

1 **The efficacy of different forms of acupuncture for the treatment of nocturnal enuresis in**
2 **children: A systematic review and meta-analysis**

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9 **Short title:** Acupuncture for nocturnal enuresis in children.

10 **Keywords:** Acupuncture, Laser acupuncture, Moxibustion, Nocturnal enuresis.

11 **Funding:** This work is supported by the start-up fund [1-ZE8G] for early-career academics at the
12 Hong Kong Polytechnic University.

13 **Acknowledgements:** We would like to thank Ms. Pun Joe Wing for her assistance with the
14 assessment of risk of bias.

15

16

17 **ABSTRACT**

18 **Background:** The efficacy of different forms of acupuncture for the treatment of nocturnal
19 enuresis in children is not known.

20

21 **Objective:** To determine the efficacy of different forms of acupuncture, such as manual
22 acupuncture, laser/electroacupuncture, acupoint injection, and moxibustion, for the treatment of
23 nocturnal enuresis.

24

25 **Methods:** A literature search was conducted on Medline, EMBASE, Web of Science, CINAHL,
26 PubMed, Physiotherapy Evidence Database, and Scopus from database inception to September
27 2020. The Cochrane risk of bias tool was utilised to evaluate the risk of bias in each included
28 study. The quality of the evidence was evaluated using the Grading of Recommendations,
29 Assessment, Development, and Evaluation tool.

30

31 **Results:** Thirteen trials (n = 890) were included. Meta-analyses revealed significantly greater
32 numbers of children reporting improved nocturnal enuresis in the moxibustion ($p=0.004$),
33 acupoint injection ($p=0.020$), and laser acupuncture ($p=0.001$) groups than in the control groups.
34 Meta-analyses showed no significant differences in the numbers of children reporting the
35 complete cure of nocturnal enuresis between laser acupuncture and desmopressin ($p=0.57$).

36

37 **Conclusions:** The review identified moxibustion, acupoint injections, and laser acupuncture as
38 effective treatments for nocturnal enuresis in children. However, the evidence for these

39 interventions is limited and of very-low-grade quality. The effects of laser acupuncture compared
40 with desmopressin remain inconclusive.

41 **Introduction**

42 Nocturnal enuresis is defined as “*nighttime bedwetting in children aged five years or older.*”^{1, 2}
43 Depending on the symptoms, nocturnal enuresis can be classified as monosymptomatic and non-
44 monosymptomatic. Monosymptomatic nocturnal enuresis is characterised by a lack of symptoms
45 during the day in children who experience bedwetting at least twice a week, consistently for a
46 minimum of three months.³ In contrast, non-monosymptomatic nocturnal enuresis is
47 accompanied by daytime symptoms (such as urgency, hesitancy, and incomplete emptying).³
48 Children with monosymptomatic nocturnal enuresis are reported to be at a higher risk of
49 developing psychosocial problems and low self-esteem.³

50
51 The aetiology of monosymptomatic nocturnal enuresis is multifactorial, and commonly
52 implicated causes include nocturnal detrusor overactivity,^{4, 5} nocturnal polyuria (excessive
53 production of urine at night), functional bladder capacity,^{6, 7} sleep characteristics,⁶ and the
54 inability to awaken in response to bladder sensation.⁴ According to Traditional Chinese Medicine
55 theory, the production and excretion of urine is associated with the lungs, kidneys, spleen, and
56 urinary bladder, and nocturnal enuresis is considered as a problem with the fluids in the body.³
57 Traditional Chinese Medicine theory accepted explanation for the pathogenesis of nocturnal
58 enuresis is a lack of ‘qi’ (energy flow) in the kidneys or ‘qi’ deficiency in the lungs and spleen.⁸

59
60 Currently available treatment options for nocturnal enuresis include medication, wetting
61 alarms, lifestyle changes, and complementary therapies, such as acupuncture.^{1, 9} Cochrane
62 reviews have reported pharmacological interventions, such as desmopressin¹⁰ and tricyclics,¹¹ as
63 effective treatments for nocturnal enuresis.^{10, 11} However, these reviews have also confirmed that

64 bedwetting in children relapses upon medication withdrawal.^{10, 11} Other reviews have reported
65 alarm interventions to be beneficial for the treatment of nocturnal enuresis¹²; however, wetting
66 alarms must be continuous, and continuous alarms have been reported to cause various degrees
67 of sleep disorders in children with nocturnal enuresis.^{4, 13} Given the disadvantages associated
68 with pharmacological and alarm interventions, parents often use complementary therapies, such
69 as acupuncture or medicinal herbs, to treat children with nocturnal enuresis.^{3, 14, 15} A number of
70 hypotheses have been proposed to explain the efficacy of various forms of acupuncture in the
71 treatment of nocturnal enuresis. Needling at urinary bladder meridian acupoints induces the
72 release of endogenous opioids, such as beta-endorphins, in both the blood plasma and the central
73 nervous system, which are thought to reduce detrusor contractions.^{3, 4} Electroacupuncture
74 represents a further advancement, in which a pulsating electrical current is applied to
75 acupuncture needles to further stimulate the acupoints.¹⁶ Electroacupuncture improves nocturnal
76 enuresis through its effects on opioid peptides, such as enkephalins, resulting in improved tonic
77 inhibitory control of the pontine micturition centre and bladder capacity regulation.^{3, 14, 17} The
78 stimulation of acupuncture points using non-thermal, low-intensity laser irradiation is commonly
79 referred to as laser acupuncture,¹⁸ which is thought to improve nocturnal enuresis by increasing
80 bladder capacity and reducing detrusor muscle contractility and maximum bladder contraction
81 pressure.^{19, 20} Moxibustion refers to the stimulation of acupoints with burning moxa wool and has
82 been proposed to regulate the autonomic nervous system, which is responsible for bladder
83 control.^{16, 21} However, there is a lack of consensus regarding the potential mechanisms
84 underlying the beneficial effects of various forms of acupuncture for the treatment of nocturnal
85 enuresis in children.

86

87 Systematic reviews and meta-analyses have previously been conducted to evaluate the
88 efficacy of acupuncture treatments in children with nocturnal enuresis.^{4, 5, 16} In 2015, a
89 systematic review of acupuncture concluded that low-quality evidence supported the efficacy of
90 acupuncture compared with placebo and pharmacological approaches for the treatment of
91 nocturnal enuresis in children.⁴ However, this review⁴ pooled multiple forms of acupuncture
92 together in the meta-analysis, making the efficacy of specific forms of acupuncture difficult to
93 assess. In 2017, a systematic review reported acupuncture as effective for the treatment of
94 nocturnal enuresis in children; however, this review also pooled multiple forms of acupuncture in
95 the meta-analysis and only included those studies comparing acupuncture with a no-treatment
96 control (inactive control).⁵ Reviews that compare an intervention group with an untreated control
97 group can only estimate absolute effects (i.e. receiving treatment vs not receiving treatment) but
98 cannot assess relative treatment efficacy (i.e. receiving one type of treatment vs another type of
99 treatment).²² The objective of this systematic review and meta-analysis was to evaluate the
100 efficacy of various forms of acupuncture in the management of nocturnal enuresis in children
101 compared with no treatment, sham treatment, placebo, pharmacological intervention, or
102 traditional Chinese medicine.

