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# Interventions for treating persistent and intractable hiccups in adults (Review)

Moretto EN, Wee B, Wiffen PJ, Murchison AG

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Interventions for treating persistent and intractable hiccups in adults.
*Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No.: CD008768.
DOI: 10.1002/14651858.CD008768.pub2.

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[Intervention Review]

# Interventions for treating persistent and intractable hiccups in adults

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**Editorial group:** Cochrane Pain, Palliative and Supportive Care Group.
**Publication status and date:** New, published in Issue 1, 2013.
**Review content assessed as up-to-date:** 10 December 2012.

**Citation:** Moretto EN, Wee B, Wiffen PJ, Murchison AG. Interventions for treating persistent and intractable hiccups in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No.: CD008768. DOI: 10.1002/14651858.CD008768.pub2.



## ABSTRACT

### Background

Persistent and intractable hiccups (typically defined as lasting for more than 48 hours and one month respectively) can be of serious detriment to a patient's quality of life, although they are relatively uncommon. A wide range of pharmacological and non-pharmacological interventions have been used for the treatment of persistent and intractable hiccups. However, there is little evidence as to which interventions are effective or harmful.

### Objectives

The objective of this review was to evaluate the effectiveness of pharmacological and non-pharmacological interventions used in the treatment of persistent and intractable hiccups of any aetiology in adults.

### Search methods

Studies were identified from the following databases: CENTRAL, CDSR, DARE, MEDLINE, EMBASE, CINAHL, PsychINFO and SIGLE (last search March 2012). The search strategy for all the databases searched was based on the MEDLINE search strategy presented in Appendix 1. No additional handsearching of journals was undertaken. Investigators who are known to be carrying out research in this area were contacted for unpublished data or knowledge of the grey literature.

### Selection criteria

Studies eligible for inclusion in this review were randomised controlled trials (RCTs) or controlled clinical trials (CCTs). Inclusion criteria: adults (over 18 years old) diagnosed with persistent or intractable hiccups (hiccups lasting more than 48 hours), treated with any pharmacological or non-pharmacological intervention. Exclusion criteria: less than ten participants; no assessment of change in hiccup frequency or intensity in outcome measures.

### Data collection and analysis

Two independent review authors assessed each abstract and title for relevance. Disagreement on eligibility was resolved by discussion. Where no abstract was available the full paper was obtained and assessed. We obtained full copies of the studies which met the inclusion criteria for further assessment. Two review authors independently collected data from each appropriate study and entered them into the software Review Manager 5. Two independent review authors assessed the risk of bias using the RevMan 5 'Risk of bias' table following guidance from the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2009).

**Main results**

A total of four studies (305 participants) met the inclusion criteria. All of these studies sought to determine the effectiveness of different acupuncture techniques in the treatment of persistent and intractable hiccups. All four studies had a high risk of bias, did not compare the intervention with placebo, and failed to report side effects or adverse events for either the treatment or control groups. Due to methodological differences we were unable to perform a meta-analysis of the results. No studies investigating pharmacological interventions for persistent and intractable hiccups met the inclusion criteria.

**Authors' conclusions**

There is insufficient evidence to guide the treatment of persistent or intractable hiccups with either pharmacological or non-pharmacological interventions.

The paucity of high quality studies indicate a need for randomised placebo-controlled trials of both pharmacological and non-pharmacological treatments. As the symptom is relatively rare, trials would need to be multi-centred and possibly multi-national.

## PLAIN LANGUAGE SUMMARY

**Interventions for treating persistent and intractable hiccups in adults.**

Hiccups involve repeated, involuntary contractions of the muscles used for breathing. They usually stop of their own accord; rarely, however, they may last for more than 48 hours. When they do persist, hiccups can cause a patient considerable upset, interfere with sleeping and eating, and can lead to other complications. Many different drugs and non-drug measures have been suggested to stop long-lasting hiccups. This review aimed to find out whether there is good evidence that any of these work. We searched for good quality studies that involved adult patients (18 or older) who had experienced hiccups for 48 hours or more. Our conclusion is that there is insufficient evidence to recommend a particular treatment for hiccups. There is a need for randomised controlled studies to identify which treatments might be effective or harmful in treating persistent hiccups.

## BACKGROUND

### Description of the condition

Hiccups, or singultus, may be defined as "repeated, involuntary, spasmodic contractions of the diaphragm and inspiratory muscles followed by sudden closure of the glottis" (Krakauer 2005). These events generate the characteristic sound from which the name 'hiccup' is derived. Hiccups are an uncommon complaint in the general hospital setting: a retrospective study of patients in a Baltimore hospital between 1995 and 2000 found that 54 of over 100,000 admissions (0.00055%) were diagnosed with hiccups (Cymet 2002). However the symptom of severe persistent or intractable hiccups in patients with advanced cancer has been reported as between 3.9% to 4.5% (Porzio 2010). Hiccups can be classified under three categories dependent on the episode duration. Hiccups are defined as acute if the episode lasts for minutes to hours, persistent if the episode lasts for more than 48 hours, and intractable in instances in which the hiccups last for more than one month. Hiccups usually occur at a frequency of four to 60 per minute, the rate usually remaining constant for a particular individual. They are thought to arise due to stimulation of a hiccup reflex arc (Bailey 1943). Whether hiccups serve any constructive function is not known; it is possible that they are a vestigial reflex. A number of self-limiting causes of acute hiccups have been identified. These include gastric distension, the consumption of alcohol or carbonated beverages, hot or cold drinks, anxiety and stress. The presence of intractable hiccups can be indicative of serious underlying pathology (Cymet 2002; Souadjian 1968). More than 100 causes of persistent and intractable hiccup have been described. These can be categorised as: lesions of the Central Nervous System, diaphragmatic irritation, irritation of the vagus nerve, drug-induced, metabolic, surgical, infectious, psychogenic, and idiopathic (Lewis 1985). Medications implicated in the onset of hiccups include benzodiazepine derivatives and corticosteroids (Thompson 1997).

