As the Satellite continues to attract even more review authors, additional capacity is required to meet the demand for training and support, and to guarantee proper management of training activities. Setting up a branch of the Australasian Cochrane Centre in Japan, similar to those that exist in Singapore, Korea, Malaysia, New Zealand and Thailand, will boost local involvement in the Cochrane Collaboration and encourage others to participate.

There has been regular contact with the Australasian Cochrane Centre about the possibility of establishing a Japanese Branch since Rintaro Mori and Steve McDonald met at the G-I-N conference in Seoul in August 2011. Further meetings have taken place at the Cochrane Colloquium in Auckland in October 2012, and in Tokyo in February 2013.

2.2 Proposed Co-Directors and Branch Manager

Rintaro Mori is the Coordinator of the Japanese Satellite of the Cochrane Pregnancy & Childbirth Group and has been an active author with the PCG since 2006 and an Associate Editor since 2011. After paediatric training in Japan, Rintaro practiced as a neonatologist in Australia, the UK and Nepal, and studied epidemiology/public health at the London School of Hygiene & Tropical Medicine, before being involved in guideline development for the UK National Institute for Health and Clinical Excellence (NICE). He has also actively been involved in research and aid-works in Nepal, Madagascar, Bangladesh and Mongolia, as well as research in women's and children's health at the global level. He has teaching roles at the University of Tokyo, Kyoto University, the London School of Hygiene & Tropical Medicine, and others, plus active roles in the Japanese Pediatric Society, including Chair of its Strategic Planning Committee, and is a Fellow of Royal College of Paediatrics and Child Health (UK).

Toshi Furukawa, Co-Director for the proposed Japanese Branch, has long been involved with the Depression, Anxiety and Neurosis Group, and has been Editor of CCDAN since December 1998. He has authored or co-authored 13 reviews and six protocols for CCDAN, and two more for other Cochrane Review Groups. For the past three years he has been particularly active in training young reviewers (see the list of review courses held in Kyoto University School of Public Health), leading to six more new protocols currently under review with various Cochrane Review Groups. He was Professor and Chair of Department of Psychiatry and Cognitive-Behavioral Medicine at Nagoya City University Graduate School of Medical Sciences between 1999 and 2010, and is currently Professor and Chair of Department of Health Promotion and Human Behavior, and Professor of Department of Clinical Epidemiology at Kyoto University Graduate School of Medicine / School of Public Health since 2010.

Erika Ota, Branch Manager for the proposed Japanese Branch, has been involved with both the Cochrane Pregnancy & Childbirth Group and HIV/AIDS Group since 2010. She has published, authored and co-authored five full reviews and seven protocols, and is presently leading more than five co-authored protocols and reviews under editorial review. Erika has a background in midwifery with a PhD in health science, and has been providing author support and training for the Cochrane PCG Japanese Satellite since April 2012. From 2010 to 2013, she worked as Research Fellow and Assistant Professor at the Department of Global Health Policy, the University of Tokyo, where she trained many young researchers and conducted a Cochrane review course. In May 2013, Erika was appointed Chief of the Epidemiology Division at the

National Center for Child Health and Development, and in this role she manages Cochrane activities for the PCG Japanese Satellite.

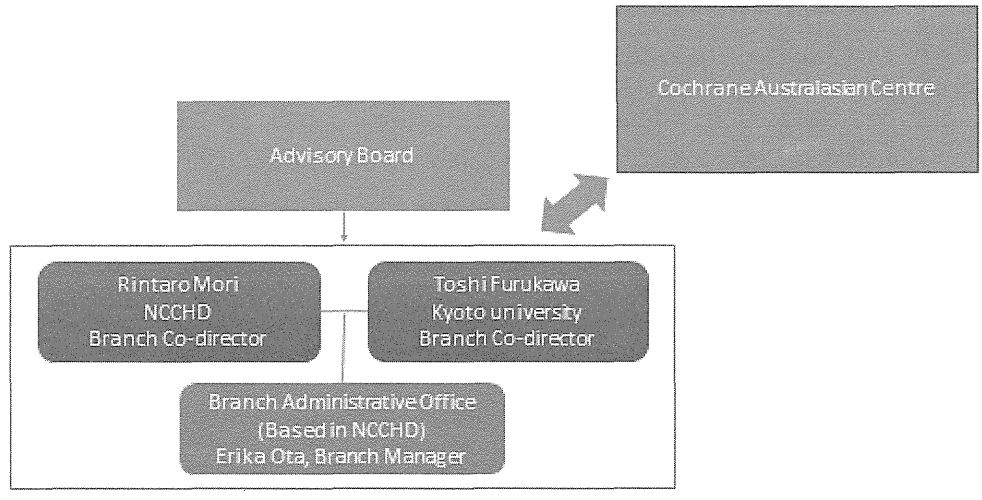
2.3 Training in Cochrane systematic reviews

Since the first Cochrane systematic review workshop in 2010 in Tokyo, which was supported by the Thai Cochrane Network, there have been numerous Cochrane courses and workshops held in Japan. The majority of workshops have been tailored to researchers who are new to Cochrane reviews and have focused specifically on title registration, protocol development and full review development.

