

## CBT to reduce healthcare use for medically unexplained symptoms:

### systematic review and meta-analysis

#### Abstract

##### Background

Studies have reported that medically unexplained symptoms (MUS) tend to be associated with increased healthcare use, which is demanding of resources and potentially harmful to patients. This association is often used to justify the funding and study of psychological interventions for MUS, yet no systematic review has specifically examined the efficacy of psychological interventions in reducing healthcare use.

##### Aim

To conduct a systematic review and meta-analysis to evaluate the effectiveness of cognitive behavioural therapies (CBT) for MUS in reducing healthcare use.

##### Design and setting

Systematic review and meta-analysis.

##### Method

The search from a previous systematic review was updated and expanded. Twenty-two randomised controlled trials reported healthcare use, of which 18 provided data for meta-analysis. Outcomes were healthcare contacts, healthcare costs, medication, and medical investigations.

##### Results

Small reductions in healthcare contacts and medication use were found for CBT compared with active controls, treatment as usual, and waiting list controls, but not for medical investigations or healthcare costs.

##### Conclusion

Cognitive behavioural interventions show weak benefits in reducing healthcare use in people with MUS. The imprecise use of MUS as a diagnostic label may impact on the effectiveness of interventions, and it is likely that the diversity and complexity of these difficulties may necessitate a more targeted approach.

##### Keywords

behaviour therapy; chronic pain; cognitive therapy; meta-analysis; somatoform disorders; systematic review.

#### INTRODUCTION

A meta-analysis in 2015 concluded that nearly half of primary care patients experience at least one medically unexplained symptom (MUS).<sup>1</sup> Various labels — psychosomatic, somatoform, functional, MUS — describe symptoms that are deemed to be unexplained or inadequately explained after investigation.<sup>2,3</sup> Doctors can find it difficult to negotiate the risks of over- or under-investigation and treatment,<sup>3,4</sup> avoidable anxiety,<sup>5</sup> and costs.<sup>6</sup>

Doubt concerning the authenticity of patients' experiences,<sup>7</sup> and patients feeling disbelieved if their symptoms are diagnosed as 'psychological',<sup>8</sup> undermine the doctor-patient relationship. Although integrated mind-body explanations are available for some long-term conditions, particularly chronic pain,<sup>9,10</sup> they are underused in general practice where models persist for which evidence is lacking — that MUS express suppressed emotion or psychosocial difficulties.<sup>11-14</sup> A model of poor adjustment focuses on illness beliefs<sup>12,13</sup> and avoidance of physical activity<sup>10,15</sup> that maintain disability.

Psychologically based rehabilitation aims to enable patients' self-management and thereby reduce healthcare use,<sup>16,17</sup> but is commonly evaluated by changes in illness beliefs, quality of life, and mood; less often by physical functioning.<sup>18</sup> A review of non-pharmacological treatments for MUS found that psychological therapies had a small benefit for MUS severity, but no effect on

healthcare use,<sup>19</sup> whereas a larger review of chronic pain<sup>20,21</sup> found a modest reduction in healthcare use after psychologically based intervention.

The aim of this review was to assess the benefits for healthcare use of interventions for MUS using cognitive behavioural therapy (CBT), given its evidence base.<sup>11,19-22</sup>

#### METHOD

This review is reported using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance.<sup>23</sup>

#### Search strategy

Trials from the review by van Dessel *et al*<sup>19</sup> with at least one CBT arm were supplemented by extending that search in three ways: a systematic search of Embase, PsycINFO, and MEDLINE, and the Cochrane Central Register of Controlled Trials CENTRAL from January 2005 to February 2018; specifying CBT interventions (cognitive therapy/treatment/rehabilitation, behavioural therapy/treatment/rehabilitation, cognitive behavioural therapy); and broadening terms for MUS conditions ('somatic', 'functional', 'medically unexplained', and specific MUS disorders of chronic fatigue syndrome, irritable bowel syndrome (IBS), chronic pain, idiopathic/unexplained pain/fatigue, and temporomandibular joint disorder). No additional restrictions were applied.

