A Systematic Review of Controlled Trials of Homeopathy in Bronchial Asthma

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Keywords

Systematic review · Homeopathy · Bronchial asthma · Controlled trials

Abstract

Homeopathy is a controversial form of complementary therapy, but is widely practised to treat asthma. The aim of this systematic review is to evaluate the controlled trials of homeopathy in bronchial asthma. Relevant trials published between Jan 1, 1981, and Dec 31, 2016, were considered. Substantive research articles, conference proceedings, and master and doctoral theses were eligible. Methodology was assessed by Jadad's scoring, internal validity by the Cochrane tool, model validity by Mathie's criteria, and quality of individualization by Saha's criteria. Sixteen trials were eligible. The majority were positive, especially those testing complex formulations. Methodological quality was diverse; 8 trials had "high" risk of bias. Model validity and individualization quality were compromised. Due to both qualitative and quantitative inadequacies, proofs supporting individualized homeopathy remained inconclusive. The trials were positive (evidence level A), but inconsistent, and suffered from methodological heterogeneity, "high" to "uncertain" risk of bias, incomplete study reporting, inadequacy of independent replications, and small sample sizes. © 2019 S. Karger AG, Basel

Schlüsselwörter

Systematische Übersichtsarbeit · Homöopathie · Asthma bronchiale · Kontrollierte Studien

Zusammenfassung

Homöopathie ist eine kontrovers diskutierte Methode der Komplementärmedizin, die in der Asthmabehandlung dennoch häufig eingesetzt wird. Mit der vorliegenden systematischen Übersichtsarbeit sollen die kontrollierten Studien zur Homöopathie bei Asthma bronchiale bewertet werden. Dabei wurden relevante Studien, die zwischen dem 1. Januar 1981 und dem 31. Dezember 2016 veröffentlicht worden waren, berücksichtigt. Stichhaltige wissenschaftliche Artikel, Kongressbände sowie Master- und Doktorarbeiten wurden in die Untersuchung eingeschlossen. Die Bewertung der Methodik erfolgte anhand der Jadad-Skala sowie durch Beurteilung der internen Validität mittels Cochrane-Tool, der Modellvalidität gemäß den Mathie-Kriterien und der Qualität der Individualisierung entsprechend den Saha-Kriterien. Sechzehn Studien wurden in die Arbeit eingeschlossen. Die meisten kamen zu positiven Ergebnissen, insbesondere jene, die komplexe Formulierungen untersuchten. Hinsichtlich der methodischen Qualität unterschieden sich die Studien, und 8 Studien wiesen ein "hohes" Verzerrungsrisiko auf. Modellvalidität und Qualität der Individualisierung waren eingeschränkt. Aufgrund der qualitativen und quantitativen Unzulänglichkeiten fanden sich keine eindeutigen Hinweise,

die die individualisierte Homöopathie stützen. Die Studien fielen positiv (Evidenzklasse A), jedoch inkonsistent, aus und waren durch ihre methodische Heterogenität, ein "hohes" bis "unklares" Verzerrungsrisiko, unvollständige Studienberichte, Unzulänglichkeit der unabhängigen Wiederholungen sowie kleine Stichprobengrößen eingeschränkt.

Introduction

Rationale

Homeopathy has remained one of the most widespread and controversial forms of complementary medicine and is used to treat asthma. The prevalence estimates of complementary therapy use for asthma vary widely, from 6 to 70% [1–3]. However, the clinical evidence remains unconvincing regarding the effectiveness of complementary therapies and homeopathy for asthma [4]. In addition, systematic reviews identified the paucity of high-quality randomized controlled trials in homeopathy [5–13]. There are several distinct forms of homeopathy in practice – “individualized,” “clinical,” “complex,” and “isopathy.” In individualized homeopathy, typically a single homeopathic medicine is selected on the basis of the “totality of symptoms” of a patient, including mental, general, and constitutional type and “miasmatic expressions.” In clinical homeopathy, one or more homeopathic medicines are administered for standard clinical conditions or conventional diagnoses. In complex homeopathy, several homeopathic medicines are combined in a fixed formulation. Isopathy, also popularly known as “homeopathic immunotherapy” (HIT), is the use of homeopathic dilutions from the causative agent of the disease itself (e.g., organisms or allergens), or from a product of the disease process, to treat the condition, strategically different from individualized homeopathic prescribing in the classic sense. However, a Cochrane systematic review [8] in the previous decade concluded that there was not enough evidence to reliably assess the possible role of homeopathy in asthma because of heterogeneity in the type of homeopathy and study designs; and until stronger evidence existed, no further recommendations could be made about homeopathic treatment. Since publication of this paper, no further systematic review has been undertaken in the concerned subject.