Table 3: Cochrane training activity in Japan (2010-2012)

Year	Type of workshop	Location
2010 Mar	Protocol development (two-day course)	Tokyo
2010 Jul	Full review development (two-day course)	Tokyo
2011 May-Jul	Cochrane review course (held 8 times)	Kyoto
2012 July	Introductory author training	Tokyo
2012 Aug	Introduction to RevMan 5	Tokyo
2012 Sep	Protocol development (two-day course)	Tokyo
2012 July-Dec	Cochrane review course (held 8 times)	Kyoto
2012 Oct-Mar	Cochrane review course (held 8 times)	Tokyo
2013 Feb	Full review development (two-day course)	Tokyo
2013 Apr	Cochrane review course (one-day course)	Kyoto
2013 Jul-Dec	Cochrane review course (held 8 times)	Kyoto

2.4 Organisational structure



2.5 Translation activities

MINDS (Medical Intervention Network Distribution Service) of the Japan Council for Quality Health Care has been translating abstracts of selected Cochrane reviews into Japanese for guideline developers and for general public for many years. We plan to explore how the new Branch can build on these efforts, and will continue to liaise with Prof Naohito Yamaguchi, the Director of MINDS, about providing translations of abstracts to a potentially wider audience in Japan. We will also liaise with the Translation Strategy Group and Cochrane Translation Exchange to investigate the most efficient ways of translating content.

2.6 Countries supported by the Branch

The Japanese Branch will have responsibility for supporting Japanese contributors. Other countries in the East Asia region are either branches of the Australasian Cochrane Centre (Korea and Singapore) or the Chinese Cochrane Centre (Hong Kong). The East Asia Cochrane Alliance (EACA) also includes Taiwan, and EACA members have met regularly for several years. It is anticipated that the increased focus on advocacy and impact of Cochrane in the new *Strategy to 2020* will lead to renewed efforts to strengthen regional links.

2.7 Vision, Mission, Goals and Activities

Vision

To achieve the best health and wellbeing possible for all through excellence and leadership in research, education, and knowledge transfer.

Goals

The goals and objectives of the Japanese Cochrane Branch are closely aligned to Cochrane's *Strategy to 2020* with respect to producing evidence, making evidence accessible and advocating for evidence:

1. To introduce new review authors and other contributors to Cochrane methods, and support Japanese authors to prepare, publish and maintain their Cochrane reviews.
2. To increase the accessibility of Cochrane Reviews and related content through translation.
3. To advocate for evidence-informed practice in Japan, particularly through promoting access to Cochrane content and facilitating the use of Cochrane Reviews to inform decision making.

Activities

The Japanese Branch will work closely with the editorial teams of the CRGs with support from the Australasian Cochrane Centre, and will facilitate the following main activities in Japan:

1. In order to generate research evidence of the highest quality that promotes the best health and wellbeing possible for all, the Branch team will:
    - support Cochrane authors on a one-to-one basis (in person, email or by phone), including editorial and language support, to produce and maintain high-quality Cochrane systematic reviews;

- organise work-ins and workshops in Japan for new and existing Japanese authors, as well as organise work-ins and workshops alongside relevant national conferences;
- monitor the number of Cochrane review titles and Cochrane publications involving contributors based in and around Japan;
- publish at least seven full Cochrane systematic reviews within two years.

2. In order to increase capacity in research synthesis, randomised trials, and implementation and translational locally and nationally, the Branch will:
   - advocate on behalf of Cochrane and promote its mission and values in relevant local and national forums;
   - hold regular local monthly meetings and training sessions;
   - disseminate information on Cochrane-related activities in Japanese, including setting up a Japanese Branch website;
3. In order to promote access to Cochrane content and increase the impact of Cochrane on health and healthcare decision making in Japan, the Branch will:
   - translate Cochrane abstracts and plain language summaries in Japanese;
   - work towards improving access to *The Cochrane Library* by pursuing a national licence;
   - collaborate with MINDS to promote utilisation of Cochrane Reviews in clinical practice guidelines developed by MINDS and other organisations.
4. In order to strengthen our existing collaborations, and to identify and communicate with new national, regional and international collaborators, the Branch will:
   - ensure communication between the team and other clinical epidemiologists and related organisations in Japan, as well as consumer organisations, the Ministry of Health, Labour and Welfare, and other relevant organisations and national agencies in Japan;
   - facilitate communication between other related organisations regionally and worldwide, for example, other relevant Cochrane groups, particularly the East Asia Cochrane Alliance, the Department of Reproductive Health and Research (WHO), and other maternal and newborn health specialists around the world.
5. To assist with the identification of relevant studies, the Branch's Information Specialist will:
   - identify relevant Japanese trials from databases and journals;
   - coordinate the translation of relevant Japanese trials into English;
   - identify search activities to enhance the Cochrane Review Groups' current search strategy for ensuring the inclusion of Japanese studies in the Group's register of trials.
6. To work towards a sustainable organisation, the Branch will:
   - identify ongoing funding opportunities;
   - support the professional and leadership development of current and future staff and contributors to the Japanese Branch.

