplicates and screening articles based on their titles and abstracts, 228 articles were selected for full text evaluation. Of these, 212 did not meet our inclusion criteria and were excluded. Finally, a total of 14 articles, based on 13 RCTs, met the full inclusion criteria.

\*\*\*Figure 2\*\*\*

### **Study characteristics**

We have summarized the details of each RCT in Appendix B. All RCTs were published from 2007 to 2018; four were conducted in Australia, three in the United States, three in the Netherlands, and one each in the United Kingdom, Sweden and Germany. The study sample sizes ranged from 55 to 5633 participants; a total of 9575 participants were enrolled in the RCTs. The age ranged from 6 to 59 years old. Eleven RCTs involved children and adolescents, and two were performed in adults. The majority of the RCTs were conducted at schools and used universal prevention (n=10, 77%). Most of the interventions were based on cognitive behavioral therapy (CBT) (n=7, 54%), whereas others used cognitive strategies (n=3, 23%), psychosocial strategies (n=2, 15%) and mindfulness (n=1, 8%). The type of control comparison groups varied across the 13 RCTs and included care as usual (n=5, 39%), placebo (n=3, 23%) and a waiting list (n=1, 7%) as well as more active control comparisons, such as psychoeducative information (n=4, 31%). The most common measure of anxiety was the reduction of anxious symptoms, and only one RCT measured the incidence of anxiety disorders. The duration of follow-up was 12 months or more in 7 studies (54%).

### **Moderator variables identified**

In Table 2, we present all the moderators studied along with the main study characteristics. We identified 27 potential moderators in the fourteen studies included. The majority of the studies evaluated more than one potential moderator. Gender/sex was the most frequently evaluated moderator (n=8), followed by age (n=5), stressful life events (n=3), number of sessions completed (n=3) and level of anxiety at baseline (n=3). The remaining potential moderators were evaluated only once. We sorted potential moderators into the following six categories: sociodemographic, clinical characteristics, cognitive variables, life events, interpersonal functioning and intervention characteristics.

#### 1. Sociodemographic characteristics

##### 1.1. Gender/sex

Eight studies evaluated gender/sex as a potential moderator, one in an adult population (Braithwaite et al., 2007) and the remaining seven in children and adolescents (Ahlen et al., 2017; Essau et al., 2012; Ginsburg et al., 2015; Johnson et al., 2017; Pophillat et al., 2016; Spence et al., 2014; Yap et al., 2018). Only one study, which compared a program composed of social, emotional, cognitive and behavioral strategies with regular health education lessons, found that male children showed a greater decrease in parent-reported anxiety symptoms

compared to female children (Pophillat et al., 2016). No moderation effects of gender/sex were found in the rest of the studies.

### 1.2. Age

Five studies investigated age as a putative moderator, all of these studies were carried out in children and adolescents and all except one showed null interactions (Ahlen et al., 2017; Essau et al., 2012; Ginsburg et al., 2015; Johnson et al., 2017; Yap et al., 2018). Essau et al. (2012) found that younger children (9-10 years old) displayed more anxiety symptoms reduction in ~~were more likely to benefit from the~~ FRIENDS program compared with a waiting list. In addition, they also observed that the FRIENDS program was more beneficial in terms of reducing anxiety symptoms for older children (11-12 years old) at the 6-12 month follow-up.

### 1.3. Ethnicity

Only one study conducted in a university adult population investigated ethnicity as a potential moderator of the intervention (Braithwaite et al., 2007). This study evaluated the efficacy of two computer-based programs compared with psychoeducative information for the reduction of anxiety symptoms. Results did not identify ethnicity as moderator of intervention effect.

### 1.4. Socioeconomic status

Socioeconomic status was evaluated as a potential moderator in one study conducted in children and adolescents where a mindfulness program with or without parental involvement was compared to a control group for the reduction of anxiety symptoms. No moderating effect of socioeconomic status was observed (Johnson et al., 2017).

### 1.5. Parents' sociodemographic characteristics

Parents gender and parent-child gender match were evaluated as potential moderators in a study where a brief psychosocial prevention program was compared to an information-monitoring control condition; no significant interaction effects were demonstrated in the reduction of the incidence of any anxiety disorder (Ginsburg et al., 2015).