### Description of the intervention

A wide range of pharmacological and non-pharmacological interventions have been used for the treatment of persistent and intractable hiccups. However, there is little evidence as to which interventions are effective or harmful. Drugs used in the treatment of hiccups have included chlorpromazine, metoclopramide, sodium valproate, haloperidol, amitriptyline, carbamazepine, magnesium sulphate, baclofen, gabapentin, peppermint water, simeticone, benzodiazepines and nifedipine. Many different non-pharmacological interventions, mostly related to pharyngeal stimulation, have also been used for the treatment of hiccups.

### Why it is important to do this review

Although relatively uncommon, persistent and intractable hiccups can be of serious detriment to a patient's quality of life. In addition to causing significant discomfort and even pain, persistent and intractable hiccups can also affect concentration, sleep and oral intake. Dehydration and weight loss can result due to an inability to tolerate food and fluids. Hiccups may also lead to anxiety and depression (Wilcock 1996), and can lead to wound dehiscence in instances of recent abdominal or thoracic surgery (Santos 1974). On occasion they have been reported to cause ventricular dysrhythmia (Lewis 1985). No data were found relating to patient satisfaction or perception of effectiveness of current treatments for persistent and intractable hiccups.

## OBJECTIVES

The objective of this review was to evaluate the effectiveness of pharmacological and non-pharmacological interventions used in the treatment of persistent and intractable hiccups of any aetiology in adults.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Studies eligible for inclusion in this review were:

- randomised controlled trials (RCTs), or
- controlled clinical trials (CCTs).

We expected that the number of RCTs would be very small, therefore we decided to include CCTs but to give special consideration to the higher risk of bias in our analysis.

Studies were excluded if:

- there were less than ten participants, or
- if the outcome measures did not include any assessment of change in hiccup frequency or intensity.

#### Types of participants

Adults (over 18 years old) who had been diagnosed with persistent or intractable hiccup (i.e. hiccup episode lasting more than 48 hours). We included studies involving participants in any care setting, and with any underlying illness or no known underlying pathology. Participants diagnosed with acute hiccups (lasting less than 48 hours) were excluded.

#### Types of interventions

Studies were included if any pharmacological intervention (any drug given by any route, in any dose, in any frequency or duration) and any non-pharmacological intervention were used for the treatment of persistent or intractable hiccups. Studies were included if the pharmacological intervention was compared to placebo or other active drugs. We planned to compare the effectiveness of different interventions where possible.

#### Types of outcome measures

The following outcomes were considered:

##### Primary outcomes

1. Cessation of hiccups within a specified time period following intervention.
2. Any change in hiccup frequency, or subjective or objective change in hiccup intensity.
3. Adverse events caused by the intervention requiring withdrawal of the intervention.

##### Secondary outcomes

1. Minor adverse events not requiring withdrawal of intervention.
2. The number of different types of interventions needed to achieve cessation.

### Search methods for identification of studies

#### Electronic searches

Studies were identified from a search of the following databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (14th November 2012 )

- The Cochrane Database of Systematic Reviews (CDSR) in *The Cochrane Library* (14th November 2012).
- Database of Abstracts of Reviews of Effectiveness (DARE) (14th November 2012).
- MEDLINE (1950 to present).
- EMBASE (1980 to present).
- CINAHL (1980 to present).
- PsychINFO (1806 to present).
- SIGLE.

Strategies for all the databases searched were based on the MEDLINE search strategy presented in Appendix 1.

### Searching other resources

We scanned the reference lists of relevant studies and review articles for possible additional studies. We undertook no additional handsearching of journals. Investigators who are known to be carrying out research in this area were contacted for unpublished data or knowledge of the grey literature.

#### Language

There was no language restriction in the selection of studies.

## Data collection and analysis

### Selection of studies

Two independent review authors assessed each abstract and title for relevance. Disagreement on eligibility was resolved by discussion. Where no abstract was available the full paper was obtained and assessed. We obtained full copies of the studies which met the inclusion criteria for further assessment.

### Data extraction and management

Two review authors independently collected data from each appropriate study and entered it into RevMan.

### Assessment of risk of bias in included studies

Two review authors independently assessed the methodological quality of each of the selected studies. The risk of bias was assessed using the RevMan 'Risk of bias' table following guidance from the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2009).

#### Data analysis

In order to assess the effectiveness of the different pharmacological interventions we planned to extract dichotomous data from the included studies. We planned to calculate the number needed to treat (NNT) hiccups if data were available. If sufficient data were available we planned to undertake a meta-analysis of the dichotomous data using risk ratio (RR) as the summary statistic. The results of the studies were to be analysed using RevMan. Heterogeneity was also to be assessed using the $I^2$ test. If the $I^2$ test results were < 50% we would have used a fixed-effect model. If the $I^2$ test results were > 50% we intended to use a random-effects model. NNT and number needed to harm (NNH) were to be calculated where appropriate. We planned to calculate NNH for both minor and major adverse events. Major adverse events were defined as those that lead to withdrawal from the study. We intended to report on the number and type of adverse events.
If there were sufficient data we intended to perform subgroup analysis in the following groups: underlying diagnoses (e.g. cancer), age, prognosis, aetiology of hiccup.

