

# BMJ Open Herbal medications for surgical patients: a systematic review protocol

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**To cite:** Arruda APN, Ayala AP, Lopes LC, *et al.* Herbal medications for surgical patients: a systematic review protocol. *BMJ Open* 2017;**7**:e014290. doi:10.1136/bmjopen-2016-014290

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2016-014290>).

Received 14 September 2016  
Revised 28 February 2017  
Accepted 20 March 2017

## ABSTRACT

**Introduction** Postoperative nausea and vomiting (PONV) affect approximately 80% of surgical patients and is associated with increased length of hospital stay and systemic costs. Preoperative and postoperative pain, anxiety and depression are also commonly reported. Recent evidence regarding their safety and effectiveness has not been synthesised. The aim of this systematic review is to evaluate the efficacy and safety of herbal medications for the treatment and prevention of anxiety, depression, pain and PONV in patients undergoing laparoscopic, obstetrical/gynaecological and cardiovascular surgical procedures.

**Methods and analysis** The following electronic databases will be searched up to 1 October 2016 without language or publication status restrictions: CENTRAL, MEDLINE, EMBASE, CINAHL, Web of Science and LILACS. Randomised clinical trials enrolling adult surgical patients undergoing laparoscopic, obstetrical/gynaecological and cardiovascular surgeries and managed with herbal medication versus a control group (placebo, no intervention or active control) prophylactically or therapeutically will be considered eligible. Outcomes of interest will include the following: anxiety, depression, pain, nausea and vomiting. A team of reviewers will complete title and abstract screening and full-text screening for identified hits independently and in duplicate. Data extraction, risk of bias assessments and evaluation of the overall quality of evidence for each relevant outcome reported will be conducted independently and in duplicate using the Grading of Recommendations Assessment Development and Evaluation classification system. Dichotomous data will be summarised as risk ratios; continuous data will be summarised as standard average differences with 95% CIs.

**Ethics and dissemination** This is one of the first efforts to systematically summarise existing evidence evaluating the use of herbal medications in laparoscopic, obstetrical/gynaecological and cardiovascular surgical patients. The findings of this review will be disseminated through peer-reviewed publications and conference presentations.

**Systematic review registration** PROSPERO CRD42016042838.

## INTRODUCTION

Postoperative nausea and vomiting (PONV) and pain account for over half of reported symptoms by surgical patients.<sup>1</sup> Defined as

## Strengths and limitations of this study

- This systematic review will provide an objective, comprehensive and systematic assessment of the use of herbal medications for surgical patients who undergo laparoscopic, gynaecological/obstetrical and cardiac surgeries.
- The results of this systematic review may assist clinicians and health professionals make clinical decisions regarding symptom prevention and management, and may guide researchers in terms of additional questions to be addressed in relation to herbal medications with this patient population.
- While systematic and robust in its methods, this systematic review is limited primarily to the peer-reviewed literature addressing herbal medications for the patient population of interest, and may not capture evidence from other sources.

nausea and/or vomiting occurring within 24 hours after surgery, reported PONV prevalences among surgical patients ranged from 25% to 30% in a number of studies, and have been reported as high as 80%.<sup>2,3</sup> In addition to decreased quality of life, PONV has also been associated with increased hospital length of stay and systemic costs.<sup>4</sup> While recommendations for pharmacological prophylaxis and treatment for PONV exist, these medications may be associated with notable side effects.<sup>5</sup>

Depression and anxiety are also very frequent worldwide in terms of perioperative symptoms for patients undergoing surgery, and have been associated with prolonged durations to recovery.<sup>6,7</sup> Reported prevalences of anxiety have been reported to be as high as 80% in the perioperative period,<sup>8,9</sup> and has been reported to be higher among those with chronic medical conditions relative to the general population.<sup>10</sup> Depression and anxiety disorders have been associated with increased rates of readmission,<sup>11</sup> morbidity<sup>12</sup> and mortality<sup>13</sup> in surgical patients.

Evidence from the USA suggests that 70% to 80% of the 23 million people who undergo surgical procedures annually experience



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moderate to severe pain.<sup>14</sup> Another study reported a postoperative pain prevalence of 52.5% in the first 24 hours and 41.1% on the second postoperative day for hospitalised surgical patients, with the most common type of pain reported by patients being musculoskeletal (54%).<sup>15</sup> Generally, pain decreases over time but may persist for days or even months postoperatively.<sup>16</sup> Postoperative pain may complicate recovery and delay discharge of patients as well.<sup>17</sup>