## 2. Clinical characteristics

### 2.1. Depressive and anxious symptoms at baseline

Only the study by Ahlen et al. (2017) conducted in children, evaluated depressive symptoms at baseline as a potential moderator. This study compared the FRIENDS program versus

treatment as usual, and depressive symptoms at baseline were not found to have a moderating role **in the decrease of anxiety symptoms**.

Three studies in children investigated anxious symptoms at baseline as a potential moderator. Ginsburg et al. (2015) found that the benefit of the brief psychosocial prevention program **in terms of reduction of the incidence of any anxiety disorder** was stronger for children with higher baseline anxiety symptoms than for those with lower baseline anxiety symptoms. However, in the remaining studies, **the decrease of anxiety symptoms was not affected by** baseline anxiety symptoms ~~were not found to have a moderating effect~~ (Ahlen et al., 2017, Yap et al., 2018).

In adults, one study, in which a cognitive behavioral intervention was compared with treatment as usual, examined mixed depressive and anxious symptoms at baseline as a potential moderator; no evidence of a moderating role in the **reduction**~~prevention~~ of anxiety **symptomatology** was found (Li et al., 2014).

## 2.2. Parents' clinical characteristics

Parent mental illness did not moderate the effects of a cognitive behavioral program called the Aussie Optimism Program **in the decrease of anxiety symptomatology** (Chen et al., 2018). Similarly, no moderation effects were found for either parent comorbidity or parent anxiety level in **a study where the outcome was the incidence of any anxiety disorder** ~~the study by~~ (Ginsburg et al., 2015).

## 3. Cognitive variables

In children and adolescents, three related studies that were part of the same large RCT included two types of attentional bias training, emotional working memory training and three corresponding placebo groups. These studies evaluated a series of cognitive moderators **for the anxiety symptomatology**. De Voogd et al. (2016a) documented that changes in working memory capacity and baseline working memory capacity were not found to be associated with prevention outcomes. In another study from the same RCT, de Voogd et al. (2016b) also did not find that changes in attentional bias, baseline attentional bias and baseline attentional control reached significance as effect moderators. The study by de Voogd et al. (2018) compared a cognitive bias modification for interpretations program with a placebo cognitive bias modification for interpretations program and examined change in interpretation bias and baseline interpretation bias as potential moderators. Neither change in interpretation bias nor baseline interpretation bias was documented to have a moderating effect. Weight and shape

concerns were not associated with **anxiety symptomatology reduction** preventive effects in a study involving a mindfulness intervention in children and adolescents (Johnson et al., 2017).

Finally, in the adult population, achieving mastery of the material taught did not prove to be a significant moderator of the intervention **for the reduction of anxiety symptoms** (Braithwaite et al., 2007).

#### 4. Life events

Stressful life events were tested in three studies belonging to the same RCT conducted in adolescents **for the decrease of anxiety symptoms**. Stressful life events were not found to have a moderating effect in any of the three studies where they were assessed (de Voogd et al., 2016a, de Voogd et al., 2016b, de Voogd et al., 2018).

#### 5. Interpersonal functioning

Three interpersonal factors were evaluated as potential moderators in three different studies conducted in children and adolescents. Adolescents who experienced low family relationship support obtained greater reductions in anxiety symptoms of a psychosocial intervention at school compared to a community forum control condition (Spence et al., 2014). Two studies from the same RCT, which compared the Aussie Optimism Program with a control group, evaluated the role of family living arrangements and family functioning as moderators in each study. No moderation effects were found for either family living arrangements or family functioning **on anxiety symptom scores** (Cheng et al., 2018, Kennedy et al., 2015).

#### 6. Intervention characteristics

Studies by de Voogd (2016a, 2016b, 2018) **to reduce symptoms of anxiety** in adolescents, examined the number of sessions of the intervention completed as a potential moderator, but the interaction between the intervention and the number of sessions completed did not reach statistical significance. Johnson et al. (2017) examined the home practice of mindfulness as a moderator of the effect of a mindfulness intervention compared to a usual curriculum control group in early adolescents. No evidence was found that this variable had a moderating effect **in the reduction of anxiety symptoms**.

