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Title page

Title

Evidence Synthesis, Practice Guidelines and Real-World Prescriptions of New Generation Antidepressants in the Treatment of Depression: A Protocol

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Abstract

Introduction

Depressive disorders are the most common, burdensome and costly mental disorders. Their treatments have developed through the past decades and we now have more than a dozen new generation antidepressants, while series of guidelines have been published to provide recommendations over the years. However, there still may exist important gaps in this evidence synthesis and implementation process. Systematic reviews may not have been conducted in the most unbiased, informative and timely manners; guidelines may not have reflected the most up-to-date evidence; clinicians may not have changed their clinical decision makings in accordance with the relevant evidence. The aim of this study is to examine the gaps between the ideally synthesized evidence, guideline recommendations and real-world clinical practices in the prescription of new generation antidepressants for major depression through the past three decades.

Methods and analysis

We will conduct cumulative network meta-analyses (cNMAs) based on the comprehensive systematic review which has identified published and unpublished head-to-head randomized controlled trials comparing the following antidepressants in the acute phase treatment of major depression: agomelatine, amitriptyline, bupropion, citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, trazodone, venlafaxine, vilazodone and vortioxetine. The primary outcomes will be the proportions of patients who responded (efficacy) and who withdrew from treatment for any reasons (acceptability). We will conduct a random effects cNMA to synthesize evidence and obtain a comprehensive ranking of all new generation antidepressants based on their surface under the cumulative ranking curves. We will identify series of international clinical practice guidelines for the treatment of major depression of adults and summarize their recommendations. We will estimate real-world prescription patterns of antidepressants in the nationally representative samples in USA in the Medical Expenditure Panel Survey. We will compare and evaluate the gaps between the rankings according to cNMAs conducted at 5-year intervals between 1990 and 2015, recommendations in guidelines published in the ensuing five years, and actual practices thereafter.

Ethics and dissemination

This review does not require ethical approval. We will disseminate our findings through publications in peer-reviewed journals and presentations at conferences.

Trial registration number

UMIN000031898.

Strengths and limitations

- This is one of the first studies to directly compare evidence derived from network meta-analyses,

recommendations from guidelines, and real-world clinical practices.

- This study will show where the gaps may lie and how big they are, which can inform future efforts to bridge the gaps from scientific evidence to real-world clinical practices.
- The cumulative network meta-analysis used in this study may evolve into prospectively designed sequential network meta-analysis which can be used as living accumulation of evidence and contribute to living guidelines.
- A major limitation of our study is that the real-world practices in nationally representative samples are available for USA only.

Key words

Network meta-analysis, Practice guidelines, Depression, Antidepressants

INTRODUCTION

Evidence-based medicine (EBM) is widely regarded as the guiding principle of today's medical practices, for it can help integrate patients' values, physicians' experiences and scientific evidence derived from large scale research to inform clinical decision-making.[1] To promote EBM, systematic reviews (SRs) including meta-analyses (MAs) should be conducted to produce a comprehensive summary of all relevant studies, clinical practice guidelines (CPGs) will be proposed based on such evidence synthesis, and physicians must update their shared decision making processes in accordance with such guidelines.[2]

Depressive disorders are the most common mental disorders, making them the second leading cause of disability accounting for 8.2% of all years lived with disability (YLDs) in 2010.[3-5] Reflecting the high prevalence of major depressive disorder (MDD) among people of working ages and the resulting dysfunctions, their economic burden was estimated at US $210.5 billion in US alone in 2010.[6] Antidepressants are widely used in the treatment of MDD, and a host of new generation antidepressants have been approved into the market in the past two to three decades. Given the enormity of burdens due to MDD on patients and society, various institutions worldwide have produced clinical practice guidelines (CPGs) for physicians. It was as early as in 1993 that American Psychiatric Association (APA)[7], British Association for Psychopharmacology (BAP)[8] and Agency for Health Care Policy and Research (AHCPR)[9] proposed the first version of their guidelines, followed by other associations like National Institute for Health and Care Excellence (NICE) from UK[10] and Canadian Network for Mood and Anxiety Treatments (CANMAT) from Canada[11]. Most of these guidelines have been updated every several years since.

