

Review of the first 20 years of the Evidence-Based Medicine Committee of the Japan Society for Oriental Medicine

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ABSTRACT

Objective/background: The Evidence-Based Medicine Special Committee of the Japan Society for Oriental Medicine was launched in 2001. We summarize the task force-specific activities of this committee over the past 20 years.

Task forces: The Evidence Reports Task Force compiles randomized controlled trials and meta-analyses on Kampo extract products. Since 2007, the collated list is available on the Japan Society for Oriental Medicine website. As of 1 February 2021, there are 478 trials and three meta-analyses.

The Clinical Practice Guidelines Task Force identifies descriptions of Kampo medicines in such guidelines. As of 1 February 2021, there are 135 guidelines (9.6%) on Kampo extract products among 1411 guidelines published in Japan. These guidelines can be classified into three types: type A ($n = 40$), references, evidence grades, and recommendation gradings; type B ($n = 51$), only references; and type C ($n = 44$), no references.

The Standards of Reporting Kampo Products Task Force manages the website (<http://mpdb.nibiohn.go.jp/stork/>) and provides information on the characteristics of 148 Kampo products marketed in Japan, acting as a simple, comprehensive reference for Kampo formulae, and promoting uniform understanding among authors, reviewers, and readers.

The Best-Case Task Force compiled remarkably effective cases as evidence of Kampo treatment in 2006. The “Kakkonto Project” collected best-case series of kakkonto. The project ended in 2011 because of the number of cases was limited.

Conclusion: The committee established significant landmarks for evidence-based Kampo medicine and collected a reliable information resource. The guidelines repository is continuously updated with new information. A standard platform for referencing Kampo formulae in research articles is also well established.

KEY WORDS: clinical practice guideline, Committee, evidence-based medicine, Kampo, randomized controlled trial

INTRODUCTION

Traditional Japanese Kampo medicine has a long history and is derived from ancient Chinese medicine [1]. This form of medicine nearly became extinct due to the government's decision to exclude Kampo medicine from the official medical educational and licensing systems in Japan in the 1870s.

Kampo medicine was reintroduced in medical education in 2001 following an amendment in the model core curriculum of medical education [1]. All medical schools in Japan have incorporated Kampo medicine into their educational curricula since then [2].

Owing to the worldwide popularity of evidence-based medicine (EBM), the number of randomized controlled trials (RCTs) using Kampo extract products has been increasing over the last two decades. Significantly, they have been published in English journals. In parallel to the increase in the number of RCTs with Kampo extract products, the number of clinical practice guidelines (CPGs) also increased and gradually handles with Kampo medicines. However, when research manuscripts on Kampo formulae are submitted to English journals, reviewers do not understand Kampo

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medicines and often ask questions on the basic characteristics of Kampo formulae. This indicates the importance of better, wider communication regarding Kampo medicine and, thus, highlights the pertinent role a dedicated committee, the EBM Special Committee of the Japan Society for Oriental Medicine (JSOM), can play. A reflective overview of the committee's activities over the past two decades is, hence, imperative to study its effectiveness and future planning.

The term 'EBM' was introduced in 1991, and the JSOM EBM Special Committee was launched in 2001. Coincidentally, this was the same year that Kampo medicine was included in the model core curriculum of medical education in Japan. The EBM Committee celebrates its 20th anniversary in 2021, marking a milestone and an opportunity to present a review of the work done by the committee. In this review, we describe how the EBM Committee of JSOM in these 20 years has tried to develop Evidence Reports of Kampo Treatment (EKAT), clarify how Kampo extract products are described and evaluated in Japanese CPGs (KCPG), and its proposal on how to cite Kampo formulae in research articles (Standards of Reporting Kampo products: STORK) (Fig. 1).

EBKAT BY THE EVIDENCE REPORTS TASK FORCE

The EBM Special Committee, launched in June 2001, published "EBM in Kampo Treatment: Interim Report 2002," [3] and subsequently, "Evidence Report of Kampo Treatment" in 2005 [4].

The first term of the committee (Chair: Dr. Tetsuo Akiba) started on 12 June 2001. According to Dr. Akiba's introductory remarks at the symposium on EBM on 24 June 2006, serious adverse drug reactions (ADRs) due to shosaikoto in its popular use for patients with chronic hepatitis and the fear that Kampo medicines might be excluded from the Japanese national health insurance system evoked the following two questions for Kampo medicine experts themselves: 'Have we established clinical evidence of Kampo medicines?' and 'Are you going to spread your individual belief about the benefit of Kampo medicine to society?' These questions prompted the committee to start the development of an Evidence Report of Kampo medicine (EKAT) Task Force.