### **Methodological quality**

#### *Risk of bias in RCTs*

The risk of bias was assessed based on the RCTs of the studies included (Table 2 and Appendix B). Forty-five percent (5/11) of the RCTs did not report enough information for sequence generation and were rated as having an 'unclear' risk of bias. We categorized the remaining 55% (6/11) as having a 'low' risk of bias. Regarding allocation concealment, 64% (7/11) reported sufficient information to judge them as having a 'low' risk of bias, 18% (2/11) were judged as having an 'unclear' risk of bias and the remaining 18% (2/11) were judged as having a 'high' risk of bias. Blinding of the participants and personnel was only possible in one RCT, so we categorized it as having a 'low' risk of bias. In another RCT, participants could be blinded, but there was insufficient information about the concealment of personnel; therefore, it was judged as having an 'unclear' risk of bias. In the majority of the RCTs (82% (9/11)) it was not possible to conceal the participants and personnel, and they were rated as having a 'high' risk of bias. Blinding of evaluator outcomes was judged as 'high' risk of bias in 55% of studies (6/11), 'unclear' risk of bias in 27% (3/11) and 'low' risk of bias in 18% (2/11). The level of incomplete outcome data was rated as 'low' risk of bias in 45% (5/11) of RCTs because they managed missing data with different strategies. Thirty-seven percent (4/11) of RCTs were judged as having an 'unclear' risk of bias, and the remaining 18% (2/11) were judged as having a 'high' risk of bias. Finally, 45% (5/11) of RCTs had reported the trial protocol or clinical trial registration. Overall, 5 RCTs (45%) were considered to have a low risk of bias, 2 (18%) showed a moderate risk of bias and 4 (37%) were found to have a high risk of bias.

#### *Quality of moderator analysis*

Half of the moderation studies (n=7, 50%) provided confirmatory evidence, 4 out of 14 studies (29%) provided insufficient evidence and the remaining study (n=3, 21%) provided exploratory evidence. Regarding the total number of criteria met by each study, 7 studies met the four criteria evaluated, six studies met three criteria, and one study met two criteria (Table 2 and Figure 3).

\*\*\*Figure 3\*\*\*

#### *Combined quality*

The combined quality between the risk of bias and the quality of the moderator studies was good in five studies (36%), satisfactory in four studies (28%) and unsatisfactory in five studies (36%) (Table 1 and Figure 4).

\*\*\*Figure 4\*\*\*

## **Global evidence**

Table 3 shows the global evidence. Insufficient evidence on the role of the different moderators evaluated was found in adults, children and adolescents.

\*\*\*Table 3\*\*\*

## **DISCUSSION**

### **Overall findings**

A systematic review of 14 moderator studies (identifying 27 potential moderators) on psychological and psychoeducational interventions for the prevention of anxiety in 13 RCTs was conducted. We found 24 potential moderators in children and adolescents and these were grouped by the following categories: sociodemographic variables, clinical variables, cognitive variables, life events, interpersonal functioning and characteristics of the intervention moderators. In addition, we identified 4 potential sociodemographic variables, clinical variables and characteristics of the intervention moderators in the adult population. The most frequently examined variables were gender/sex, age and baseline anxiety symptoms. We did not find sufficient evidence for any moderator evaluated. ~~However, low family relationship support was significantly associated with better outcomes for psychological and psychoeducational interventions in the only study that evaluated this relationship; this study was conducted in children and adolescents. In addition, higher levels of anxiety symptoms at baseline were significantly associated with higher effectiveness in one of the three studies in which this moderator was evaluated; this study was also conducted in children and adolescents.~~

### **Study strengths and limitations**

To our knowledge, this study is the first synthesis of moderators of psychological and psychoeducational intervention effects in the prevention of anxiety. We rigorously followed the PRISMA guidelines. With the aim of not missing any relevant studies, we applied broad terms for the search strategy; in addition, multiple complementary electronic databases with supplementary manual searching were used, and a consultation with experts was performed. Regarding our selection criteria, we included only RCTs (since this design is the least biased to provide evidence of causality) with at least one interaction test to ensure that the RCTs

included met minimum quality standards. A variety of interventions (psychological and psychoeducational) and potential moderators (individual characteristics and circumstantial variables) were covered in this systematic review, **providing a new body of research that will guide the development of new meta-analyses focused on more specific interventions, populations or type of moderators.** The selection of studies, data collection, and assessment of the risk of bias and quality of the moderating effect analyses were performed by trained independent authors. We clearly defined the methods used to assess the methodological quality of the studies included and employed a combined assessment of quality based on the risk of bias of RCTs and the quality of the moderator studies. Our conclusions are based on both the number of significant results and the methodological quality of the studies, so, we gave greater value to those studies of higher quality.

