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I don't want you to be only
a doctor but I also want you
to be a man
A quotation by His Royal Highness Prince Mahidol of Songkla

the clinical academia

Aim and Scope

Our journal is an opened access international journal devoted to peer-reviewed contributions dealing with clinical medicine and medical education from experimental to clinical aspects. Our journal publishes only high quality research, review and other types of original articles, technical and clinical reports every two months. Reviews of various global and Asian aspects will be solicited. Innovation or epidemiological aspects as well as health system research will be addressed. Rigorous systematic review and neglected tropical diseases are our priority

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message from the editor

Dear readers,

This is the final issue of volume 44. In this issue, you will learn about agents that we use for pain and agitation control and their risks for death in patients with tuberculosis that required long-term mechanical ventilation. Another article is a systematic review regarding the use of balastine for seasonal allergic rhinitis. Hope you enjoy reading and gain more knowledge from these two articles.

Happy New Year to you all!

Thammasorn Jeeraaumponwat, M.D., Ph.D.
Editor-in-Chief of The Clinical Academia

submission

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Our issues of each volume will be published online
IN
March, June, September, and December

reviewing process

All accepted articles are classified into two main categories;
"***standard submission***" with the approximated processing time of 3-4 months and "***expression submission***" with the approximated processing time of 1-2 months. For the latter category, the author must submit as standard submission with notifying our journal for express submission.

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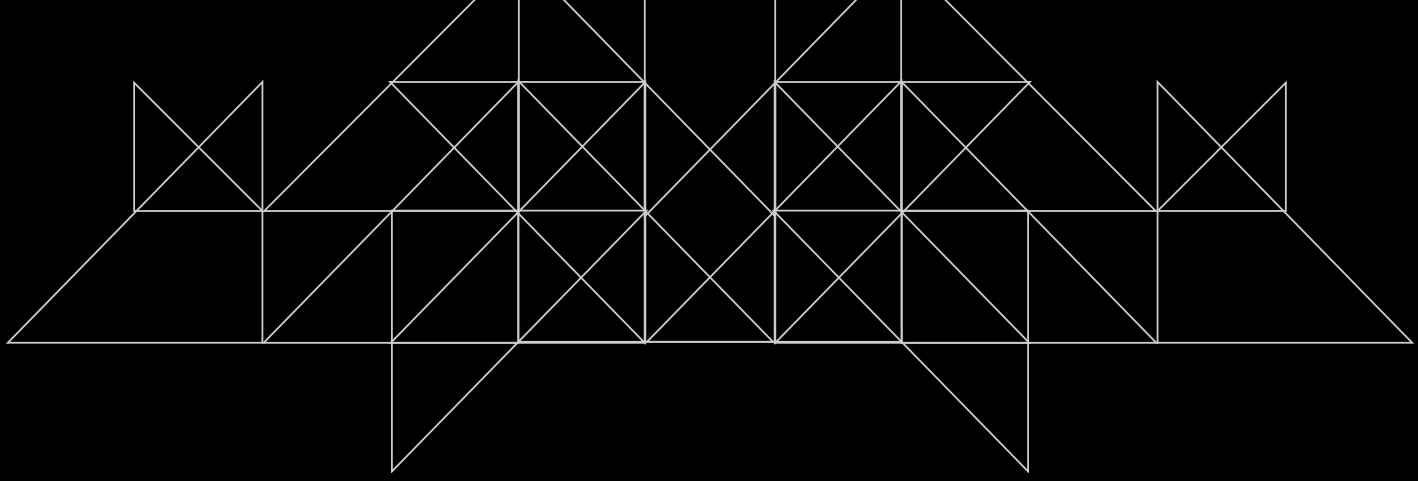
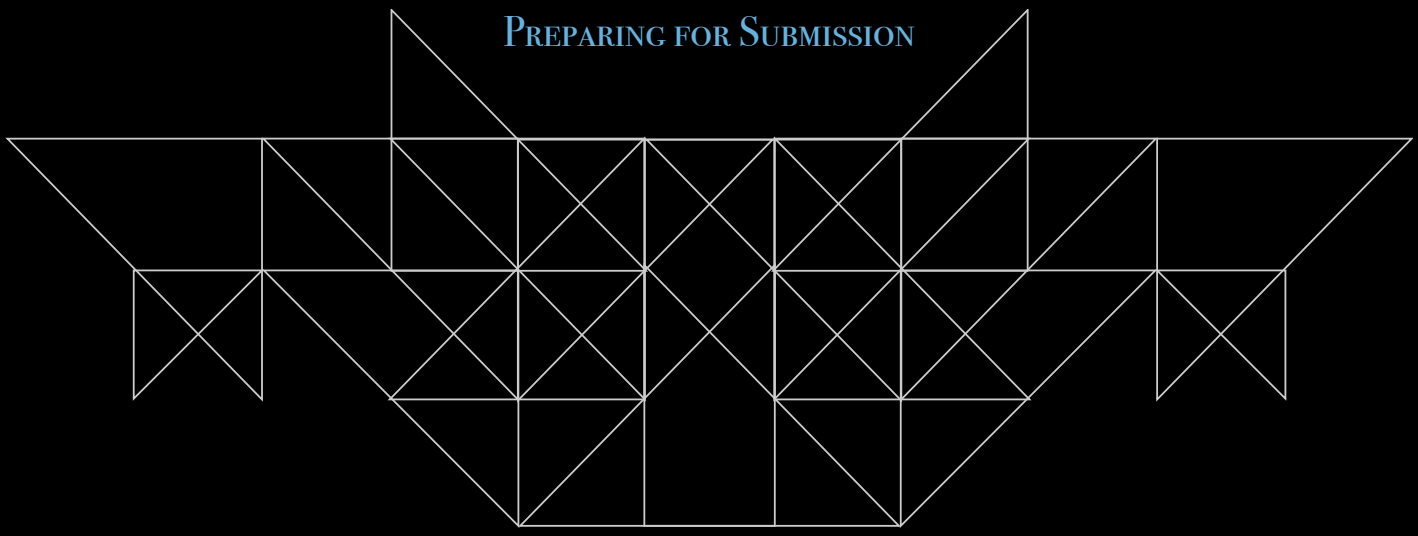
Contents



International Committee of Medical Journal Editors (ICMJE)

Recommendation for Preparing for Submission



1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT for randomized trials, STROBE for observational studies, PRISMA for systematic reviews and meta-analyses, and STARD for studies of diagnostic accuracy. Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, select¬ing, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network and the NLM's Research Reporting Guidelines and Initiatives.

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

Author information: Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

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Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the Abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of Figures and Tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because Tables and Figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

Conflict of Interest declaration. Conflict of interest information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform conflict of interest disclosure form for use by ICMJE member journals and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require conflict of interest declarations on the manuscript title page to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not over-interpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential. Funding sources should be listed separately after the Abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a

registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository, authors should state at the end of the abstract the data set name, repository name and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer)." Authors should define how they measured race or ethnicity and justify their relevance.

ii. Technical Information

Specify the study's main and secondary objectives–usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your finings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations Related to References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests.Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

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References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Reference Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References webpage and detailed in the

NLM's Citing Medicine, 2nd edition. These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

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For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

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k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Agents for pain and agitation control and risk for death in patients with pulmonary tuberculosis infection requiring long-term mechanical ventilation

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the association between agents for pain and agitation control and risk for death in patients with pulmonary tuberculosis infection requiring long-term mechanical ventilation.

METHODS

We conducted a retrospective cohort study of those with PTB infection requiring long-term mechanical ventilation admitted at Khon Kaen Hospital, Thailand. The agents for pain and agitation control were our interested exposure. Our primary outcome was the all-cause mortality within 90 days of admission. Our secondary outcomes included cardiac arrest, ventilator-associated pneumonia, acute respiratory distress syndrome (ARDS), shock, tracheostomy, and barotrauma.

RESULTS

Among 393 patients with PTB infection requiring long-term mechanical ventilation between January 2013 and August 2017. We found that the use of the agents for pain and agitation control were not significantly associated with the all-cause mortality within 90 days of admission (crude hazard ratio (HR), 0.98; 95% confidence interval [CI], 0.77 to 1.24; adjusted HR, 1.08; 95% CI, 0.84 to 1.39)). For the secondary outcomes, the use of the agents were not significantly associated with cardiac arrest (relative risk [RR], 1.47; 95% CI, 0.99 to 2.19), ventilator-associated pneumonia (RR, 1.86; 95% CI, 0.58 to 6.00), ARDS (RR, 3.10; 95% CI, 0.28 to 33.94), shock (RR, 0.91; 95% CI, 0.76 to 1.09) and barotrauma. However, we found the use of the agents was significantly associated with the tracheostomy (RR, 7.05; 95% CI, 1.43 to 34.66).

CONCLUSION

The exposure to the agents for pain and agitation control were not significantly associated with all-cause mortality within 90 days of admission in patients with PTB infection requiring long-term mechanical ventilation.

INTRODUCTION

Tuberculosis (TB) is still one of the most important global health problems worldwide; about 10 million people per year are infected with *Mycobacterium tuberculosis* and develop TB disease, in 2016 nearly 1.3 million deaths were associated with TB.1 Pulmonary TB (PTB) accounts for 85% of all TB.[1] Severe PTB infection can develop into acute respiratory failure, which requires mechanical ventilation and carries a high mortality rate.[2–8] In those with mechanical ventilation 96 hours or longer is considered to be long-term ventilation and it is associated with a higher mortality rate.[9,10] Pain, agitation, and delirium (PAD) were common in patients with mechanical ventilation.[11] Consequently, the sedative agent is one of the treatments usually prescribed to the patients to relieve PAD.[12] However, the agent is found to be associated with prolonged duration of mechanical ventilation and higher mortality rate; a Spanish prospective cohort in 2005 found that sedative use was associated with prolonged duration of mechanical ventilation and higher mortality rate in 5,183 adults[13] as well as a later Danish trial in 2010 in 428 clinically ill adults, similar results were also observed.[14] However, there is no study that ascertains the association between agents for pain and agitation control and mortality rate within 90 days of admission in those with long-term ventilation with PTB infection. Thus, the aim of this study was to assess the association between the agents for pain and agitation control and all-cause mortality within 90 days of admission in PTB with long-term mechanical ventilation.