The purpose of the project was to promote EBM in Kampo medicine, create further understanding regarding Kampo medicine, and sharing comprehension about medical treatments with Western medicine through the concept of EBM [5].

The first step was to collect clinical reports on Kampo treatments in various medical fields. The methods and inclusion criteria were as follows: (i) sample size of more than 10; (ii) good case series were included in addition to RCTs; (iii) use of a database developed by the Japan Kampo Manufacturers Association (JKMA); and (iv) studies published after 1986. The year 1986 saw the implementation of new manufacturing guidelines for Kampo products, which

included the use of at least two chemical-biological indicators to maintain a certain level of quality. As a result, 905 articles qualified for the evaluation, and 93 reports were selected as good clinical evidence. Some challenges, such as deciding on the selection criteria for articles, were experienced during the process, as have been mentioned for previous studies as well [6].

The second term of the committee (Chair: Dr. Kiichiro Tsutani) started in 2005 and lessons from the previous term were utilized. Taking over their predecessor's achievements, the second phase of the project adopted a systematic approach, focusing on comprehensiveness and transparency. The methods of developing structured abstracts (SAs) for RCTs needed consideration. Development of SAs was limited to RCTs, in accordance with worldwide standards. The following steps were used for the development of SAs:

Three criteria for reference selection

References that satisfied all of the following three criteria were included: (i) references using Kampo formulae approved for manufacture and sale in Japan; (ii) RCTS, quasi-RCTS, crossover trials, and meta-analyses; and (iii) references published in or after 1986.

Search and screening

The following databases were included: (i) CENTRAL in The Cochrane Library; (ii) Ichushi Web; and (iii) the JKMA database. All the searched formulae were included in EKAT. A list of excluded studies, with reasons for exclusion, was compiled and included in each EKAT report.

Preparation of SAs

The eight-item SA format of RCTs proposed by Altman and Gardner [7] was employed. The globally adopted items are as follows: (i) objectives; (ii) design; (iii) setting; (iv) participants; (v) intervention; (vi) main outcome measures; (vii) main results; (viii) conclusions; furthermore, a further four items used specifically for EKAT included the following: (ix) description of the 'Kampo medicine perspective', such as 'sho' (pattern diagnosis), used in patient inclusion and/or exclusion criteria, also including post-randomized stratified 'sho' analysis; (x) safety assessment; (xi) abstractor's comments; and (xii) abstractor's name and date.

Development of a website for EKAT

Each SA was documented on A4 size documents and uploaded on the newly developed website of JSOM (<http://www.jsom.or.jp/medical/ebm/ere/index.html>). Every three years, such as 2010, 2013, and 2016, full and updated versions of EKAT are published together with annual appendices. English versions are also available.

EKAT has been linked to a government-sponsored website: 'evidence-based Japanese integrative medicine' (eJIM: <https://www.ejim.ncgg.go.jp/en/index.html>) [9–11]. EKAT has been

History of EBM Committee, JSOM (2001-2013)

2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Committee Chair: T. Akiba				K. Tsutani								
EBM in Kampo Treatment				Evidence Report Task Force (ER-TF) (Chair: T. Okabe) EKAT				Evidence Report/Clinical practice guidelines Task Force (ER/CPG-TF) (Chair: T. Okabe) EKAT, KCPG			Evidence Report/Clinical practice guidelines Task Force (ER/CPG-TF) (Chair: K. Tsutani) EKAT, KCPG	
EKAT: Evidence Report of Kampo Treatment KCPG: Description of Kampo in clinical practice guidelines KCONSORT: Kampo-CONSORT				Clinical practice guidelines Task Force (CPG-TF) (Chair: K. Tsutani) In response to CPG projects for traditional Medicine by WHO/WPRO KCPG								
1) 2006.6.25. Symposium: How should EBM of Kampo be? 2) 2007.6.16 RTD: Dramatically effective cases with Kampo 3) 2007.6.17 WS: How to make adequate comments in EKAT 4) 2008.6.7 RTD: In order to make dramatically effective cases clinical evidence: from the analysis of effective cases with kakkonto” 5) 2009.6.21 Forum: “Communicate” evidence of Kampo								KCONSORT Task Force (Chair: K. Tsutani) KCONSORT				
RTD: Round Table Discussion WS: Workshop				Best Case Task Force (BC-TF) (Chair: H. Kimoto) “Kakkonto Project”				Best Case Task Force (BC-TF) (Chair: M. Ogawa) “Kakkonto Project”			*Each term starts in June	
JSOM												
Managing director: T. Akiba				M. Sugiyama		K. Tsutani		T. Okabe		S. Muramatsu		
President: A. Ishibashi				S. Ishino		K. Terasawa		T. Ishikawa				

