Effectiveness and safety of Ayurvedic medicines in type-2 diabetes management: a systematic review protocol

Abstract

Objective: To evaluate and synthesize evidence on the effectiveness and safety of Ayurvedic medicines for managing type-2 diabetes (T2DM).

Introduction: Several randomized controlled trials (RCTs) have been conducted to assess the effectiveness and safety of Ayurvedic medicines for managing T2DM. Systematic reviews have been conducted on this topic but need to be updated. The findings from the review will be used to develop a clinical guideline for managing T2DM by Ayurvedic practitioners in India.

Inclusion criteria: RCTs assessing the effectiveness and safety of Ayurvedic medicines for managing T2DM in adults will be included in this systematic review.

Methods: We will search for a wide range of sources to find both published and unpublished studies, including, but not limited to, MEDLINE, Embase, CINAHL, PsycINFO, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and Allied and Complementary Medicine Database (AMED). No language restrictions will be applied. The Joanna Briggs Institute systematic review methodology will be followed to conduct the review. Data synthesis will be conducted using narrative synthesis and meta-analyses, where appropriate.

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Keywords: Ayurveda; effectiveness; safety; type-2 diabetes

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Introduction

Type-2 diabetes (T2DM) in India

T2DM is a complex disorder, which has major health, social and economic consequences. Chronic hyperglycaemia is associated with macro- and micro-vascular complications and even death.[1,2] Currently, India has the world's second-largest T2DM epidemic, with around 73 million adults living with T2DM.[1] It has been estimated that by 2045, India will have approximately 134 million adults with T2DM.[1] In terms of deaths attributable to T2DM, India is the largest contributor to the regional mortality, with around one million deaths, of which approximately 50% being premature in people under 60 years.[1]

Ayurveda for T2DM management

Like many other South Asian countries, Ayurveda is the dominant traditional medical system in India, especially for meeting the primary healthcare needs of people.[3] It has been in use for thousands of years.[3] In Ayurveda, the corresponding term for diabetes mellitus is madhumeha (madhu means sweetness and meha means excessive urination).[4,5] Classical Ayurvedic texts, written in Sanskrit, have described this condition and its management in details.[4,5] T2DM is one of the main diseases for which patients consult Ayurvedic practitioners and use Ayurvedic treatments, often from diagnosis to throughout their lives.[6-11] Ayurveda is commonly used due to how it fits with their health beliefs and culture; thus, its acceptability, satisfaction and perceived relief are usually high, especially among rural, poor, older and tribal populations.[9,12] Many T2DM patients in India prefer not to use western medicines due to avoiding associated side-effects, costs and the mode of administration (for example, injections). Additionally, there is a lack of availability of western medical system doctors within rural areas.[8-11,13] In recognition of these facts, the Indian government actively promotes Ayurveda and deploys Ayurvedic practitioners in the health system, often as the main clinical provider.[8,13] Around 430,000 Ayurvedic practitioners are registered with the government's medical council in India.[14]

Clinical effectiveness and safety of Ayurvedic medicines in T2DM management

Previous systematic reviews of clinical trials suggest beneficial effects of several Ayurvedic medicines on T2DM-related outcomes, including improvement in blood glucose levels; with no major safety issues. Their mechanisms of actions have been reported, with some intriguingly suggesting the potential to regenerate beta cells.[15-21]

Existing problems in T2DM management by Ayurvedic practitioners

Strong concerns have been raised about the lack of consistency in how Ayurvedic practitioners manage T2DM, where any of the steps within the care pathway are largely left to

the judgement of the individual Ayurvedic practitioner (including screening for complications and referral to specialists), thus, resulting in these unacceptable variations.[7,13,22] Despite the clinical effectiveness and safety of several Ayurvedic medicines for managing T2DM found in trial settings, many non-evidence based medicines are being prescribed in clinical practice, which can have serious adverse effects on patients, including heavy metal poisoning.[23] It is exceedingly difficult for them to be versed with the latest data on the most effective and safe Ayurvedic medicines. Many poor-quality studies continue to be published particularly in "predatory journals", and Ayurvedic practitioners tend to lack knowledge and skills of how to critically appraise articles.[24,25] Furthermore, Ayurvedic practitioners can struggle to make sense of the results from studies, which are at times conflicting in their findings, to optimise disease management of patients, and therefore, can blindly follow the claims made by others or use a 'trial and error' approach.[22,24,25] One of the major challenges identified by Ayurvedic practitioners is the absence of a good quality clinical guideline to aid their clinical decision-making process and delivery of high-quality care to T2DM patients.[22]