# RESULTS

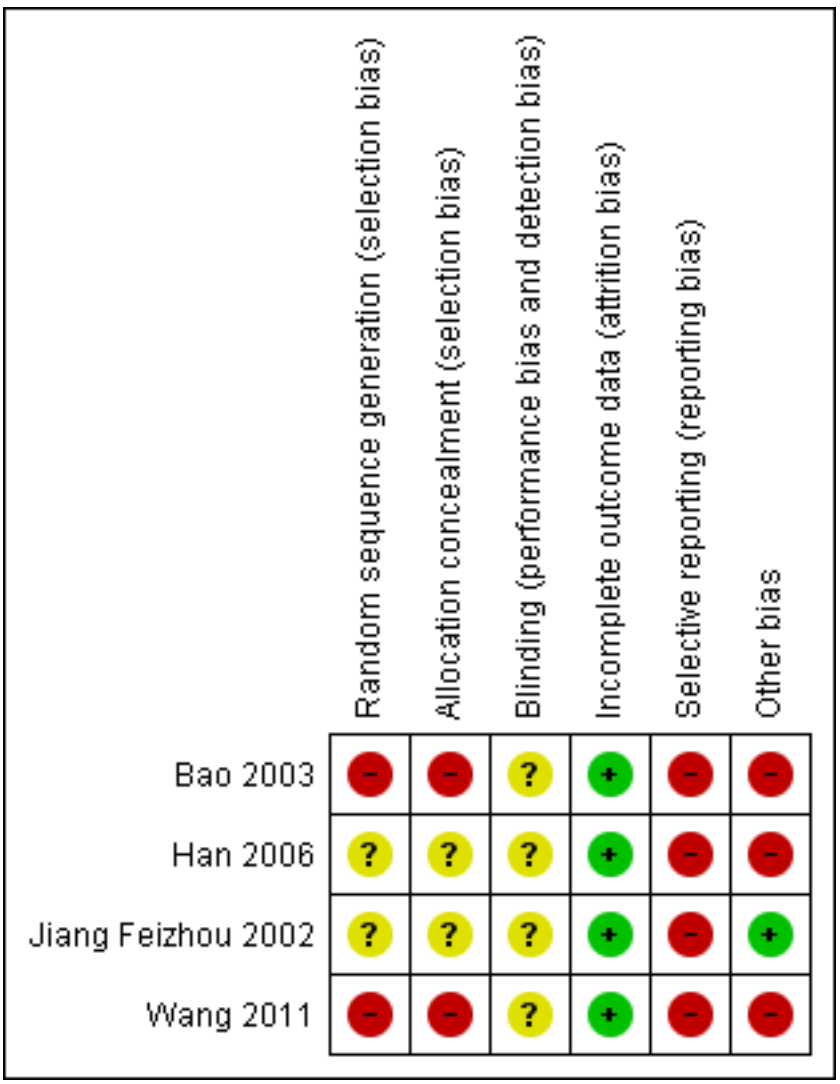
## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
The first search performed on 16th October 2010 revealed 1080 references (some duplicates). The vast majority of studies were case reports and case series. We obtained seven full articles and only one study fulfilled the inclusion criteria. One double blind randomised placebo controlled trial was excluded due to insufficient power (four patients) (Ramirez 1992). We repeated the search in March 2012. It was revealed that the initial search of the CENTRAL database had been incomplete. This yielded a further 21 studies, of which three met the inclusion criteria. There were seven articles for which we have been unable to obtain abstracts or a full article from the British Library. We are currently trying to obtain the full articles from China. These studies have been included in Studies awaiting classification.
A total of four studies met the inclusion criteria; due to methodological differences we were unable to perform a meta-analysis of the results. Details of the four studies which met the inclusion criteria of this review are given in the Characteristics of included studies section. Details of the excluded studies are given in the Characteristics of excluded studies

## Risk of bias in included studies

Risk of bias has been assessed in the included studies (see Characteristics of included studies and Figure 1). All studies were assessed as having high risk of bias. None of these studies appeared to be blinded, and none described the method of random sequence generation or whether there was allocation concealment.

**Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**




## Effects of interventions

Only four studies (305 participants) met the criteria for inclusion in the review. All of these studies sought to determine the effectiveness of differing acupuncture techniques as a treatment intervention for persistent and intractable hiccups.

In the first study, 85 patients with hiccups for more than three

days received acupuncture at multiple body points, scalp points and otopoints (Bao 2003). In the control group the acupuncture needles were retained for 30 minutes. In the treatment group the needles in the body acupoints were retained for one hour and at the scalp point retained for more than six hours. Treatment was conducted once daily for five days. The results were analysed after two weeks. In the treatment group (45 patients), 40 patients were cured (hiccup disappeared without relapse in 2 weeks following treatment). In the control group (40 patients), 26 were cured. There was a statistically significant difference in total cure rate between the groups ($P < 0.05$).

The second study compared the effectiveness of acupuncture with injection of toad extract (treatment) to acupuncture with injection of vitamin B6 (control) (Han 2006). 40 patients were randomised to each group. In the treatment group, 100% of patients were cured (hiccups stopped within 24 hours). In the control group, 12 patients were cured, 17 relieved (hiccup improved, but lasting more than 24 hours) and 11 patients had no improvement. The difference between the groups was statistically significant ($P < 0.05$). This trial did not use a placebo control.