103

104 **Methods**

105 This systematic review is registered in the PROSPERO registry (CRDXXXXXX).

106 *Search strategy and study selection*

107 The electronic databases Medline (EBSCO host), EMBASE, Web of Science, CINAHL,
108 PubMed, Physiotherapy Evidence Database (PEDro), and Scopus were searched from database
109 inception to September 2020. Abstract proceedings from China acupuncture and moxibustion

110 association were also searched. Because each electronic database uses unique Medical Subject
111 Headings (MeSH), each database was searched independently. The search terms used were either
112 keywords or database-specific MeSH relating to three major themes: nocturnal enuresis,
113 acupuncture, and RCTs. A description of the search terms used is summarised in Supplementary
114 Table A.1. Reference lists from the included studies were hand-searched to identify any
115 additional potentially relevant studies. The screening and selection of studies were performed by
116 two independent reviewers. Conflicts were resolved by discussions between the two reviewers; a
117 third reviewer was consulted for any unresolved conflicts.

118

119 *Study selection criteria*

120 This review was developed and is reported following the PRISMA guidelines for the reporting of
121 reviews evaluating randomised trials.²³ Study selection criteria are presented in Table 1. The
122 research team did not have a member with proficiency in the Chinese language; therefore, we did
123 not include Chinese databases in our search strategy. Identified studies published in the Chinese
124 language were translated into English by a physiotherapy student with proficiency in the Chinese
125 language. The student was an independent individual with no other involvement in the study.

126

127 *Data extraction and assessment of the risk of bias and quality*

128 Two independent reviewers extracted the information from each included study, including author
129 names, publication year, study design, mean age (and standard deviation [SD]), the sample size
130 of each study group, outcome measures, intervention, control, and post-intervention means.

131 Extracted data were then compared, and any disagreements were resolved by discussion between
132 the two reviewers.

133 The risk of bias in each included study was evaluated using the Cochrane risk of bias
134 tool.²⁴ Risk of bias was assessed for the following six domains: sequence generation, allocation
135 concealment, blinding of participants, personnel and outcome assessors, incomplete outcome
136 data, selective outcome reporting, and other sources of bias (validity of outcome measure,
137 baseline comparability, and other potential confounding factors).²⁴ The assessment was based on
138 the statement from the authors of each study. This systematic review used ‘+’, ‘-’, ‘?’ as keys of
139 the judgments of Cochrane categories. The answer ‘+’ indicated a low risk of bias, ‘U’ indicated
140 an uncertain risk of bias, and an “-” indicated a high risk of bias. Studies were classified as
141 having a high risk of bias if they had a high risk of bias for random allocation, allocation
142 concealment, incomplete outcome data, and selective reporting.

143
144 The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)
145 tool²⁵ was utilised to evaluate the quality of evidence, using GRADEpro software.²⁶ Based on the
146 GRADE system, studies were rated as either ‘high’, ‘moderate’, ‘low’ or ‘very low’ quality.²⁷
147 The quality of evidence was rated based on the following factors: risk of bias,²⁸ indirectness,²⁹
148 imprecision,³⁰ inconsistency,³¹ and publication bias.³² Although the lack of blinding was not
149 considered a methodological flaw (given the nature of the intervention), studies were
150 downgraded for lack of therapist and assessor blinding. Industry-sponsored studies and studies in
151 which authors disclosed conflicts of interest were downgraded for publication bias; a funnel plot
152 was planned if more than ten studies were included in the meta-analysis.³²

153
154 The reporting quality of each acupuncture study was evaluated based on the Standards for
155 Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist.³³ Each item on

156 the STRICTA checklist was scored as either ‘yes’, ‘no’, or ‘partially reported’ (PR), to determine
157 whether the details were reported in accordance with STRICTA requirements.^{34, 35} The number
158 and percentage of studies that met the STRICTA standards were calculated for each item.³⁵

159

160 *Data synthesis and statistical analysis*

161 Comprehensive meta-analysis software (version 2.2.027) was used to perform the meta-
162 analysis.³⁶ Separate meta-analyses were conducted for each form of acupuncture. Studies
163 comparing similar outcome measures and control conditions were grouped together for pooling.
164 The treatment effect size (standardised mean difference [SMD]) and 95% confidence interval
165 (CI) were calculated for continuous data, and the risk ratio (RR) and 95% CI were calculated for
166 dichotomous data. Statistical heterogeneity was determined using the Chi-square test. If
167 heterogeneity was less than 50%, a fixed-effects model was used; a random-effects model was
168 used in cases of high heterogeneity (>50%).³⁷ A p -value ≤ 0.05 was considered significant.

169

170 **Results**

171 Figure 1 summarises the review process and the reasons for study exclusion at each stage.
172 Electronic and hand-searching yielded 209 potentially relevant articles (Supplementary Table
173 A.2. summarises the reasons for exclusion in the abstract and full-text screening stages). Among
174 these studies, 13 studies met the inclusion criteria and were included in the review. The
175 characteristics of each included study are summarised in Table 2. Among these 13 studies, we
176 identified six studies examining laser acupuncture, three examining acupoint injection, and four
177 examining moxibustion for the treatment of nocturnal enuresis in children. The 13 included
178 studies provided data for 890 participants.

179 Out of the 13 included studies, only one study was at low risk of bias.³⁸ The risk of bias
180 of the included studies is summarized in Figure 2. Seven out of 13 studies provided information
181 on random sequence generation.^{9, 20, 38-42} Methods used for allocation concealment were
182 described in one study.³⁸ Two studies each reported blinding of participants^{6, 43} and outcomes
183 assessors.^{6, 44} Five studies^{9, 38-40, 45} reported the completeness of outcome data for each main
184 outcome and nine^{6, 9, 20, 38-41, 44, 45} reported exclusions from the analysis. Eight^{6, 9, 38, 40, 42-44, 46} out
185 of 13 studies were free of other biases (such as the validity of outcome measure, baseline
186 comparability, or other potential confounding factors).

187
188 The reporting quality for each included study, based on STRICTA guidelines, can be
189 found in Supplementary Table A.3. All 13 included studies reported the names of the acupoints
190 used and a description of the control condition. Of the 13 studies, 12 studies reported the number
191 of treatment sessions, and ten studies reported information regarding the style of acupuncture and
192 the frequency and duration of acupuncture treatment. The overall quality of the included studies,
193 based on the GRADE assessment tool, was ‘very low’. Serious risk of bias (lack of random
194 allocation, allocation concealment, and participant blinding) was the main factor contributing to
195 the downgraded quality of evidence. The GRADE quality assessments for the included studies
196 are presented in Table 3.