METHODS

STUDY DESIGN

This retrospective cohort was conducted to evaluate the association between the use of agents for pain and agitation control and the 90-day mortality rate after admission in those with PTB infection requiring long-term mechanical ventilation at Khon Kaen Hospital, Thailand. We reviewed data from medical records of hospitalized patients who were diagnosed with PTB. All patient's data were concealed. Access to our data collection form was restricted. Confidentiality was kept. Our study protocol was approved by Khon Kaen Hospital Institutional Review Board (IRB) for ensuring that was ethically acceptable (KE 60146).

PATIENTS

Medical records of those with PTB infection requiring long-term mechanical ventilation admitted from January 2013 through August 2017 in Khon Kaen Hospital were reviewed. For PTB, all of them had to have positive chest radiological findings from chest radiography given the impression by radiologists. They were categorized into three groups following criteria; (i) confirmed TB diagnosed by positive for acid-fast bacilli (AFB) smear in multiple sputum samples (at least two, possibly three samples) and polymerase chain reaction (PCR) for TB,[15,16] (ii) probable TB for those who negative for all of above investigation but have clinical symptoms, radiographic features that suggest TB infection, and (iii) possible cases for those without the criteria mentioned above but anyhow have been diagnosed by international classification 0f disease, 10th revision (ICD-10) for TB (codes A15).[17,18] Our exclusion criterion was PTB patients with mechanical ventilation for less than 96 hours.

EXPOSURE

Agents for pain and agitation control including types (benzodiazepines, opioid, other sedative drugs). Their data were collected promptly after mechanical ventilation use including their dosage and duration. The data were extracted from real findings of drug prescription from medical records with no protocol of PAD treatment was applied.

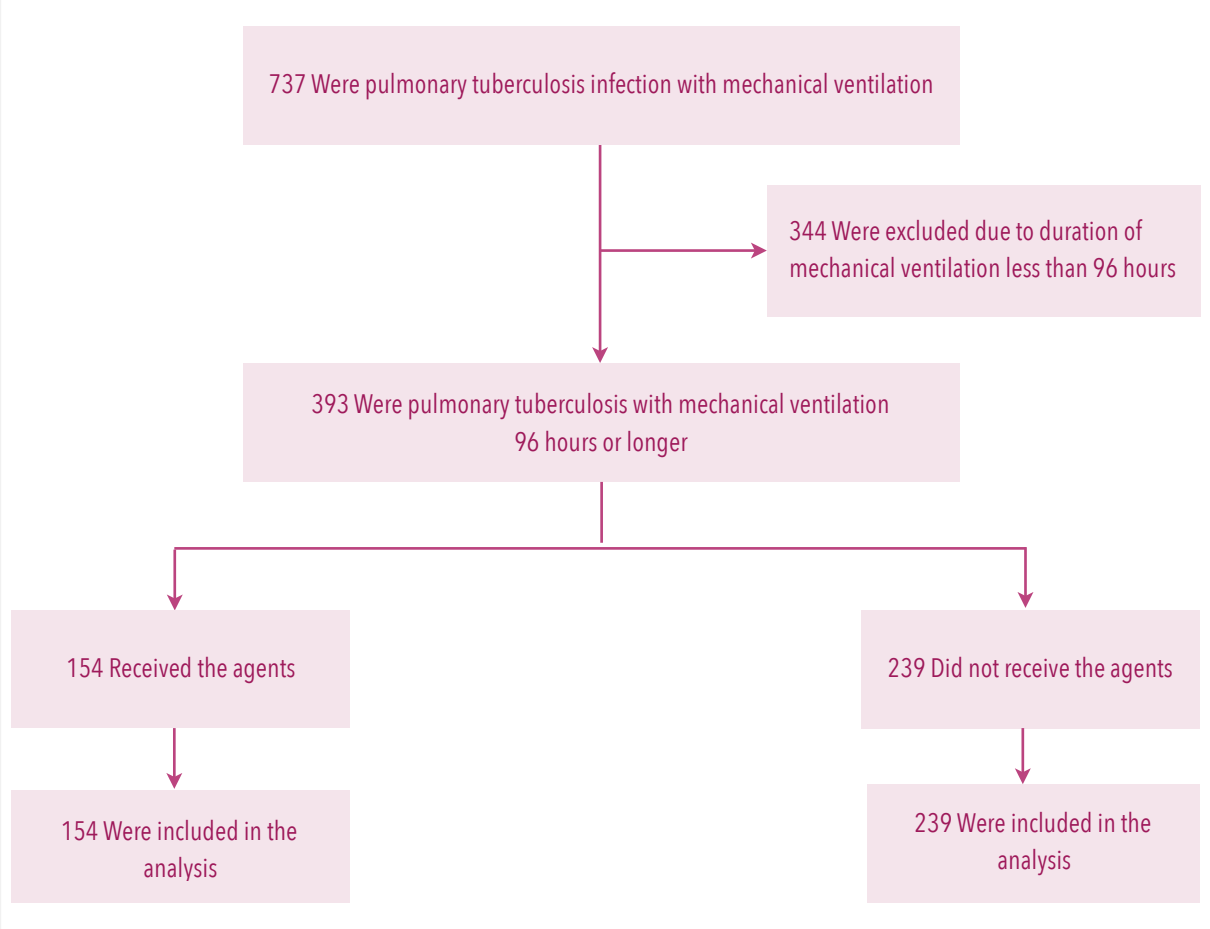

Figure 1. The patients flow in the analysis

OUTCOMES

The primary outcome was all-cause mortality within 90 days of admission. Our secondary outcomes were cardiac arrest, ventilator-associated pneumonia, ARDS, shock, tracheostomy, and barotrauma.

DATA COLLECTION

Apart from our exposures of interest and outcomes, we also collected patients' characteristics and laboratory investigations i.e., age, sex, weight, coexisting condition (pulmonary diseases, cardiovascular diseases, cerebrovascular diseases, diabetes mellitus, hypertension, chronic kidney disease, underlying malignancies, HIV infected, ARDS before mechanical ventilation), history of TB, the pattern of PTB, types of the hospital ward, systemic corticosteroids use during admission, arterial blood gas profile (ratio of partial pressure arterial oxygen and the fraction of inspired oxygen, pH, bicarbonate) and serum creatinine.

STATISTICAL ANALYSIS

We divided patients into two groups; with and without the agents for pain and agitation control. For variable analysis, we used descriptive statistics to summarize characteristic variables in each group; numbers and percentages for presenting categorical variables mean with standard deviation (SD) for normally distributed continuous variables

Table 1. Characteristics of patients

Characteristics	Exposed to the agents (N = 154)	Not exposed to the agents (N = 239)	P Value
Age -yr			
Median	56.6	64.3	0.002
Interquartile range	41.4-69.3	46.0-75.6	
Male–no. (%)	106 (68.8)	178 (74.5)	0.222
Weight-kg *			
Median	52	48	0.046
Interquartile range	45-60	41-53	
Coexisting conditions-no. (%)			
Pulmonary disease	27 (17.5)	30 (12.6)	0.171
Diabetes mellitus	27 (17.5)	42 (17.6)	0.992
Hypertension	27 (17.5)	50 (20.9)	0.409
Human immunodeficiency virus infection	25 (16.2)	32 (13.4)	0.434
Intensive care unit admission-no. (%)	41 (26.6)	34 (14.2)	0.002
Systemic corticosteroid use-no. (%)	65 (42.2)	102 (42.7)	0.927
Miliary TB-no. (%)	4 (2.6)	9 (3.8)	0.527
Confirmed cases-no. (%)	43 (27.9)	23 (9.6)	<0.001
Probable cases-no. (%)	85 (55.2)	165 (69.0)	0.005
ARDS on admission-no. (%)	2 (1.3)	0	0.153
PaO2/FiO2 ratio			
Median	709.3	842.3	0.295
Interquartile range	447.9-1148.8	455.5-1176.1	
pH§			
Median	7.38	7.41	0.002
Interquartile range	7.28-7.45	7.33-7.50	
HCO^3 (mEq/l)¶			
Median	19.8	19.0	0.713
Interquartile range	15.2-22.7	14.7-23.2	

Table 1. (continued)

Characteristics	Exposed to the agents (N = 154)	Not exposed to the agents (N = 239)	P Value
Creatinine (mg/dl)**			
Interquartile range	0.87	0.89	0.49
Interquartile range	0.57-2.31	0.62-1.26	

* 111 patients in agents group and 177 patients in non-agents group had missing data.
† Pulmonary disease was included chronic obstructive pulmonary disease, asthma, and Bronchiectasis.
‡ 18 patients in agents group and 56 patients in non-agents group had missing data.
§ 18 patients in agents group and 56 patients in non-agents group had missing data.
¶ 18 patients in agents group and 18 patients in non-agents group had missing data.
** 2 patients in agents group and 2 patients in non-agents group had missing data

and median with interquartile range (IQR) for non-normally distributed continuous variables. For inferential statistics, we used either Pearson's chi-squared or Fisher's exact test for categorical variables and t-test or Mann-Whitney U test for distributed continuous variables comparing. Crude relative risk (CRR) and adjusted relative risk (ARR) were applied for comparing event rates of the primary and secondary outcomes calculated using Cox proportional regression analysis. For the mortality rate (within 90 days of admission) as our primary outcome, the hazard ratio (HR) were calculated using Cox proportional regression analysis. Either P or 95% confidence intervals (CI) were demonstrated together with all inferential statistical analysis tests. Subgroup analysis was also conducted to identify the association of our primary outcome and each type of agents for pain and agitation control as well as the three groups of PTB diagnosis.