Objectives

The aim of the present analysis was to systematically review the literature on homeopathic controlled clinical studies of bronchial asthma published between 1980 and 2016 and to evaluate whether homeopathy treatment (alone or as additive to standard therapy) could produce any different effect from control (placebo or standard therapy) in the reported outcomes. Reporting of this systematic review was compliant to the PRISMA statement [14–16].

Materials and Methods

Protocol and Registration

The review protocol was adherent to the PRISMA-P guidelines [17, 18] and was registered in the PROSPERO database (International Prospective Register of Systematic Reviews, National Institute for Health Research, Centre for Reviews and Dissemination, University of York, UK) prospectively (Reg. No. 42017071609).

Inclusion/Exclusion Criteria

Controlled trials (randomized, non-randomized, or observational) of any form of homeopathy in patients suffering from persistent and chronic bronchial asthma, published between Jan 1, 1981, and Dec 31, 2016, without any language restriction.

Information Sources

Substantive research articles (either peer-reviewed or not) as well as conference proceedings and master and doctoral theses were eligible for screening. Book chapters and abstracts were excluded. A list of reprint articles is presented in Appendix I. Articles excluded due to insufficient reporting are listed in Appendix II.

Searches

Different medical databases including MEDLINE (via PubMed), EMBASE (Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley interface), CORE-Hom (Carl and Veronica Carstens-Stiftung), ChiroACCESS (MANTIS interface), LILACS (Biblioteca virtual em salud interface), and Google Scholar were used for the literature search. Various search terms were used for different databases, for example:

MEDLINE: homeopath* OR homoeopath* AND “randomized controlled trial” OR “controlled clinical trial” OR “randomized” OR “placebo”

EMBASE: homeopath\$ OR homoeopath\$

CENTRAL: homeopathy (MeSH)

CORE-Hom: Specifying the field “Respiratory tract disorder” (138 hits)

ChiroACCESS: homeopath* OR homoeopath*

LILACS: homeopath\$ AND random\$

Besides, hand search was made into different journals, magazines, meeting abstracts, and bibliographic sections of reviews, meta-analyses, and original trial papers. The most recent search was carried out in August 2017.

Study Selection

Selection included randomized and non-randomized controlled trials and controlled observational studies of any form of homeopathy in bronchial asthma.

Data Collection Process

Data extraction was performed utilizing standardized Microsoft Excel files. Two reviewers (M.K. and S.S.) extracted the data and double-checked the information independently. Discrepancies, if any, were resolved by consulting with another independent reviewer (C.N.). The classification of the therapeutic approaches was made according to a grade of evidence in six levels, which had been developed by Natural Standard, an international research collaboration that aggregates and synthesizes data on complementary and alternative therapies (<http://www.naturalstandard.com/index.asp>). A summary of these criteria is reported in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000494621).

Data Items

The following data was extracted from the included studies:

- 1 Publication type (substantive research article peer-reviewed; substantive research article non-peer-reviewed; minor research article peer-reviewed; thesis; minor research article non-peer-reviewed; master thesis; doctoral thesis; conference proceedings); the levels of evidence of the studies and publications are graded as per criteria mentioned in online supplementary Tables 2 and 3.
- 2 Study aim and target population
- 3 Inclusion and exclusion criteria
- 4 Study design (randomized controlled trials, controlled cohort study, case-control study)
- 5 Intervention details (potency; type of homeopathy (individualized/classical; clinical; complex; isopathy; preventive)
- 6 Control details: placebo or conventional treatment as control; homeopathy as additive or not
- 7 Number of patients that have participated, and that have been evaluated in each group; attrition rate; intention-to-treat or per-protocol analysis
- 8 Statistical reporting: measures of central tendency and dispersion for continuous data, number of favourable events for dichotomous data, etc. As we expected considerable variety in outcomes – both primary and secondary, those were planned to be reported in all data formats (e.g., dichotomous, continuous).
- 9 Funding and declared conflicts of interest.

Risk of Bias in Individual Studies

Two reviewers (M.K. and S.S.) independently assessed the methodological aspects of the included studies. Disagreements on data extraction were resolved by discussion and participation of another reviewer (C.N.). If information was missing, the study authors were contacted by e-mail.