However there are still several important barriers that may impede physicians and patients from making optimal clinical decisions. First, it has become increasingly known that a substantive amount of trials of antidepressants remain unpublished and were not included in contemporary SRs, a fact which most likely introduces publication bias into the results of SRs and thus undermines the credibility of guidelines.[12] Second, it has been reported that there is approximately eight months to more than one year's lag between the last search date in the literature and the publication of an SR,[13] [14] and in total 2.5-6.5 years' interval between the publication dates of the latest primary studies and the publication date of SRs,[15] which makes most SRs already out of date at the time of their publication. Third, few of the available CPGs provide specific and precise recommendations in the choice of antidepressants, as pooled evidence has been given conflicting interpretations.[16] [17] Fourth, physicians' behaviors are notoriously difficult to influence.[18-20] The road from randomized evidence to actual practices thus appears formidable.[21]

The aim of the present study is to examine how the accumulating body of evidence should have been assembled, and reflected in guidelines, and then transferred into real practices in the prescription of new generation antidepressants for MDD through the past three decades. The evidence we will consider comes from a uniquely comprehensive dataset prepared by GRISELDA (Group of Researchers Investigating Specific Efficacy of individual Drugs for Acute depression). [22] [23] It

comprises data from 522 published and unpublished double-blind randomized controlled trials of new generation and other antidepressants in the acute treatment of depression. Capitalizing on this, we will use cumulative network analysis (cNMA) to summarize the development of accumulated evidence over time. [24-26] When two or more treatment alternatives are available, as in the case of MDD, NMA can summarize the relative effects of all treatments options by combining both direct and indirect comparisons[27]; because they utilize all direct and indirect evidence, they can produce strong evidence concerning relative efficacy more often and earlier than conventional, pairwise meta-analyses[28]. We will examine the specific recommendations in the internationally representative CPGs. The real-world prescription practices will be collated from Medical Expenditure Panel Survey (MEPS) in USA, which is a large-scale yearly healthcare survey of representative samples of families and individuals in the United States. [29] We predict that there are important gaps in the evidence synthesis and implementation process. Our study will evaluate and narratively summarize how big these gaps are and where mainly they exist, and will provide valuable information necessary to direct future paths to bridge the gaps from scientific evidence to real-world clinical practice.

METHODS

Systematic reviews of RCTs of new generation antidepressants and cumulative network meta-analysis

Study eligibility

The cNMAs in this study will be based on the systematic review which has identified all published and unpublished double-blinded head-to-head RCTs comparing any of the following new generation antidepressants in the acute phase treatment of adults with MDD up to January 2016[22 23]: we will consider all new generation antidepressants approved by drug agencies of US, Europe or Japan including agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone and vortioxetine.

The GRISELDA dataset also contains two older tricyclic antidepressants (TCAs) recommended by WHO Model List of Essential Medicines (amitriptyline and clomipramine) and two drugs with distinct effect and side-effect profiles (trazodone and nefazodone): they will constitute evidence set[30] in the NMAs which serves to connect and strengthen the network.

We will include in the meta-analysis only study arms which administered the drugs within dose ranges approved by the regulatory agencies. Because the inclusion of placebo-controlled trials may violate the transitivity assumption of NMA in depression studies[31-35], and because we will be comparing the evidence from cNMA with real-world practice, we will only include RCTs comparing active drugs and exclude placebo-controlled studies in the current cNMAs.

Study identification and data extraction

GRISELDA has searched the following databases without language restrictions for published articles: Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, EMBASE, LiLACS, MEDLINE, MEDLINE In-Process, and PsycINFO up to January 2016. We performed manual searches of references of included articles. We also searched for published, unpublished and ongoing RCTs in drug-approval agencies' documents, company websites, international trial registries, and through contact with pharmaceutical companies and other relevant organizations. Where necessary, we contacted study authors directly to get supplementary materials for further information. The risk of bias of each included study was assessed according to the guide proposed in the Cochrane Collaboration Handbook.[36]

Study identification, data extraction and risk of bias assessment of the included studies were all performed independently by two researchers, and any disagreements were resolved through discussion or in consultation with a third reviewer. For further details of the systematic review process, please see the published protocol and the main GRISELDA paper.[22 23]

Statistical analyses

We will conduct cNMA every 5 years in consideration of the speed of accumulating new trials and publication of guidelines for MDD. According to previous studies which indicated that the latest search of database was about one year before publication of SRs,[13-15] cNMA at any time point will include all trials completed up to 1 year before. For trials whose completion year is not available, publication date will be used; when neither is known, the date of approval of the drug by regulatory agencies will be used as the study completion date.