2.8 Funding

The administrative office will be set up in the NCCHD, where the core staff will be based. We will continue to seek financial support. Currently, the Pregnancy and Childbirth Group Satellite in Japan receives a research grant from the Japan Ministry of Health, Labour and Welfare (¥12,000,000 (approx. US$120,000) per year, including overheads, for three years). The NCCHD can provide office space, support for workshops, and allow staff to spend time on Cochrane author support.

2.9 Staffing and personnel

The following staff will support and undertake activities on behalf of the Branch, supported by NCCHD and the other organisations.

Branch Co-Directors	• Rintaro Mori, *Associate Editor*, Pregnancy and Childbirth Group, Chair of PCG Japan Satellite • Toshiaki Furukawa, *Editor*, Depression, Anxiety and Neurosis Group
Branch Manager (NCCHD)	• Erika Ota, *Chief*, Division of Epidemiology
Trainer (Kyoto Uni. and NCCHD)	• TBC
Statistician	• Hisashi Noma, *Associate Researcher*, Department of Health Policy (Biostatistics)
Information specialists (NCCHD)	• Miwako Segawa, *Associate Researcher*, Department of Health Policy (Information specialist) • Chiemi Kataoka, *Information Specialist*, NCCHD
Linguistic support (NCCHD)	• Emma Barber, *Research Fellow*, Department of Health Policy (Editor)
Administrative assistants (NCCHD)	• TBC

2.10 Advisory Board

The Advisory Board will be established to provide advice and suggestion on the management and strategic direction of the Branch. Board members will be expected to advocate the work of Cochrane in Japan. We are keen to appoint a chair who has standing within Japanese medical societies and influence among other key stakeholders, such as the Ministry. We have begun informal discussions with potential Board members, and plan to finalise the membership and terms of reference after the Branch application has been approved. We anticipate the Advisory Board will have at least one face-to-face meet annually.

2.11 Communication

There are three forms of communication we will establish to support interaction with the Australasian Cochrane Centre:

1. *Face-to-face meetings*

We will hold annual face-to-face meeting to discuss any issues above to proceed with our work more effectively and efficiently, most likely during the Cochrane Colloquium.

2. *Regular teleconferences*
   Apart from the annual face-to-face meeting above, we will hold telephone conferences quarterly to catch up on all the activities that the Branch and the Centre work together on.
3. *Email and/or telephone meetings*
   In daily situations and when necessary, we will communicate via email or by setting up extra telephone conference.

We see the main areas of support from the Australasian Cochrane Centre as:

- Providing advice and support with fulfilling the activities of the Branch strategic plan, and ensuring we are integrated within the broader activities and priorities of Cochrane, as set out in the *Strategy to 2020*;
- Support for training activities through sharing of materials and facilitating workshops;
- Acting as a link between the Japanese Branch and the rest of Cochrane, particularly when issues arise involving other groups in Cochrane;
- Helping to establish the Branch website, updating Archie records, completing monitoring obligations, and other tasks required by Cochrane.

3. SUPPORTING DOCUMENTATION

3.1 Declarations of interest

Declarations based on the questions required of Steering Group members. The term 'related organisation' in the questions below means any organisation related to health care or medical research. Responses from Rintaro Mori and Toshi Furukawa (current September 2013, covering previous five years).

1. Received research funding: any grant, contract or gift, commissioned research, or fellowship from a related organisation to conduct research?

RM *Yes, from World Health Organization for grants relating to systematic reviews, guideline development and surveys in maternal and newborn health; Ministry of Health, Labor and Welfare of Japan on development of neonatal clinical database, systematic reviews and clinical practice guidelines; Ministry of Education, Culture, Sports, Science and Technology of Japan on birth cohort study in Mongolia; Gates Foundation on health system in Japan; Ministry of Foreign Affairs of Japan on systematic reviews for global women's and children's health; and Save the Children on the global burden of diseases project.*

TF *Yes, the Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, and the Japan Foundation for Neuroscience and Mental Health have funded his research projects.*

2. Had paid consultancies: any paid work, consulting fees (in cash or kind) for a related organisation?

RM *Yes, as an external tutor at the London School of Hygiene & Tropical Medicine; consulting fees from Japan International Cooperating Agency on its programme on maternal and newborn health in Bangladesh.*

TF *Yes, on advisory board for Sekisui Chemicals and Takeda Science Foundation.*

3. Received honoraria: one-time payments (in cash or kind) from a related organisation?

RM *Yes, payments from The University of Tokyo, Kyoto University, Nagasaki University and Tokyo Women's Medical University for lecturing.*

TF *Yes, received honoraria for speaking at CME meetings sponsored by Asahi Kasei, Eli Lilly, GlaxoSmithKline, Mochida, MSD, Otsuka, Pfizer, Shionogi and Tanabe-Mitsubishi.*

4. Served as a director, officer, partner, trustee, employee or held a position of management with a related organisation?