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**Submitted:** 9 July 2018; **Editor's response:**

22 August 2018; **final acceptance:** 2 October 2018.

©British Journal of General Practice

This is the full-length article (published online 29 Jan 2019) of an abridged version published in print. Cite this version as: **Br J Gen Pract 2019;** DOI: <https://doi.org/10.3399/bjgp19X701273>

## How this fits in

Increasing numbers of patients present with medically unexplained symptoms (MUS) and high levels of associated healthcare use. GPs are under pressure to identify effective interventions that reduce use of healthcare services. This meta-analysis reviews the effectiveness of cognitive behavioural interventions in reducing healthcare use in patients with MUS.

### Inclusion and exclusion criteria

**Study population and design.** Included were full reports of randomised controlled trials (RCTs) or cluster RCTs, published in peer-reviewed scientific journals. Participants were at least 18 years old with MUS as their primary problem (MUS included diagnoses of single or multiple MUS, somatoform disorders, fibromyalgia, chronic fatigue syndrome, IBS, temporomandibular disorders, and chronic pain — of at least 3 months' duration in any body site). Participants with pain or symptoms associated with medical diagnoses, such as rheumatoid arthritis, were excluded.

**Interventions.** Studies had a primary face-to-face CBT intervention, such as behavioural therapy, and included third-wave CBT (such as mindfulness or acceptance and commitment therapy) and rehabilitation or 'stress reduction' programmes with a major CBT component. Interventions were delivered or supervised by a healthcare professional with a recognised CBT qualification. Comparator arm/s could be active intervention, attention or waiting list control (a group of participants assigned to a waiting list who receive the intervention after the active treatment group), or treatment as usual.

**Outcomes.** Included trials assessed healthcare use as an outcome after the end of treatment; any form of healthcare use was eligible (for example, health service visits, medication use, diagnostic procedures, or treatments), regardless of referral route or recording method.

### Data collection and management

**Study selection.** After de-duplication, potentially eligible studies were selected on titles and abstracts, then on full texts, combining multiple versions of single studies. Reasons for study exclusion were recorded.

**Data extraction and management.** Data on characteristics of participants, treatments,

and outcome measures were extracted, and further data obtained for four studies.<sup>24-27</sup>

### Risk of bias

Each study was individually assessed for bias using adapted Cochrane principles. Ratings of selection bias, detection bias, and reporting bias were used as described in Cochrane guidance.<sup>28</sup> Performance bias was excluded because it is not possible to blind therapists and patients to delivery or receipt of psychological therapy. Three items were added: treatment of incomplete data (attrition bias), bias related to insufficient size and power, and treatment quality. Attrition bias is particularly important in research on psychological treatments for MUS because of differences in understanding of the problem between doctors and patients leading many patients to stop treatment. Studies were categorised as 'low risk' of bias if <10% of participants failed to complete treatment or an intention to treat analysis was completed with the conservative 'baseline measure carried forward'; as 'unclear risk' if >10% of participants did not complete the study and an algorithm to estimate missing values was used; or as 'high risk' if >10% dropped out and only completers' data were analysed.

For power calculations and adequate size of trials to detect treatment effects, studies were categorised as having a 'low risk' of bias if they reported a power analysis and met the sample size requirement; as having an 'unclear risk' if they reported a power analysis but did not meet the size requirement; and as having a 'high risk' if they did not report a power analysis and the size of the study appeared inadequate by comparison with studies reporting power calculations.

One further rating was made on treatment quality. Particularly for psychological treatments, it is important that the specified intervention was actually delivered to participants and contained cognitive and/or behavioural interventions of known efficacy. Interventions not delivered by qualified healthcare professionals were excluded, and those delivered by a qualified healthcare professional but without checking fidelity of treatment to the specified model were assessed as having a 'high risk' of bias. Studies were rated as having an 'unclear risk' if they referred to checks for treatment fidelity but provided insufficient information, and as having 'low risk' where the quality of interventions was assessed and adequately reported. The 'risk of bias' tool in the Cochrane Collaboration's RevMan software (version 5.3) was used to complete a risk of bias table for each study.

### Meta-analysis of treatment effect

RevMan (version 5.3) was used for meta-analysis of data. Treatment effects were estimated using standardised mean differences (continuous data) and odds ratios (dichotomous data), both using random effects. All estimates included 95% confidence intervals (CI).