The third study compared acupuncture in 60 patients with hiccups lasting more than 3 days (Jiang Feizhou 2002). The treatment and control groups received acupuncture at different sites. A treatment schedule consisted of the insertion of acupuncture needles for one hour every day, turning them every 10 minutes. This was continued for 10 days. The number of patients cured after one treatment in the treatment group (24) compared to the control group (14) was statistically significant ($P > 0.01$). However, the difference between patients cured in total in the two groups is not significant at the level $P < 0.05$.

The last study compared a control group, which received acupuncture at three sites, with a new intervention group, which received acupuncture at these sites and an additional fourth site (Wang 2011). All 80 patients had hiccups present for more than three days which were unresponsive to drug treatment. Acupuncture was given once daily for two periods of five days separated by a two day rest period, and the outcome was assessed at the end of treatment. The total effective rate (hiccups cured or improved) was 97.5% in the new intervention group and 85% in the control group ($P < 0.01$). In patients who were cured, time to improvement and time to cure was also reduced in the new intervention group ($P < 0.05$) compared to the control group. As the trial was not placebo controlled it is impossible to say whether either intervention was more effective than placebo.

No adverse events or side effects were reported in any group of any of the included studies.

Due to methodological differences we were unable to perform a meta-analysis of the results.

## DISCUSSION

Persistent and intractable hiccups can be of serious detriment to a patient's quality of life, although they are relatively uncommon. A wide range of pharmacological and non-pharmacological treatments have been reported in the literature. The aim of this review was to evaluate the effectiveness of these interventions for the treatment of persistent and intractable hiccups of any aetiology.

In order to capture as many studies as possible we included those looking at both non-pharmacological and pharmacological treatments for persistent and intractable hiccups. We also included studies of persistent and intractable hiccups of any aetiology. Despite this only four studies met the inclusion criteria. The vast majority of published papers were case reports and case series reporting the outcome of single interventions or, in a few cases, multiple different interventions.

The four studies which fulfilled the inclusion criteria all examined the effect of different types of acupuncture treatment for persistent and intractable hiccups. As the studies varied greatly in terms of treatments and study design a meta-analysis of the results could not be performed.

In Bao's study 85 patients with hiccups of more than three days duration received acupuncture at a scalp point, multiple body points and otopoints (Bao 2003). The same points were used for both groups (see original article). In the treatment group needles were retained for one hour in body acupoints, and more than six hours in the scalp point. In the control group needles were retained for 30 minutes. The total cure rate was 88.9% in the treatment group compared to 65% in the control group ($P < 0.05$). This study is subject to a high degree of bias. Patients were randomised on visiting time and there were not equal numbers in each group. Furthermore, some patients received acupuncture at supplementary sites depending on the different type of hiccup. It is not stated how many patients with these different types of hiccup were in each group and therefore it is difficult to be certain that the two groups were comparable or that all patients within a group received the same treatment. In addition, some of the treatment involved pressing on otopoints at least five times a day and whenever hiccup occurred, and the scalp needle was to be retained in the treatment group for more than six hours and removed at bed time; both of these factors could have been variable between patients.

This study further subdivided the results of both groups into two different syndrome types (deficiency syndrome type and excess syndrome type) which were not specified in the methodology. The study also sought to find out if there was a relationship between the cure rate and the duration of disease, by comparing the cure rate in patients who had deficiency-syndrome hiccups for less than two weeks and more than two weeks. The shorter the duration of disease the higher the cure rate in the treatment group ($P < 0.05$). However, the subdivision of the types of hiccup and duration were not stated in the methodology and the P value for the difference in the control group has not been provided.

Therefore, due to the high risk of bias, it was difficult to draw any conclusions from this study about where acupuncture should be applied and how long the needles should be retained. Furthermore, as there was no placebo control, treatment may not be better than placebo and no side effects or adverse events have been recorded.

In Han's study the effectiveness of acupuncture with injection of toad extract (treatment) was compared to acupuncture with injection of vitamin B6 (control) (Han 2006). In the treatment group, 100% of patients were cured with hiccups stopping within 24 hours. In the control group, 12 patients were cured, 17 relieved (hiccup improved, but lasting more than 24 hours) and 11 patients had no improvement. The difference between the groups was statistically significant ($P < 0.05$). With no placebo control it was impossible to be certain that either of the acupuncture treatments were more effective than placebo. This study was also subject to a high degree of bias; the method of randomisation and allocation concealment was not recorded, nor was there any reporting of blinding of the participants or outcome assessors. In addition this study stated the duration of hiccups prior to entry into study in 72 of the 80 patients. No side effects or adverse events were recorded.

In Jiang Feizhou's study 60 patients with hiccups lasting more than three days were randomised into treatment and control groups and received acupuncture at different sites (Jiang Feizhou 2002). A treatment schedule consisted of the insertion of acupuncture needles for one hour every day, turning them every 10 minutes. The treatment was repeated daily for 10 days. The number of patients cured after one treatment in the treatment group (24) compared to the control group (14) was statistically significant ($P > 0.01$). However, the difference between patients cured in total was not significant at the level $P < 0.05$. The different acupuncture sites which were used were not specified in the paper. It was not clear whether this study examined the difference in effectiveness of two different acupuncture regimes that were thought to be effective, or if it compared the effectiveness of acupuncture treatment compared to placebo with sham acupuncture. This study would appear to suggest that the acupuncture given to patients in the treatment group had a more immediate effect but that at the end of treatment there was not a significant difference in the number of cured patients in the control and treatment groups. This study was subject to a high degree of bias; the method of randomisation and allocation concealment is not recorded, nor was there any reporting of blinding of the participants or outcome assessors. No side effects or adverse events were recorded.