RM *No.*

TF *No.*

5. Possessed share-holdings, stock, stock options, equity with a related organisation (excludes mutual funds or similar arrangements where the individual has no control over the selection of the shares)?

RM *No.*

TF *No.*

6. Received personal gifts from a related organisation?

RM *No*

TF *No.*

7. Had an outstanding loan with a related organisation?

RM *No.*

TF *No.*

8. Received royalty payments from a related organisation?

RM *Yes, royalty payments for books published from Iwanami Shoten Publisher, Igaku-shoin Publisher and Medicus Shuppan Publisher.*

TF *Yes, royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha.*

9. Do you have any other competing interests that could pose a conflict of interest that would reasonably appear to be related to the primary interest?

RM *No.*

TF *No.*

3.2 CVs of Co-Directors

See Appendix 1.

3.3 Letters of support

See Appendix 2 for letters of support from the following:

- Cochrane Pregnancy and Childbirth Group
- National Center for Child Health and Development (NCCHD)
- Kyoto University

3.4 Application checklist

☒	Information about the applicants - Evidence of support for evidence-based practice and promotion of systematic reviews - Expertise and competencies in systematic reviewing
☒	Statement of the resources available to support the Branch
☒	Rationale for establishing a Branch
☒	List of countries the Branch will support (if applicable)
☒	Proposed membership of Advisory Board or description of how stakeholders will be engaged
☒	Strategic plan (2 year)
☒	Funding sources of the Branch
☒	Proposed staffing of the Branch
☒	Outline of communication plan between Centre and Branch
☒	Description of the support the Centre will provide the Branch
☒	Declarations of interest of Director(s)
☒	Curriculum vitae of Director(s)
☒	Letters of support

UNIVERSITY OF LIVERPOOL

Professor J Neilson, BSc MD FRCOG
NIHR Dean for Faculty Trainees;
Professor of Obstetrics & Gynaecology

Department of Women's and Children's Health
Institute of Translational Medicine
University of Liverpool

University Department, First Floor
Liverpool Women's Hospital
Crown Street
Liverpool
L8 7SS

T 0151 795 9551
F 0151 795 9599
E jneilson@liv.ac.uk

www.liv.ac.uk

2 October 2013

To whom it may concern

I am very happy to add my support to the application by Rintaro Mori and Toshiaki Furukawa (with Steve McDonald) for recognition of a Japanese Branch of the Australasian Cochrane Centre.

Japan is, of course, a very important country in terms of population size, culture, language and influence but, until recently, there has been less engagement with the Cochrane Collaboration in Japan than we would all like to see. The Cochrane Pregnancy & Childbirth Group has a long-standing link with Rintaro Mori since his secondment with NICE in the UK some years ago. This relationship has developed since to the point at which Rintaro has become an Editor of the Group and Rintaro and colleagues, notably Erika Ota, have established a satellite of the Cochrane Pregnancy & Childbirth Group in Tokyo. I was privileged to visit the satellite in July this year and was able to see the enthusiasm and commitment of those involved. I was also able to meet Professor Furukuwa, who has been a longstanding Cochrane contributor in the area of depression.

I have no doubt that this team will build on current considerable achievements and make a real difference, through training and support, to increasing Japanese contribution to the work of the Cochrane Collaboration.

I support this application without any reservation.

Yours Sincerely,

Professor J P Neilson
NIHR Dean for Training,
Professor of Obstetrics & Gynaecology

National Center for Child Health and Development
2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, JAPAN
Tel. 81-3-3416-0181 Fax. 81-3-5727-1075

Takashi Igarashi, M.D., Ph.D.
Chief Executive Officer

28 October 2013

Dear Sir or Madam

On behalf of the National Center for Child Health and Development, I am pleased to support the application of the Japanese Branch of the Australasian Cochrane Centre. Our Center has been hosting the Japanese Satellite of the Cochrane Pregnancy and Childbirth Group since last year. Awareness of the need to promote clinical research and evidence-based medicine has substantially increased as a result of the Satellite's activities, not only within our Center, but within other hospitals/facilities in women's and children's health, as well as other disciplines.