For network meta-analysis, transitivity assumption is the principle. Since we have confirmed the transitivity assumption of the whole data set in the final network meta-analysis [23], we will not validate it at every time point re-analysis. In our previous study, we investigated the distribution of the following potential effect modifiers across treatment comparison: (1) study year; (2) sponsorship; (3) depressive severity at baseline; (4) dosing schedule; (5) proportion of participants allocated to placebo; (6) number of recruiting centers (single-center vs multi-centric studies). We evaluated consistency and heterogeneity in the entire network using various tests and metrics and we have found little evidence of inconsistency and heterogeneity.[23]

Our primary outcomes are (i) efficacy of the intervention in terms of response rate defined as the proportion of patients who showed a reduction of at least 50% on the total depression severity score compared to baseline, and (ii) acceptability of the intervention in terms of all-cause discontinuation rate defined as the proportion of patients who leave the study early for any reason. We have extracted the outcome data at a time point as close to 8 weeks as possible: if outcomes at 8 weeks were not available, we recorded data between 4 and 12 weeks.

We will not adjust for multiple comparisons in successive NMAs as we are not testing particular hypotheses for specific comparisons among antidepressants.

We will use the surface under the cumulative ranking curve (SUCRA) to estimate ranking probabilities for each intervention with regard to the two primary outcomes. We will show ranked forest plots of ORs with 95% CI in comparison with a common comparator as a sensitivity analysis: we will use fluoxetine as the common comparator as it is the most frequently used drug in the trials network.[23]

We will use STATA (Stata Corp 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp) to conduct cNMA. [37 38]

Identification and extraction of recommendations in guidelines

We will use a series of CPGs as our benchmark in comparisons. We will extract recommendations for specific antidepressants or for specific classes of antidepressants from internationally representative guidelines listed below:

1) Practice guidelines for the treatment of patients with major depressive disorder published by American Psychiatric Association (APA), in 1993, 2000, 2010 respectively.[7 39 40]
2) Guidelines for management of depression proposed by National Institute for Health and Care Excellence (NICE), in 2004, 2009 and 2018.[10 41 42]
3) Guidelines for treating depressive disorders with antidepressants proposed by British Association for Psychopharmacology (BAP), in 1993, 2000, 2008 and 2015. [8 43-45]
4) Clinical guidelines for the management of major depressive disorder in adults proposed by Canadian Network for Mood and Anxiety Treatments (CANMAT), in 2001, 2009 and 2016.[46-48]

We will extract recommendations with respect to acute phase treatment for adult patients with a primary diagnosis of unipolar non-psychotic major depression. We define recommendations as statements used in CPGs involving the words like “recommend”, “must”, “necessary”, “should”, “appropriate” or other words indicating instructions from guidelines. We will also collect the quality of evidence and strength of recommendations backing extracted recommendations. Two researchers will independently identify recommendations and extract information from CPGs. Any disagreement will be resolved through discussion or in consultation with a third researcher.