Table 2. Primary and secondary outcomes

Outcome	Exposed to the agents (N=154)	Not exposed to the agents (N=239)	Crude relative risk (95% CI)
Primary outcome			
All-cause mortality	118 (77.1)	201 (84.1)	0.91 (0.73-1.15)
Secondary outcome			
Cardiac arrest	38 (24.7)	40 (16.7)	1.47 (0.99-2.19)
Ventilator-associated pneumonia	6 (3.9)	5 (2.1)	1.86 (0.58-6.00)
ARDS during mechanical ventilation	2 (1.3)	1 (0.4)	3.10 (0.28-33.94)
Shock	83 (53.9)	141 (59.0)	0.91 (0.76-1.09)
Tracheostomy	6 (3.9)	2 (0.8)	7.05 (1.43- 34.66)
Barotrauma	2 (1.3)	0	

Table 3. Factors associated with all-cause mortality

Factor	Relative risk		Hazard ratio	
	Crude analysis (95% CI)	Adjusted analysis (95% CI)	Crude analysis (95% CI)	Adjusted analysis (95% CI)
Age-yr	1.00 (1.00 - 1.01)	1.01 (1.00-1.01)	1.00 (1.00-1.02)	1.01 (1.00-1.02)
Male	0.95 (0.73-1.23)	0.98 (0.75-1.28)	0.90 (0.70-1.17)	0.95 (0.73-1.24)
Exposed to the agents	0.97 (0.77-1.24)	1.01 (0.79-1.30)	0.98 (0.77-1.24)	1.08 (0.84-1.39)
Diabetes mellitus	1.05 (0.78-1.42)	1.05 (0.74-1.49)	1.11 (0.82-1.50)	1.14 (0.80-1.61)
Hypertension	1.05 (0.79-1.40)	0.99 (0.70- 1.39)	1.07 (0.80-1.42)	0.91 (0.65-1.28)
Human immunodeficiency virus infection	1.08 (0.78-1.49)	1.26 (0.87- 1.84)	1.05 (0.76-1.45)	1.36 (0.94-1.98)
Intensive care unit admission	0.90 (0.67-1.23)	0.90 (0.66-1.23)	0.75 (0.55-1.02)	0.74 (0.55-1.01)
Systemic corticosteroids use	0.97 (0.77-1.23)	0.96 (0.76-1.23)	0.90 (0.71-1.14)	0.88 (0.69-1.13)
Miliary TB	1.06 (0.57-2.00)	1.03 (0.54-1.96)	1.22 (0.65-2.30)	1.17 (0.61-2.23)

RESULTS

CHARACTERISTIC OF PATIENTS

A total of 2,869 hospitalized patients with PTB infection were diagnosed between January 2013 and August 2017. Only 737 were on mechanical ventilation and 393 required mechanical ventilation 96 hours or longer; 66 confirmed PTB, 250 probable PTB, and 77 possible PTB. Out of these 393 patients, 154 (39.2%) were exposed to the agents for pain and agitation control and 239 (60.8%) did not expose the agents (Figure 1). The patients in the two groups were similar with respect to the ratio of sex, coexisting conditions, miliary PTB, systemic corticosteroids use, ARDS on admission, PaO2/FiO2 ratio, HCO3, and creatinine. However, the group with the agents tended to be younger (P=0.018), higher weight (P=0.046), a higher proportion of intensive care unit (ICU) admission, a higher proportion of confirmed cases(P<0.001), lower proportional of probable cases (P=0.005) and lower pH in arterial blood gas (P=0.002) (Table 1).

STUDY OUTCOMES

Among 393 patients with PTB infection requiring long-term mechanical ventilation, the mortality rates within 90 days of admission were similar between the two groups (CRR, 0.91; 95% CI 0.73 to 1.15) (Table 2). For the secondary outcomes, the agents were significantly associated with a higher rate of tracheostomy (CRR, 7.05; 95% CI 1.43 to 34.66) (Table 2). On the other hand, cardiac arrest, ventilator-associated pneumonia, ARDS during mechanical ventilation, and shock were not significantly different between the two groups. The Kaplan-Meier curve showing no association between survival and exposure to the agents in PTB with long-term mechanical ventilation (P=0.831; log-rank test) (Figure 2).

FACTORS DETERMINE OUTCOME

From the Cox proportional hazard regression, we found that exposure to the agents was not significantly associated with the all-cause mortality within 90 days of admission (CHR, 0.98; 95% CI,

0.77 to 1.24; AHR, 1.08; 95% CI, 0.84 to 1.39). Furthermore, there were no factors associated with the all-cause mortality within 90 days of admission as shown in Table 3.

SUBGROUP ANALYSIS

The patients were recategorized into three groups; confirmed PTB, probable PTB, and possible PTB, we found that the agents were not significantly associated with the all-cause mortality within 90 days of admission (AHR, 0.73; 95% CI, 0.10 to 5.43) (AHR, 1.08; 95%CI, 0.79 to 1.48) (AHR, 0.80; 95% CI, 0.44 to 1.46) (Table 4). Then, we analyzed the association between each type of the agents and the outcomes; all-cause mortality within 90 days on admission, cardiac arrest, and shock. We found that there were no significant differences for all of the outcomes regarding each type of agents (Figure 3).

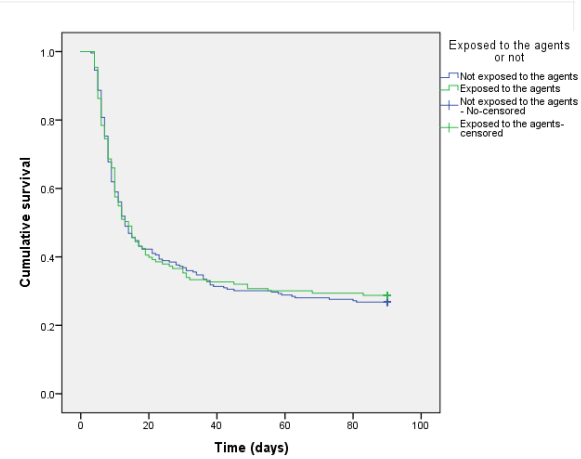

Figure 2. Kaplan-Meier curve was generated to compare survival between exposure of the agents in PTB with long-term mechanical ventilation..

DISCUSSION

MAIN FINDINGS

Our retrospective cohort study showed that the exposure to the agents for pain and agitation control were not significantly associated with all-cause mortality within 90 days of admission in patients with PTB infection requiring long-term mechanical ventilation. In the same way, the agents were not significantly associated with cardiac arrest, ventilator-associated pneumonia, and shock in patients with PTB infection requiring long-term mechanical ventilation.

COMPARISON WITH OTHER STUDIES

According to the treatment of PAD, the agents were prescribed depends on the physician's preference. While other studies had a protocol to treat the patients with PAD. Our study showed that agents for pain and agitation control tended to lower the mortality rate. On the other hand, Few previous studies were designed to examine between sedative use and duration of mechanical ventilation and mortality rate in critically ill patients.13,14 The Spanish cohort study in 2005 and the Danish trial in 2010 found that sedative use had a higher mortality rate. The probable reason for the difference was explained as follows. First, they included only patients older than 18-year-old but our study included all-aged from one-day infant to ninety-year-old elderly patients. Second, all patients in their studies were admitted only to the ICU but most of our patients admitted to the general ward, thus, the findings from those studies were based on more severe patients. Nevertheless, neither those two studies nor our study showed a significant association between the agents and the mortality rate. Possible reasons for this outcome may indicate that the agents for pain and agitation control use are not related or very lightly related to the mortality rate of patients

Table 4. Hazard ratios of exposure to the agents regarding types of tuberculosis diagnosis

Outcome	Hazard ratio (95% confidence interval)		
	Confirmed cases (N=66)	Probable cases (N=250)	Possible cases (N=77)
All-cause mortality	0.73 (0.10-5.43)	1.08 (0.79-1.48)	0.80 (0.44-1.46)
Cardiac arrest	2.07 (0.49-8.76)	1.60 (0.87-2.95)	0.94 (0.31-2.84)
Ventilator-associated pneumonia	10.31 (0.49-217.42)		4.19 (0.04-499.51)
Shock	0.77 (0.34-1.76)	1.17 (0.81-1.68)	0.82 (0.39-1.73)
Tracheostomy		9.89 (0.18-557.47)	1.05 (0.05-23.10)

with long-term mechanical ventilation, so to find a significant difference, a larger sample size should be required. For the other outcomes, ventilator-associated pneumonia was not significantly similar to our study. In terms of tracheostomy rate, the Danish trial showed that there was no significant association between the sedative and non-sedative group. On the contrary, our study was significantly associated with a higher tracheostomy rate. The probable reason for the difference was our study included patients with mechanical ventilation 96 hours or longer that prone to do a tracheostomy. The findings implied that clinicians tended to prescribe the agents to the patients that prone to do a tracheostomy.

STRENGTHS AND LIMITATIONS OF STUDY

This study is the first to identify the association between the exposure to the agents for pain and agitation control and the all-cause mortality within 90 days of admission in a large number of PTB infection patients. Furthermore, our study also analyzed the outcomes, agent types, and patient groups. However, this study held many limitations; first of all, we only used the database from medical records, which was the secondary source of information, contained several limited-quality documents leading to missing data, unclear evidence of the diagnosis of PTB, and inaccuracy receiving the agent dosage. However, the use of the agents was always recorded. Secondly, some patients received more than one type of agent for pain and agitation control, which could not be interpreted as the true outcome of each of the agent types. Thirdly, most of the patients in this study were probable and possible cases of PTB. Although, there is a standard protocol for PAD treatment, practically prescribing the agents for pain and agitation control still depends on the physician's preference. We also did not provide the information of adverse effects of agents for pain and agitation control and last, the all-cause mortality within 90 days of admission was reviewed from the National Statistical Office of Thailand which cannot differentiate causes of death.