Where an eligible study had two or more treatment or comparison groups, these were combined into a single treatment or comparison group depending on content. Between-study heterogeneity of data (as indicated by the  $I^2$  statistic) was calculated in RevMan and interpreted using Cochrane principles.<sup>28</sup>

Studies that did not provide usable data for the meta-analysis were included in the narrative review.

## RESULTS

### Search

The literature search and study selection is shown in Figure 1. One study from the review by van Dessel *et al*<sup>19</sup> met criteria.<sup>29</sup> The expanded and updated search produced 22 eligible trials.<sup>24–27,29–46</sup> Full details of the trials are available from the authors on request.

Where a follow-up or economic analysis contributed most data, it was used

rather than the original trial. Details of excluded trials are also available from the corresponding author on request.

### Participants

The 22 studies had 3809 participants (mean = 173) at start of treatment, and 3208 (mean = 145) at the end; the mean completion rate was 84%.

Two studies were conducted in the US,<sup>30,39</sup> and the rest in Europe. Participants' ages ranged from 18 to 75 years, with a mean of 41 years (standard deviation = 16.5). As is common in research on MUS, most participants were female (76%).

### Diagnoses

The broad and overlapping nature of MUS conditions and symptoms was represented in the 22 eligible trials. Four studies ( $n = 441$ ) recruited patients using DSM-IV diagnostic criteria,<sup>47</sup> most commonly undifferentiated somatoform disorder ( $n = 173$ ), somatisation disorder ( $n = 133$ ), and pain disorder ( $n = 56$ ).<sup>29,30,42,45</sup> Of these four, two did not report the specific physical complaints of participants,<sup>29,30</sup> one<sup>42</sup> reported most frequent complaints of pain, dizziness, heart palpitations, and fatigue, and the fourth<sup>45</sup> provided details of complaints, including pain ( $n = 57$ ), fatigue ( $n = 31$ ), gastrointestinal symptoms ( $n = 13$ ), and neurological symptoms ( $n = 11$ ).

One study ( $n = 569$ ) recruited participants with multiple and persistent bodily symptoms assessed as medically unexplained and deemed to be the primary treatment issue by their GP, but did not specify the complaints.<sup>35</sup>

Five studies included participants ( $n = 1172$ ) with chronic pain or fibromyalgia,<sup>26,27,31,33,34</sup> and four included only participants with fibromyalgia ( $n = 482$ ).<sup>24,25,36,44</sup> Among these nine studies, back and/or neck pain was the dominant complaint ( $n = 541$ ).

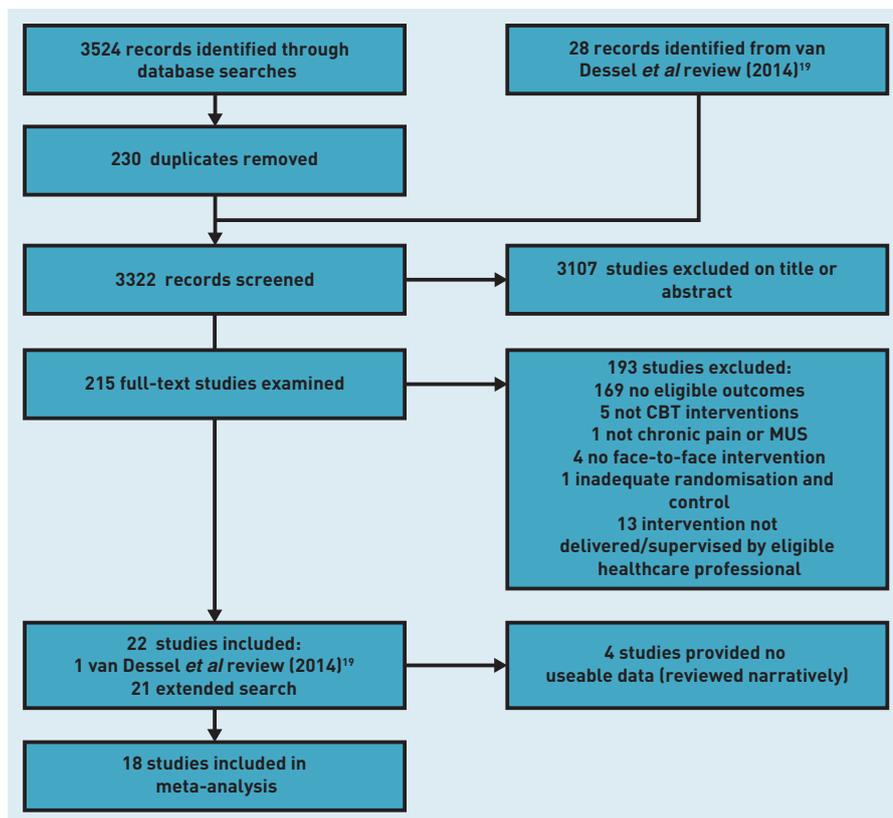
Several studies focused on specific disorders classified as medically unexplained: four treated chronic fatigue ( $n = 1026$ ),<sup>38,39,41,46</sup> one treated IBS ( $n = 149$ ),<sup>37</sup> and one treated tinnitus ( $n = 304$ ).<sup>40</sup>