Conventional medications are the general treatment for this set of symptoms. Premedication with anxiolytic and sedative drugs may reduce preoperative anxiety.<sup>18</sup> However, the role of anxiolytic premedication for surgical patients remains unclear and postoperative side effects may result from routine premedication.<sup>19</sup> Recently, new generations of antiemetic and shorter-acting anaesthetic drugs have been used in PONV.<sup>20</sup> Opioid agonists are the current mainstay of pain treatment after surgery, but opioid therapy is severely limited by side effects at effective doses.<sup>21</sup> Preoperative cognitive behavioural therapy (CBT) has been associated with less postday surgery pain and a lower risk of chronic postoperative pain.<sup>22</sup> Postoperative CBT has also been associated with decreased postoperative depression rates relative to conventional medications.<sup>23</sup>

Use of herbal medications by surgical patients is quite common worldwide for a number of these indications as well, although geographic variability exists. A study of hospitalised patients in a public medical centre in Israel found that 44% reported using herbal remedies in the last year; 89 different remedies were reportedly used.<sup>24</sup> In comparison, the estimated prevalence of herbal medicine use for patients undergoing surgery in the USA has been reported to range from 32% to 51%.<sup>25</sup> Eighty-five per cent of the Brazilian population has been reported to use medicines involving plants or plant-based preparations as part of their healthcare.<sup>26</sup> Reported prevalence rates for herbal medicine use in the European countries range from 5.9% to 48.3% across the UK, Germany, Turkey, Switzerland, Sweden, Norway, Denmark, Italy, Israel, Finland and Spain.<sup>27</sup>

While herbal medications have been associated with positive effects on postoperative pain, anxiety and PONV,<sup>28–30</sup> they have been associated with side effects of their own. In addition, there may also be concerns regarding interactions with conventional medications and associated perioperative adverse events such as bleeding, cardiovascular instability, coagulopathy, excessive somnolence, photosensitivity and endocrine and electrolyte disturbances.<sup>31–37</sup> Despite growing knowledge about herbal medications and drug interactions, most of these concerns have arisen based on theoretical data rather than clinical evidence from surgical patients.<sup>38</sup>

The American Society of Anaesthesiology recommends discontinuing herbal remedies consumption 2 weeks prior to surgery.<sup>39</sup> Nevertheless, a recent study showed that only around 23% of preoperative surgical patients

discontinue their herbal medication regimens prior to surgery.<sup>40</sup>

No recent systematic reviews evaluating herbal medications in patients undergoing surgical procedures for perioperative and postoperative symptom control were identified. As such, we plan to undertake a systematic review summarising the efficacy and safety of herbal medications for the treatment and prevention of anxiety, depression, pain and PONV in patients undergoing laparoscopic, obstetrical/gynaecological and cardiovascular surgical procedures.

## METHODS AND ANALYSIS

### Standards

The Cochrane Handbook for Intervention Reviews<sup>41</sup> will guide our choice of methods. This review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.<sup>42</sup>

### Protocol and registration

This review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42016042838).

### Search methods for primary studies

#### Electronic searches

We will search the following electronic databases without language and publication status restrictions, up to 1 October 2016: Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), Ovid MEDLINE, Ovid Embase, LILACS, ISI Web of Science, EBSCO CINAHL and clinicaltrials.gov. Search terms describing laparoscopic, obstetrical/gynaecological and cardiovascular surgeries and herbal medication interventions will be combined. The search strategy will be designed with the assistance of a trained librarian.

#### Search strategy

We will use the following MeSH terms, with associated keywords: (1) intervention (phytotherapy, herb therapy, herbal therapy, plant extracts, herbal medicine, herbalism, medicinal plants, pharmaceutical plants, pharmaceutical plant, healing plants, healing plant, medicinal herbs, medicinal herb); (2) condition (laparoscopies, peritoneoscopy, peritoneoscopies, celioscopy, celioscopies, laparoscopic surgical procedures, laparoscopic surgical procedure, laparoscopic surgery, laparoscopic surgeries, cardiac surgical procedure, cardiac surgical procedures, heart surgical procedures, heart surgical procedure, cardiovascular surgical procedure, cardiovascular surgical procedures, gynaecological surgical procedure, gynaecologic surgical procedures, gynaecological surgeries, gynaecological surgery, gynaecologic surgery, gynaecologic surgeries, obstetric surgical procedure, obstetric surgical procedures, obstetrical surgical procedures, obstetrical surgical procedure, obstetric surgeries, obstetric surgery, obstetrical surgery, obstetrical surgeries). The search strategy will be adapted