History of EBM Committee, JSOM (2014-2021)

2014	2015	Sept* 2016	2017	2018	2019	June	2020	2021
Committee Chair: K. Tsutani			Y. Motoo			T. Kogure		
Evidence Report/ Clinical practice guidelines Task Force (ER/CPG-TF) (Chair: K. Tsutani) EKAT, KCPG	Evidence Report Task Force (ER-TF) (Chair: K. Tsutani) EKAT		Evidence Report Task Force (ER-TF) (Chair: Y. Motoo) EKAT			Evidence Report Task Force (ER-TF) (Chair: T. Kogure) EKAT		
	Clinical practice guidelines Task Force (CPG-TF) (Chair: Y. Motoo) KCPG		Clinical practice guidelines Task Force (CPG-TF) (Chair: I. Arai) KCPG					
KCONSORT Task Force (KC-TF) (Chair: K. Tsutani) KCONSORT			KCONSORT Task Force (KC-TF) (Chair: T. Hakamatsuka) KCONSORT		STORK Task Force (STORK -TF) (Chair: T. Hakamatsuka) STORK STORK: Standards of Reporting Kampo products			
6) 2014.6.29 Symposium: The era of post-EBM has come? 7) 2015.6.13 Symposium: Clinical practice guidelines and Kampo 8) 2018.6.9 Special Session: Up-to-date of English writing: Let's send information on Kampo to the world						*The Chairs of ER-TF and CPG-TF changed in September only in 2015.		
JSOM			Managing director: S. Muramatsu			Y. Motoo		
President: T. Ishikawa			H. Sato			T. Itoh		

Figure 1 | History of the EBM Committee of the Japan Society for Oriental Medicine.

analyzed in terms of the design of RCTs, published journals, and current status [12,13].

We also struggled to utilize a variety of means to obtain support from ordinary members of JSOM. The first agenda was organizing a workshop for the developers of SA to use the positive-negative-positive (PNP) method [8] in writing

reviewer's comments in each SA. Therefore, even if serious problems were included in the article, we started by acknowledging points (positive issue: P) such as developing unique research questions and combating difficulties in the recruitment of study participants. Thereafter, we highlighted a few (not many) negative (N) problems; lastly, we included

a few points on future trials hoping for positive results (P). The PNP method was originally developed for education of medical students' communication skills. That is, simulating patients' attitudes toward medical students should be based on the PNP methods, so that students can learn communication skills smoothly. The EBM committee members also wished to maintain friendly relations with other members of JSOM. The second agenda was to hold a symposium on EBM wherein ongoing activities were introduced and significant dialogue was generated between the EBM Committee members and the audience.

As of 1 February 2021, the latest version of EKAT is EKAT Appendix 2018. The history of upgrade is shown on the website of JSOM in English as follows: The Japan Society for Oriental Medicine | History of version upgrades (jsom.or.jp). As of 1 February 2021, there are 478 RCTs and three meta-analyses (MAs). Since 2007, EKAT has been an open-source repository on the website of JSOM (<http://www.jsom.or.jp/medical/ebm/er/index.html>). One may search for any RCT that used Kampo products on the website of EKAT.

KAMPO PRODUCTS IN CPG (KCPG) BY THE CPG TASK FORCE

The 'Clinical Practice Guidelines Project for Traditional Medicine' was launched by the World Health Organization (WHO) Regional Office for the Western Pacific in 2004. Japan pointed out the difficulties and problems of CPG for traditional medicine in 2005 [14]. This project itself eventually stopped its activities in 2007. Although several conferences were canceled, CPGs for traditional Chinese medicine were developed in various medical fields [15]. CPGs for traditional medicine in east Asian countries have been analyzed [16]. However, CPGs for Kampo medicine have never been tried, rather Japan attempts not to develop CPGs for Kampo medicine alone. This reflects that Japan respects the diversity of medical approaches, including Kampo medicine.