CONCLUSION AND IMPLICATIONS

In conclusion, the exposure to the agents for pain and agitation control in PTB infection with long-term mechanical ventilation was not significantly associated with all-cause mortality within 90 days

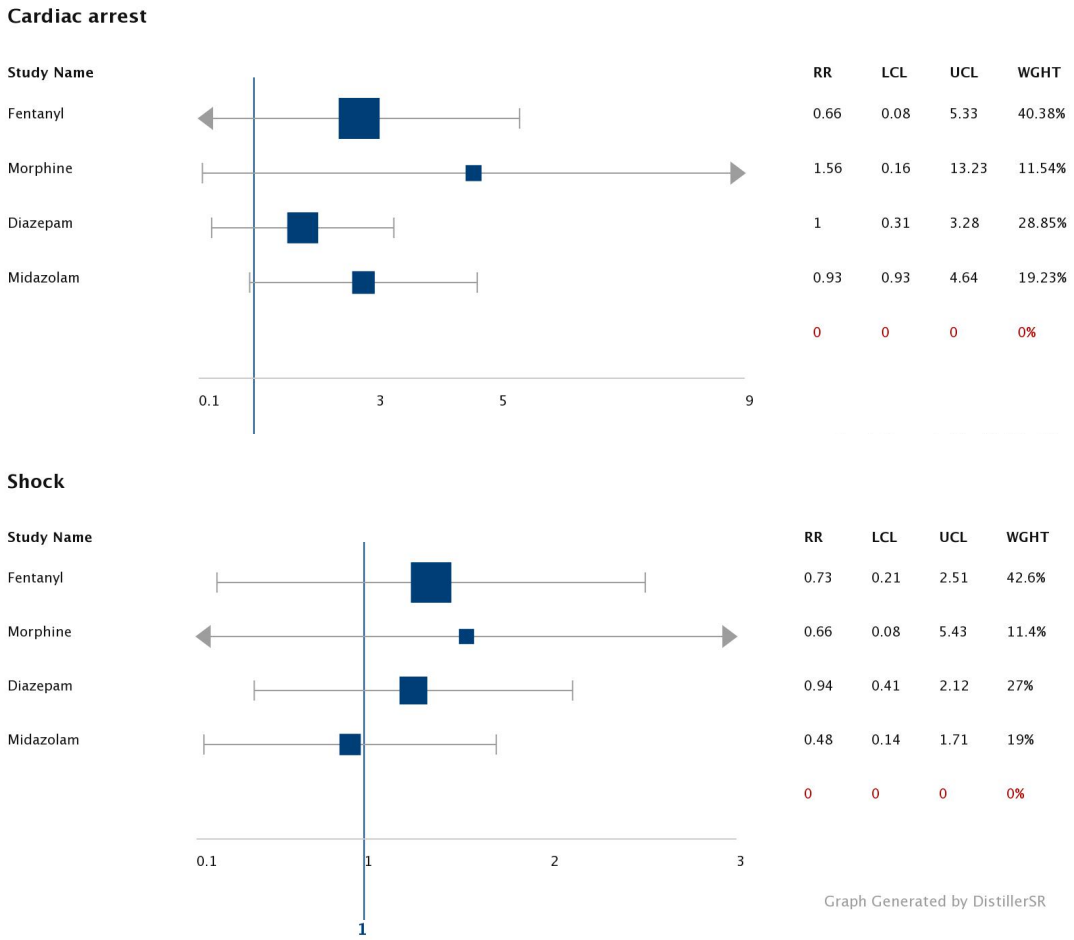

Figure 3. Kaplan-Meier curve was generated to compare survival between exposure of the agents in PTB with long-term mechanical ventilation.

of admission. Due to the limitation of the standard protocol for PAD treatment practice, for further studies, the practical application of the standard protocol for PAD treatment should be strongly reinforced. Also, the association between the adverse effects and type, dosage, and duration of the agents should be observed. The all-cause mortality within 90 days of admission as shown in Table 3.

SUBGROUP ANALYSIS

The patients were recategorized into three groups; confirmed PTB, probable PTB, and possible PTB, we found that the agents were not significantly associated with the all-cause mortality within 90 days of admission (AHR, 0.73; 95% CI, 0.10 to 5.43) (AHR, 1.08; 95%CI, 0.79 to 1.48) (AHR, 0.80; 95% CI, 0.44 to 1.46) (Table 4). Then, we analyzed the association between each type of the agents and the outcomes; all-cause mortality within 90 days on admission, cardiac arrest, and shock. We found that there were no significant differences for all of the outcomes regarding each type of agents (Figure 3).

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COMPETING INTERESTS: This study has no competing on interest.

FUNDING:No

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Bilastine for seasonal allergic rhinitis: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

Bilastine is a second-generation oral H1-antihistamine that has therapeutic value in patients with seasonal allergic rhinitis. It shows efficacy and safety for the reduction of symptoms of seasonal allergic rhinitis. Nevertheless, no systematic review compares the efficacy and safety of bilastine and other second-generation oral H1-antihistamines for the reduction of symptoms of seasonal allergic rhinitis.

METHODS

We conducted a retrospective cohort study using medical records of outpatients with the diagnosis of TB/HIV co-infection in Khon Kaen Hospital, Thailand between January 2007 and August 2017. We included the patients who started tuberculosis treatment and various times of starting ART with CD4 count less than 350 cells/mm^3. We separated patients into 3 groups by the time of initiated ART starting within the first 4 weeks, 5 to 8 weeks, and 9 to12 weeks after starting tuberculosis treatment. We compared the risk of all-cause mortality within 1 year after start tuberculosis treatment among three groups as our primary outcome. Our secondary outcomes were sputum conversion at 2 months after starting tuberculosis treatment and rate of CD4 count increasing in 1 year after tuberculosis treatment.

RESULTS

Two RCTs were included in the meta-analysis with 1401 patients with seasonal allergic rhinitis; bilastine (n=460), other second-generation oral H1-antihistamines (n=470), and placebo (n=471). It showed that no statistically significant difference among bilastine and other second-generation oral H1-antihistamines regarding the change from baseline in TSS-AUC of 0-14 days for the intention-to-treat (ITT) population (mean difference (MD), 2.69; 95% confidence interval (CI), -2.94 to 8.22; I2=0%). It showed the change from baseline

in TSS-AUC of 0-14 days for ITT population was a significantly greater reduction in those using bilastine than those using placebo (MD, -17.73; 95% CI, -30.46 to -5.00; I2=78%). Adverse events (AEs) reported over 2 weeks, bilastine had no statistically significant difference compared with other second-generation oral H1-antihistamines and placebo for incidence 2% or more AEs in any treatment group including headache,somnolence and fatigue (relative risk (RR), 1.11; 95% CI, 0.76 to 1.62; I2=0%, RR, 0.51; 95% CI, 0.12 to 2.20; I2=77%, RR, 0.48; 95% CI, 0.02 to 11.50; I2=85%), drug-related AEs (RR, 0.78; 95% CI, 0.45 to 1.37; I2 =78%) and withdrawals due to AEs (RR, 0.98; 95% CI, 0.14 to 6.64; I2=0%) but patients reporting 1 or more AE were found significantly lower in those using bilastine (RR, 0.77; 95% CI, 0.62 to 0.98; I2 =26%) and bilastine had no statistically significant difference compared with placebo for incidence 2% or more AEs in any treatment group including headache,somnolence and fatigue (RR, 0.91; 95% CI, 0.64 to 1.31; I2=0%; RR, 1.02; 95% CI, 0.48 to 2.18; I2=0%; RR, 0.47; 95% CI, 0.07 to 3.38; I2=65%), drug-related AEs (RR, 0.90; 95% CI, 0.64 to 1.26; I2 =34%) and withdrawals due to AEs (RR, 0.26; 95% CI, 0.06 to 1.23; I2=0%) but patients reporting 1 or more AE were found significantly lower in those using bilastine (RR, 0.97; 95% CI, 0.72 to 1.29; I2 =47%).

CONCLUSION

Our systematic review showed that the efficacy of bilastine and other second-generation oral H1-antihistamines in the reduction of symptoms of seasonal allergic rhinitis was similar in patients with seasonal allergic rhinitis and secondary outcome including incidence 2% or more AEs in any treatment group, drug-related AEs, and withdrawals due to AEs were similar in those using other second-generation oral H1-antihistamines but patients reporting 1 or more AEs were found significantly lower in those using bilastine.

of admission. Due to the limitation of the standard protocol for PAD treatment practice, for further studies, the practical application of the standard protocol for PAD treatment should be strongly reinforced. Also, the association between the adverse effects and type, dosage, and duration of the agents should be observed.

the all-cause mortality within 90 days of admission as shown in Table 3.

SUBGROUP ANALYSIS

The patients were recategorized into three groups; confirmed PTB, probable PTB, and possible PTB, we found that the agents were not significantly associated with the all-cause mortality within 90 days of admission (AHR, 0.73; 95% CI, 0.10 to 5.43) (AHR, 1.08; 95%CI, 0.79 to 1.48) (AHR, 0.80; 95% CI, 0.44 to 1.46) (Table 4). Then, we analyzed the association between each type of the agents and the outcomes; all-cause mortality within 90 days on admission, cardiac arrest, and shock. We found that there were no significant differences for all of the outcomes regarding each type of agents (Figure 3).

INTRODUCTION

Allergic rhinitis is a common inflammatory disease affecting about 10 to 40% of the population worldwide.1–11 Although it is not a life-threatening condition,1,10 it causes fatigue, headache, diminished cognition, sleep disruption, and other systemic symptoms.4,5,9–16 Due to histamine playing a major role in the manifestation of nasal symptoms,11,17 oral histamine H1-receptor antagonists (H1-antihistamines) of both first-generation and second-generation (e.g., cetirizine, desloratadine and bilastine) with less sedative, and anticholinergic effects have been used as first-line pharmacotherapy for seasonal and perennial allergic rhinitis.11,16–22

There were prior trials stated that bilastine was well tolerated and effective in reducing the nasal and ocular symptoms of seasonal allergic rhinitis; a randomized controlled trial (RCT) in 2009 in 683 patients with seasonal allergic rhinitis demonstrated that bilastine 20 mg once daily for 2 weeks was similar in efficacy to cetirizine 10 mg once daily and had a lower incidence of drug-related adverse events compared to cetirizine,23 another RCT in 2009 in 721 patients with seasonal allergic rhinitis found that bilastine 20 mg once daily for 2 weeks was efficacious, safe and not different from desloratadine 5 mg once daily.24 However, there is no systematic review comparing the efficacy and safety of bilastine and other second-generation oral H1-antihistamines. Thus, we systematically reviewed all evidence to analyze any treatment outcomes in terms of efficacy and safety with bilastine against other second-generation H1-antihistamines and placebo.

METHODS

SEARCH STRATEGIES

We systematically searched through electronic databases including PubMed, Scopus, Cochrane Library, and Trip Database. We also applied MeSH searching strategies in terms of ("Rhinitis, Allergic, Seasonal"[Mesh]) AND ("Bilastine" [Supplementary Conc]) to identify studies in PubMed. The keywords were "seasonal allergic rhinitis" and "bilastine" to identify studies in Scopus. The key search terms were ("Rhinitis, Allergic, Seasonal"[Mesh]) AND "Bilastine" to identify studies in Cochrane Library. We used the PICO search strategy in Trip Database; P: "seasonal allergic rhinitis" and I: "bilastine" with no specific C and O. We also performed hand searching through Clinicaltrials.gov, Web of Science, and WorldCat. The search terms were "seasonal allergic rhinitis" and "bilastine". All searches were done as of March 1, 2017.