Real-world prescriptions data extraction

We will extract real-world prescription data from the Medical Expenditure Panel Survey (MEPS) database. [29]MEPS is a database composed of large-scale surveys of families and individuals and their medical providers, collecting data on the use of specific health services, the cost, and the health insurance in the United States. The survey started in 1996. MEPS has two major components, the household component and the insurance component, both of which provide data on a yearly basis. In the household component a representative sample of families and individuals are interviewed every year and detailed information including demographic characteristics, health status, use of medical services, specific medications, cost for each person is collected. Each annual MEPS household

sample size is about 15,000 households. This set of households is a subsample of households participating in the previous year's National Health Interview Survey (NHIS) led by the National Center for Health Statistics. The NHIS sampling frame gives a nationally representative sample of the non-institutionalized population in the US, and oversamples of Blacks and Hispanics. In 2006, after implementing a new sample design, Asian population has been included in order to deal with the oversampling issues. To correct for oversampling and for non-response, each participant is given a weight adjusting for nonresponse over time and some poststratification variables (region, race/ethnicity, sex, age, poverty status and etc.), in order to produce national estimates.[29] MEPS database has been used for the analysis of health expenditures and real-world prescriptions of specific drugs in several studies.[49-51]

Participants

We will include those who have been classified as "Depressive disorders" in the category of "657 Mood disorder", of either sex and aged 18 years or older. The corresponding ICD-10 numbers are: 29383 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 3004 311. MEPS database only code the diagnosis for the first 3 digits using ICD numbers (293, 296, 300, 311).

Interventions

Of the 21 antidepressants included in the GRISELDA network, the following drugs will not be included among the drugs prescribed for depressive disorders in MEPS: agomelatine and reboxetine have not been approved by FDA for marketing in USA, fluvoxamine has an indication for obsessive-compulsive disorder but not for depression, and milnacipran for fibromyalgia only. On the other hand, there are many antidepressants, other than new generation antidepressants, which may have been prescribed especially in older days, such as imipramine, desipramine, doxepin or nortriptyline. Although our focus of comparison is new generation antidepressants, we will extract the frequency of prescription of all antidepressants in the MEPS study. Using the National Drug Code Directory[52], which included all registered drugs in FDA, we identified all antidepressants ever used in the USA as the following: 1) Tricyclic Antidepressants [EPC]: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine; 2) Serotonin Reuptake Inhibitor [EPC]: citalopram, escitalopram, fluoxetine, nefazodone, paroxetine, sertraline, trazodone; 3) Serotonin and Norepinephrine Reuptake Inhibitor [EPC]: desvenlafaxine, duloxetine, venlafaxine, levomilnacipran; 4) No Pharm Class: bupropion, mirtazapine, vilazodone, vortioxetine. All the 24 listed antidepressants will be searched in MEPS during data extraction.

Data extraction

We will extract prescription data for antidepressants listed above in the year 1996, 2000, 2005, 2010 and 2015 (Table 1). Since diagnostic labels available MEPS data cannot distinguish unipolar

depression from bipolar depression and psychotic depression, both of which require different drug treatments than unipolar depression, we will exclude those patients who are concomitantly taking mood stabilizers or any antipsychotics. According to the National Drug Code Directory [52], Mood Stabilizer [EPC] include: carbamazepine, divalproex, lamotrigine, lithium, valproate, valproic acid; and Phenothiazine [EPC], Typical Antipsychotics [EPC] and Atypical Antipsychotics [EPC] include: aripiprazole, asenapine, brexipiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperido, iloperidone, loxapine, lurasidone, molindone, olanzapine, paliperidone, perphenazine, pimavanserin, quetiapine, risperidone, thioridazine, thiothixene, ziprasidone. We will exclude all participants taking any of these drugs concomitantly with an antidepressant.

Every participant in one MEPS cohort (called 'panel' in MEPS) is interviewed five times (called 'rounds') for 2 years. For example, the file of 2015 contains the 2015 portion of Round 3 and Rounds 4 and 5 for Panel 19, as well as Rounds 1, 2 and the 2015 portion of Round 3 for Panel 20 (see Figure 1).[29] We will check the prescription of antidepressants at round 2 from panel 20 and round 4 from panel 19 (similar patterns in other given years), because each participant, either from panel 19 or 20, must have this intermediate round of interview within 2015, and we will use it as a cross-sectional investigation. We will use the total number of patients with the diagnosis of depression and who are on antidepressants at this round as denominator, and the prescription for a particular drug as numerator. Given lack of precise information for medication schedule (e.g. start time of diagnosis, primary medication, time of start and change of medication), we will not be able to restrict the prescriptions to inception prescriptions in the acute phase treatment of MDD, and the results will include both incident and prevalent uses. As MEPS data set give each participant a sample weight according to nonresponse and poststratification variables, we will use the sample weights to estimate the nationally representative number of patients on a specific therapy. Finally the ranking of the of prescriptions will then be based on the estimated numbers of prescriptions in the general US population.