As of 1 January 2021, there are 135 CPGs (9.6%) that include descriptions on Kampo products among 1411 CPGs published in Japan. The 135 CPGs were classified into three types — type A includes references, evidence grades, and recommendation gradings (40 CPGs); type B includes references but no evidence grades or recommendation gradings (51 CPGs); type C has no references and no recommendation gradings (44 CPGs) [17]. Figure 2 shows the trend in changes in the number of CPGs containing descriptions of Kampo medicines. CPGs containing descriptions of Kampo medicines, especially type A, are increasing, but not enough to provide strong recommendations of Kampo medicines in clinical practice. Some CPGs lack descriptions of Kampo medicines while there is evidence on that matter. The Evidence Reports Task Force (ER-TF) developed 467 SAs (RCT: 465, MA:2). Among 565 articles for these 467 studies, only 53 articles were cited in CPGs. The KCPG has been revised

every year. As of 1 February 2021, the latest version of KCPG is KCPG 2019. The upgrade history is shown on the website of JSOM in English (<http://www.jsom.or.jp/medical/ebm/cpg/about.html>). JSOM hopes that Kampo medicine will be well evaluated in CPGs for modern medicine.

STANDARDS OF REPORTING KAMPO PRODUCTS (STORK) TASK FORCE

Standards of Reporting Kampo Products (STORK) is the website (<http://mpdb.nibiohn.go.jp/stork/>) for Kampo products, formerly called KCONSORT (Kampo-CONSORT). The CONSORT Statement 2010 comprises a 25-item checklist and a flow diagram. There are no standard methods to cite a Kampo formula. For example, some articles show lists of the crude drugs, while others show detailed descriptions including a 'fingerprint' using high-performance liquid chromatography. We sought to create a simple and comprehensive way of citing Kampo formulae.

The STORK website provides information on the characteristics of 148 ethical Kampo products marketed in Japan [18]. It is based on the Standard Kampo Formula Nomenclature [19] which is developed for the use in the Japanese pharmacopeia (JP) and ADR data from the Japanese government reported to the Uppsala Monitoring Centre (WHO Collaborating Centre for Drug Monitoring). STORK corresponds to Item 5 (Intervention) of the CONSORT Statement 2010. Thus, reporters of RCT and other types of clinical research involving Kampo drugs are recommended to include the correct URL of STORK to describe characteristics for each Kampo drug involved in the study in the manuscript, such as (anchusan: see <http://mpdb.nibiohn.go.jp/stork/>). However, currently it only shows the top page of STORK. The link for each formula will be developed in the future.

Recent articles handling Kampo drugs utilize STORK in their Materials (or Patients) and Methods section in addition to the Introduction section [20–23].

BEST-CASE TASK FORCE

The Best-Case Task Force (BC-TF) of JSOM has compiled remarkably effective cases as evidence of Kampo treatment since 2006. At first, the 'Kakkonto Project' was launched to collect a best-case series of kakkonto formula [24,25]. It was proposed to the ethics committee of JSOM on 6 March 2007, and was approved as an ethically adequate project on 30 March 2007. The case reports were collected through the JSOM website. However, only five cases were collected, and eventually, this project was stopped in March 2011. In addition, the 'Kakkonto Project' was a retrospective approach, not a prospective intervention. The BC-TF was continued for the purpose of developing a database of case reports of Kampo treatment as a new mission; however, the activities