Finally, two studies<sup>32,42</sup> recruited patients who met criteria for a newly proposed diagnosis of bodily distress syndrome ( $n = 119$ ), covering chronic fatigue, fibromyalgia, non-cardiac chest pain, IBS, hyperventilation syndrome, and tension headache.

### Interventions

Most trial interventions ( $n = 13$ ) included both cognitive and behavioural elements; three were mainly behavioural,<sup>27,36,39</sup> three

Figure 1. PRISMA study flow diagram. CBT = cognitive behavioural therapy. MUS = medically unexplained symptoms.



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Blinding of outcome assessment (detection bias)	Selecting reporting (reporting bias)	Size and power bias	Treatment quality bias
Allen, 2006 <sup>30</sup>	+	-	+	?	+	-	+
De Boer, 2014 <sup>31</sup>	+	+	+	?	?	?	-
Fjorback, 2013 <sup>32</sup>	+	+	?	+	+	+	+
Jensen, 2005 <sup>33</sup>	?	+	-	-	+	+	?
Kääpä, 2006 <sup>34</sup>	+	+	+	-	+	+	-
Konnopka, 2016 <sup>35</sup>	+	-	+	+	+	+	-
Luciano, 2013 <sup>36</sup>	+	+	+	+	+	+	-
Martin, 2007 <sup>29</sup>	+	-	+	-	+	-	-
McCracken, 2013 <sup>24</sup>	+	-	?	?	?	-	?
McCrone, 2008 <sup>37</sup>	+	?	?	-	+	+	?
McCrone, 2012 <sup>38</sup>	+	+	+	+	-	+	+
Meng, 2014 <sup>39</sup>	+	?	?	+	?	+	+
Nyenhuis, 2013 <sup>40</sup>	+	+	?	+	?	+	-
O'Dowd, 2006 <sup>41</sup>	+	+	?	+	+	+	-
Schmidt, 2011 <sup>25</sup>	+	?	?	+	+	+	-
Schröder, 2013 <sup>42</sup>	?	-	+	-	+	-	+
Schröder, 2017 <sup>26</sup>	+	+	?	+	+	+	+
Siemonsma, 2013 <sup>43</sup>	+	+	?	+	+	-	?
Sleptsova, 2013 <sup>27</sup>	+	+	-	?	?	-	?
Thieme, 2006 <sup>44</sup>	-	-	+	-	?	-	-
van Ravesteijn, 2013 <sup>45</sup>	+	+	?	-	+	+	-
Vos-Vromans, 2017 <sup>46</sup>	+	+	+	+	+	+	+

+ Low risk of bias   
? Unclear risk of bias   
- High risk of bias

Figure 2. Risk of bias by item for each included study.

used mindfulness or mindfulness-based cognitive therapy/stress reduction,<sup>25,32,45</sup> and one delivered acceptance and commitment therapy.<sup>24</sup>

### Risk of bias analysis

Methodologically, the main problems were of inadequate power, questionable treatment quality, and attrition bias (Figure 2).