We will use Python 3.6 to extract data from MEPS dataset.

Comparison between cNMA, CPGs, and real-world prescriptions

We propose that a cNMA at a specific time point (e.g. 2000) should be taken as a reference for any guidelines that are going to be published in the next five years (e.g. 2000 through 2004), and then inform real world prescriptions afterwards (e.g. 2005 and after). We will therefore compare the results of NMA, CPG recommendations and real-world practice in these corresponding years. Table 1 shows the time periods for comparisons. We will assess if the recommendable sets estimated from cNMA (i.e. drugs which have good balance between efficacy and acceptability) are reflected in the drugs recommended by guidelines, which then will be compared with the rankings in actual clinical practice. We will describe the possible differences and explore the time lag from the ideally available evidence to guideline recommendations and from guideline recommendations to the real world practices. We will also investigate the potential factors which may influence the actual prescriptions

including side-effects profiles of specific drugs, year of FDA approval, the price of the drug while on patent, and the year of patent expiration of each drug.

Table 1. Time periods for comparisons in our study.

Trials (completion year*)	Cumulative NMAs	CPGs (publication year)	Real world prescriptions (MEPS data file year)
~present	present	2016~present	-
~2009	2010	2010~2014	2015
~2004	2005	2005~2009	2010
~1999	2000	2000~2004	2005
~1994	1995	1995~1999	2000
~1989	1990	1990~1994	1996**

* For trials whose completion year is not available, publication date will be used; when neither is known, the date of approval of the drug by regulatory agencies will be used as its completion date.

**As MEPS database started with 1996, so we will use data from 1996 for the analysis of prescriptions.

DISCUSSION

We have presented the study protocol for investigating the gaps between ideally synthesized evidence, guideline recommendations and real-world clinical practices in the prescriptions of new generation antidepressants for unipolar major depressive disorders.

Our study has several strengths. It is one of the first studies to make comparisons between pooled evidence derived from cumulative network meta-analyses, recommendations from guidelines, and real-world clinical practices. In the cNMA, we will use the comprehensive dataset from our previous study [23], which included both published and unpublished trials. And we will use MEPS database, which collect detailed information of health status and specific medications from a representative sample in the US, as a reflection of real world prescription profile. We expect this study to show the gaps between evidence and practice, and our findings will inform future developments of evidence-based medicine. For instance, the cNMA used in this study may eventually evolve into prospectively designed sequential network meta-analysis which can be used to continuously update evidence and contribute to living guidelines.

There are some limitations to our study. First, as we will use a database to reflect the real-world prescription patterns, we are not able to extract very precise information from the database, such as the specific diagnosis of the patients, or whether the therapy was used as first-line or later treatments, which to some extent may lower the comparability between the cNMA of acute phase treatment studies of unipolar depression and the real world practices. Second, MEPS is a US study and we were not able to make comparisons between guideline recommendations and actual practices in other countries. Last, the reasons behind the differences between evidence and practice may be so

complicated that we will need to factor in various potential confounding factors such as the side-effects, price of a particular drug and marketing efforts of pharmaceutical companies. [53 54]
In conclusion, our study represents a unique inquiry into gaps from evidence to real-world practices, and may provide valuable insights into future developments of EBM.

Ethics and dissemination

This study does not require institutional review board approval. We have registered it in the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR): UMIN000031898.

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Competing interests

TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has received research support from Mitsubishi-Tanabe and Mochida. ACi is supported by the NIHR Oxford Cognitive Health Clinical Research Facility, and was expert witness for Accord Healthcare for a patent issue about quetiapine extended release. All the other authors report no competing interests to declare.

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Contributors

YL and TAF conceived the study and drafted the protocol. ACh, YK, EGO, YO, ACi and GS assisted in the study design and critically revised the protocol. All authors gave final approval of the version to be published.