197

198 **Effects of interventions**

199 *Effects of laser acupuncture for the treatment of nocturnal enuresis*

200 Meta-analysis of the reported data from three^{9, 38, 42} very-low-grade studies found a non-
201 significant effect of laser acupuncture compared to pharmacological intervention (desmopressin)

202 on self-reported complete cure rate during the 9-month follow-up period (RR 1.15 [95% CI: 0.70
203 to 1.89]; $p = 0.578$; $n = 193$; Fig. 3.). Meta-analysis of two^{6, 20} very-low-grade studies revealed
204 no significant differences in the number of children reporting complete cure during the 3–6-
205 month follow-up period between groups receiving laser acupuncture and sham acupuncture (RR
206 2.09 [95% CI: 0.52 to 8.32]; $p = 0.294$; $n = 109$; Fig. 4.). Meta-analysis of two^{20, 40} very-low-
207 grade studies revealed a significant reduction in the number of wet nights in the laser
208 acupuncture group than in the sham group during the 2-6-month follow-up period (SMD -0.69
209 [95% CI: -1.09 to -0.28]; $p = 0.001$; $n = 112$; Fig. 5.).

210

211 *Effect of moxibustion for the treatment of nocturnal enuresis*

212 Meta-analysis of four^{39, 41, 44, 45} very-low-grade studies, involving 224 children, demonstrated that
213 a significantly increased number of children in the moxibustion group reported improvement
214 compared with the control group that received Chinese medicine (RR 1.47 [95% CI: 1.13 to
215 1.91]; $p = 0.004$; Fig. 6.).

216

217 *Effect of acupoint injection for the treatment of nocturnal enuresis*

218 The pooled analysis of three^{43, 46, 47} very-low-grade studies, involving 252 children, revealed a
219 significantly increased number of children reporting improvement in the acupoint injection group
220 compared with the control group that received Chinese medicine (RR 1.45 [95% CI: 1.06 to
221 1.98]; $p = 0.020$; Fig. 7.).

222

223 **Discussion**

224 This systematic review evaluated the efficacy of various forms of acupuncture compared with
225 control treatments for the management of nocturnal enuresis in children. A literature search
226 identified 209 potentially relevant studies, 13 of which met the criteria for inclusion in this
227 review.

228

229 Laser light has been used as an alternative to needles for the stimulation of traditional
230 acupuncture points for many decades.⁴⁸ When treating children, laser stimulation is preferred
231 over needle stimulation because lasers are pain-free and non-invasive.¹⁶ The pooled analyses of
232 data from two laser acupuncture trials of very-low-grade quality revealed a significantly greater
233 number of children reporting improved nocturnal enuresis in the intervention group than in the
234 sham laser acupuncture group. Although the effect of laser acupuncture was significant, with a
235 moderate effect size (0.69),⁴⁹ the evidence for the efficacy of this intervention was provided by
236 two small studies of very-low-grade quality. However, because laser acupuncture is a pain-free
237 and non-invasive intervention, it could be considered for the treatment of nocturnal enuresis in
238 children. The laser trials included in the current review used widely variable parameters;
239 therefore, no recommendations can be made regarding the optimal laser parameters for nocturnal
240 enuresis therapy. Future well-designed studies remain necessary to fully determine the efficacy
241 of laser acupuncture to treat nocturnal enuresis in children.

242

243 Although the aetiology of nocturnal enuresis is multifactorial, three important factors
244 known to contribute to nocturnal enuresis pathogenesis are nocturnal polyuria, nocturnal bladder
245 overactivity, and the failure to awaken in response to bladder sensations.^{4, 7} Research evidence

246 suggests that these factors might be attributable to altered brainstem control mechanisms.^{4, 14} The
247 pontine micturition centre, located in the brainstem, regulates the micturition reflex and is
248 connected both functionally and anatomically with the locus coeruleus, which plays an important
249 role in arousal from sleep.^{4, 50} During acupuncture at the ST36 (Zusanli) acupoint, functional
250 magnetic resonance imaging showed the activation of the hypothalamus,⁵¹ suggesting that
251 acupuncture might improve bladder function through the activation of the brainstem-thalamus-
252 cortex reticular system.¹⁴

253
254 A review exploring the rationale for acupuncture in the treatment of nocturnal enuresis in
255 children¹⁴ reported that the acupoints BL23, BL28, BL32, RN3, RN4, RN6, and RN12 coincide
256 with the micturition centre in the spinal cord (S2, S3, and S4), and stimulating this region
257 restored bladder function in children with nocturnal enuresis.⁵² The stimulation of acupoints
258 UB20, UB13, SP6, ST36, KI3, and LU9 is thought to improve bladder function by invigorating
259 the spleen, vital energy, and blood.¹⁴ The treatment techniques utilised by all of the
260 moxibustion,^{39, 41, 44, 45} acupoint injection,^{43, 46, 47} and laser acupuncture^{6, 9, 20, 38, 40, 42} studies
261 included in the review involved the stimulation of at least one acupoint recommended for the
262 restoration of bladder function.¹⁴ Commonly utilised acupoints in the included moxibustion,
263 acupoint injection, and laser acupuncture studies included BL23 (Shenshu), BL28 (Bladder Shu),
264 SP6 (Sanyinjiao), ST36 (Zusanli), REN3 (Zhong Ji), and REN4 (Guan Yuan).

265
266 Meta-analysis of data from four trials^{39, 41, 44, 45} of very-low-grade quality showed a
267 significantly increased number of children in the moxibustion group reporting improvement
268 compared with the control group that received traditional Chinese medicine. However, the

269 application of moxibustion directly over the skin has been associated with adverse effects,
270 including burns, blisters, allergic reactions, itching, and infections, in newborns and adults.^{53, 54}
271 The safety of moxibustion for the treatment of nocturnal enuresis in children remains uncertain.
272 In the absence of specific knowledge of the adverse effects of moxibustion on children, no
273 recommendations can be made regarding the efficacy of this intervention in the management of
274 nocturnal enuresis in children.

275
276 Acupoint injections were found to have beneficial effects on nocturnal enuresis compared
277 with traditional Chinese medicine, based on^{43, 46, 47} three studies of very-low-grade quality.
278 Acupoint injection is frequently used as a complementary therapy for the treatment of various
279 conditions in children.³ Commonly reported adverse effects associated with acupoint injection in
280 children include pain, nausea, vomiting, bleeding, and fever; however, these complications are
281 typically transient, resolving within two weeks.^{55, 56} Although the effects of acupoint injection on
282 nocturnal enuresis were significant in the current study, the evidence for this intervention should
283 be interpreted with caution. The estimate was calculated using a small number of studies (n = 3)
284 of very-low-grade quality. However, because no long-term adverse effects are known for
285 acupoint injection, it may be considered in clinical practice for the treatment of nocturnal
286 enuresis in children.