The other study which met the inclusion criteria compared acupuncture at three sites to acupuncture at four sites (an additional site to control) for the treatment of 80 patients with hiccups present for more than three days and unresponsive to drug treatment (Wang 2011). The types of drug treatment which had been used and the cause of hiccup was not reported. This study demonstrated that there was an improved total effective rate (hiccups cured or improved) in patients treated with the four sites of acupuncture compared to three sites of acupuncture. In patients who were cured the time to improvement and time to cure was also reduced in the intervention group with four sites. This study did not investigate whether either treatment was more effective than placebo. Furthermore no adverse events or side effects were reported in either group. The study was at high risk of bias due to the method of randomisation, and it was not reported whether the patients or assessors were blinded.

In summary all of the studies that fulfilled the inclusion criteria appeared to be prone to a high risk of bias and therefore it was difficult to draw any conclusion from these studies. Furthermore, as none of the studies had a placebo arm it was difficult to ascertain whether the hiccups would have improved without any treatment. None of the included studies measured or reported side effects or adverse events for either the treatment or control groups. There is therefore the potential that treatment with these interventions could be no better than placebo, and could cause harm.

A double-blind randomised controlled cross-over study treating intractable hiccups with baclofen (Ramirez 1992) did not meet the inclusion criteria due to insufficient power, however the study design had a low risk of bias and in light of the paucity of evidence may be helpful when considering drug treatments for intractable hiccups. Four male patients with hiccup for more than six months and unresponsive to previous medical therapy (including diazepam, chlorpromazine and metoclopramide) were studied. Following a two day baseline observation period patients were randomly assigned to receive either baclofen 5 mg three times daily or placebo for three days. The dose was then increased to 10 mg three times daily for an additional three days. The patients were discharged and dose reduced to zero over a period of a week. After an additional week "wash out" period the patients were readmitted and the procedure repeated as a cross-over. Nurses evaluated the frequency of hiccup, severity of hiccup and the number of 10 minute periods free of hiccup at nine predefined times per day. Patients evaluated hiccup severity. When patients received baclofen the hiccup-free period assessed by a nurse increased by 69% with the dose of 15 mg/day and 120% with the dose of 30 mg/day (statistically significant) whereas it remained the same or worse with the placebo. There was an improvement in the severity of hiccup noted by patients (subjective) when they were receiving baclofen, and when receiving baclofen 30 mg/day the improvement in subjective severity of hiccup was statistically significant. However, baclofen at either dose did not effect the actual hiccup frequency compared to placebo. Side effects were monitored and no side effects were reported by any patients in the study.

In a large case series patients with chronic hiccup (present for more than seven days) were divided into two groups based on the identified cause of hiccup (Guelaud 1995). The majority of patients had persistent hiccups for more than one year and multiple previous drug treatments (most commonly metoclopramide, chlor-

promazine and amitriptyline) had been ineffective. Patients with evidence of gastro-oesophageal disease (55) identified on OGD (oesophagogastroduodenoscopy) were treated with cisapride and omeprazole for one week. The majority of cases were clinically silent. 35 patients responded to this treatment. Patients with no evidence of gastro-oesophageal disease (17) were treated with baclofen (doses ranging from 15 to75 mg/day). Patients who failed to respond to treatment with cisapride and omeprazole after a week (20) were also given baclofen. Of the 37 patients that were treated with baclofen, complete resolution of hiccup was seen in 18 patients within a few days of commencing baclofen and a considerable decrease in 10 cases. Three patients were lost to follow up. In the few patients requiring doses higher than 45 mg/day of baclofen, nausea and somnolence were at times noted but disappeared when doses decreased. As this is not a case controlled study there is a high risk of bias and the improvement could have been coincidence.

Pharmacological interventions for persistent and intractable hiccups discussed in case reports include metoclopramide, gabapentin, baclofen, chlorpromazine, haloperidol, amitriptyline, benzodiazepines, steroids, nifedipine, nimodipine, sodium valproate, carbamazepine, lidocaine, nefopam, amantadine, olanzapine, alpha-2-delta ligands, sertraline, mirtazapine, marijuana, mexilitine, diphenylhydantoin and methylphenidate. Some larger case series have looked at the use of gabapentin (Porzio 2010, Moretti 2004), baclofen (Boz 2001, Guelaud 1995,) and chlorpromazine (Friedgood 1955). A number of case series that did not meet inclusion criteria for this review used a combination of drug treatments, for instance cisapride, omeprazole and baclofen (Guelaud 1995, Petroianu 1997). Some case series used aetiology of hiccup to determine treatment, for example omeprazole and cisapride in hiccups of gastro-oesophageal origin, and baclofen in cases of non gastro-oesophageal origin (Guelaud 1995).

Many non-pharmacological interventions for persistent and intractable hiccups have been described in case reports and case series. As already highlighted there are a large number of studies reporting the use of acupuncture for the treatment of persistent and intractable hiccups. There were eight articles for which we have been unable to obtain abstracts or a full article from the British Library. We are currently trying to obtain the full articles from China. These studies have been included in Studies awaiting classification.