This application fits well within our mission to promote evidence-based children's families' health care and promotion in Japan. I am sure that establishing the Japanese Branch of the Australasian Cochrane Centre will enhance the movement and also contribute to promoting health in Japan and around the world.

Yours sincerely,

Takashi Igarashi
CEO and President
National Center for Child Health and Development

〒157-8535 東京都世田谷区大蔵2-10-1 独立行政法人国立成育医療研究センター

DEPARTMENT OF EPIDEMIOLOGY AND HEALTHCARE RESEARCH
GRADUATE SCHOOL OF MEDICINE AND PUBLIC HEALTH
KYOTO UNIVERSITY
YOSHIDA KONOE-CHO, SAKYO-KU, KYOTO, 606-8501 JAPAN

SHUNICHI FUKUHARA, MD, MSc, FACP
PROFESSOR AND CHAIR

September 3, 2013

Re: Application for the Creation of the Japan Branch of the Australasian Cochrane Centre: Letter of support

To the Monitoring and Registration Group:

In my capacity as Dean of the School of Public Health at Kyoto University, I am pleased to support the establishment of the Japan Branch of the Australasian Cochrane Centre. One of the co-directors of the proposed Centre, Professor Furukawa, is Professor of the departments of Health Promotion and Human Behavior and of Clinical Epidemiology at our School, and many of the review authors of completed Cochrane reviews, protocols and registered titles are current students and graduates of our School who were supervised by Professor Furukawa and other professors here. We have also had the honor of hosting a number of Cochrane workshops for systematic reviews at Kyoto University.

Given the past efforts and achievements of Professor Furukawa and Dr. Mori (National Center for Child Health and Development, Tokyo) in their coordination of Cochrane activities in Japan, and their strong vision to advance the role of Cochrane in Japan, as outlined in the Proposal, I am convinced that the Japan Branch will greatly enhance the presence of the Cochrane Collaboration throughout Japan and lead to a rapid increase in the participation of many Japanese authors in various aspects of Cochrane activities.

京都大学大学院 医学研究科　医療疫学分野
〒606-8501 京都市左京区吉田近衛町　Phone:+81-75-753-4646　Fax:+81-75-753-4644　http://www.epikyoto-u.jp

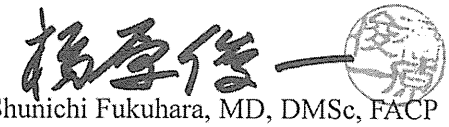
DEPARTMENT OF EPIDEMIOLOGY AND HEALTHCARE RESEARCH
GRADUATE SCHOOL OF MEDICINE AND PUBLIC HEALTH
KYOTO UNIVERSITY
YOSHIDA KONOE-CHO, SAKYO-KU, KYOTO, 606-8501 JAPAN

SHUNICHI FUKUHARA, MD, MSc, FACP
PROFESSOR AND CHAIR

I look forward to the approval of this proposal by the Cochrane Collaboration, to the establishment of the Japan Branch of the Australasian Cochrane Centre in Kyoto and Tokyo, and to the increased presence and recognition of the Cochrane Collaboration in Japan. I would feel honored to collaborate in this great endeavor.

Please feel free contacting me for any questions and comments.

Sincerely,



Shunichi Fukuhara, MD, DMSc, FACP
Professor and Dean, Kyoto University School of Public Health and Graduate School of Medicine

京都大学大学院 医学研究科　医療疫学分野
〒606-8501 京都市左京区吉田近衛町　Phone:+81-75-753-4646　Fax:+81-75-753-4644　http://www.epikyoto-u.jp

Ⅱ．分担研究報告書

平成 25 年度 厚生労働科学研究費補助金（成育疾患克服等次世代育成基盤研究事業）
「母子保健に関する国際的動向及び情報発信に関する研究」分担研究報告書

ネットワークメタアナリシスの批判的吟味

研究分担者 古川壽亮（京都大学大学院医学研究科　教授）

研究要旨

複数の治療選択肢を同時に比較するネットワークメタアナリシスの発表が急激に増えている。たとえば、大うつ病の急性期の薬物療法について、すでに 3 本のネットワークメタアナリシスが発表されている。しかし、医学文献のコンシューマ（医師、患者、政策立案者など）から見ると、異なるネットワークメタアナリシスが異なった結論を導いているように読め、実際に結論が異なるのか、もしそうだとしたらどのネットワークメタアナリシスを信用すべきなのか、批判的吟味の指針がほしい。本研究は、上記の大うつ病のネットワークメタアナリシスを例に、批判的吟味の指針を提示する。

A. 研究目的

新世代のエビデンス統合方法として、ネットワークメタアナリシス network meta-analysis の発表が急激に増えている。ネットワークメタアナリシスは、複数治療メタアナリシス multiple treatments meta-analysis, 混合治療メタアナリシス mixed treatment meta-analysis などとも呼ばれる。