287 288 *Strengths and weaknesses*

289 The use of a highly sensitive search strategy and a psychometrically valid quality assessment
290 tool, as well as the inclusion of unpublished studies that may present insignificant results, are the
291 strengths of this systematic review. Significant benefits for the treatment of nocturnal enuresis in

292 children were identified for several types of acupuncture, including laser acupuncture (compared
293 with sham without active laser light but with skin contact), acupoint injection, and moxibustion.
294 These findings also highlighted the acupoints associated with bladder function. However, the
295 limitations of the current systematic review are (1) the inclusion of small and very-low-grade
296 studies with high risks of bias; (2) the involvement of only a few studies in each meta-analysis;
297 (3) the lack of Chinese medical database searches, which might have resulted in the omission of
298 additional relevant studies; and (4) a language bias due to the selection of studies published only
299 in English and simplified and traditional Chinese.

300

301 **Conclusions**

302 Meta-analysis of two very-low-grade studies revealed significant effects for laser acupuncture
303 treatment compared with sham laser acupuncture in reducing the number of wet nights in
304 children with nocturnal enuresis. Laser acupuncture is a pain-free, non-invasive, and safe
305 intervention and could, therefore, be considered for the treatment of nocturnal enuresis in
306 children. The review identified moxibustion and acupoint injections as effective treatments for
307 nocturnal enuresis in children. However, the evidence for these interventions is limited and of
308 very-low-grade quality.

309

310 **Implications for future research**

311 The laser acupuncture parameters varied greatly across the trials included in this review, and
312 additional research remains necessary to determine the optimal parameters for improving
313 nocturnal enuresis in children. The safety of moxibustion in children has not been validated, and
314 future studies are required to determine the safety of moxibustion for the treatment of children

315 with nocturnal enuresis. Further adequately powered, high-quality research examining other
316 forms of acupuncture, such as electroacupuncture which may improve bladder function through
317 the activation of the neuroendocrine response, is warranted. Future RCTs examining acupuncture
318 are recommended to abide by the STRICTA recommendations for reporting. Existing
319 acupuncture trials for the management of nocturnal enuresis in children are small and associated
320 with a high risk of bias. Therefore, future studies evaluating the effectiveness of acupuncture
321 must be conducted with larger sample sizes and high methodological rigour.

322

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481 **Table 1.** Study selection criteria

	Inclusion criteria	Exclusion criteria
Population	Children (boys and girls) in the age group of 5 to 18 years with monosymptomatic nocturnal enuresis	Adults with monosymptomatic nocturnal enuresis
Intervention	Manual acupuncture, laser/electroacupuncture, acupoint injection, and moxibustion	Acupressure
Comparison	No treatment, sham, placebo, pharmacological interventions, or Chinese medicine	Studies comparing active interventions (such as acupoint injection vs moxibustion or laser acupuncture vs electroacupuncture)
Outcomes	Self- or parent-reported complete or partial recovery from nocturnal enuresis or the number of wet nights	Studies that assessed quality of life or adverse effects of acupuncture
Study	RCTs (pilot, cluster, or cross-over [with data before cross-over]) or unpublished theses published English or Chinese (traditional or simplified) languages	Case series, single-group studies, or non-RCTs

482 Note: RCTs = Randomised Controlled Trials.

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Table 2. Characteristics of included studies ($n = 13$)

Author, year, country of study	The mean age/ age range of participants (yrs); sample size	Intervention	Control	Outcome measure(s)	Results: Time points of assessment; Mean (SD) (or) n/N
Alsharnoubi et al. ³⁸ 2017 Egypt	Mean: 15.7* Exp: $n = 15$ Con: $n = 15$	LA <i>Parameters:</i> wavelength, 905 nm; spot size diameter, 5 mm; frequency, 2,500 Hz; average power, 15 W; energy, 225 mJ; pulse width, 100 ns for 1 min/point. <i>Acupoints:</i> REN 2, 3, 4, and UB23, 28, 32 (bilateral), and SP6 (bilateral). <i>Duration/ frequency of treatment:</i> 3 months (twice weekly).	Desmopressin, 60 µg. <i>Duration/frequency of treatment:</i> 3 months (once daily).	Self/parent/caregiver-reported complete cure	<u>6 months</u> Complete cure Exp: 11/15 Con: 3/15
Dong et al. ⁴³ 2012 China	Exp: 8.6 (5 to 12)* Con: 8.6 (5 to 13)* Exp: $n = 57$ Con: $n = 26$	Acupoint injection <i>Acupoints:</i> Zhongji, Guanyuan, and Sanyinjiao (bilateral). <i>Injection:</i> Astragalus. <i>Duration/ frequency of treatment:</i> 5 weeks (twice daily).	Meclofenoxate <i>Dose:</i> 0.1 g. <i>Duration/frequency of treatment:</i> 5 weeks (thrice daily).	Self/parent/caregiver-reported complete cure	<u>6 months</u> Exp: 46/60 Con: 36/60
Chen and Gu ⁴⁷ , 2003 China	Exp: 5 to 14# Exp: $n = 40$ Con: $n = 32$	Acupoint injection <i>Acupoints:</i> Shenshu, Jiaji, Ba, Zusanli, Sanyinjiao. <i>Injection:</i> Chuankezhi. <i>Duration/frequency of treatment:</i> 2 weeks (once daily).	Chinese medicine <i>Duration/frequency of treatment:</i> 2 weeks (once daily).	Self/parent/caregiver-reported complete cure	[^] Exp: 36/40 [^] Con: 14/32
Hong et al. ³⁹ 2011 China	5 to 13# Exp: $n = 33$ Con: $n = 33$	Moxibustion <i>Acupoints:</i> Baihui, Mingmen, Shenshu, Bladder Shu, Guanyuan shu <i>Duration/frequency of treatment:</i> Two course treatment each lasting for 14 days. Once daily for 14 consecutive days.	Con: Chinese Medicine <i>Duration/frequency of treatment:</i> 2 courses, each lasting for 2 weeks (twice daily).	Self/parent/caregiver-reported complete cure	<u>1 Month</u> Exp: 20/33 Con: 19/33