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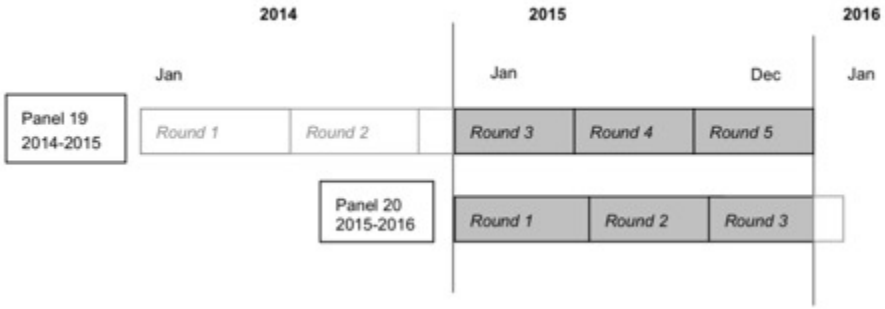

Figure 1. Survey structure of 2015 file in MEPS.[29]

171x61mm (72 x 72 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (UMIN000031898, see Main document Page 2)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (see Main document Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (see Main document Page 11)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review (see Main document Page 11)
Sponsor	5b	Provide name for the review funder and/or sponsor (see Main document Page 11)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (see Main document Page 4)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (see Main document Page 4)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (see Main document Page 5)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (see Main document Page 5)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (see Main document Page 6)
Study records:		

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (see Main document Page 6)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (see Main document Page 6)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (see Main document Page 6)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (see Main document Page 5-6)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (see Main document Page 6)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (see Main document Page 6)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (see Main document Page 6-7)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (see Main document Page 6-7)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (see Main document Page 6-7)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (see Main document Page 6-7)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (see Main document Page 5-6)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (see Main document Page 6-7)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Evidence Synthesis, Practice Guidelines and Real-World Prescriptions of New Generation Antidepressants in the Treatment of Depression: A Protocol for Cumulative Network Meta-analyses and Meta-epidemiological Study.

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Title page

Title

Evidence Synthesis, Practice Guidelines and Real-World Prescriptions of New Generation Antidepressants in the Treatment of Depression: A Protocol for Cumulative Network Meta-analyses and Meta-epidemiological Study

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Abstract

Introduction

Depressive disorders are the most common, burdensome and costly mental disorders. Their treatments have developed through the past decades and we now have more than a dozen new generation antidepressants, while series of guidelines have been published to provide recommendations over the years. However, there still may exist important gaps in this evidence synthesis and implementation process. Systematic reviews may not have been conducted in the most unbiased, informative and timely manners; guidelines may not have reflected the most up-to-date evidence; clinicians may not have changed their clinical decision makings in accordance with the relevant evidence. The aim of this study is to examine the gaps between the ideally synthesized evidence, guideline recommendations and real-world clinical practices in the prescription of new generation antidepressants for major depression through the past three decades.

Methods and analysis

We will conduct cumulative network meta-analyses (cNMAs) based on the comprehensive systematic review which has identified published and unpublished head-to-head randomized controlled trials comparing the following antidepressants in the acute phase treatment of major depression: agomelatine, amitriptyline, bupropion, citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, trazodone, venlafaxine, vilazodone and vortioxetine. The primary outcomes will be the proportions of patients who responded (efficacy) and who withdrew from treatment for any reasons (acceptability). We will conduct a random effects cNMA to synthesize evidence and obtain a comprehensive ranking of all new generation antidepressants based on their surface under the cumulative ranking curves. We will identify series of international clinical practice guidelines for the treatment of major depression of adults and summarize their recommendations. We will estimate real-world prescription patterns of antidepressants in the nationally representative samples in USA in the Medical Expenditure Panel Survey. We will compare and evaluate the gaps between the rankings according to cNMAs conducted at 5-year intervals between 1990 and 2015, recommendations in guidelines published in the ensuing five years, and actual practices thereafter.

Ethics and dissemination

This review does not require ethical approval. We will disseminate our findings through publications in peer-reviewed journals and presentations at conferences.