Firstly, the methodological quality was assessed by the Jadad scoring system [19] in the following domains:

- 1 Randomization
 - 2 Blinding
 - 3 Description of withdrawals and drop-outs
- The internal validity of the trials was evaluated by the Cochrane Collaboration tool for assessing the risk of bias in randomized trials [20] for the seven following domains:
- 1 Random sequence generation
 - 2 Allocation concealment
 - 3 Blinding of participants and personnel
 - 4 Blinding of outcome assessors
 - 5 Incomplete outcome data, i.e., whether all the randomized patients are accounted for in the analysis
 - 6 Selective reporting
 - 7 Anything else

The internal validity of the observational studies was assessed by the Cochrane risk of bias assessment tool for non-randomized studies of interventions [21, 22] for the seven following bias domains:

- 1 Confounding
- 2 Selection of participants into the study
- 3 Measurement of interventions
- 4 Departures from intended interventions
- 5 Missing data
- 6 Measurement of outcomes
- 7 Selection of reported results.

By the standard Cochrane approach, each trial is designated as follows:

- (a) low risk of bias for all key domains;
- (b) uncertain risk of bias for one or more key domains; and

- (c) high risk of bias for one or more key domains.

The novel method of nomenclature was adopted based on the Cochrane approach for rating risk-of-bias characteristics across all domains per trial as proposed by Mathie et al. [23] (2014) as follows:

A = Low risk of bias in all seven domains

Bx = Uncertain risk of bias in x domains; low risk of bias in all other domains

Cy.x = High risk of bias in y domains; uncertain risk of bias in x domains; low risk of bias in all other domains.

The homeopathic model validity was evaluated by the six judgemental domains proposed by Mathie et al. [24] (2015):

- 1 Rationale for the choice of the particular homeopathic intervention
- 2 Homeopathic principles reflected in the intervention
- 3 Extent of homeopathic practitioner input
- 4 Nature of the main outcome measure
- 5 Capability of the main outcome measure to detect change
- 6 Length of the follow-up to the endpoint of the study.

The quality of homeopathic individualization was evaluated by the six judgemental criteria proposed by Saha et al. [25] (2014):

- 1 Single medicine prescription when required on each occasion
- 2 Medicine individualization
- 3 Proper description of approach to medicine individualization
- 4 Dose individualization
- 5 Proper description of approach to dose individualization
- 6 Subsequent prescriptions as per Kent's observations and/or Hering's law.

Summary Measures

Keeping in mind the heterogeneity in homeopathy trials in terms of intervention, study designs, and outcome reporting, as identified in the earlier meta-analyses as well, it seemed inappropriate to draw any summary measure (e.g., odds ratio, risk ratio, etc.) and to combine them into quantitative meta-analytic models comparing treatment effects of homeopathic medicines with those of placebo or standard therapies.

Synthesis of Results

A narrative synthesis of the findings from the included studies, structured around outcome and intervention/comparator was provided.

Risk of Bias across Studies and Additional Analyses

None planned.

Results

Study Selection

A total of 1,218 records were identified by electronic and manual searches between 1981 and 2016 of which 55 records were screened further. Among these, 27 were excluded and 28 records were considered further. Of these, there were 16 controlled trials and 12 uncontrolled observational studies (see study flow diagram; Fig. 1).

Study Characteristics

Sixteen controlled trials [26–41] (online suppl. Table 4) and 12 uncontrolled observational studies [42–53] (online suppl. Table 5) of homeopathy in bronchial asth-

Fig. 1. Study flow diagram.

ma were identified. Thus, the level of evidence was graded as A (strong scientific evidence, i.e., statistically significant evidence of benefit from more than 2 properly conducted randomized trials; online suppl. Table 1). For each controlled trial, the following characteristics – study and publication type, aim, population and setting, exclusion and inclusion criteria, design, intervention, control, number of patients, and attrition and analysis (per protocol/PP or intention to treat/ITT), key results, study funding, and declared conflict of interest – were extracted and are arranged with citations in online supplementary Table 4. Among the 16 controlled trials, 6 were of complex homeopathy, 5 of individualized homeopathy, 3 of HIT, and 2 of clinical homeopathy. Data for the observational uncontrolled studies was also extracted and is presented in online supplementary Table 5. Among these 12 uncontrolled studies, individualized, clinical, and HIT were tested in 8, 3, and 1 study, respectively.

Risk of Bias within Studies

Methodological quality, as analysed by Jadad scoring, was judged to be diverse, ranging from 1 to 5 (online suppl. Table 6). Risk of bias in each controlled trial, as evaluated by using seven domains of Cochrane Collaboration

tool (detailed in Materials and Methods) is elaborated in online supplementary Table 7. Eight trials had “high” risk of bias, while 8 had “uncertain” risk of bias. Model validity was also compromised – only 3 had “acceptable” rating, two were “uncertain,” and the remaining 11 were “inadequate” (online suppl. Table 8). Similar evaluation was also performed using the individualization scoring method – the trials having model validity designated as “acceptable” and “uncertain” got a score of 2 or 3 out of 6, respectively; the rest of the trials got a score of 0 to 1 (online suppl. Table 9). Similarly, risk of bias, model validity, and quality of individualization were also assessed for the uncontrolled observational studies (online suppl. Tables 10–12). All the studies had “high” risk of bias (online suppl. Table 10), “inadequate” model validity (except 2 studies; online suppl. Table 11) with variable scores of 1–4 on individualization (online suppl. Table 12).