We also should consider a series of limitations in this study. We found a very small number of moderators that were consistently assessed across the studies. It was difficult to draw conclusions about specific groups that can benefit most from preventive interventions when the most frequent moderators studied was gender/sex and age, and they were measured in 8 and 5 studies, respectively. In addition, the limited number of studies included in this systematic review suggests that effectiveness is frequently not assessed for specific subgroups. In relation to this limitation, another weakness of our study is that the majority of the studies were not originally designed to examine moderators. Instead, they were studies examining the effectiveness of several interventions (mainly CBT) for the prevention of anxiety.

This qualitative synthesis is based on the number of significant results and we are aware that this measure is highly influenced by sample size. RCTs are mostly underpowered for moderator analysis; usually a sample at least three to four times larger is needed to evaluate a treatment  $\times$  outcome interaction (Brookes et al; 2004). Only a minority of the included studies reported an *a priori* power analysis for the study of moderators. Therefore, the lack of statistical association could just as easily be related to a problem of sample size as to a lack of association. This is especially a problem in the prevention field, as effects in prevention are typically smaller, compared to the treatment field, and therefore the necessary sample size is larger.

Another limitation was that some variables related to the onset of anxiety in the literature were not assessed in the included studies. These variables are worse physical and

mental quality of life, dissatisfaction with paid and unpaid work, perception of financial strain, smoking and alcohol problems, personality and physical diseases suffered among others (Moreno-Peral et al., 2014; Moreno-Peral, Conejo-Cerón et al., 2014; King et al., 2011).

The risk of bias of the RCTs was considered moderate/high in six RCTs; although, the combined quality of the studies included, which was assessed based on the risk of bias plus the quality of the moderating effect analyses, was good in five studies.

Only two studies were carried out in the adult population, so the conclusions in this population are very limited and premature. This small number shows that the prevention of anxiety in the adult population has not received as much attention as in children and/or adolescents. This is evident in the systematic reviews and meta-analyses carried out in the field (Fisak et al., 2011; Moreno-Peral et al., 2017; Teubert and Pinquart, 2011; Werner-Seidler et al., 2017; Zalta, 2011).

### **Comparison with the literature and explanation of the results**

The majority of the findings showed non-significant associations between putative moderators and intervention outcome. These findings suggest that there is no evidence regarding sociodemographic variables, clinical variables, cognitive variables, life events or interpersonal factors that moderate anxiety prevention outcomes. Similarly, the characteristics of the intervention were also not associated with the intervention outcome. This apparent lack of association has been found in other reviews of the psychological treatment of anxiety disorders (Nilsen et al., 2013; Schneider et al., 2015). Nilsen et al. (2013) conducted a systematic review of moderators in the treatment of anxiety disorders and concluded that the majority of findings for anxiety studies showed non-significant associations between demographic or clinical factors and treatment outcome. Similarly, Schneider et al. (2015) conducted another systematic review of treatment moderators for anxiety disorders; few consistent treatment moderators were identified. Demographic variables, as well as the majority of clinical variables, failed to moderate outcomes. In this systematic review, **higher baseline anxiety symptomatology** ~~baseline anxiety disorder severity~~ was significantly associated with the outcome in over one-third of the moderator tests, but no clear pattern of findings emerged. ~~In our systematic review, we found that higher baseline anxiety symptomatology was a significant moderator in less than forty percent of studies (1/3 of studies).~~ More research is needed to draw conclusions about baseline symptomatology as a moderator of anxiety disorders prevention outcomes. ~~Only~~ The low family relationship support

variable moderated the effect of psychological or psychoeducational interventions to prevent anxiety in the **only** one study where this variable was studied; there were greater preventive effects in adolescents with low family relationship support. This could be explained by the fact that adolescents found in the intervention the support they did not receive from their families, and therefore, may have been more motivated and adherent to the intervention. ~~The intervention provided in this trial aimed to build a supportive school climate stimulating positive social relationship. Additionally, this intervention provided information to the families to identify problems so that they could seek help for themselves and help their peers.~~