Hong and Zhang ⁴⁵ , 2009 China	8 to 12# Exp: <i>n</i> = 15 Con: <i>n</i> = 15	Moxibustion <i>Acupoints (acupuncture)</i> : Chengjiang, Qugu, Henggu (bilateral), Sanyinjiao (bilateral), Taichong (bilateral). <i>Acupoints (moxibustion)</i> : Qugu, Henggu, Sanyinjiao. <i>Duration/frequency of treatment</i> : 20 sessions (once daily).	Con 1: Chinese Medicine <i>Duration/frequency of treatment</i> : Children <12 years: five days (once daily); Children >12 years: 10 days (once daily)	Self/parent/caregiver-reported complete cure	<u>1 Month</u> Exp: 13/15 Con: 5/15
Karaman et al. ²⁰ 2011 Turkey	Exp: 8.5 (3.2) Con: 8.9 (3.3) Exp: <i>n</i> = 57 Con: <i>n</i> = 26	LA <i>Parameters</i> : wavelength between 635 and 670 nm, power 5 mW. <i>Acupoints</i> : CV3, CV4, CV6, and bilateral SP6, ST36. <i>Duration/frequency of treatment</i> : 4 weeks (thrice-weekly).	Sham LA without active laser light <i>Parameters, acupoints and duration/frequency of treatment</i> : same as for the experimental group.	Self/parent/caregiver-reported complete cure No. of wet nights	<u>Self-reported complete cure; 6 months</u> Exp: 31/57 Con 1: 3/26 <u>No. of wet nights; 6 months</u> Exp: 1.7 (1.3) Con 2: 3.1 (2.2)
Jodorkovsky ⁶ , 2003; Korea	Mean: 6.5 (SD not reported) Exp: <i>n</i> = 11 Con: <i>n</i> = 15	LA <i>Parameters</i> : E-beam, 0-200UA, using two cords for 20 s. <i>Acupoints</i> : I-19, I-22, J-23, A-3, J-3, I-37, H-2/I-38). <i>Duration/frequency of treatment</i> : 5 sessions (twice weekly).	Sham LA <i>Parameters</i> : E-beam with non-functioning cords, without active laser light and skin contact. <i>Acupoints</i> : same as the experimental group. <i>Duration/frequency of treatment</i> : 5 sessions (twice weekly).	Self/parent/caregiver-reported complete cure	<u>3 months</u> Exp: 10/11 Con: 12/15
Ling and Chen ⁴⁶ , 2011 China	Exp: 9.2 (5 to 16)# Con: 9.1 (5 to 15)# Exp: <i>n</i> = 30 Con: <i>n</i> = 30	Acupoint injection <i>Acupoints</i> : Shenshu, bladder Shu, Sanyinjiao (bilateral). <i>Injection</i> : Human placenta tissue fluid injection. <i>Duration/frequency of treatment</i> : 1st course: 10 sessions (once daily). 2nd	Chinese medicine <i>Dose</i> : Yizhiren 10 g, Wuyao 6 g, and Chinese Yam 15 g. <i>Duration/ frequency of treatment</i> : 1st course: 10 sessions (once	Self/parent/caregiver-reported complete cure	[^] Exp: 18/30 [^] Con: 15/30

		course: 10 sessions (10-day intervals).	daily). 2nd course: 10 sessions (10-day intervals).		
Moursy et al. ⁹ 2014 Egypt	Mean: 15.7 Exp: <i>n</i> = 62 Con: <i>n</i> = 62	LA <i>Parameters</i> : wavelength, 808 nm; power, 200 mW, 26 s, energy < 4 J/cm. <i>Acupoints</i> : REN2, REN3, REN4, SP6, ST29, ST36, UB23, UB28, UB32, UB40. <i>Duration/ frequency of treatment</i> : 3 months (twice weekly).	Desmopressin <i>Dose</i> : 120 g <i>Duration/frequency of treatment</i> : 3 months (once daily).	Self/parent/caregiver-reported complete cure	<u>9 months</u> Exp: 33/62 Con: 35/62
Radvanska et al. ⁴⁰ 2011 Denmark	Mean: 8.8 (1.4) Exp: <i>n</i> = 16 Con <i>n</i> = 13	LA <i>Parameters</i> : wavelength, 670 nm. <i>Acupoints</i> : Du20, H7, ST36, SP6, Liv3, K3, Ren3, Ren4, B23, Du4. <i>Duration/ frequency of treatment</i> : 5 weeks (thrice weekly for the first two weeks followed by twice a week for the next three weeks).	Sham LA without active laser light but with skin contact. <i>Parameters and acupoints</i> : same as for the experimental group. <i>Duration/ frequency of treatment</i> : NR	No. of wet nights per week	<u>5 weeks</u> Exp: 5.4 (2.0) Con: 6.0 (2.0)
Radmayr et al. ⁴² 2001 Austria	Exp: 8.6 Con: 8.0 Exp: <i>n</i> = 19 Con: <i>n</i> = 20	LA <i>Parameters</i> : wavelength, 670 nm; power, 10 mW. <i>Duration/ frequency of treatment</i> : 5 weeks (thrice-weekly- 10–15 sessions).	Desmopressin <i>Dose</i> : 20-40 µg. <i>Duration/ frequency of treatment</i> : 3 months (frequency of treatment NR).	Self/parent/caregiver-reported complete cure	<u>9 months</u> Exp: 13/19 Con: 15/20
Tong and Zhan ⁴⁴ , 2009	6 to 20# Exp: <i>n</i> = 30 Con: <i>n</i> = 30	Moxibustion <i>Acupoints</i> : Qihai, Zhongji, Shenshu, Bladdershu, Yinlingquan, Sanyinjiao, Zusanli. <i>Duration/frequency of treatment</i> : 5 days (once daily).	Chinese medicine <i>Duration/ frequency of treatment</i> : Children <13 years: five days (4 times daily); Children >13 years: 5 days (thrice daily).	Self/parent/caregiver-reported complete cure	[^] Exp: 17/30 [^] Con: 10/30

Yang et al. ⁴¹ 2012	3 to 15# Exp: <i>n</i> = 34 Con: <i>n</i> = 34	Moxibustion <i>Acupoints</i> : Guanyuan, Zhongji, Shenshu, Bladder Shu and Sanyinjiao. <i>Duration/ frequency of treatment</i> : 20 sessions (once daily with 2-day intervals between every 5 sessions).	Chinese medicine <i>Duration/ frequency of treatment</i> : 4 weeks (thrice daily).	Self/parent/caregiver- reported complete cure	<u>4 weeks</u> Exp: 21/34 Con: 12/34
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Note: Con = Control group; EA = Electroacupuncture; Exp = Experimental group; LA = Laser Acupuncture; NE = Not Evaluated; NR = Not

*SD not reported; #Mean and SD of individual groups not reported; ^Assessment time point not reported.