Clinical guidelines for the management of T2DM by Ayurvedic practitioners have been developed in India.[4,5,26-28] However, the quality of the guidelines is questionable due to unclear development processes being used, including whether the best available evidence was considered. Additionally, the majority of such guidelines are extremely brief and limited in their scope, with heterogeneous content and no clear recommendations for actions at the stages of the T2DM care pathway. Poor-quality clinical guidelines can lead to the use of ineffective interventions, inefficient use of scarce resources and most importantly, harm to patients.[29]

Good quality clinical guideline: a potential solution

Clinical guidelines have been effectively used in improving the clinical care of T2DM in western medicine.[30,31] However, their existence in Ayurvedic clinical practice remains extremely limited. Many stakeholders, including Ayurvedic practitioners, patient groups, the Indian government and the World Health Organization (WHO), advocate for good-quality clinical guidelines for Ayurvedic practitioners.[10,11] Thus, a good-quality clinical guideline, based on the best available evidence, to manage T2DM by Ayurvedic practitioners may address the problems mentioned above. Whilst the clinical guideline will be created for Indian Ayurvedic practitioners, it will also be highly relevant to other South Asian countries, such as Nepal and Sri Lanka and countries with South Asian ethnic minorities who often rely heavily on Ayurvedic treatments.

The rationale for systematic review

A preliminary search was carried out in PubMed and Google Scholar to identify prior systematic reviews on this topic. Although a number of systematic reviews have been published on this topic, these are outdated now, with the two most recent systematic reviews being published around a decade ago in 2011.[15-21] One of the most recent was a Cochrane systematic review, which was limited in scope through solely focusing on multi-herbal formulations and Ayurveda as a whole system, thereby excluding single herbs and their extracts.[20] Similarly, the other systematic review included only two Ayurvedic single herbs and excluded other forms of Ayurvedic medicines.[21] Additionally, the evidence base since the publication of these systematic reviews has substantially grown over the past decade; thereby highlighting the need to re-focus and update the reviews to provide contemporary estimates of effect and safety for all Ayurvedic medicines for the management of T2DM. The findings from the review will be used to develop a clinical guideline for managing T2DM by Ayurvedic practitioners in India.

The objective of the proposed systematic review and main review questions

The objective of the proposed systematic review is to evaluate and synthesize evidence on the effectiveness and safety of Ayurvedic medicines for managing T2DM as compared to no intervention, placebo, any non-pharmaceutical intervention or pharmaceutical intervention. The main review questions are:

1. Whether Ayurvedic medicines are effective in controlling blood glucose levels of T2DM patients?
2. Whether Ayurvedic medicines are effective in improving health-related quality-of-life of T2DM patients?
3. Whether Ayurvedic medicines are safe to be used by T2DM patients?

Inclusion criteria

Population

The systematic review will include studies conducted among adults (≥18 years) with T2DM, irrespective of associated comorbidities (such as overweight/obesity, hypertension and hyperlipidaemia) or T2DM complications (such as macro- and micro-vascular). Both newly diagnosed T2DM (i.e., not yet treated with antidiabetic drugs), as well as existing cases (i.e., treated earlier with antidiabetic drugs), will be eligible. Where populations include children, the study will be included in the review if the mean age of the participants is ≥18 years or where the study findings are stratified into adults and children. Studies which include participants with type-1 diabetes will be excluded unless it is possible to extract the data on T2DM

participants. Studies in which the major goal of the intervention is to manage the associated comorbidities and T2DM complications are beyond the scope of this review and will be excluded. To be consistent with the changes in classification and diagnostic criteria of T2DM over the years, the diagnosis should be based on the standard criteria valid at the time of the study. Authors' definition of T2DM will be used in case the diagnostic criteria are not described.

Intervention

Studies will be included if they assess any classical and/or proprietary Ayurvedic medicine (containing plant-, animal- and/or mineral-origin ingredients – single or in combination) in any form (e.g., tablets, capsules, decoction). Cross-checking of eligibility of the Ayurvedic medicine (to distinguish it from traditional Chinese and Western medicines) will be performed by Ayurveda experts via searching the Indian Medicinal Plants Database (http://medicinalplants.in), Encyclopedia on Indian Medicinal Plants (http://envis.frlht.org/implad), Traditional Knowledge Digital Library (http://www.tkdl.res.in), Ayurvedic Pharmacopoeia of India and Ayurvedic Formulary of India. Studies on multimodal interventions that include Ayurvedic medicine will be included if it is possible to extract data relating to Ayurvedic medicine.