The non-significant results found, as stated above, could be considered inconclusive rather than negative findings or a lack of association due to the small sample size of the studies included in this systematic review. It is of note that the absence of a significant moderator effect does not allow to conclude that the respective pretreatment characteristic is not associated with intervention effect. As outlined above the sample size needed for such analyses is much greater, compared to when investigating simply effects on symptom change or disorder onset. All studies included here, were not adequately powered to detect moderator effects and only one study had a sample size above 700. In order to overcome this problem individual patient meta-analyses can be used, which should be considered in future studies. In order for such studies been able to provide meaningful results, we encourage that a wide range of pre-treatment characteristics that might potentially be associated with differential prevention effects are included in future randomized controlled trials, even if studies are not designed to analyze these research questions.

Another explanation can be established for this lack of association; samples from the included studies may be relatively homogeneous due to the exclusion criteria applied, which hinders the possibility of detecting significant moderator effects (Steketee and Chambless, 1992) (if upper limits of moderators are missed, statistical power for testing moderation is limited). The inclusion and exclusion criteria set for a particular study affect the ability to test for particular moderators.

For some moderators (gender/sex, age and anxiety symptoms at baseline), we found opposite results across studies. The inconsistent moderator findings might be because some studies included tested variant interventions and compared them to each other. Additionally, moderators may work differently across anxiety disorders. Further studies should examine whether these moderators work differently depending on the type of anxiety disorder

targeted in the prevention efforts. Furthermore, related to the previous aspect, many putative moderators were defined differently across studies, and when they were defined, they were often measured in different ways. Finally, the methodologic quality and sample size were also very different across studies.

### **Future direction and conclusions**

The results obtained in this synthesis highlight the need for more methodologically robust studies to identify the subgroups of patients and circumstances required for psychological and psychoeducational interventions to be effective in preventing anxiety. More research is clearly needed to develop personalized preventive approaches. The need for large sample sizes might be one reason for the limited number of studies that examined moderators in anxiety prevention studies to date, since there are still surprisingly few studies examining this topic.

We can conclude that there is little consistent knowledge concerning for whom and under what conditions interventions work for the prevention of anxiety. Consequently, the study of moderators of intervention outcome in the prevention of anxiety must be given increased priority. However, various aspects are to be taken into account: 1) common measurements for moderators and outcome assessment should be used to allow for combination of results across studies; 2) moderator studies should be specifically designed with special attention given to assuring appropriate statistical power; 3) studies should consider the replication and validation of previous research results, particularly the variables identified as putative moderators in this systematic review such as sociodemographic variables, initial anxiety or depression symptom level, social support, psychological difficulties in family members, worse physical and mental quality of life, dissatisfaction with paid and unpaid work, perception of financial strain, smoking and alcohol problems, personality and physical diseases suffered; and 4) future studies should include a wide range of putative moderators (specially which we commented before), **even if the primary trial is underpowered to investigate such research questions**, in order to apply an individual patient data approach based on appropriate machine learning techniques to deliver the most effective intervention for a specific individual. **Furthermore, with the challenge of accumulating large data sets across studies and increase transparency and trust in the studies conducted, we suggest to share the data sets with a research data repository.**

Considering the state of the evidence for this topic, it may seem premature to suggest any clinical implications. However, a potential clinical implication based on these results is that

psychological and psychoeducational interventions for the prevention of anxiety are equally effective regardless of the gender/sex and age of the population. The findings found in this systematic review highlight the nascent state of this topic and the need for more consistent knowledge concerning for whom and under what conditions psychological and psychoeducational interventions work in the prevention of anxiety.

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### **Contributors**

PMP, JAB and SCC designed the study and the other authors collaborated on the design. PMP, JAB, EM, HCP, CMG, DDE, CB, MG, and SCC acquired, analyzed and interpreted the data.