ネットワークメタアナリシスでは、複数の治療選択肢を比較した無作為割り付け比較試験(RCT)をすべて集めてきて、従来のメタアナリシスのように 1 対 1 で比較するのではなく、エビデンスのネットワーク全体を同時に統合する。すなわち、A という治療選択肢と B という治療選択肢を比較するには、A と B とを直接に比較した直接比較に加えて、A と B とのあいだの効果の差は、A とまた別の治療選択肢 C との間の差、マイナス、B と C との間の差と同じなるはずであるので、このような関節比較の結果も統合することができる。ネットワークの全体について直接比較と関節比較の統合を行うのがネットワークメタアナリシスである。

B. 研究方法

大うつ病の急性期薬物療法についてのネットワークメタアナリシスは、

- Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, Watanabe N, Nakagawa A, Omori IM, McGuire H, Tansella M & Barbui C (2009) Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet, 373, 746-758.
- Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Van Noord M, Mager U, Thieda P, Gaynes BN, Wilkins T, Stobelberger M, Lloyd S, Relchenpfader U & Lohr KN (2011) Comparative benfits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Annals of Internal Medicine, 155, 772-785.
- Ramsberg J, Asseburg C & Henriksson M (2012) Effectiveness and cost-effectiveness of

antidepressants in primary care: a multiple treatment comparison meta-analysis and cost-effectiveness model. PLoS ONE, 7, e42003.

の3本が発表されている。Cipriani らは、有効性では mirtazapine がベストであったが、有効性と受容性のバランスを勘案すると escitalopram と sertraline が優れていると結論した。Garlehner らは、効果の差に基づいて特定の抗うつ剤を推奨するだけのエビデンスはないと結論した。Ramsberg らは、エスシタロプラムがもっとも有効であると結論した。

本研究では、これらの差異がどこから生じたのか、どのネットワークメタアナリシスがより妥当なのかを、表1のガイドラインに則って批判的に吟味した。

（倫理面への配慮）

出版されたデータの二次利用であるので、倫理委員会の承認は要さない。

C. 研究結果

C1. 単純な比較

3つのネットワークメタアナリシスの臨床疑問は表2のようにまとめることができる。

ほぼ同じ臨床疑問（うつ病の急性期の薬物療法）を扱ったレビューであるのに、PECO にまとめると、この段階で微妙だが結果に影響を及ぼすかもしれない差異があることが分かる。Gartlehner と Ramsberg はプライマリケアに焦点を当てているのに対し、Cipriani はそうではない。また、具体的に包含されている薬剤も重なっているが、まったく同一ではない。ネットワークメタアナリシスでは包含される薬が違えば当然ネットワークと、そして答えが違ってくる可能性がある Cipriani と Gartlehner ではアウトカムは「反応」だが、Ramsberg では「寛解」であった。すべてのレビューは実薬間の RCT を中心としたが、Gartlehner は必要とあればプラセボ対照の RCT も包含した。

次に、実際に包含された研究をリストアップしてみた（表3）。3つのレビューを比較するために3つのレビューのすべてに含まれた薬剤のみについて表にした。順番に 2009 年、2011 年、2012 年に発表されたレビューだが、venlafaxine を除くと、2009 年に発表された Cipriani のネットワークが最も包括的であるようだ。

さて、ネットワークメタアナリシスの最大の特徴は、治療選択肢の間のランキングを出すことが出来ることである。そこで、上記の包含された薬剤をランキングすると、表4のようになる。これではまったく順番が異なり、3つのレビューはほとんどお互いに一致しないように見える。第一に、もっとも有効な薬剤がレビューごとに異なっている。Cipriani でや mirtazapine であり、Gartlehner では citalopram であり、Ramsberg では escitalopram である。Ioannidis もこの点をもってネットワークメタアナリシスの結果は合致しないと批判した。[1]

C2. ランク付フォレストプロットによる比較

これらの差異は、表2で見たような微妙な PECO の差異、あるいは表3で見たような包含された研究や薬剤の差異に由来するのかもしれない。しかし、効果サイズの点推定がごく近くて 95%信頼区間が重なっているような場合でも、かなり離れていて 95%信頼区間が全く重なっていない場合でも、ランキング上は1つの違いにしかならない場合がある。そこで、効果サイズの推定の不確実さまで表すことの出来る、ランク付けフォレストプロットを描いてみた。それが表5である。ここではもっともよく対照薬として使われている fluoxetine を1といたオッズ比(OR)とその 95%信頼区間をプロットしてある。

すると、今度は全然違った全体像が見えてくる。Cipriani と Gartlehner を比較すると、後者で 95%信頼区間が非常に広くなっている 2 つの薬を除いて両者のランキングは驚くほど一致している。また、Gartlehner では OR がより大きく、しかし 95%信頼区間もより広くなっている。信頼区間が広いのは、Gartlehner のほうが包含された RCT が少ないためであろう。