Table 3. Summary of findings (GRADE) for included studies ($n = 13$)

Laser acupuncture compared to Desmopressin					
<i>Outcomes</i>	<i>Illustrative comparative risks* (95% CI)</i>		<i>Relative effect (95% CI)</i>	<i>No of Participants (studies)</i>	<i>Quality of the evidence (GRADE)</i>
	<i>Assumed risk</i>	<i>Corresponding risk</i>			
Self-reported complete cure	Study population 546 per 1000	634 per 1000 (377 to 1000)	RR 1.15 (0.70 to 1.89)	193 (3 studies) ^{9, 38, 42}	⊕⊕⊕⊕ very low ^{a,b}
	Moderate 565 per 1000	655 per 1000 (390 to 1000)			
Laser acupuncture compared to sham (self-reported complete cure)					
<i>Outcomes</i>	<i>Illustrative comparative risks* (95% CI)</i>		<i>Relative effect (95% CI)</i>	<i>No of Participants (studies)</i>	<i>Quality of the evidence (GRADE)</i>
	<i>Assumed risk</i>	<i>Corresponding risk</i>			
Self-reported complete cure	Study population 366 per 1000	820 per 1000 (73 to 1000)	RR 2.09 (0.52 to 8.32)	109 (2 studies) ^{6, 20}	⊕⊕⊕⊕ very low ^{b,c,d}
	Moderate 458 per 1000	1000 per 1000 (92 to 1000)			
Laser acupuncture compared to sham (number of wet nights)					
<i>Outcomes</i>	<i>Illustrative comparative risks* (95% CI)</i>		<i>Relative effect (95% CI)</i>	<i>No of Participants (studies)</i>	<i>Quality of the evidence (GRADE)</i>
	<i>Assumed risk</i>	<i>Corresponding risk</i>			
Number of wet nights		The mean number of wet nights in the intervention groups was 0.69 lower (1.09 to 0.28 lower)		112 (2 studies) ^{20, 40}	⊕⊕⊕⊕ very low ^{b,e}
Moxibustion compared to Chinese medicine					
<i>Outcomes</i>	<i>Illustrative comparative risks* (95% CI)</i>		<i>Relative effect (95% CI)</i>	<i>No of Participants (studies)</i>	<i>Quality of the evidence (GRADE)</i>
	<i>Assumed risk</i>	<i>Corresponding risk</i>			
Self-reported complete cure	Study population 312 per 1000	628 per 1000 (463 to 856)	RR 1.47 (1.13 to 1.91)	224 (4 studies) ^{39, 41, 44, 45}	⊕⊕⊕⊕ very low ^{b,f}
	Moderate 333 per 1000	669 per 1000 (493 to 912)			
Acupoint injection compared to Chinese medicine					

<i>Outcomes</i>	<i>Illustrative comparative risks* (95% CI)</i>		<i>Relative effect (95% CI)</i>	<i>No of Participants (studies)</i>	<i>Quality of the evidence (GRADE)</i>
Self-reported complete cure	Study population		RR	252	⊕⊕⊕⊕ very low ^{b,d,g}
	533 per 1000	767 per 1000 (655 to 884)	1.45 (1.06 to 1.98)	(3 studies) <small>^{43, 46, 47}</small>	
	Moderate 500 per 1000	720 per 1000 (615 to 830)			

Note: CI: Confidence interval; RR: Risk ratio. *The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

^a Allocation concealment and assessor blinding not reported in three studies (Moursy 2014, Alsharnoubi 2017, and Radmayr 2001).

^b Wide or no overlap of CI.

^c Allocation concealment not reported in two studies (Jodorkovosky 2002 and Karaman 2011); and lack of assessor blinding and dropout rate >15% in one study (Karaman 2011).

^d Evidence of clinical/methodological heterogeneity ($I^2 > 50\%$) across studies.

^e Allocation concealment, lack of assessor blinding, and dropout rate >15% in two studies (Radvanska 200 and Karaman 2011).

^f Lack of random allocation in two studies (Hong 2011 & Ahang 2009 and Yang 2012); lack of allocation concealment and blinding in four studies (Hong & Zhang 2009, Yang 2012, Tong & Zhan, and Hong 2011).

^g Lack of random allocation in two studies (Dong 2012, Ling and Chen 2011); lack of allocation concealment, therapist and participant blinding in three studies (Dong 2012, Ling and Chen 2011, and Chen and Gu 2003)

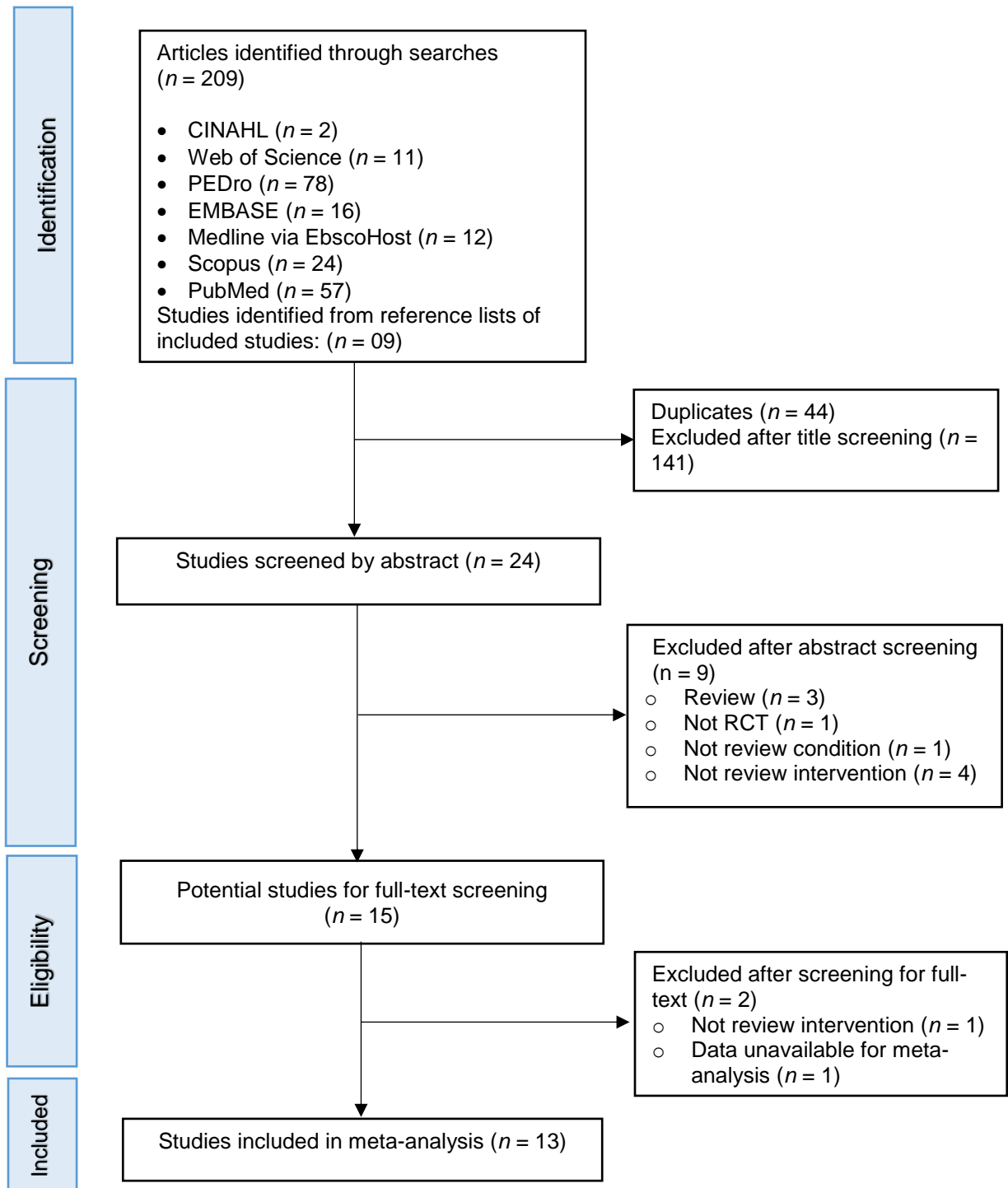
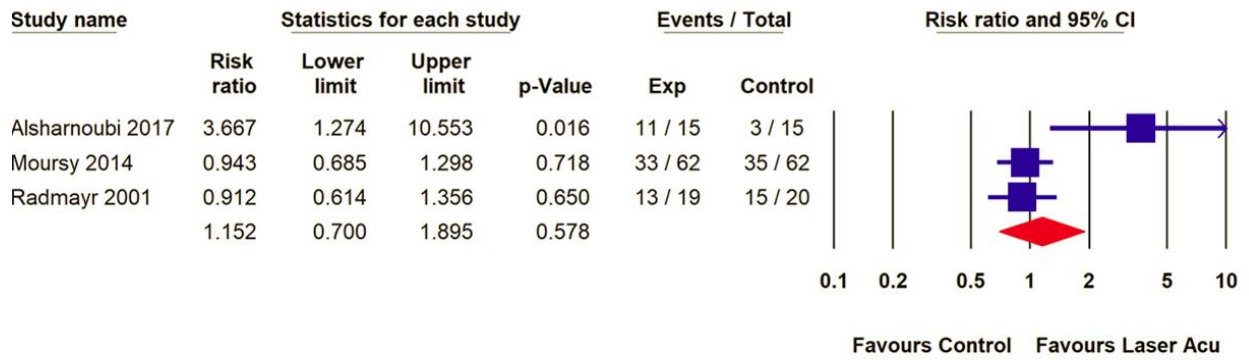