INCLUSION CRITERIA

STUDY DESIGN

RCT

PATIENTS

Patients with seasonal allergic rhinitis

INTERVENTION

Bilastine 20 mg

OUTCOMES

Any treatment outcomes in terms of efficacy and safety

EXCLUSION CRITERIA

We excluded RCTs that had patients with a history of perennial or allergen-induced allergic rhinitis.

QUALITY OF REPORTING AND RISK OF BIAS

We used Cochrane Collaboration's tool for Assessing Risk of Bias to assess the quality of the included RCTs and to present the risk of bias demonstrated as random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel

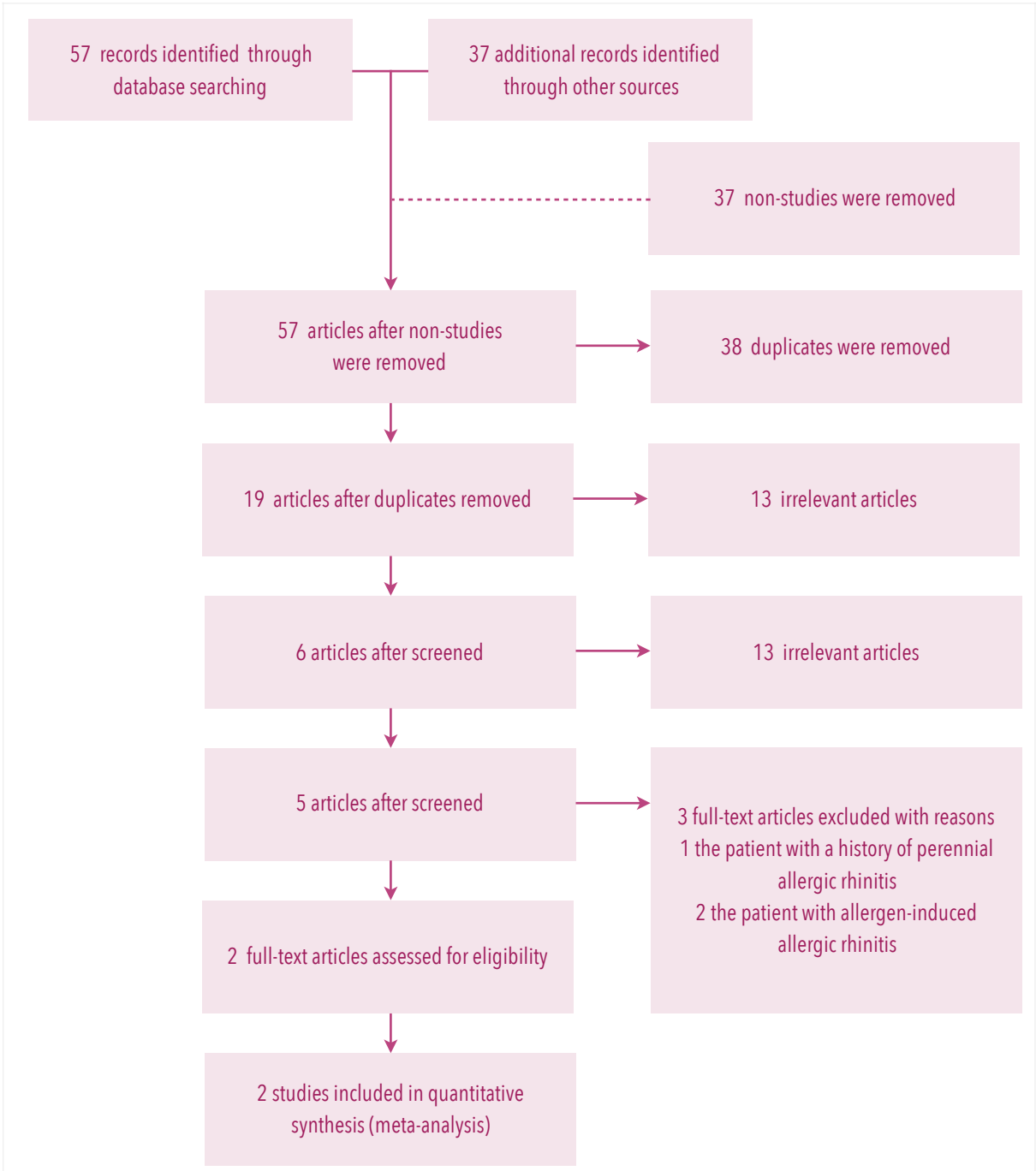

Figure 1. Flow of Studies by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Table 1. Characteristics of the included RCTs and study treatments

Author, year	Number of patients (intervention/ control)	Patients' age (years)	Doses and treatment duration		Outcomes
			Intervention	Control	
Bachert et al, 2009	233/242	12-70	Bilastine 20 mg once daily (14 days)	Desloratadine 5 mg once daily (14 days) Placebo 10 mg once daily (14 days)	Bilastine 20 mg once daily was efficacious, safe and not different from desloratadine 5 mg once daily. Bilastine 20 mg once daily had lower incidence of drug-related adverse effects compared to desloratadine 10 mg once daily. Bilastine 20 mg once daily was significant difference in efficacy to placebo 10 mg once daily (P<0.001).
Kuna et al, 2009	227/228	12-70	Bilastine 20 mg once daily (14 days)	Cetirizine 10 mg once daily (14 days) Placebo 10 mg once daily (14 days)	Bilastine 20 mg once daily was similar in efficacy to cetirizine 10 mg once daily. Bilastine 20 mg once daily is safe and a safety profile is not different to cetirizine 10 mg once daily for patients with seasonal allergic rhinitis. Bilastine 20 mg once daily significantly reduced AUC of TSS compared to placebo 10 mg once daily (P<0.001).

(performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias and classified the included trials as low risk, high risk, and unclear risk.25

DATA EXTRACTION

We extracted data regarding the first author's name, year of publication, a number of participants and baseline data, duration of both treatments, duration of studies, interventions as bilastine as

well as other second-generation H1-antihistamines and any treatment outcomes in terms of efficacy and safety from each study.

DATA ANALYSIS

We calculated the mean difference (MD) and 95% confidence interval (CI) for the efficacy of bilastine and other second-generation oral H1-antihistamines while calculated relative risk (RR) and 95% CI for AEs among bilastine and other second-generation oral H1-antihistamines and placebo in the patients with seasonal allergic rhinitis. All data were analyzed by using Review Manager 5.3 statistical software. We used the mean AUC of TSS to present the primary outcome. We calculated I2 to present the heterogeneity of associations of the effect sizes between both RCTs. Moreover, the results from the meta-analysis of our systematic review were shown as a forest plot. The publication bias was shown as funnel plots. The statistical test for heterogeneity is significant if the P-value of the Chi-Square test is less than 0.05.

RESULTS

Initially, there were 94 records identified by the reviewers. Of these, 37 records were removed due to non-studies. Of the remaining 57 articles, 38 articles duplicates were removed. Of the remaining 19 articles, we removed 13 irrelevant articles. Of those remaining 6 articles after screened, we removed one article due to no full-text. Of those remaining 5 full-text articles the predefined inclusion criteria and were screened in detail. We later excluded 3 articles as our exclusion criteria. We finally assented to have two related studies to be included in the quantitative analysis (Figure 1).

CHARACTERISTICS OF THE PATIENTS

Two RCTs comprising 1401 patients with seasonal allergic rhinitis comparing bilastine (n=460) with other second-generation oral H1-antihistamines (n=470) and placebo (n=471) were included in this systematic review. Both RCTs examined the efficacy of bilastine for the reduction of symptoms of seasonal allergic rhinitis. Both RCTs used 20 mg once daily of bilastine. One of them used 10 mg once daily of cetirizine while another RCT used 5 mg once daily of desloratadine. The characteristics of the included RCTs are shown in Table 1.

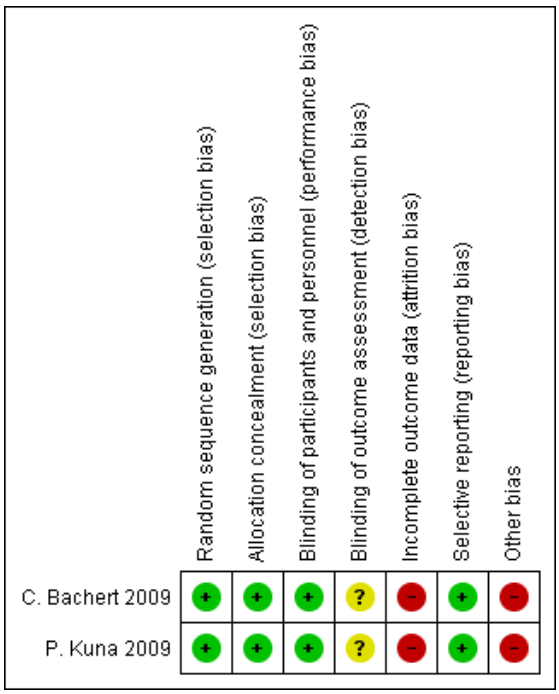

Figure 2. Risk of bias summary

BIAS RISK ASSESSMENT

The risk of bias assessed using the Cochrane Collaboration tool for both trials is summarized in Figure 2 and the risk of bias graph is shown in Figure 3 and descriptive results are shown below.

RANDOM SEQUENCE GENERATION

Both RCTs reported the methods of generating the random sequence. They were described as low risk of bias.