Comparator

Studies comparing Ayurvedic medicines with no intervention, placebo, any non-pharmaceutical intervention (such as diet, exercise or yoga) or pharmaceutical intervention (such as antidiabetic drugs or insulin or another Ayurvedic medicine) will be included in this systematic review. Co-intervention(s) will be allowed as long as all the study arms received the same co-intervention(s). If a study includes multiple arms, we will include the arms that meet the review inclusion criteria.

Outcome

Studies which assess any of the following outcomes will be included:

Primary outcomes

- Blood glucose levels (i.e., glycated haemoglobin (HbA1c), fasting blood glucose)
- Health-related quality-of-life
- Adverse effects (e.g., incidence of hypoglycaemia, macro- and micro-vascular complications of T2DM, hospitalization, death)

Secondary outcomes

- Postprandial blood glucose level

- Fasting and stimulated insulin levels
- Fasting and stimulated C-peptide levels
- Insulin sensitivity (homeostasis model assessment of insulin resistance (HOMA-IR))
- Bodyweight, body mass index (BMI) and waist circumference
- Blood pressure and heart rate
- Serum lipid levels (i.e., total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides)

Timing of outcome measurement

At least two months from randomisation will be considered as the primary timing of outcome measurement.

Study design

Considering the feasibility and practicality of the proposed work and hierarchy of study designs, only randomized controlled trials (RCTs) will be included in this systematic review. Our preliminary work has identified more than 125 potentially eligible RCTs.

Methods

The systematic review process will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Joanna Briggs Institute (JBI) systematic review methodology guidelines.[32,33]

Search

We will search for a wide range of sources to find both published and unpublished studies via the following electronic databases and grey literature sources:

- MEDLINE (1946-present)
- Embase (1974-present)
- CINAHL (1937-present)
- PsycINFO (1806-present)
- Web of Science (1900-present)
- Cochrane Central Register of Controlled Trials (CENTRAL) (1996-present)
- Allied and Complementary Medicine Database (AMED) (1985-present)
- International Pharmaceutical Abstracts (1970-present)
- Turning Research Into Practice (TRIP) (1997-present)
- AYUSH Research Portal (a database of Ayurveda (and other) research articles) (http://ayushportal.nic.in)
- Digital Helpline for Ayurveda Research Articles (DHARA) (http://dharaonline.org)

- A Bibliography of Indian Medicine (ABIM) (http://indianmedicine.eldoc.ub.rug.nl)
- CAM-QUEST (a database of complementary and alternative medicine research articles) (https://www.cam-quest.org/en)
- Directory of Open Access Journals (https://doaj.org)
- EthOS (a database of theses) (https://ethos.bl.uk)
- OpenGrey (a grey literature database) (http://opengrey.eu)
- ProQuest Dissertations and Theses (a database of dissertations and theses) (https://www.proquest.com/products-services/dissertations)
- Researches in Ayurveda and Ayurvedic Research Database (ARD) (databases of Ayurveda-related dissertations and theses) (https://ayurvedahealthcare.info)

We will also contact (twice through email) relevant experts to find out any relevant studies, including the Central Council for Research in Ayurvedic Sciences (Ministry of AYUSH, India). Authors of the included studies and/or manufacturers of the included Ayurvedic medicines will be contacted (twice through email) to identify further eligible studies. The reference list of previous reviews and included studies will be screened for additional studies.

The search strategy, to be used in MEDLINE, is detailed in Appendix I. The search strategy has been developed based on the following: (i) T2DM component of the search strategy is based on the search strategies reported in the UK's National Institute for Health and Care Excellence (NICE) guideline for managing T2DM and previous Cochrane systematic review on this topic, (ii) Ayurvedic medicine component is based on Ayurvedic medicines mentioned in previous systematic reviews (on this topic) and guidelines for managing T2DM, and (iii) study design component is based on the search strategy reported in the NICE guideline for managing T2DM.[4,5,15-21,26-28,34] This search strategy will be adopted for other databases, in consultation with an information specialist/librarian. No language restrictions will be applied, and translations will be sought where necessary.

Study selection

Following the searches, all identified citations will be collated and uploaded into Endnote 8.2 (Clarivate Analytics, PA, USA), and duplicate citations will be removed. Titles and abstracts will be screened for eligibility by two independent reviewers. Studies identified as potentially eligible or those without an abstract will have their full text retrieved, and their details will be imported into the JBI System for Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia). Full texts of the studies will be assessed for eligibility by two independent reviewers. Any disagreements that arise between the two reviewers will be resolved through discussion. If consensus is not reached, then a third reviewer will be

involved. Full text of the studies that do not meet the inclusion criteria will be excluded, and reasons for exclusion will be reported.