PMP and SCC drafted the manuscript and JAB, EM, HCP, CMG, DDE, CB and MG conducted a critical revision of the manuscript for important intellectual content. All authors discussed and approved the final version. PMP is the guarantor.

**Declarations of interest:** None

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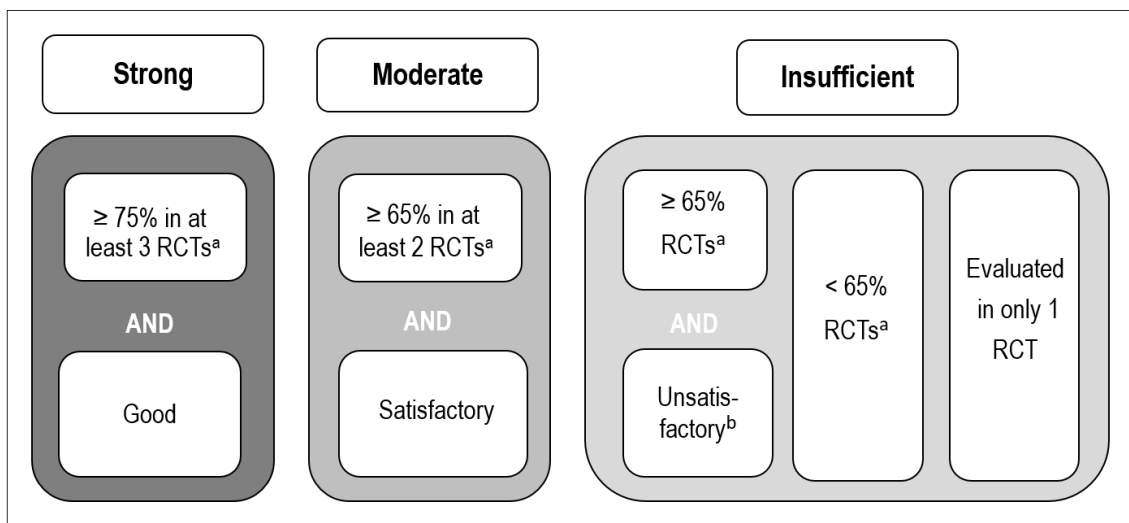
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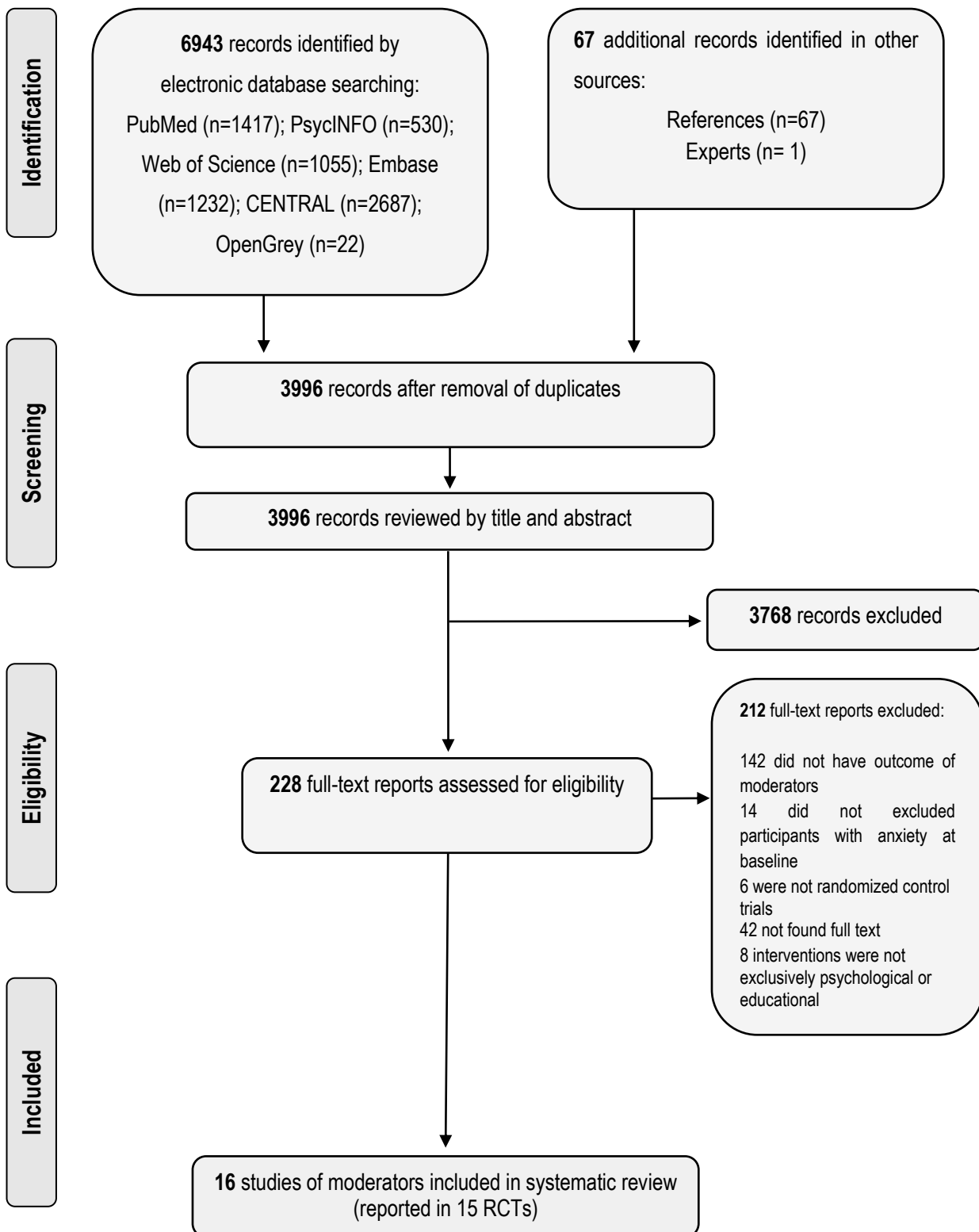
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**Figure 1.** Level of global scientific evidence.