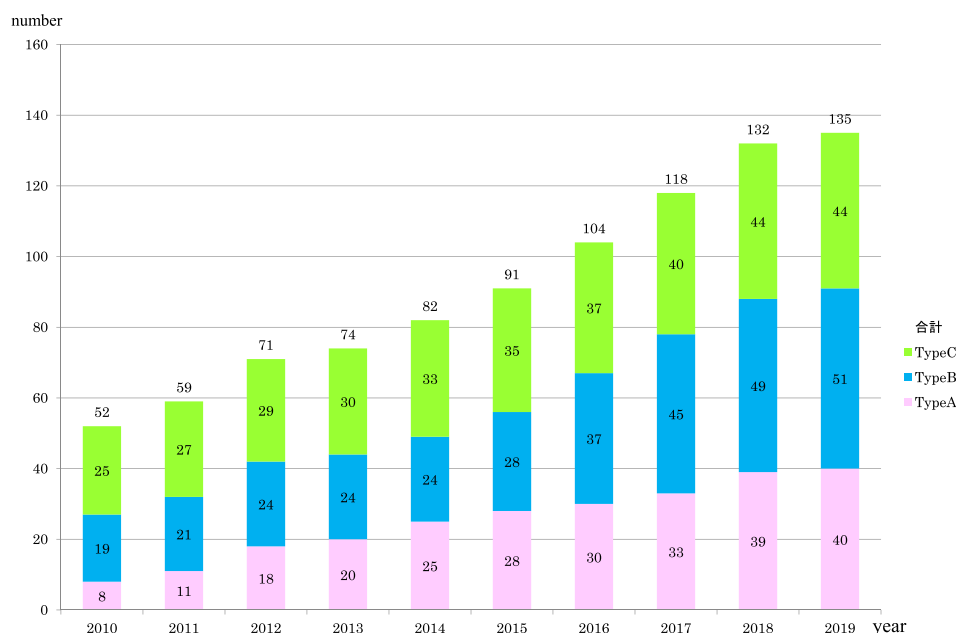


Figure 2 | Change in the number of clinical practice guidelines (CPGs) for the various types of Kampo description. The CPGs were classified into three types: type A includes references, evidence grades, and recommendation gradings; type B includes references but no evidence grades or recommendation gradings; type C has no references and no recommendation gradings [17].

of this TF were low due to the difficulties of developing SA and an actual workflow, member changes, and restrictions on the budget.

REMAINING ISSUES: SAFETY AND EDUCATION

Several physicians complained of the lack of evidence for Kampo medicine during the early 2000s, but we believe that such physicians are now few. We are proud that JSOM-EKAT contributes to the increasing positive recognition of Kampo medicine. It is now imperative and the correct time to make use of evidence and lessons in each specific area. Thanks to the inclusion of Kampo medicine in the model core curriculum in 2001, physicians under 40 years of age do not have ‘anti-Kampo medicine reactions’, as was the case earlier.

From the history of EKAT, we observe that the quality of evidence for Kampo medicine’s effectiveness has improved over the last few decades. Articles of high-quality trials using Kampo medicine are being published in English journals in various areas of medicine. EKAT also contributed to the inclusion of Kampo medicine into CPGs, although some are still neglected at the CPG developing stage.

Two issues still remain. One is that of safety. Frequent use of limited kinds of Kampo formulae and insufficient attention to adverse reactions might lead to severe adverse events, such as acute liver failure or life-threatening interstitial pneumonitis [26,27]. Some oncologists do not recommend

the use of Kampo formulae in combination with modern anti-cancer agents, being concerned about the occurrence of adverse events (AE). JSOM accordingly established a Medical Safety Committee in 2017. Rational drug selection should be based on benefit, risk, and cost effectiveness. Research evidence on safety should be studied and made available as well. We expect that this new committee will develop certain monitoring systems and AEs can be avoided in the future.

The second issue is that of education. A minimum of education regarding Kampo medicine already started in all medical schools in Japan in 2001. It has been observed that significant numbers of patients prefer nature-derived drugs such as Kampo medicines over conventional modern drugs. An EBM process flow has evolved over time. Haynes *et al.* [28] illustrated EBM using three factors, i.e., research evidence, patient preference and actions, and clinical state and circumstances; it is governed by the clinical expertise of physicians and caregivers. It would be of great importance in clinical settings to understand the indications and limitations of modern medicine and Kampo medicine, considering the above factors. A good model that includes Kampo medicine should be developed in medical education.

According to the WHO Traditional Medicine (TM) Strategy 2014–2023 [29], there are great expectations that TM will contribute to health, wellness, and people-centered health care. Promoting the safe and effective use of TM through regulation and education will lead to appropriate integration of TM into modern health systems.

CONCLUSION

The EBM Committee of JSOM has established significant landmarks for EBM of Kampo medicine in the history of TM in Japan. EKAT is now utilized as a reliable information resource of RCT on Kampo extract products. KCPG is continuously renewed in parallel with the development of new CPGs in modern medicine. STORK has become a standard platform for references of Kampo formulae in research articles. Continuous improvement of these activities is warranted. Further, this review of activities can now be used to objectively and systematically plan further steps for this committee.

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CONFLICTS OF INTEREST

YM received lecture fees from Tsumura & Co.; the other co-authors have no conflicts of interest to report.

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