Assessment of methodological quality

Included studies will be critically assessed using the standardized critical appraisal tool for RCTs incorporated within JBI SUMARI and assigned a score as met (yes), not met (no), unclear or not applicable (n/a).[33] Two reviewers will independently answer each question and comment on it. Any disagreements that arise between the two reviewers will be resolved through discussion. If consensus is not reached, then a third reviewer will be involved. The critical appraisal results will be presented in a table and narrative form. All studies, regardless of their methodological quality, will be included in the review.

Data extraction

Two reviewers will independently extract data from the included studies, using the standardized data extraction tool incorporated within JBI SUMARI.[33] Any disagreements that arise between the two reviewers will be resolved through discussion. If consensus is not reached, then a third reviewer will be involved. Data extraction will include study characteristics (e.g., country, setting/context, participant characteristics, sample size), intervention and comparator details (e.g., ingredient(s) (including taxonomic details, part(s) used, manufacturing process, voucher specimen provided or not), form of administration, dose, duration), outcomes and timings (including quantitative results).

Data synthesis

Initially, narrative syntheses will be conducted to describe the studies. Where possible, meta-analyses based on random-effects models will be conducted to provide a weighted measure of treatment effect for each Ayurvedic medicine.

Measures of treatment effect

For binary outcomes, risk ratios (RR) with 95% confidence intervals (CI) will be reported. For continuous outcomes, mean differences (MD) with 95% CI will be reported where the same scale is used across studies. Where different scales are used across studies, standardised mean differences (SMD) with 95% CI will be reported. Where there is a marked difference in the continuous outcomes at baseline between the intervention groups, we will also use change from baseline to account for this. Where appropriate, we will calculate the number needed to treat (NNT) and number needed to harm (NNH) for binary primary outcomes.

Unit of analysis issues

We will take into account the level at which randomization occurred within our analyses for studies with the unit of analysis issue, for example, crossover or cluster designed trials. Where this is not possible, for example, where the intracluster correlation coefficient from a cluster designed trial is not available, the results for these studies will not be pooled with those from parallel study designs. For studies with more than one active treatment group, the comparisons will be included in separate meta-analysis models to avoid the issue of double-counting of the comparator group.

Dealing with missing data

The corresponding author of the included study will be contacted by email (two times per author) to obtain relevant missing data. Where possible, analyses will be based on intention-to-treat (ITT). Sensitivity analyses will be conducted to assess the robustness of the results using per-protocol (PP) data.

Assessment of heterogeneity

Clinical and methodological heterogeneity (diversity) will be assessed by descriptively comparing trial and participant characteristics between the studies. We will quantify heterogeneity using the I^2 statistic and categorize heterogeneity as substantial where values are greater than 50%.

Assessment of reporting biases

Where there is a sufficient number of studies included in the meta-analysis (at least 10), we will use funnel plots to assess for small study bias.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be conducted to investigate reasons for heterogeneity for primary outcomes based on the following study level factors:

- Intervention (form of administration, dose and duration)
- Definition of the comparator (no intervention versus placebo versus active comparator)
- Methodological quality (allocation concealment, blinding of outcome measure and attrition)
- Country.

Sensitivity analysis

Sensitivity analyses will be performed to explore the influence of the following factors on primary outcomes through:

- Excluding unpublished studies

- Excluding studies not written in English
- Excluding studies with industry funding.

Assessing certainty in the findings

We will generate evidence statements (which contains a descriptor, strength and direction (positive or negative)) for each outcome. A modified version of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method will be used to determine the strength of evidence for each outcome.[35] Since only RCTs will be included in this systematic review, the findings will be initially ranked as high and will be downgraded to moderate, low or very low, if there is evidence of the following: risk of bias, imprecision, the inconsistency of evidence, indirectness and/or publication bias. Reasons will be provided for the ratings. Two independent reviewers will be involved in this process. Any disagreements that arise between the two reviewers will be resolved through discussion. If consensus is not reached, then a third reviewer will be involved. The results will be reported in a summary of findings table.

Conflicts of interest

The authors have no conflicts of interest to declare. Jo Leonardi-Bee is a Senior Associate Editor for the journal and has been blinded to the editorial processes and decisions associated with this manuscript.