Fig. 1. Flow diagram of searches and study selection.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alsharnoubi 2017	+	+	-	-	+	+	-
Chen and Gu 2003	?	?	-	?	-	-	-
Dong 2012	?	-	+	?	-	-	+
Hong 2011	+	-	-	-	+	+	?
Hong and Zhang 2009	?	?	-	?	+	+	?
Jodorkovsky 2003	?	-	+	+	-	+	+
Karaman 2011	+	-	-	-	-	+	?
Ling and Chen 2011	-	?	-	?	-	-	+
Moursy 2014	+	-	-	-	+	+	-
Radmayr 2001	+	-	-	-	-	-	+
Radvanska 2011	+	-	-	-	+	+	+
Tong and Zhan 2009	-	-	-	+	-	+	+
Yang 2012	+	-	-	-	-	+	?

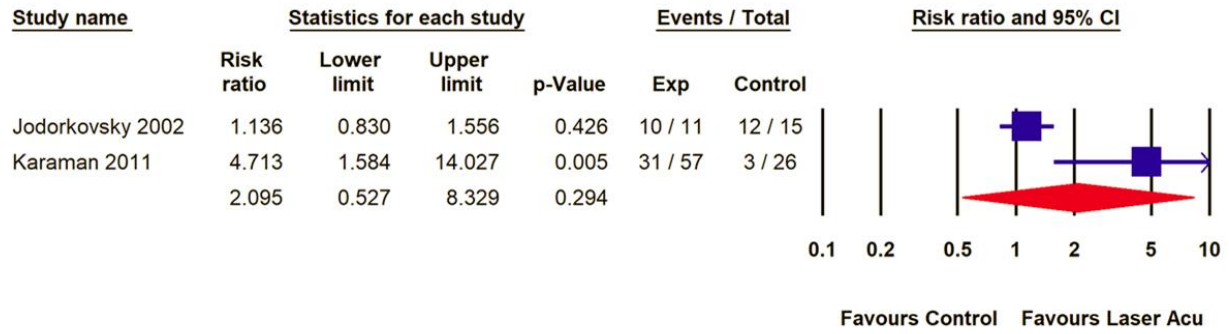
Fig. 2. Risk of bias assessment for each included study (based on review author’s judgment)

+ = low risk of bias; - = high risk of bias; U = uncertain risk of bias.



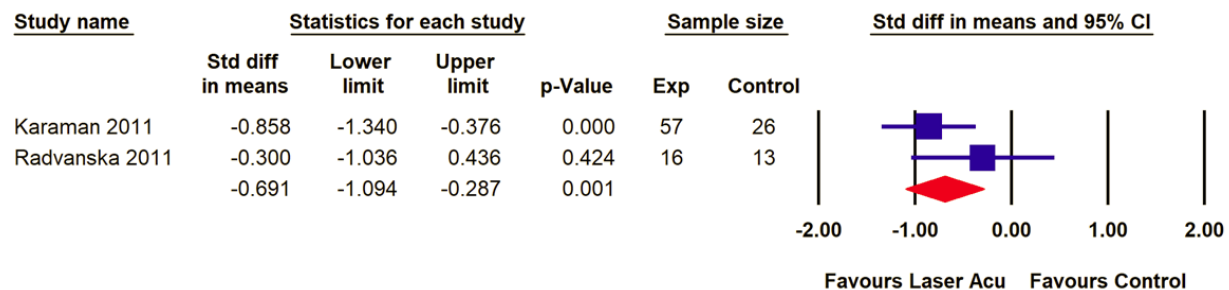
($I^2 = 67.42$)

Fig. 3. Laser Acupuncture Vs. Desmopressin for self-reported complete cure of nocturnal enuresis at 9 months follow-up.



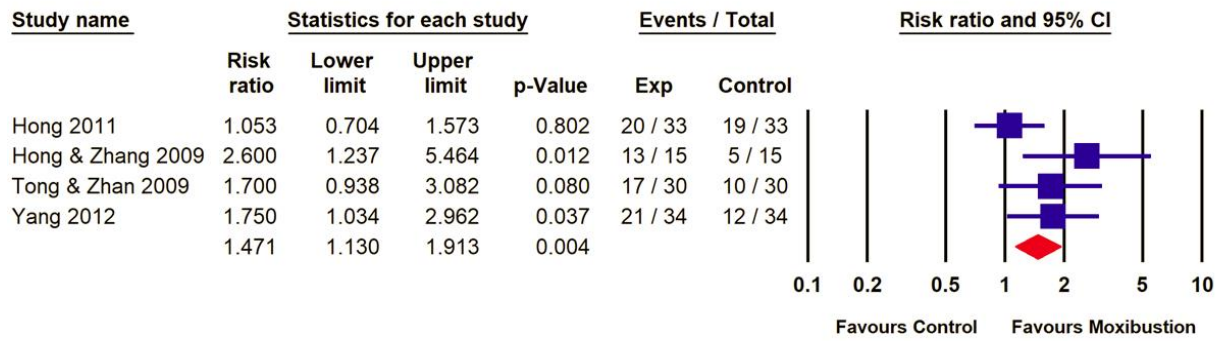
($I^2 = 83.43$)

Fig. 4. Laser Acupuncture Vs. Sham laser for self-reported complete cure of nocturnal enuresis at 3-6 months follow-up.