**Size and power.** Five trials had no power analysis,<sup>29,30,37,43,44</sup> two estimated power (initially or post hoc) but were underpowered,<sup>31,42</sup> and one estimated using clinical experience and was probably underpowered.<sup>27</sup>

**Treatment quality.** Ten studies did not assess treatment quality or fidelity,<sup>25,29,31,34-36,40,41,44,45</sup> and a further four were weak or not fully reported.<sup>24,33,37,43</sup> One study with a high dose of treatment (25 × 90 minute sessions) provided supervision to check treatment quality with limited information on the treatment protocol.<sup>43</sup>

**Attrition bias.** Most studies had more than 10% attrition (maximum 44%;<sup>31</sup> mean 16%). Two used completer analyses,<sup>27,33</sup> eight estimated missing values,<sup>25,31,37,39-42,45</sup> and one did not specify.<sup>43</sup>

### Outcomes

Of the 215 full-text studies examined in the literature search, 114 cited high healthcare use as a rationale for research on MUS, but few assessed it as an outcome.

Of the 22 eligible trials, 18 studies contributed usable data for meta-analysis of healthcare use outcomes; contact with six of these studies<sup>26,30,31,40,42,46</sup> provided data for two.<sup>26,46</sup> All assessed healthcare use at follow-up (8 weeks to 3 years); the latest complete measurement was used where there was more than one. Most trials ( $n = 16$ ) collected data through self-report, five directly from medical records,<sup>26,30,32,41,44</sup> and one from insurance company records.<sup>27</sup>

**Healthcare contacts and resource use.** Eighteen studies with usable data contributed to the meta-analysis of healthcare contacts and resource use.

Sixteen trials had continuous data analyses. Ten referred to contacts with healthcare professionals,<sup>24,27,29,33,34,36,38,39,44,45</sup> three to costs,<sup>26,32,35</sup> and three to both contacts and costs;<sup>37,38,41</sup> for these three, contacts were used rather than costs for consistency. The overall effect showed a just significant difference between intervention and control in reduction of healthcare use: standardised mean difference (SMD) = -0.18 (95% CI = -0.35 to -0.01);  $z = 2.07$ ,  $P = 0.04$ . Heterogeneity was 75%.

Raw data for three studies<sup>24,25,27</sup> showed non-normal distribution; four other

trials may have had skewed data,<sup>6,32,37,45</sup> with no evidence of attempts to correct them. One study tried to correct highly skewed cost data in the analysis.<sup>26</sup> Because analysis should be reasonably robust in handling deviations from normality, no trial was excluded, but it raises doubts over interpretation of some individual study findings. Two trials with event-related data on healthcare contacts and resource use<sup>33,43</sup> were analysed separately but showed no significant difference between treatment and control groups: odds ratio [OR] = 0.75 (95% CI = 0.34 to 1.65);  $z = 0.70$ ,  $P = 0.48$ . Heterogeneity was moderate, at 58%. Four studies without usable data reported contacts with healthcare professionals or costs,<sup>30,31,40,42</sup> two<sup>40,42</sup> reported no significant difference between groups, one<sup>30</sup> reported a significant difference in healthcare costs favouring CBT but no significant difference in physician visits between groups, whereas the third<sup>31</sup> reported a marginal difference in costs favouring the control group, although a large dropout among controls rendered the difference 'negligible'.

**Medication use.** Eleven trials contributed data to the meta-analysis of medication use.

Nine trials contributed continuous data, seven as medication counts<sup>27,39</sup> or cost,<sup>26,35,36,38,41</sup> one calculated days of medication use,<sup>29</sup> and the last predicted medication use and associated costs using an algorithm.<sup>41</sup> The overall effect showed a just significant reduction in medication use in favour of the intervention: SMD = -0.32 (95% CI = -0.60 to -0.05);  $z = 2.28$ ,  $P = 0.02$ . Heterogeneity was 86%. Two trials contributed event-related data on medication use, one as the number of patients taking pain medication,<sup>43</sup> and one as the use of antidepressants, analgesics, or sleep medication.<sup>25</sup> The combined effect showed no significant difference between groups: OR = 0.69 (95% CI = 0.25 to 1.91);  $z = 0.71$ ,  $P = 0.47$ . Heterogeneity was moderate, at 33%.