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Appendix I: Search strategy

Ovid MEDLINE

1 exp Diabetes Mellitus, Type 2/
2 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.
3 ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw.
4 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw.
5 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.
6 (NIDDM or T2DM or T2D).tw.
7 Prameha.mp.
8 Madhumeha.mp.
9 or/1-8
10 exp Medicine, Ayurvedic/
11 Ayurved*.tw,ot.
12 *Medicine, Traditional/
13 exp Complementary medicine/tu [Therapeutic use]
14 ((plant* or herb* or medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*) adj6 (Ayurved* or Hindu or Indian)).tw,ot.
15 exp Plants, Medicinal/tu [Therapeutic use]
16 exp Plant Extracts/tu [Therapeutic use]
17 exp Plants/tu [Therapeutic use]
18 ((plant* or herb*) adj6 (medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*)).tw,ot.
19 exp Ethnobotany/
20 exp Ethnopharmacology/
21 (ethnobotan* or ethno botan* or ethnopharmacolog* or ethno pharmacolog*).tw,ot.
22 *Phytotherapy/
23 (phytotherap* or phyto therap*).tw,ot.
24 exp Acanthaceae/
25 exp Aegle/
26 exp Aloe/
27 exp Artocarpus/
28 exp Azadirachta/
29 exp Butea/
30 exp Cassia/

31 exp Catharanthus/
32 exp Cinnamomum/
33 exp Cinnamomum aromaticum/
34 exp Cinnamomum zeylanicum/
35 exp Clerodendrum/
36 exp Cucurbitaceae/
37 exp Curcuma/
38 exp Cyamopsis/
39 exp Ficus/
40 exp Garlic/
41 exp Ginger/
42 exp Gymnema/
43 exp Gymnema sylvestre/
44 exp Ipomoea batatas/
45 exp Momordica charantia/
46 exp Murraya/
47 exp Nigella sativa/
48 exp Ocimum sanctum/
49 exp Onions/
50 exp Phyllanthus/
51 exp Phyllanthus emblica/
52 exp Piper/
53 exp Plantago/
54 exp Psyllium/
55 exp Pterocarpus/
56 exp Punicaceae
57 exp Salacia/
58 exp Solanum/
59 exp Syzygium/
60 exp Tamarindus/
61 exp Tinospora/
62 exp Trigonella/
63 exp Lead/
64 exp Tin/
65 (Aegle marmelos or Crateva marmelos or Allium cepa or Allium sativum or Aloe vera or Artocarpus heterophyllus or Azadirachta indica or Melia azadirachta or Butea monosperma or Cassia auriculata or Catharanthus roseus or Vinca rosea or

Cinnamomum aromaticum or Cinnamomum cassia or Cinnamomum tamala or Cinnamomum verum or Cinnamomum zeylanicum or Clerodendrum phlomides or Coccinia grandis or Coccinia cordifolia or Coccinia indica or Curcuma longa or Cyamopsis tetragonoloba or Emblica officinalis or Phyllanthus emblica or Enicostemma axillare or Enicostemma littorale or Ficus carica or Gymnema lactiferum or Gymnema sylvestre or Hygrophila schulli or Asteracantha longifolia or Ipomoea batatas or Momordica charantia or Murraya koenigii or Nigella sativa or Ocimum tenuiflorum or Ocimum sanctum or Phyllanthus amarus or Phyllanthus nirurii or Piper longum or Plantago arenaria or Plantago psyllium or Pterocarpus marsupium or Pterocarpus santalinus or Punica granatum or Salacia chinensis or Salacia reticulate or Solanum torvum or Syzygium cumini or Eugenia jambolana or Syzygium jambolanum or Syzygium jambos or Eugenia jambos or Tamarindus indica or Tinospora cordifolia or Trigonella foenum-greacum or Zingiber officinale).tw,ot.

66 (Lead or Tin or Black bitumen or Black asphalt*).tw,ot.

67 (Arogyavardhini* or Arogyvardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantar* or Gokshuradi* or Goksuradi* or Jambudyarisht*or Jambudyarist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vasanta Kusumakar* or Vashanta Kushumakar* or Vasantkusumakar* or Vashantkushumakar* or Vasantakusumakar* or Vashantakushumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkushumakar* or Basantakusumakar* or Bashantakushumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijaysharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijaysharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*).tw,ot.

68 (Ayush 82 or Ayush-82 or Cogent DB or Diabecon or D 400 or D-400 or GS4 or Gurmar or Hyponidd or Inolter or M 93 or M-93 or MA 471 or MA-471 or Nosulin or Pancreas Tonic).tw,ot.

69 or/10-68

70 Randomized Controlled Trial.pt.

71 Controlled Clinical Trial.pt.

72 Clinical Trial.pt.

73 exp Clinical Trials as Topic/
74 Placebos/
75 Random Allocation/
76 Double-Blind Method/
77 Single-Blind Method/
78 Cross-Over Studies/
79 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
80 (random$ adj3 allocat$).tw.
81 placebo$.tw.
82 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
83 (crossover$ or (cross adj over$)).tw.
84 or/70-83
85 9 and 69 and 84