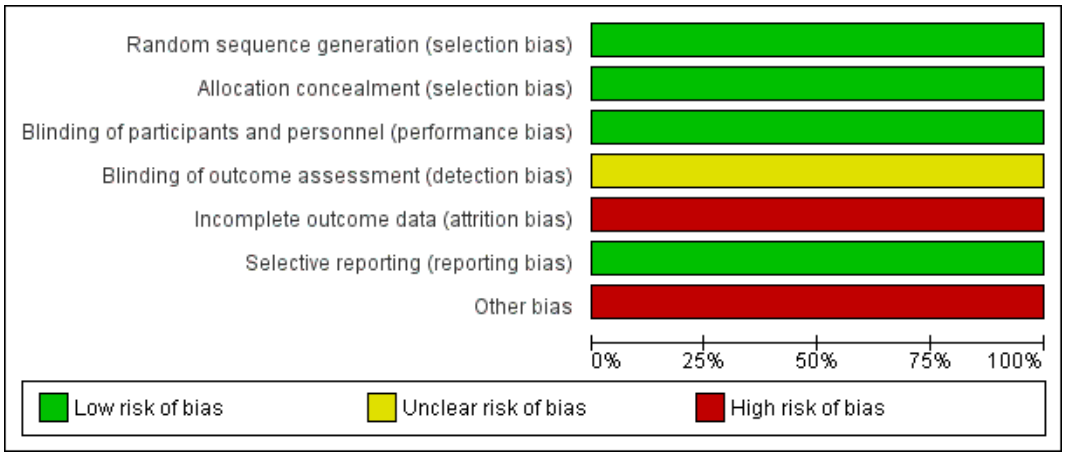

Figure 3. Risk of bias graph

ALLOCATION CONCEALMENT

Both RCTs reported the methods of generating the random sequence. They were described as low risk of bias.

BLINDING OF PARTICIPANTS

Both RCTs reported that participants were blinded. They were described as low risk of bias.

BLINDING OF OUTCOME ASSESSMENT

Both RCTs were described as unclear risk of bias as they did not describe the process of blinding of outcome assessors.

INCOMPLETE OUTCOME DATA

Both RCTs were described as high risk of bias as there were missing participants with an improper description of lost to follow up.

SELECTIVE REPORTING

Both RCTs properly reported adverse events. They were described as low risk of bias.

OTHER POTENTIAL SOURCES OF BIAS

The study by Bachert et al, 2009, was supported by FAES FARMA, Spain, and the study by Kuna et al, 2009, was supported by MDS Pharma Services Inc. They reported many conflicts of interest and their data were analyzed by their sponsor company. Thus, they were described as high risk.

PRIMARY OUTCOME

The meta-analysis of both RCTs showed no statistically significant difference among bilastine and other second-generation oral H1-antihistamines regarding the reduction of TSS-AUC on Day 14 from baseline for ITT population (MD, 2.64; 95% CI, -2.94 to 8.22; I2=0%) and it also showed that reduction of TSS-AUC on Day 14 from baseline for ITT population of those using bilastine was significantly greater than that of using a placebo (MD, -17.73; 95% CI, -30.46 to -5.00; I2=78%) (Figure 4).

ADVERSE EVENTS (AES) REPORTED OVER 2 WEEKS OF TREATMENT

BILASTINE VS. OTHER SECOND-GENERATION ORAL H1-ANTIHISTAMINES

Patients reporting ≥ 1 AE

The meta-analysis of both RCTs comparing bilastine with other second-generation oral H1-antihistamines, patients reporting 1 or more AEs

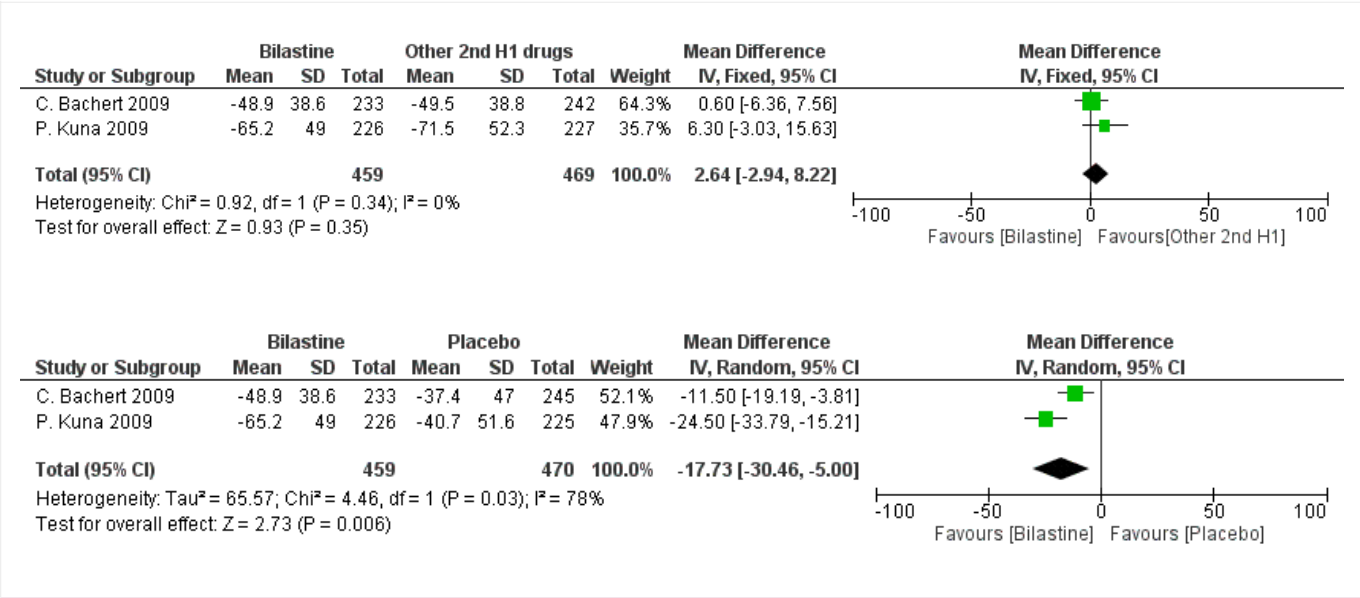

Figure 4. The forest plot of comparison: bilastine 20 mg versus other second-generation oral H1-antihistamines and bilastine 20 mg versus placebo respectively, outcome: reduction of TSS-AUC on Day 14 from baseline for ITT population

was found significantly lower in those using bilastine (RR, 0.77; 95% CI, 0.64 to 0.98; I2=26%) (Figure 5).

Drug-related AEs

The meta-analysis of both RCTs showed no statistically significant difference among bilastine and other second-generation oral H1-antihistamines regarding drug-related AEs (RR, 0.78; 95% CI, 0.45 to 1.37; I2=78%) (Figure 5).

Withdrawals due to AEs

The meta-analysis of both RCTs showed no statistically significant difference among bilastine and other second-generation oral H1-antihistamines regarding withdrawals due to AEs (RR, 0.98; 95% CI, 0.14 to 6.64; I2=0%) (Figure 5).

Incidence of ≥2% in any treatment group

The meta-analysis of both RCTs showed no statistically significant difference among bilastine and other second-generation oral H1-antihistamines regarding incidence 2% or more in any treatment group, adverse events, including headache, somnolence and fatigue, and (RR, 1.11; 95% CI, 0.76 to 1.62; I2=0%, RR, 0.51; 95% CI, 0.12 to 2.20; I2=77%, RR, 0.48; 95% CI, 0.02 to 11.50; I2=85%) (Figure 5).

BILASTINE VS. PLACEBO

Patients reporting ≥ 1 AE

The meta-analysis of both RCTs showed no statistically significant difference between bilastine and placebo regarding patients reporting 1 or more AEs (RR, 0.97; 95% CI, 0.72 to 1.29; I2=47%) (Figure 6).

Drug-related AEs

The meta-analysis of both RCTs showed no statistically significant difference between bilastine and placebo regarding drug-related AEs (RR, 0.90; 95% CI, 0.64 to 1.26; I2=34%) (Figure 6).

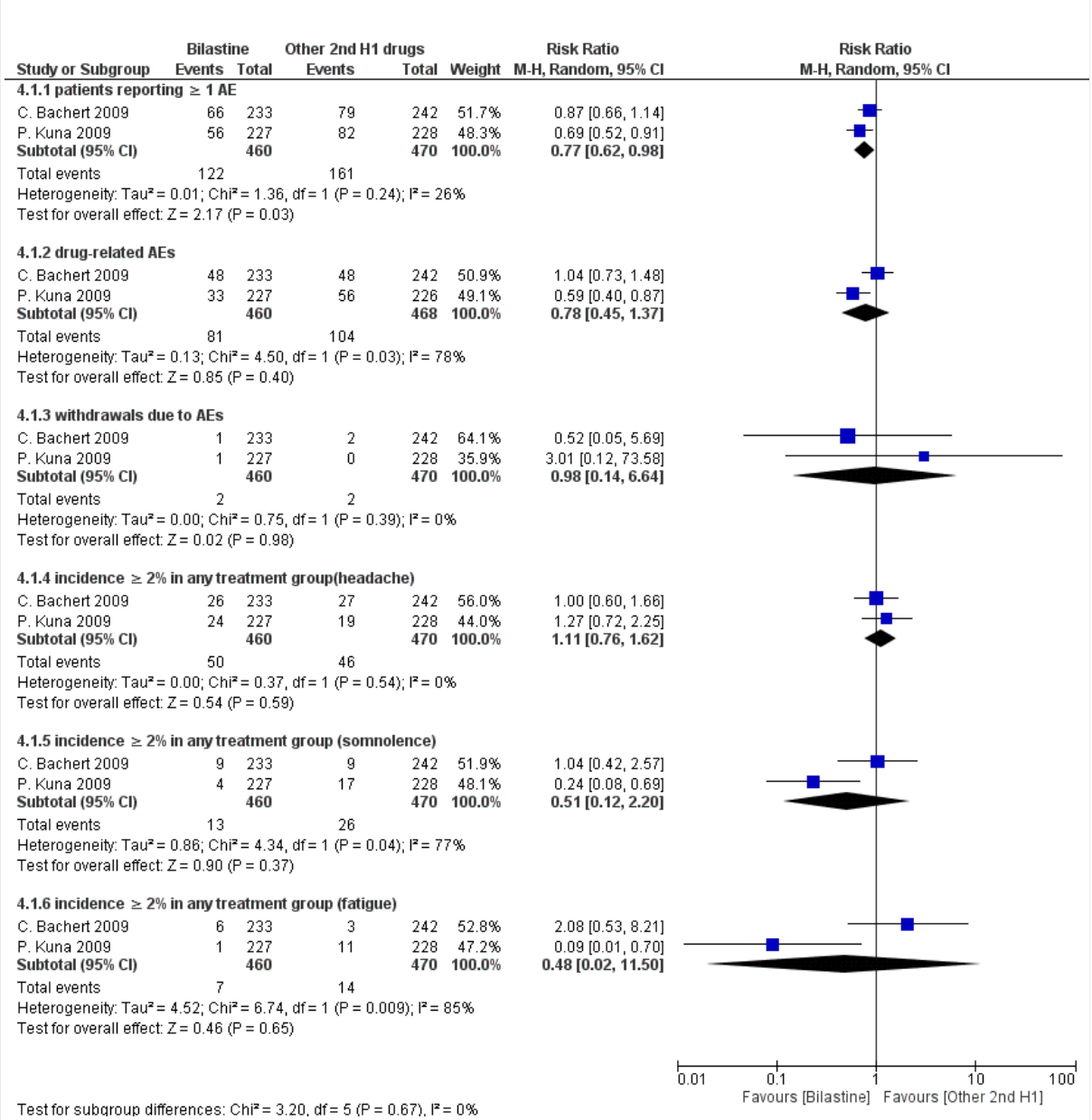

Figure 5. The forest plot of comparison: bilastine 20 mg versus other second-generation oral H1-antihistamines, outcome: AEs reported over 2 weeks of treatment

Withdrawals due to AEs

The meta-analysis of both RCTs showed no statistically significant difference with bilastine and placebo regarding withdrawals due to AEs (RR, 0.26; 95% CI, 0.06 to 1.23; I2=0%) (Figure 6).