Discussion

Summary of Evidence

Sixteen controlled trials of homeopathy in bronchial asthma were identified. The trials were heterogeneous in

terms of type of homeopathy used, methodological qualities, risk of bias, model validity, and quality of individualization. Most of them were double blind, randomized, parallel arm, and placebo controlled, and homeopathy was mostly used as additive to standard care. The majority of the studies were positive, and the level of evidence could be graded as A (strong scientific evidence). All the controlled trials testing complex homeopathic products were funded and yielded positive results, thus raising additional concern regarding whether these studies were free from vested interest or not. Proof in support of individualized homeopathy remained equivocal and inconclusive. Evidence in support of HIT or clinical homeopathy remained sparse. Besides, due to wide variability and incompleteness in study reporting, “high” to “uncertain” risk of bias, inadequacy of independent replications, and small sample sizes, quantitative pooling of the effect sizes into a meta-analytic model seemed inappropriate and improbable. Considerable heterogeneity was also identified in terms of the selected outcome measures – ranging from objective to different subjective outcomes. Objective outcomes included spirometry readings, granulocyte functions, etc., whereas subjective measures included symptom intensity measuring visual analogue scales, frequency of asthma attacks and medication use, number of withdrawals and drop-outs, clinical assessments and scorings, quality of life questionnaire, patient-rated relief, etc. The target sample included both children and adults. Intervention was also varied in terms of individualized, clinical, complex, immunotherapy, and often as adjunctive to usual care. Positive responses were elicited predominantly on symptom severity subjective outcomes, frequency of asthmatic attacks and use of standard medications, and immunological markers, whereas responses obtained on lung functions were equivocal and negative on quality of life outcomes. Outcomes from controlled trials were always favourable for complex homeopathy, but ambivalent in cases of other forms of homeopathy – classic or individualized, immunotherapy or clinical. Contrarily, evidence from non-controlled trials was in support of both individualized and clinical homeopathy, against immunotherapy, but none existed of complex homeopathy. We recommend both placebo-controlled (in the mutual context of usual care) and pragmatic models testing the efficacy and effectiveness of homeopathy, respectively, by using both subjective and objective measures and allowing practitioners to prescribe freely in their usual way. It is important to test homeopathy in the form in which it is commonly practised rather than in a form specially curtailed for clinical trials. The trials should keep provision for input of more than one experienced homeopath in order to counter any negative result attributed to lack of competence of a single therapist.

Limitations

All the relevant papers were captured by electronic and manual searches into all available databases and bibliographies; nevertheless, retrieval may be incomplete. At this stage, any meta-analysis of the existing results is not possible; rather, further adequately powered trials and replications are recommended.

Conclusion

Overall, the findings of this review seem to be promising enough and qualitatively suggest a definite role of homeopathy beyond placebo in the treatment of bronchial asthma; however, they are not adequately supported by level A evidence. Though few trials were rated as 1a or 1b, they still suffered from many important caveats including inadequate power and sample size and less robust designs in terms of randomization, blinding, and choice of outcome measures. Independent replications and further evaluation in appropriate and rigorous designs are warranted.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare. The review was carried out as part of a PhD thesis of the corresponding author.

Funding Sources

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Author Contributions

M.Q. and S.M.S. were involved in the concept, design, literature search, data extraction and interpretation, and preparation of the article. C.N., M.K., and S.S. participated in data extraction and interpretation, and preparation of the article. All the authors edited, reviewed, and approved the final article.

Appendix I

List of Reprint Articles

- Matusiewicz R. The effect of a homeopathic preparation on the clinical condition of patients with corticosteroid-dependent bronchial asthma [Die Wirkung einer homöopathischen Präparation auf den klinischen Zustand von Patienten mit kortikosteroidabhängigem Bronchial asthma]. *Biomed Ther.* 1997;15:70–4.
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Appendix II

Articles Excluded due to Insufficient Reporting

- Blackie MG. Asthma. *Br Homeopath J.* 1932;22:179.
- Zotou P. Statistical study of the results of treatment of childhood asthma by homeopathic remedies. *Proceedings of the 43rd LMHI Congress; 1988; Athens, Greece; p. 284–305.*

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