Cipriani と Ramsberg を比較すると、95%信頼区間までを勘案するととくに上位の薬剤は両者で重なる部分が大きい。顕著な差異は、Ramsberg では duloxetine が fluoxetine より有意に勝っている点である（Cipriani でも Gartlehner でも有意差はついていない）。表 3 で分かるように、3 つのネットワークメタアナリシスは全く同じ dluoxetine のトライアルを包含しており、もちろん他に包含された RCT が異なるので異なった数字が出てきてもおかしくはないのだが、有意差がつくほどにはならないはずである。ここで原典に当たると、この RCT では対 fluoxetine で「反応」では有意差がなく「寛解」で有意差がついたようであった。よってこの差異は、アウトカムの差異に帰すことが出来る。

D. 考察

一定のチェックポイントに従って、同じまたは似通った臨床疑問を取り扱ったネットワークメタアナリシスを比較し、批判的に吟味した。そして結果をランク付きフォレストプロットで提示した。結果、いっけん互いに異なる結果を出したネットワークメタアナリシスが、実はかなり似通った結果に基づいていることが図示された。

3 つのネットワークメタアナリシスのあいだの差異は、ネットワークメタアナリシスの結果の差と言うよりも、その解釈の差であったようである。Gartlehner のように差がないと結論をすることの方が、ある意味、安易であろうが、「どのお薬がうつ病の治療の第一選択であるか」という実践的な疑問に答えることにはならないであろう。

E. 結論

同一の疾患に対して複数の治療を比較するネットワークメタアナリシスは臨床判断に不可欠になってくるであろう。今後、ネットワークメタアナリシスを臨床家が利用できるためには、

（1） ネットワークメタアナリシスの論文がカバーすべき項目などのガイドラインが必要である

（2） ランキングよりも、95%信頼区間を重視すべきである。

（3） もし同様のテーマについての先行レビューがある場合、新しいレビューの著者は、それぞれに包含された研究の一覧表を用意し、ウェブ付録などで公表すべきである

引用文献

1) Ioannidis JP. Ranking antidepressants. Lancet. May 23 2009;373(9677):1759-1760; author reply 1761-1752.
2) Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. Jan 28 2009;373:746-758.
3) Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benfits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann. Intern. Med. 2011;155:772-785.
4) Ramsberg J, Asseburg C, Henriksson M. Effectiveness and cost-effectiveness of

antidepressants in primary care: a multiple treatment comparison meta-analysis and cost-effectiveness model. PLoS ONE. 2012;7(8):e42003.

F. 研究発表

1. 論文発表

1) Churchill R, Moore TH, Furukawa TA, Caldwell DM, Davies P, Jones H, Shinohara K, Imai H, Lewis G & Hunot V (2013) 'Third wave' cognitive and behavioural therapies versus treatment as usual for depression. Cochrane Database of Systematic Reviews, 10, CD008705.

Furukawa TA & Leucht S (2013) Can we inflate effect size and thus increase chances of producing "positive" results if we raise the baseline threshold in schizophrenia trials? Schizophrenia Research, 144, 105-108.

Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, Johnston BC, Karanicolas P, Akl EA, Vist G, Kunz R, Brozek J, Kupper LL, Martin SL, Meerpohl JJ, Alonso-Coello P, Christensen R & Schunemann HJ (2013) GRADE guidelines: 13. Preparing Summary of Findings tables and evidence profiles-continuous outcomes. Journal of Clinical Epidemiology, 66, 173-183.

Honda M, Kuriyama A, Noma H, Nunobe S & Furukawa TA (2013) Reply to Letter: "Hand-Sewn Versus Mechanical Esophagogastric Anastomosis After Esophagectomy: A Systematic Review and Meta-Analysis". Annals of Surgery.

Honda M, Kuriyama A, Noma H, Nunobe S & Furukawa TA (2013) Hand-sewn versus mechanical esophagogastric anastomosis after esophagectomy: A systematic review and meta-analysis. Annals of Surgery, 257, 238-248.

Hunot V, Moore TH, Caldwell DM, Furukawa TA, Davies P, Jones H, Honyashiki M, Chen P, Lews G & Churchill R (2013) 'Third wave' cognitive and behavioural therapies versus other psychological therapies for depression. Cochrane Database of Systematic Reviews, 10, CD008704.

Kinoshita Y, Furukawa TA, Kinoshita K, Honyashiki M, Omori IM, Marshall M, Bond GR, Huxley P, Amano N & Kingdon D (2013) Supported employment for adults with severe mental illness. Cochrane Database of Systematic Reviews, 9, CD008297.

Magni LR, Purgato M, Gastaldon C, Papola D, Furukawa TA, Cipriani A & Barbui C (2013) Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database of Systematic Reviews, 7, CD004185.