In addition to the included studies, a retrospective case series (Ge 2010) reported the use of acupuncture in 16 adult male patients with cancer and persistent hiccups. Patients were given one to three acupuncture sessions within a seven day period. Eight acupuncture sites were used (Ge 2010) and treatment administered for 30 minutes. The treatment efficacy was evaluated using a hiccup assessment instrument (HAI) which was devised to evaluate the severity of hiccup pre- and post-treatment. Patients' subjective ratings of severity, discomfort, distress and fatigue were measured on 0-10 numerical scales. The mean hiccup severity was moderate (defined as interfering significantly with activities of daily living). Of the 16 patients, 13 had complete remission of hiccups after acupuncture treatments: 8 achieved these results after one treatment session, two after two sessions and three required three sessions. Three patients were excluded from the study after the first acupuncture session due to medical conditions which precluded further treatment; all of these patients had experienced reduction of hiccup symptoms following a single session. The difference in hiccup severity pre- and post-acupuncture treatment was highly significant. The study also reported that following acupuncture treatment there were significant reductions in discomfort, distress and fatigue in all 16 subjects. Following disappearance of hiccups there was also reported cessation of symptoms such as difficulties in swallowing, sleeping, breathing, speech, pain in the diaphragm area, cough, nausea and vomiting. No patients reported any adverse effects from acupuncture. As a case series the results are subject to high risk of bias. The study also proposed an instrument with which to assess hiccup severity; this would need to be validated prior to use in other studies.

Other case series reported the use of near-infrared irradiation in custom-set acupoints (Chang 2008), ultrasound-guided phrenic nerve block and diaphragmatic pacing for the treatment of persistent and intractable hiccups.

A recent systematic review has been published assessing the effectiveness of acupuncture for treating hiccups in patients with cancer(Choi 2012). This systematic review searched Chinese and Korean databases (DBPIA, KISS, KISTI, RISS, KoreaMed, the Koreaan National Assembly Library and the Chinese Medical Database in addition to the databases which we have searched(Electronic searches). Five studies met their inclusion criteria for the systematic review, all of these were from the Chinese and Korean databases. Of the five studies, three studies did not state the duration of hiccup, and in another study participants had hiccups present for less than 48 hours and therefore would be excluded from our systematic review. The remaining study(Wang 2006) may fulfil our inclusion criteria and therefore is also included in Studies awaiting classification.This systematic review has highlighted the possibility that there may be further studies within the Chinese and Korean databases which might fulfil our inclusion criteria and therefore we aim to run searches in these databases in the near future and update the review as soon as we have this information.

A further systematic review of the treatment of chronic hiccups in cancer patients reached the conclusion that there is a paucity of evidence concerning the effectiveness of treatments for hiccups in cancer patients (Calsina-Berna 2012). The report recommended that further clinical trials were required to compare the effectiveness of baclofen, gabapentin and chlorpromazine in the treatment of hiccups in cancer patients.

In conclusion there is very little evidence to guide the treatment

of persistent or intractable hiccups either pharmacologically or non-pharmacologically. Four randomised controlled trials demonstrated that acupuncture may be effective in the treatment of persistent and intractable hiccups. However these results should be interpreted with caution as the studies were not blinded or placebo-controlled, and did not report potential side effects, therefore these treatments may be no better than placebo.

The lack of randomised controlled trials of interventions for hiccups is likely to reflect that persistent and intractable hiccups occur rarely, and are potentially under-reported. The incidence of persistent and intractable hiccups is not known. However, there is evidence that hiccups can be very disabling for patients, having a large impact on quality of life and interfering significantly with activities of daily living. In order to guide treatment there is a need for randomised placebo-controlled studies to be undertaken. These may need to be multi-centred in order to gain sufficient power.

### Summary of main results

In summary there are four randomised controlled trials which demonstrate that acupuncture may be effective in the treatment of persistent and intractable hiccups. However, these studies do not appear to be blinded or placebo-controlled and did not report any side effects of treatment. The results should be interpreted with caution as the treatments may be no better than placebo. No studies investigating pharmacological interventions for persistent and intractable hiccups met the inclusion criteria. The vast majority of published studies of pharmacological interventions for persistent and intractable hiccups were case reports and case series.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is insufficient evidence to guide the treatment of persistent or intractable hiccups either pharmacologically or non-pharmacologically. Four randomised controlled trials demonstrated that acupuncture may be effective in the treatment of persistent and intractable hiccups. However these results should be interpreted with caution as the studies were not blinded or placebo-controlled, and did not report potential side effects, therefore these treatments may be no better than placebo.There are several larger case series looking at the use of baclofen or gabapentin for the treatment of persistent and intractable hiccups.

### Implications for research

There is a paucity of high quality studies examining the effectiveness of pharmacological or non-pharmacological interventions for persistent and intractable hiccups. This may be because persistent and intractable hiccups are a relatively rare and under-reported symptom. In order to guide the treatment of this disabling condition there is a need for randomised placebo-controlled trials of both pharmacological treatments and non-pharmacological treatments. As the condition is relatively rare, trials would probably have to be multi-centred and possibly multi-national. Ideally, the comparison of pharmacological versus non-pharmacological treatments would enable clinicians to make more informed decisions, giving information about effectiveness of the different treatment options and potential side effects. Furthermore, longer-term follow-up would allow the length of action of the treatments and the burden of treatments to be compared.