**Medical investigations.** Three trials contributed data to the meta-analysis of medical investigations. Two reported the mean number of investigations,<sup>27,39</sup> and one their costs.<sup>36</sup> The overall effect showed no significant reduction between groups: SMD = -0.26 (95% CI = -0.74 to 0.23);  $z = 1.03$ ,  $P = 0.3$ . Heterogeneity was high, at 76%. One study without usable data reported medical investigations<sup>30</sup> with no difference in diagnostic procedures between groups.

**Healthcare costs.** Nine trials contributed data to the meta-analysis of healthcare costs.<sup>6,26,27,32,36,37,38,41,46</sup>

One study<sup>46</sup> included the cost of the intervention in the total healthcare costs, so it was subtracted for consistency with other trials in this analysis. The overall effect showed no difference in healthcare costs between groups: SMD = 0.17 (95% CI = -0.15 to 0.49);  $z = 1.04$ ,  $P = 0.3$ . Heterogeneity was 90%. One study without usable data reported a greater reduction in healthcare costs for those receiving CBT than for controls.<sup>30</sup>

## DISCUSSION

### Summary

Eighteen studies contributed data on the effectiveness of CBT-based interventions in reducing healthcare use quantified variously as healthcare contacts ( $n = 18$ ), healthcare costs ( $n = 9$ ), medication use ( $n = 11$ ), and medical investigations ( $n = 3$ ). Most analyses showed no effect, with small benefits for the effect of treatment on healthcare contacts and medication use. These results agree with the narrative review of studies without usable data ( $n = 4$ ), all of which reported small or non-significant reductions in healthcare use. Taken together, these findings suggest that CBT-based treatments on average make only small reductions in healthcare use in people with MUS. Most trials evaluated outcome by symptom reduction with the assumption that healthcare use would reduce proportionately, but this assumption may be false.

### Strengths and limitations

The multiple conditions and symptoms covered by the label MUS risks missing studies described in specific terms, but this search built on a previous review<sup>19</sup> and is transparent.

Between-study heterogeneity was moderate to high in most analyses, but has no serious implications for the interpretation of results except, possibly, for medication consumption, where assessment methods appeared also to vary conceptually, not only metrically, so caution in interpretation is warranted.

### Comparison with existing literature

This review is in line with previous Cochrane reviews on MUS, both in finding few studies that measured healthcare use,<sup>3</sup> and in finding non-significant or borderline effects.<sup>19</sup> The results here are less positive than those of a recent review on chronic

pain alone;<sup>20,21</sup> it may be that a more condition-specific intervention, with clearer theory underpinning it, can achieve more consistent changes in this outcome.

### **Implications for research and practice**

One of the most revealing findings of this review was the considerable discrepancy between healthcare use as a justification for treatment trials and as an outcome of those trials. Given that a high level of healthcare use likely indicates poorly treated symptoms, as well as aggregating costs and risking harm, it is disappointing that healthcare use is so rarely assessed as an outcome in trials. It is not clear to what extent healthcare use is targeted in interventions aimed at changing beliefs and behaviours, despite its importance.<sup>3,48,49</sup> Some standardisation of assessment of healthcare use would be helpful.

Apart from failure to collect data on healthcare use by self-report or independent records, costed where possible, there were other shortcomings of trial design. Underpowered studies (including through attrition) are of questionable value, as are

those delivered by unqualified staff.

Ideally, future studies would attempt to elucidate what factors contribute to reduced healthcare use. Patients with MUS tend to have difficult relationships with healthcare providers, so there may be multiple reasons why a patient consults healthcare providers less. The desired outcome is that improved self-management skills render healthcare use less necessary, but disillusionment with the healthcare system or resort to alternative/complementary health provision are also possible.

As CBT encompasses a variety of different interventions, an update on this review could consider whether specific treatment content is associated with reduction of healthcare use.

The authors would further argue that treatment effects will be strengthened by interventions that are specific to problems (as in chronic pain), and that recognise the differences between the many conditions described as MUS. Use of a more specific term than MUS to describe those problems might also help patients feel that treatment is designed around their needs.

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### **Funding**

This research received no funding.

### **Ethical approval**

Ethical approval was obtained through the University College London Research Ethics Committee (reference: 2584/001).

### **Provenance**

Freely submitted; externally peer reviewed.

### **Competing interests**

The authors have declared no competing interests.

### **Acknowledgements**

The authors are grateful to the authors who responded to requests for information or data.

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