**Table 1** Search strategy for Ovid MEDLINE, designed as of 2 September 2016

No	Searches	Results
1	gynecology/ obstetrics/ thoracic surgery/ Minimally Invasive Surgical Procedures/	61 687
2	laparoscopy/ hand-assisted laparoscopy/	69 622
3	thoracic surgical procedures/ exp cardiac surgical procedures/	195 024
4	expGynecologic/obstetric Surgical Procedures/	72 904
5	Cholecystectomy, Laparoscopic/	10 733
6	((gynecolog* or cardiac or cardio* or thoracic or heart or coronary or obstetric* or gynae* or laparoscop* or OBGYN or uter* or vaginal or cervical* or ovarian*) adj5 (surger* or operation* or operate*)).tw,kf.	153 069
7	Herbal Medicine/	1629
8	((herb* or plant* or flower* or phyto* or tree or mineral* or botan*) adj5 (treat* or therap* or intervention* or medicin* or remed* or extract* or cure* or oil* or heal*)).tw,kf.	101 339
9	(herbalism or botany or herbology).tw,kf.	1255
10	Phytotherapy/	33 568
11	(phyto-therap* or phytotherap*).tw,kf.	1680
12	exp Plant Preparations/pd, tu, ad, st [Pharmacology, Therapeutic Use, Administration & Dosage, Standards]	103 896
13	/1–6 [Surgery]	457 564
14	/7–12 [Herbal medicine]	194 482
15	13 and 14	1296
16	adult.mp. or middle aged.sh. or age:.tw.	7 608 507
17	15 and 16	470

for each of the aforementioned electronic databases (see [table 1](#) for the search strategy adapted for Ovid MEDLINE).

### Searching other resources

In addition to an electronic database search, we will manually search the reference lists of every study deemed eligible to identify additional trials which may be includable; any potentially eligible studies will be screened in duplicate. Furthermore, coauthors of all eligible trials and/or pharmaceutical companies leading the conduct of eligible trials will be contacted for additional data and information regarding any additional trials which may be includable.

### Eligibility criteria

#### Inclusion criteria

##### Patients

Adults ( $\geq 18$  years of age) undergoing laparoscopic, obstetrical/gynaecological and/or cardiac surgeries.

### Interventions

Any herbal medicines from any of the following plant preparations (whole, powder, extract, crude drug, standardised mixture, drug extract ratio and solvent) will be compared against conventional treatment, placebo, no intervention, other type of complementary and alternative therapy (eg, acupuncture, homeopathy) or another herbal medication. We will consider the following routes of administration: oral (eg, dropping pills, aqueous decocts), topical and intravenous. We will only consider herbal medications preoperatively administered.

### Study designs

Randomised controlled trials (RCTs) and quasi-RCTs.

### Exclusion criteria

#### Patients

Studies where the majority of participants are HIV-positive or transplant patients will not be considered eligible for inclusion.

#### Interventions

Studies involving combination herbal medication regimens as interventions and/or combination pharmacological medications as control arms will not be considered eligible for inclusion.

### Measure outcomes

We will include studies that report any of the following outcomes:

#### Primary outcomes

- ▶ Anxiety (Spilberger Anxiety Inventory—IState-Trait Anxiety Inventory (STAI) and other validated instruments)
- ▶ Depression (Depression Scale—Hospital Anxiety and Depression Scale (HADS-D) and other validated instruments)
- ▶ PONV (visual analogue scale (VAS) and other validated instruments)
- ▶ Overall pain (VAS and other validated instruments)

#### Secondary outcomes

- ▶ Adverse events—primarily withdrawals and serious adverse events (eg, death, life-threatening, hospitalisation, disability or permanent damage)
- ▶ Number of patients reporting adverse events (as defined above)
- ▶ Quality of life (Short Form-36 and other validated instruments)
- ▶ Satisfaction with herbal medications
- ▶ Need for rescue medication
- ▶ Duration of symptoms (intervention costs with descriptive analysis)

### Screening, extraction and risk of bias

Three pairs of reviewers will independently screen all titles and abstracts identified by the literature search. Full-text articles for potentially eligible studies will be obtained and screened independently by reviewer pairs

using the same eligibility criteria as with the title and abstract screening.

Once a final set of eligible studies has been identified, reviewer pairs will independently extract data for the following variables from each study using a prestandardised data extraction form: characteristics of the study design, participants, interventions, outcomes event rates (for aforementioned primary and secondary outcomes) and duration of follow-up.

Reviewers will independently assess risk of bias by using a modified version of the Cochrane Collaboration's tool. The tool includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting and the presence of other potential sources of bias not accounted for in the previously cited domains.<sup>43,44</sup> For incomplete outcome data, loss to follow-up of less than 10% and a difference of less than 5% in missing data in intervention and control groups is considered low risk of bias.

Consensus for both stages of screening, data extraction and risk of bias assessments will be established by discussion and adjudication by a third reviewer as necessary.