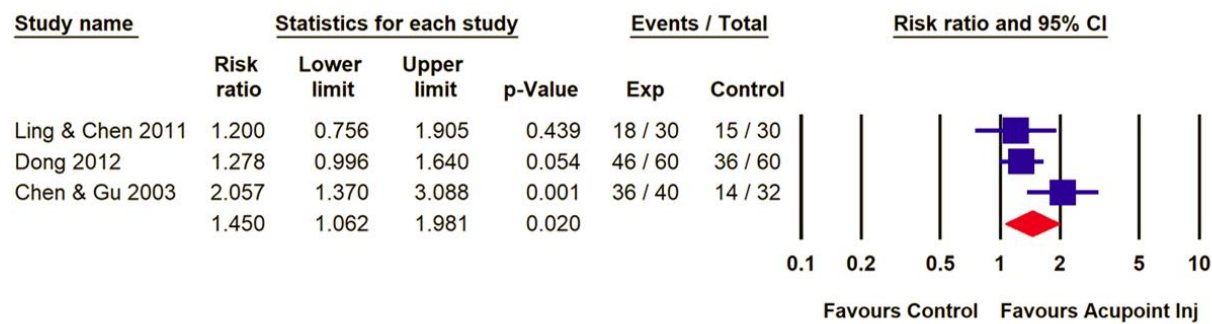
(I² = 35.32)

Fig. 5. Laser Acupuncture Vs. Sham laser for number of wet nights in children with nocturnal enuresis at 2-6 months follow-up.



($I^2 = 46.13$)

Fig. 6. Moxibustion Vs. Chinese herbal medicine for curate rate in children with nocturnal enuresis.



($I^2 = 54.43$)

Fig. 7. Acupoint injection Vs. Chinese herbal medicine for curate rate in children with nocturnal enuresis.

Supplementary Table A.1. Search terms and search strategy

Subject areas	Search terms used
Urinary incontinence	(nocturnal enuresis) OR (nocturnal enuresis in children) OR (bedwetting in children)
AND	
Mind-body and complementary therapies	(acupuncture) OR (electroacupuncture) OR (laser acupuncture) OR (moxibustion) OR (acupoint injection) OR (hand acupuncture) OR (body-acupuncture) OR (scalp acupuncture) OR
AND	(Japanese acupuncture) OR (Meridian acupuncture) OR (Korean acupuncture) OR (Saam acupuncture) OR (auricular acupuncture)
Randomised Controlled Trial	(RCT) OR (random allocation) OR (randomised controlled tria*) OR (randomised controlled clinical trial)

Supplementary Table A.2. Studies excluded (on abstract and full-text screening) and reasons for exclusion

Abstract screening			
No.	First author and year	Title	Reason for exclusion
1.	Abd 2018	Acupuncture as a treatment for nocturnal enuresis	Not review intervention
2.	Longstaffe2000	Behavioral and self-concept changes after six months of enuresis treatment: a randomized, controlled trial	Not review intervention (alarm intervention vs. medication)
3.	Ma 2007	A randomized controlled clinical trial for treatment of children with primary nocturnal enuresis	Not review intervention (alarm intervention)
4.	Dommelen 2009	The Short- and Long-term Effects of Simple Behavioral Interventions for Nocturnal Enuresis in Young Children: A Randomized Controlled Trial	Not review intervention
5.	Bosson S. 2002	Nocturnal enuresis	Review
6.	Bower 2010	Acupuncture as a treatment for nocturnal enuresis	Review
7.	Wei 2013	A meta analysis of acupuncture combined with traditional Chinese medicine in the treatment of nocturnal enuresis in children	Review
8.	Honjo	Treatment of monosymptomatic nocturnal enuresis by acupuncture: A preliminary study	Not RCT
9.	Carmona 2013	Percutaneous tibial nerve stimulation versus neurostimulation of SP 6 (Sanyinjiao) in urge incontinence	Not review condition
Full-text screening			
1.	Mogahed 2016	Response of bladder reservoir function to low level laser acupuncture in primary monosymptomatic nocturnal enuresis	Data not reported for review outcome
2.	Yukse 2003	Acupressure versus oxybutinin in the treatment of enuresis	Not review intervention

Supplementary Table A.3. Reporting quality of each included study ($n = 13$), according to STRICTA

Items description	Study reference													Number of RCTs reporting details (%)
	Alsharnoubi et al. 2017	Chen & Gu, 2003	Dong	Hong & Zhang, 2009	Hong & Law, 2011	Jodorkovsky, 2003	Karaman et al. 2011	Ling & Chen	Moursy et al. 2014	Radmayr et al. 2001	Radvanska et al. 2010	Tong & Zhang, 2009	Yang et al. 2012	
Acupuncture rationale														
1a	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	10 (76.9%)
1b	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	6 (46%)
1c	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	2 (15.4%)
Details of needling														
2a	NA	No	No	No	No	No	NA	No	NA	NA	NA	No	NA	0
2b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13 (100%)
2c	NA	No	Yes	No	Yes	No	NA	No	NA	NA	NA	No	NA	2 (15.4%)
2d	NA	No	Yes	Yes	Yes	No	NA	No	NA	NA	NA	Yes	NA	4 (30.8%)
2e	NA	No	No	No	Yes	No	NA	No	NA	NA	NA	Yes	NA	2 (15.4%)
2f	NA	No	No	Yes	Yes	Yes	NA	No	NA	NA	NA	Yes	NA	4 (30.8%)
2g	NA	No	Yes	No	Yes	No	NA	Yes	NA	NA	NA	Yes	NA	4 (30.8%)
Treatment regimen														
3a	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12 (92%)
3b	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10 (76.9%)
Other components of treatment														
4a	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes	4 (30.8%)
4b	Yes	No	No	No	No	PR	No	No	Yes	No	No	No	No	2 (15.4%)
Practitioner background														
5a	No	No	No	No	No	No	No	No	No	No	Yes	No	No	0
Control or comparator interventions														
6a	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	PR	9 (69%)
6b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13 (100%)

Note: 1a, Style of acupuncture; 1b, Reasoning for treatment provided with references where appropriate; 1c, Extent to which treatment was varied; 2a, Number of needles insertions per subject per session; 2b, Names of points used; 2c, Depth of insertion; 2d, Response sought; 2e, Needle stimulation; 2f, Needle retention time; 2g, Needle type; 3a, Number of treatment sessions; 3b, Frequency and

duration of treatment sessions; 4a, Details of other interventions administered to the acupuncture group; 4b, Setting and context of treatment; 5a, Description of participating acupuncturists; 6a, Rationale for the control or comparator; 6b, Precise description of the control or comparator.

Yes = Details reported; No = Not Reported; PR = Partially Reported; NA = Not Applicable.