Incidence of ≥2% in any treatment group

The meta-analysis of both RCTs showed no statistically significant difference between bilastine and placebo regarding incidence 2% or more in

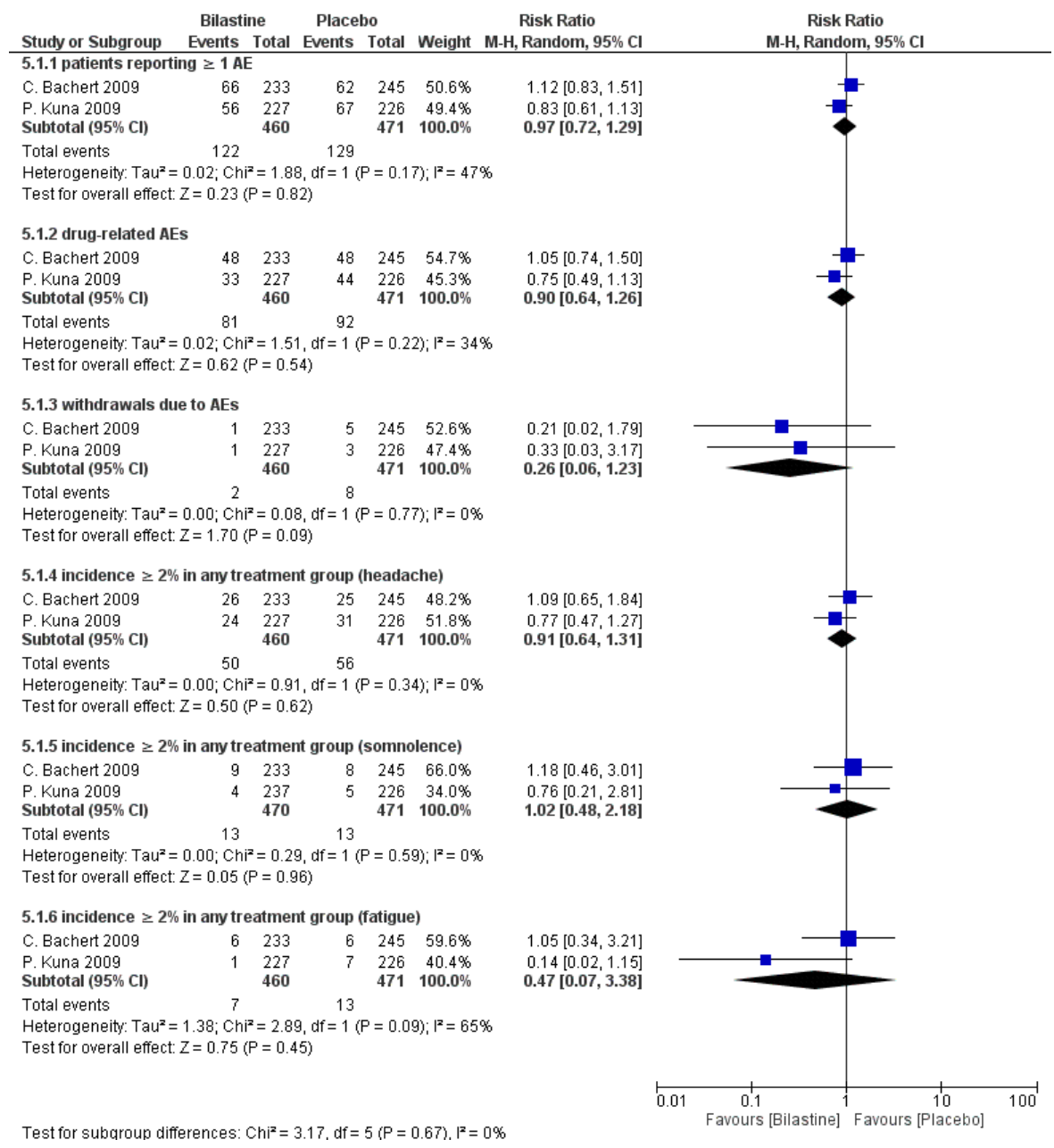

Figure 6. The forest plot of comparison: bilastine 20 mg versus placebo, outcome: AEs reported over 2 weeks of treatment.

any treatment group, adverse events, including headache, somnolence and fatigue (RR, 0.91; 95% CI, 0.64 to 1.31; I2=0%; RR, 1.02; 95% CI, 0.48 to 2.18; I2=0%; RR, 0.47; 95% CI, 0.07 to 3.38; I2=65%) (Figure 6).

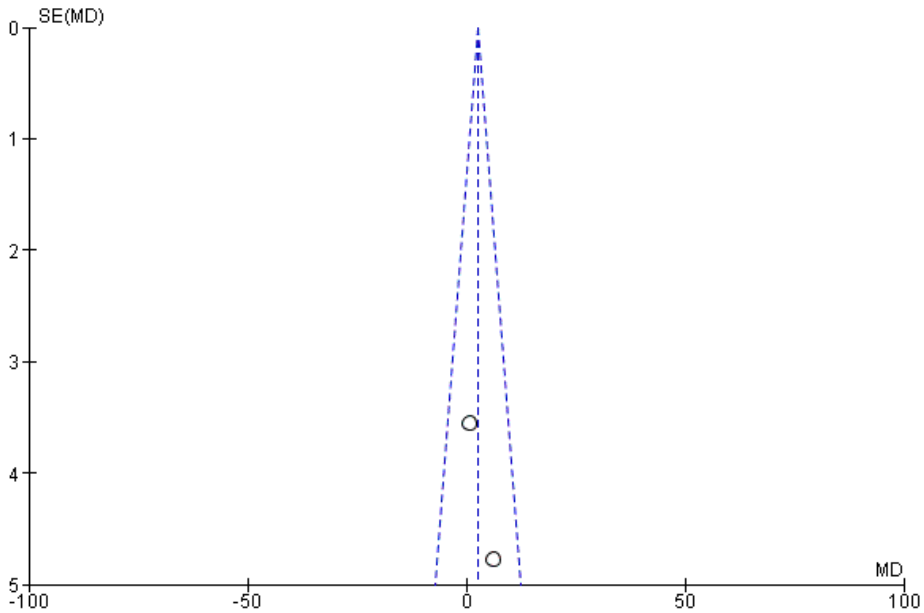

Figure 7. Funnel plot of comparison: bilastine versus other second-generation oral H1-antihistamine, outcome: reduction of TSS-AUC on Day 14 from baseline for ITT population

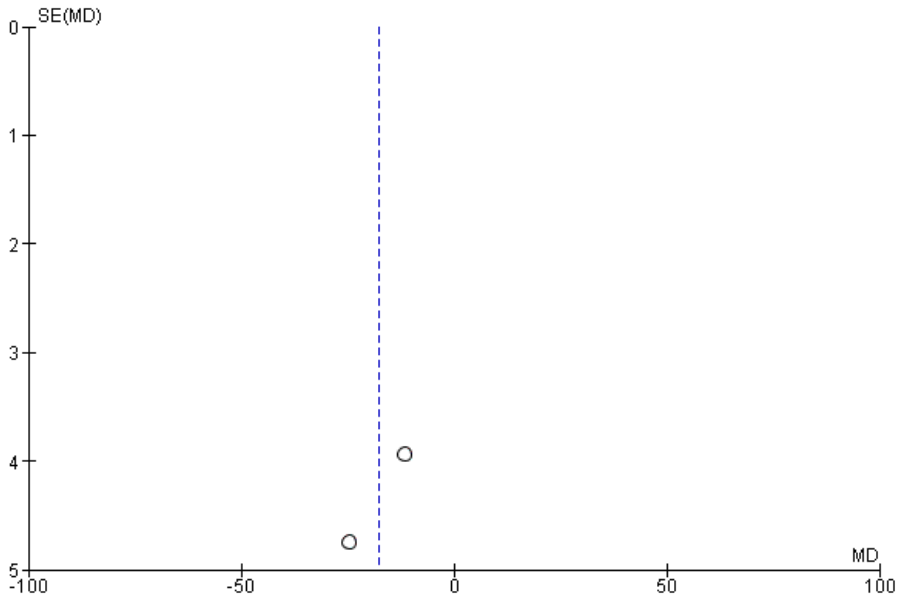

Figure 8. Funnel plot of comparison: bilastine versus placebo , outcome: reduction of TSS-AUC on Day 14 from baseline for ITT population