## ACKNOWLEDGEMENTS

We would like to thank Kuei-Chang HSU for his help in translation of many of the articles.

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Bao 2003**

| | |
|---|---|
| Methods | Quasi-randomised trial. |
| Participants | 85 participants with hiccups for greater than 3 days and not relieved with intramuscular injection of ritalin or 654-II (Anisodaminum)<br>Treatment group: 45 cases. 42 male, 3 female. Mean age 61 years<br>Hiccup duration < 2 weeks 33 cases; > 2 weeks 12 cases.<br>Control group: 40 cases. 38 male, 2 female. Mean age 59 years<br>Hiccups duration < 2 weeks 30 cases; > 2 weeks 10 cases. |
| Interventions | Acupuncture needles placed in scalp point and multiple body acupoints (see original article); the same points were used for both groups. However additional points/methods were used depending on the different type of hiccup - deficiency syndrome, liver-*qi* attacking the stomach, and type of stomach-cold. For example, for deficiency syndrome three additional points were used. Treatment was conducted once daily for 5 days. Otopoints were also used with vaccaria seeds-plaster pressed by patients more than five times a day and especially when hiccup occured. Results were analysed after two weeks of follow up survey<br>Control group: acupuncture needles were retained for 30 minutes<br>Treatment group: acupuncture needles in the body acupoints retained for one hour, in scalp point retained for more than six hours |
| Outcomes | Cured: Following treatment the hiccup disappeared without relapse within two weeks<br>Non-cured: Hiccup did not stop completely within two weeks.<br>Treatment group (45 patients): 40 patients cured, five non-cured; total cure rate 88.9% (deficiency syndrome 85.3%)<br>Control Group (40 patients): 26 cured, 14 non-cured; total cure rate 65% (deficiency syndrome 53.3%)<br>Statistically significant difference in total cure rate between groups (P < 0.05) |
| Notes | Further subdivision of groups into excess syndrome type and deficiency syndrome. The cure rates in both groups for excess syndrome was 100% (no significant difference) There is a significant difference in the cure rate between the two groups for the deficiency syndrome (P < 0.05) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Randomisation according to visiting time. Unequal numbers in each group |
| Allocation concealment (selection bias) | High risk | Randomisation according to visiting time. Unequal numbers in each group |

**Bao 2003** (*Continued*)

| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | No description or evidence of blinding of participants or outcome assessors |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcomes of all participants reported |
| Selective reporting (reporting bias) | High risk | No evidence adverse events monitored or recorded. No prespecified outcome measures recorded in methodology |
| Other bias | High risk | Additional acupoints used according to type of hiccup - no indication if same numbers of each type of hiccup in each group<br>Acupressure use by patient encouraged at least five times a day and when hiccups occur - likely to vary between individuals<br>Scalp needles in treatment group retained for > 6 hours until patient went to bed - likely to vary<br>"Results analysed after two weeks of follow-up survey". Treatment was for 5 days - as outcomes were measured nine days after treatment, resolution of hiccups may be due to other treatments or natural course of disease<br>Subgroups of excess and deficiency syndromes not defined in protocol |

**Han 2006**

| | | |
|---|---|---|
| Methods | Randomised controlled trial. | |
| Participants | Treatment group: 40 cases. 31 male, nine female. Mean age 55 years. Hiccups lasted five to seven days in 20 patients and two to five days in 16 patients<br>Control group: 40 cases. 32 male, eight female. Mean age 56 years. Hiccups lasted more than five days in 21 cases and two to five days in 15 cases | |
| Interventions | Treatment group: acupuncture and injection of toad extract<br>Control group: acupuncture at same sites (see original article) and injection of vitamin B6 | |
| Outcomes | Cured: stopped in 24 hours.<br>Relieved: improved but hiccups lasted more than 24 hours.<br>Treatment group (40 patients): 40 patients cured<br>Control Group (40 patients): 12 cured, 17 relieved, 11 no effect<br>Statistically significant difference between groups, $P < 0.05$ | |
| Notes | No adverse events or side effects reported with either group | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |

**Han 2006** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No description of randomisation |
| Allocation concealment (selection bias) | Unclear risk | No description |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | No description or evidence of blinding of participants or outcome assessors |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcomes of all participants reported |
| Selective reporting (reporting bias) | High risk | No evidence adverse events monitored or recorded |
| Other bias | High risk | Duration of hiccups prior to intervention was not recorded for four patients in the treatment group and four patients in the control group |

**Jiang Feizhou 2002**

| | |
|---|---|
| Methods | Randomised controlled trial. |
| Participants | 30 patients in treatment group, 30 in control group.<br>Hiccups lasting 3 or more days.<br>Ages 26-75 years. |
| Interventions | Acupuncture.<br>Treatment and control groups use different acupuncture sites (see original article). Control uses sham acupuncture technique<br>A treatment schedule consisted of the insertion of acupuncture needles for one hour every day,turning them every 10 minutes. This was continued once a day for 10 days |
| Outcomes | Cured: absence of symptoms, with no recurrence (follow up to 1 month)<br>Relieved: hiccups less common or of reduced intensity.<br>Treatment group: 24 patients cured after one treatment , 27 cured in total, 2 relieved, 1 no effect<br>Control group: 14 cured with one treatment, 21 cured in total,7 relieved, 2 no effect<br>Difference between patients cured in total is not significant at the level $P < 0.05$. Statistically significant difference between number of patients cured after one treatment $P < 0.01$ |
| Notes | No adverse events or side effects reported with either group |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Jiang Feizhou 2002** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No description of randomisation |
| Allocation concealment (selection bias) | Unclear risk | No description |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | No description or evidence of blinding of participants or outcome assessors |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcome of all participants reported |
| Selective reporting (reporting bias) | High risk | No evidence adverse events monitored or recorded |
| Other bias | Low risk | |