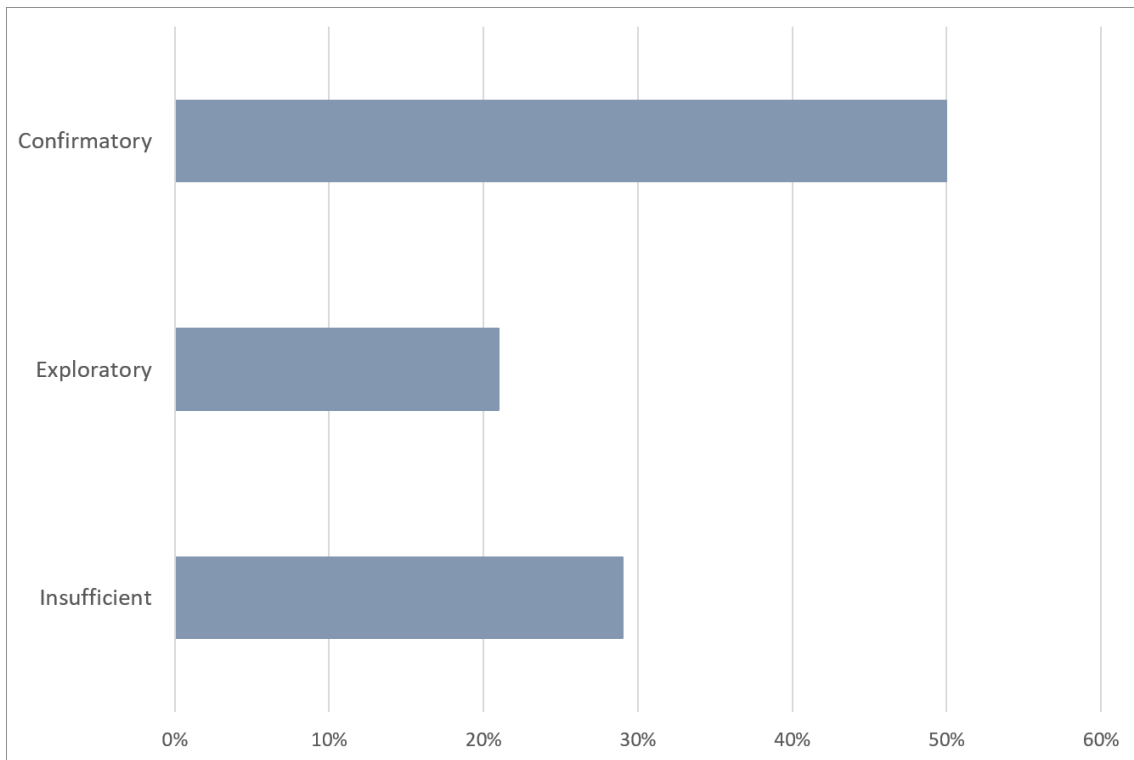


<sup>a</sup>:Statistical significance. <sup>b</sup>:Combination of methodological quality.

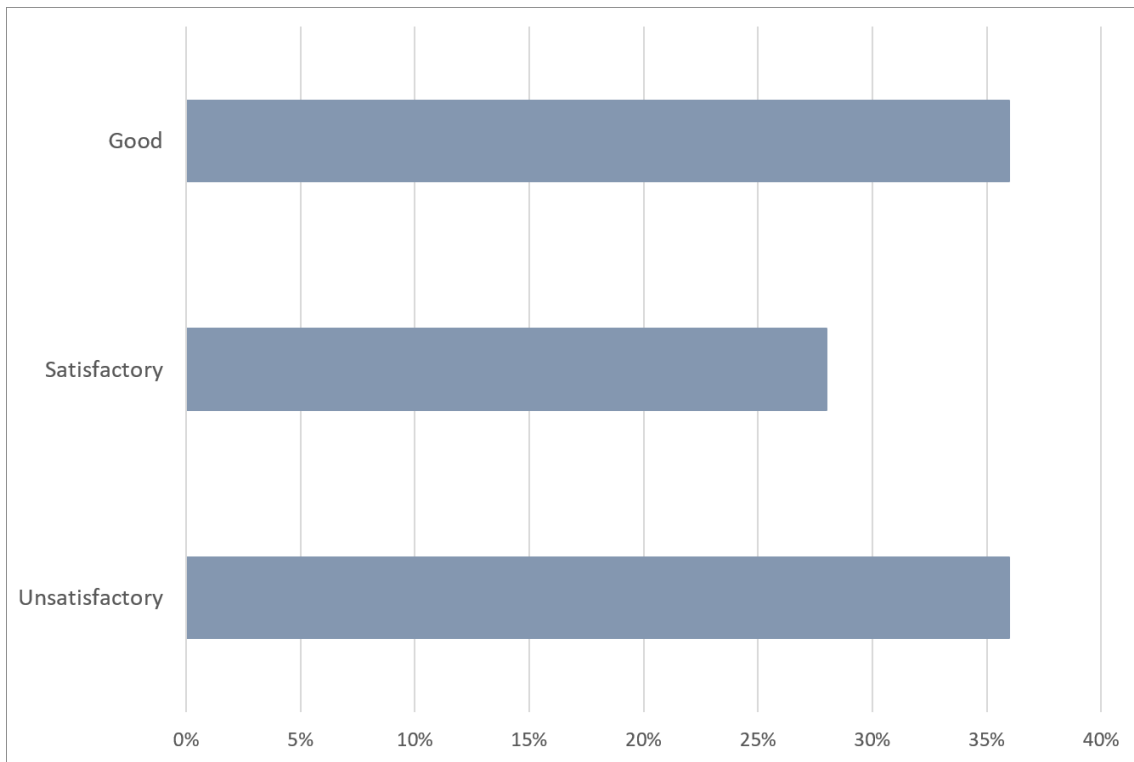
**Figure 2.** PRISMA Flowchart of the studies reviewed and included.



**Figure 3.** Quality of moderator analysis.



**Figure 4.** Combined quality.



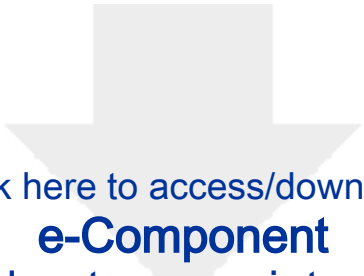


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**Table**

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**e-Component**

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**e-Component**

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