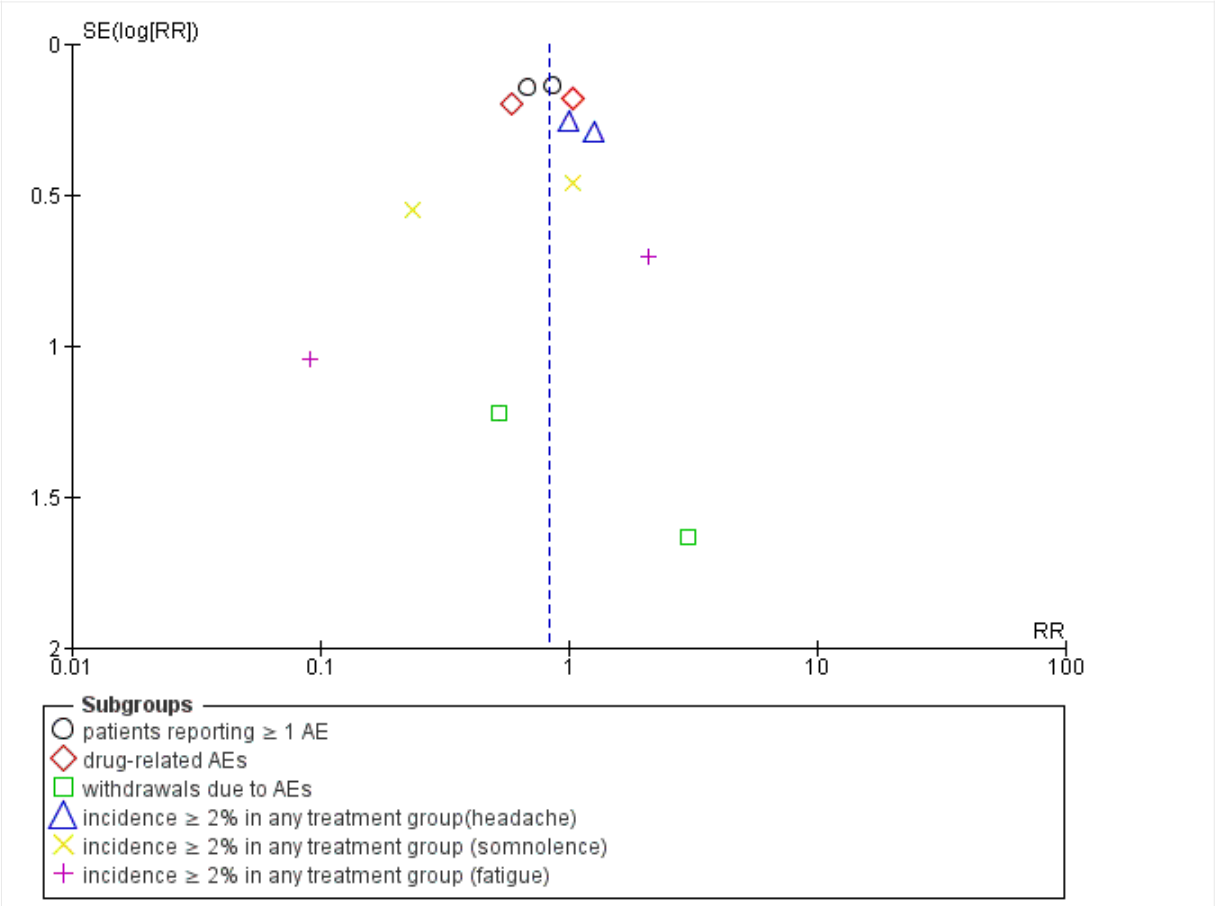

Figure 9. The funnel plot of comparison: bilastine 20 mg versus other second-generation oral H1-antihistamines, outcome: AEs reported over 2 weeks of treatment

PUBLICATION BIAS

We present funnel plots of the outcomes (Figure 7-10). However, we did not interpret them regarding publication bias due to a small number of trials.

DISCUSSION

This was the first review investigating the efficacy and safety of bilastine for the reduction of symptoms of seasonal allergic rhinitis comparing bilastine with other second-generation oral H1-antihistamines as well as placebo. From the two included studies with 1401 patients with seasonal allergic rhinitis, we found that there was no statistically significant difference in the reduction of symptoms of seasonal allergic rhinitis between using bilastine and other second-generation oral H1-antihistamines with low heterogeneity. We also found that the reduction of symptoms of seasonal allergic rhinitis of those using bilastine was significantly greater than that of using a placebo with high heterogeneity. In both trials, we found that adverse events, including headache, somnolence, and fatigue in those using bilastine were also similar to that of other second-generation oral H1-antihistamines and placebo except the rate of patients reporting 1 or more AEs were found

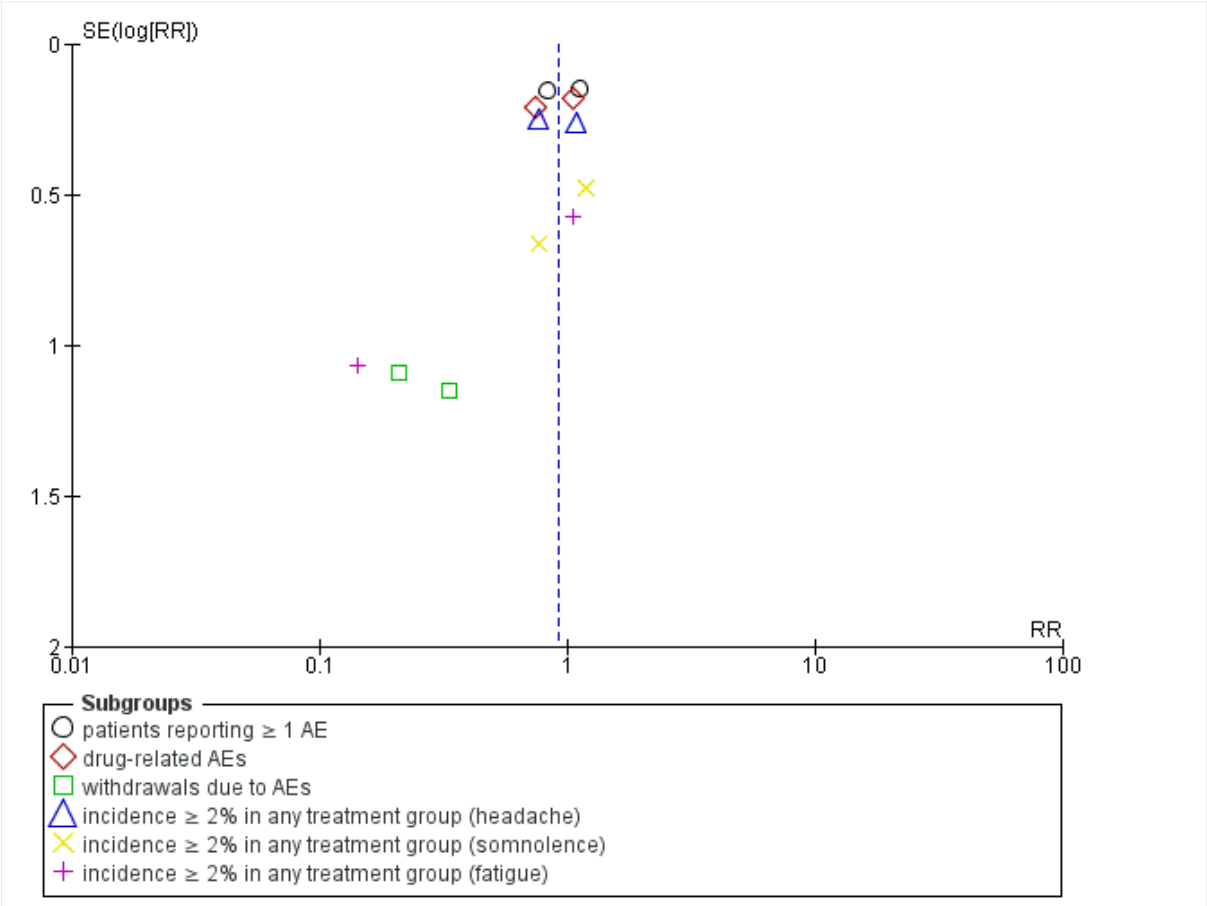

Figure 10. The funnel plot of comparison: bilastine 20 mg versus placebo, outcome: AEs reported over 2 weeks of treatment

significantly a bit lower in those using bilastine comparing to other second-generation oral H1-antihistamines.

STRENGTH AND LIMITATIONS

Our review is a systematic review comparing the efficacy and safety of bilastine for the reduction of symptoms of seasonal allergic rhinitis. We systematically searched databases and other sources for published and unpublished trials. We applied a comprehensive search with no language restrictions. We tended to identify all relevant trials. We conducted this review with the Cochrane handbook. Our search was comprehensive, our included studies had a low risk of bias.

There were several limitations in our systematic review. Firstly, the limitation was the small number of participants as we found only two RCTs that met our inclusion and exclusion criteria. Secondly, because of the limited data on other drugs from our enrolled trials, we were able to analyze only 2 drugs and other drugs were not considered for analysis. Thirdly, our study had a different duration of the assessment and they did not combine with outcome analysis for dyspnea. Finally, we had to exclude one potential study found from

ClinicalTrial.gov and the attempt to contact the author was made, however, there was no response.

COMPARISON WITH OTHER STUDIES

Our review demonstrated bilastine and other second-generation H1-antihistamines were similar in the efficacy of the reduction of symptoms of seasonal allergic rhinitis at 14 days. According to a study of Okubo et al, 2016, they found the efficacy of bilastine on rhinorrhea was similar to that of fexofenadine for perennial allergic rhinitis at 14 days and they reported that bilastine had a rapid onset of action at one hour.26 According to a study of Zuberbier et al, they found the efficacy of bilastine on reducing the symptom was similar to that of levocetirizine for chronic urticaria.27 Nevertheless, allergic rhinitis is an inflammatory respiratory disease caused by inflammatory mediators, including histamine mediating its effect via H1-receptor. Pathophysiology of seasonal, perennial allergic rhinitis and chronic urticaria is the same mechanism, therefore, second-generation H1-antihistamines, bilastine, and fexofenadine should be similar in the reduction of symptoms of seasonal and perennial allergic rhinitis.

CONCLUSION

Our systematic review showed that the efficacies using bilastine and other second-generation oral H1-antihistamines in the reduction of symptoms of seasonal allergic rhinitis were similar in patients with seasonal allergic rhinitis as well as the adverse events including incidence 2% or more AEs in any treatment groups. Rates of drug-related AEs and withdrawals due to AEs were similar in those using bilastine and other second-generation oral H1-antihistamines except the rate of patients reporting 1 or more AEs were found significantly lower in those using bilastine. For further study, we suggest larger RCTs with clearer study design, methods and assess long-term efficacies and adverse events.

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"I shall either find a way or make one"

-Hannibal Barca

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