**Wang 2011**

| | |
|---|---|
| Methods | Quasi-randomised controlled trial. |
| Participants | 80 patients with hiccups that had been present for more than three days and refractory to oral/intramuscular treatment<br>40 patients in new intervention group, 40 patients in control group |
| Interventions | Control group: Acupuncture at three sites.<br>New intervention group: Acupuncture at a fourth main site in addition to above three sites<br>Needles retained for thirty minutes. Acupuncture given once daily for five days. Followed by two day rest period. Then a further five day treatment once daily<br>Effectiveness assessed at the end of treatment. |
| Outcomes | Cure: Hiccups stopped without recurrence for at least five days<br>Improvement: reduction in sound of hiccups, reduction in duration of hiccup, or reduction in abdominal discomfort<br>No change.<br>New Intervention Group (40 patients): Cure 77.5%, improvement 20%, no change 2.5%<br>Control group (40 patients): Cure 50%, improvement 35%, no change 15%<br>Statistically significant difference between groups ($P < 0.01$)<br>In patients who were cured, time to improvement and time to cure was also reduced in new intervention group ($P < 0.05$)<br>New Intervention Group (31 patients) Time to improvement (days) 1.9 ± 0.5, time to cure 4.1 ± 2.0<br>Control Group (20 patients) Time to improvement (days) 2.2 ± 0.6, time to cure 5.3 ± 2.2 |
| Notes | No adverse events or side effects reported with either group |

**Wang 2011** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | High risk | Randomised by order of outpatient attendance |
| Allocation concealment (selection bias) | High risk | Randomised by order of outpatient attendance. Lack of detailed description |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | Lack of detailed description, no record of blinding of participants or assessors |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants accounted for |
| Selective reporting (reporting bias) | High risk | No evidence adverse events monitored or recorded |
| Other bias | High risk | No placebo control therefore unclear if hiccups resolving spontaneously |

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Boz 2001 | Open label prospective study 10 patients |
| Chang 2008 | Case series 35 patients |
| Chen 2006 | No mention of hiccup duration |
| Chen 2007 | No mention of hiccup duration |
| Dai 2003 | Acute hiccups less than 48 hours duration prior to intervention |
| Dore 2007 | Not specifically investigating treatment of hiccups |
| Friedgood 1955 | Case series 50 patients |
| Ge 2010 | Case series 16 patients |
| Guelaud 1995 | Case series 72 patients |

(*Continued*)

| | |
|---|---|
| Huang 2003 | No mention of hiccup duration |
| Jun 2003 | Case series 15 patients |
| Liu 2007 | Includes acute hiccups, less than 48 hours duration |
| Luo 2007 | No mention of hiccup duration |
| Moretti 2004 | Case series 15 patients |
| Petroianu 1997 | Case series 15 patients |
| Porzio 2010 | Case series 43 patients |
| Ramirez 1992 | Insufficient power: four patients in this double blind cross-over RCT |
| Wang 1994 | No mention of hiccup duration. Randomised |
| Wang 2004 | No mention of hiccup duration |
| Wu 2003 | No mention of hiccup duration. Quasi-randomised |
| Xie 2006 | No mention of hiccup duration |
| Yan 2002 | No mention of hiccup duration |
| Yang 2004 | Hiccups present for 24 hours or more prior to intervention. Quasi-randomised |
| Yang 2007 | Acute hiccups less than 48 hours duration |
| Zhao 2004 | Hiccups present for 12 hours prior to intervention |

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix 1. Search strategy

Search strategy and study design filter for MEDLINE which was adapted for EMBASE, CINAHL, PsychINFO and SIGLE:
#1 Hiccup/
#2 (hic*up* or hic*ough* or singult*).mp.
#3 #1 or #2
Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format. (Box 6.4.c of The Cochrane Handbook of Systematic Reviews of Interventions)
# 1. randomized controlled trial.pt.
# 2. controlled clinical trial.pt.
# 3. randomized.ab.
# 4. placebo.ab.
# 5. drug therapy.fs.
# 6. randomly.ab.
# 7. trial.ab.
# 8. groups.ab.
# 9. or/1-8
# 10. exp animals/ not humans.sh.
# 11. 9 not 10

## CONTRIBUTIONS OF AUTHORS

| | |
|---|---|
| Draft the protocol | AM/EM/PW/BW |
| Develop a search strategy | AM/EM/BW |
| Search for studies | AM/EM |
| Obtain copies of studies | AM/EM |
| Select which studies to include | AM/EM/PW/BW |
| Extract data from studies | AM/EM |
| Enter data into RevMan | AM/EM |
| Carry out the analysis | AM/EM |
| Interpret the analysis | AM/EM/PW/BW |

(*Continued*)

| | |
|---|---|
| Draft the final write-up of the review | AM/EM |
| Update the review | AM/EM |
| Content expert name | BW |
| Methodologist name | PW |

## DECLARATIONS OF INTEREST

None known

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acupuncture Therapy [*methods]; Hiccup [*therapy]; Randomized Controlled Trials as Topic

### MeSH check words

Adult; Humans