To measure agreement between reviewers, we will use kappa statistics. Kappa values between 0.40 and 0.59 are considered to demonstrate fair agreement, while values between 0.60 and 0.80 demonstrate good agreement and values greater than or equal to 0.75 demonstrate excellent agreement.<sup>45</sup>

### Confidence in pooled estimates of effect

The reviewers will use the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology to rate the quality of evidence for each outcome. Quality ratings will be assigned as high, moderate, low or very low.<sup>46</sup> Detailed GRADE guidance will be used to assess overall risk of bias,<sup>47</sup> imprecision,<sup>48</sup> inconsistency,<sup>49</sup> indirectness<sup>50</sup> and publication bias.<sup>51</sup> Consensus will be established by discussion and adjudication by a third reviewer as necessary, and final results will be summarised in an evidence profile.

### Data synthesis

We will calculate pooled risk ratios (RRs) for dichotomous outcomes and standardised mean differences (SMD) for continuous variables with the associated 95% CIs using random effects models with the Mantel-Haenszel statistical method. Absolute effects and 95% CI will be calculated by multiplying pooled RRs and 95% CI by baseline risk estimates derived from the largest included RCTs in the meta-analysis.

We will address variability in results across studies by using  $I^2$  statistic and the p value obtained from the Cochran  $\chi^2$  test. Our primary analyses will be based on eligible patients who have reported outcomes for each study (complete case analysis). We will assess publication bias through visual inspection of funnel plots for

outcomes addressed in 10 or more studies. We will use Review Manager (*RevMan*) V.5.3 (Nordic Cochrane Centre, Cochrane) for all analyses.<sup>52</sup>

We will calculate the SMD with a sensitivity analysis in cases where studies report the same construct using different measurement instruments. SMDs show the intervention effect in SD units, rather than the original units of measurement, and depend on the size of the effect (the difference between means) and the SD of the outcomes (the inherent variability among participants). We will use anchor-based minimally important difference (MID) to convert the SMD into an OR and risk difference.<sup>53</sup>

To address missing participant data for dichotomous outcomes<sup>54</sup> and continuous outcomes,<sup>55</sup> we will use newly developed approaches. These approaches will be only applied to outcomes which show a significant treatment effect and report sufficient missing participant data to potentially introduce clinically important bias. Thresholds for important missing participant data will be determined on an outcome-by-outcome basis.

If there are sufficient studies available, we will offer a subgroup analysis for doses (lower vs higher dose) and risk of bias (lower vs higher risk of bias). We will construct summary tables and provide a narrative synthesis if the meta-analysis is not appropriate due to excessive heterogeneity in populations, interventions, comparators, outcomes or methodologies.

### Summarising evidence

We will follow the recommendation by the GRADE Working Group, presenting cumulative findings in evidence profiles.<sup>51,56</sup> These evidence profiles will provide succinct, easily understandable summaries of quality of evidence and magnitude of effects. We will use a software programme, GRADEpro (<http://ims.cochrane.org/grade>) to build these evidence profiles. The following seven elements will be included: (1) a list of up to seven important outcomes, including both outcomes of benefit and harm; (2) a measure of the typical burden of these outcomes (eg, control group, estimated baseline risk); (3) a measure of the difference between risks with and without intervention; (4) the relative magnitude of effect; (5) numbers of participants and studies addressing these outcomes, as well as follow-up time; (6) a rating of the overall confidence in the estimate of effect for each outcome; and (7) additional comments, which will include the MID if available.

### Ethics and dissemination

Ethical approval is not required for this systematic review protocol because it does not involve the gathering or presentation of any individual-level patient data and, as such, does not involve any privacy concerns.

Findings will be disseminated in the form of manuscripts submitted to peer-reviewed journals and presentations at research conferences with a relevant readership/audience.

## DISCUSSION

Our review will evaluate the available evidence for herbal medications for adult surgical patients, provide estimates of the effectiveness of treatments and their associated harms and evaluate the quality of the evidence in a rigorous and consistent manner using the GRADE approach.<sup>57</sup>

This work addresses an important gap in summarising available evidence regarding a potential management strategy for the prophylaxis and treatment of anxiety, depression, pain and PONV. Our findings may assist clinicians and health professionals make clinical decisions regarding symptom prevention and management, and may guide researchers in terms of additional questions to be addressed in relation to herbal medications with this patient population.

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**Contributors** APNA is the guarantor, led the writing of the manuscript and will participate in data extraction. RED and LCL are the project managers, coinvestigators, contributed to the writing and revision of the protocol and will participate in data extraction. APA is the Trial Search Coordinator responsible for the search strategy. CCB is coinvestigator, helped to revise the protocol and will participate in data extraction. CG, MDG, LARR and AA contributed to the writing and revision of the manuscript and will participate in data extraction. All authors read and approved the final manuscript.

**Funding** RED was supported by Brazilian Research Council (CNPq) scholarship grant number (CNPq 310953/2015-4). CNPQ is not involved in any other aspect of the project, such as the design of the project's protocol and analysis plan.

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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