Samara MT, Spineli LM, Furukawa TA, Engel RR, Davis JM, Salanti G & Leucht S (2013) Imputation of response rates from means and standard deviations in schizophrenia. Schizophrenia Research, 151, 209-214.

Shinohara K, Honyashiki M, Imai H, Hunot V, Caldwell DM, Davies P, Moore TH, Furukawa TA & Churchill R (2013) Behavioural therapies versus other psychological therapies for depression. The Cochrane database of systematic reviews, 10, CD008696.

2. 学会発表

1) Furukawa TA, Noma H, Hunot V, Churchill R (2013) Waiting list may be a

nocebo condition in psychotherapy trials: a network meta-analysis.7th World Congress of Behavioural and Cognitive Therapies, Lima, Peru 2013.7.23.

2. Furukawa TA, Noma H, Honyashiki M, Shinohara K, Imai H, Churchill R, Hunot V, Caldwell D (2013) Waiting list may be a 'nocebo' condition in psychotherapy trials. 21st Cochrane Colloquium, Quebec City, Canada 2013.9.19-23.

G. 知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

表 1。ネットワークメタアナリシスの相違の原因

臨床疑問	患者：診断基準、病期、重症度、併存症 介入と対照：包含された介入、介入の投与量 アウトカム：定義、時期
研究選択	文献検索
質の吟味	バイアスのリスクの評価項目
データ抽出	評定者間の信頼性
データ統合	異質性 ネットワークメタアナリシスの方法 結果の提示の仕方

表 2. 3 つのネットワークメタアナリシスの臨床疑問

Cipriani[2]	Gartlehner[3]	Ramsberg[4]
Patients: Adults with acute phase treatment of major depression as diagnosed with standard operationalized diagnostic criteria **Interventions**: Any one of the pre-defined 12 new generation antidepressants used as monotherapy (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine) **Outcome**: Response defined as reduction of at least 50% from the baseline score on the Hamilton depression rating scale (HAMD) or Montgomery-Asberg depression rating scale (MADRS), or as scoring much or very much improved on the clinical global impression scale at 8 weeks (6-12 weeks) **Study design**: Head-to-head double-blind RCTs	**Patients**: Adults with major depressive disorder in primary care **Interventions**: Commonly used 13 medications or placebo for depression (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine), with preferably flexible dose design **Outcome**: Response at >6 weeks study duration, defined as a 50% improvement of depression scores **Study design**: Head-to-head double-blind RCTs, Placebo-controlled RCTs only when head-to-head RCTs are not sufficient	**Patients**: Adults with a diagnosis of major depressive disorder in primary care receiving the first-line treatment **Interventions**: Monotherapy with 17 antidepressants including citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine plus less commonly used amitriptyline, dosulepin, imipramine, lofepramine, maprotiline, milnacipran, and nortriptyline. **Outcomes**: Remission at 6-12 weeks, defined as HAMD score =<7 or 8 or as MADRS score =<12. **Study design**: Head-to-head double-blind RCTs

表 3. 3 つのネットワークメタアナリシスに包含された RCT

	Cipriani[2]	Gartlehner[3]	Ramsberg[4]
mirtazapine	Amini2005 Hong2003 Leinonen1999 Versiani2005 Wheatley1998 Winokur2003	 Hong2003 Versiani2005 Wheatley1998	Amini2005 Hong2003 Versiani2005 Wheatley1998
escitalopram	SCT-MD-16 Kasper2005	Mao2008 European518	 Kasper2005
venlafaxine	Alves1999 Clerc1994 Costaesilva1998 DeNayer2002 DiazMaritinez1998 Dierick1996 Rudolph1999 Silverstone1999 Tylee1997 Tzanakaki2000 Schtzberg2006 Nemeroff2007	Alves1999 DeNayer2002 Dierick1996 Rudolph1999 Silverstone1999 Nemeroff2005	Alves et al 1999 Clerc et al 1994 Costa e Silva 1998 De Nayer et al 2002 Dierick et al 1996 Rudolph & Feiger 1999 Silverstone et al 1999 Tzanakaki et al 2000 Schatzberg et al 2006 Nemeroff & Thase 2007 Rudolph & Feiger 1997 Kornaat 1998 S332 Rudolph et al 1998 S606 S102 Keller et al 2007 Mehtonen 2002 Stevens 1997 Cantillon & Daley 2000
sertraline	Sechter1999 Bennie1995 Fava2000 Fava2002 Newhouse2000 Van Moffaert1995 Aguglia1993 Suri2000	Sechter1999 Bennie1995 Fava2002 Newhouse2000	[none]
citalopram	Khanzode2003 Stahl2000 Bourgerol1997	 Patris1996	 Patris1996
bupropion	Coleman2001 Feighner1991	Coleman2001 Feighner1991	[none]