Trial registration number

UMIN000031898.

Strengths and limitations

- This is one of the first studies to directly compare evidence derived from network meta-analyses,

recommendations from guidelines, and real-world clinical practices.

- This study will show where the gaps may lie and how big they are, which can inform future efforts to bridge the gaps from scientific evidence to real-world clinical practices.
- The cumulative network meta-analysis used in this study may evolve into prospectively designed sequential network meta-analysis which can be used as living accumulation of evidence and contribute to living guidelines.
- A major limitation of our study is that the real-world practices in nationally representative samples are available for USA only.

INTRODUCTION

Evidence-based medicine (EBM) is widely regarded as the guiding principle of today's medical practices, for it can help integrate patients' values, physicians' experiences and scientific evidence derived from large scale research to inform clinical decision-making.[1] To promote EBM, systematic reviews (SRs) including meta-analyses (MAs) should be conducted to produce a comprehensive summary of all relevant studies, clinical practice guidelines (CPGs) will be proposed based on such evidence synthesis, and physicians must update their shared decision making processes in accordance with such guidelines.[2]

Depressive disorders are the most common mental disorders, making them the second leading cause of disability accounting for 8.2% of all years lived with disability (YLDs) in 2010.[3-5] Reflecting the high prevalence of major depressive disorder (MDD) among people of working ages and the resulting dysfunctions, their economic burden was estimated at US $210.5 billion in US alone in 2010.[6] Antidepressants are widely used in the treatment of MDD, and a host of new generation antidepressants have been approved into the market in the past two to three decades. Given the enormity of burdens due to MDD on patients and society, various institutions worldwide have produced clinical practice guidelines (CPGs) for physicians. It was as early as in 1993 that American Psychiatric Association (APA)[7], British Association for Psychopharmacology (BAP)[8] and Agency for Health Care Policy and Research (AHCPR)[9] proposed the first version of their guidelines, followed by other associations like National Institute for Health and Care Excellence (NICE) from UK[10] and Canadian Network for Mood and Anxiety Treatments (CANMAT) from Canada[11]. Most of these guidelines have been updated every several years since.

However there are still several important barriers that may impede physicians and patients from making optimal clinical decisions. First, it has become increasingly known that a substantive amount of trials of antidepressants remain unpublished and were not included in contemporary SRs, a fact which most likely introduces publication bias into the results of SRs and thus undermines the credibility of guidelines.[12] Second, it has been reported that there is approximately eight months to more than one year's lag between the last search date in the literature and the publication of an SR,[13] [14] and in total 2.5-6.5 years' interval between the publication dates of the latest primary studies and the publication date of SRs.[15] It was estimated that 7% of the published SRs were already out of date at the time of publication[16]. Third, few of the available CPGs provide specific and precise recommendations in the choice of antidepressants, as pooled evidence has been given conflicting interpretations.[17] [18] Fourth, physicians' behaviors are notoriously difficult to influence.[19-21] The road from randomized evidence to actual practices thus appears formidable.[22]

The aim of the present study is to examine how the accumulating body of evidence should have been assembled, and reflected in guidelines, and then transferred into real practices in the prescription of new generation antidepressants for MDD through the past three decades. The evidence we will consider comes from a uniquely comprehensive dataset prepared by GRISELDA (Group of Researchers Investigating Specific Efficacy of individual Drugs for Acute depression). [23] [24] It

comprises data from 522 published and unpublished double-blind randomized controlled trials of new generation and other antidepressants in the acute treatment of depression. Capitalizing on this, we will use cumulative network analysis (cNMA) to summarize the development of accumulated evidence over time. [25-27] When two or more treatment alternatives are available, as in the case of MDD, NMA can summarize the relative effects of all treatments options by combining both direct and indirect comparisons[28]; because they utilize all direct and indirect evidence, they can produce strong evidence concerning relative efficacy more often and earlier than conventional, pairwise meta-analyses[29]. We will examine the specific recommendations in the internationally representative CPGs. The real-world prescription practices will be collated from Medical Expenditure Panel Survey (MEPS) in USA, which is a large-scale yearly healthcare survey of representative samples of families and individuals in the United States. [30] We predict that there are important gaps in the evidence synthesis and implementation process. Our study will evaluate and narratively summarize how big these gaps are and where mainly they exist, and will provide valuable information necessary to direct future paths to bridge the gaps from scientific evidence to real-world clinical practice.

METHODS

Systematic reviews of RCTs of new generation antidepressants and cumulative network meta-analysis

Study eligibility

The cNMAs in this study will be based on the systematic review which has identified all published and unpublished double-blinded head-to-head RCTs comparing any of the following new generation antidepressants in the acute phase treatment of adults with MDD up to January 2016[23 24]: we will consider all new generation antidepressants approved by drug agencies of US, Europe or Japan including agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone and vortioxetine.

The GRISELDA dataset also contains two older tricyclic antidepressants (TCAs) recommended by WHO Model List of Essential Medicines (amitriptyline and clomipramine) and two drugs with distinct effect and side-effect profiles (trazodone and nefazodone): they will constitute evidence set[31] in the NMAs which serves to connect and strengthen the network.

We will include in the meta-analysis only study arms which administered the drugs within dose ranges approved by the regulatory agencies. Because the inclusion of placebo-controlled trials may violate the transitivity assumption of NMA in depression studies[32-36], and because we will be comparing the evidence from cNMA with real-world practice, we will only include RCTs comparing active drugs and exclude placebo-controlled studies in the current cNMAs.

Study identification and data extraction

GRISELDA has searched the following databases without language restrictions for published articles: Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, EMBASE, LiLACS, MEDLINE, MEDLINE In-Process, and PsycINFO up to January 2016. We performed manual searches of references of included articles. We also searched for published, unpublished and ongoing RCTs in drug-approval agencies' documents, company websites, international trial registries, and through contact with pharmaceutical companies and other relevant organizations. Where necessary, we contacted study authors directly to get supplementary materials for further information. The risk of bias of each included study was assessed according to the guide proposed in the Cochrane Collaboration Handbook.[37]

Study identification, data extraction and risk of bias assessment of the included studies were all performed independently by two researchers, and any disagreements were resolved through discussion or in consultation with a third reviewer. For further details of the systematic review process, please see the published protocol and the main GRISELDA paper.[23 24]

Statistical analyses

We will conduct cNMA every 5 years in consideration of the speed of accumulating new trials and publication of guidelines for MDD. According to previous studies which indicated that the latest search of database was about one year before publication of SRs,[13-15] cNMA at any time point will include all trials completed up to 1 year before that date. For trials whose completion year is not available, publication date will be used; when neither is known, the date of approval of the drug by regulatory agencies will be used as the study completion date. Thus studies with a known completion year before the proposed cNMA will be included in the relevant cNMA even if the data were published after that year. Only such cNMA can present the best available, publication bias-free evidence, upon which practice guidelines should ideally be founded.

For network meta-analysis, transitivity assumption is the principle. Since we have confirmed the transitivity assumption of the whole data set in the final network meta-analysis [24], we will not validate it at every time point re-analysis. In our previous study, we investigated the distribution of the following potential effect modifiers across treatment comparison: (1) study year; (2) sponsorship; (3) depressive severity at baseline; (4) dosing schedule; (5) proportion of participants allocated to placebo; (6) number of recruiting centers (single-center vs multi-centric studies). We evaluated consistency and heterogeneity in the entire network using various tests and metrics and we have found little evidence of inconsistency and heterogeneity.[24]

Our primary outcomes are (i) efficacy of the intervention in terms of response rate defined as the proportion of patients who showed a reduction of at least 50% on the total depression severity score compared to baseline, and (ii) acceptability of the intervention in terms of all-cause discontinuation rate defined as the proportion of patients who leave the study early for any reason. We have extracted

the outcome data at a time point as close to 8 weeks as possible: if outcomes at 8 weeks were not available, we recorded data between 4 and 12 weeks.

We will not adjust for multiple comparisons in successive NMAs as we are not testing particular hypotheses for specific comparisons among antidepressants.

We will use the surface under the cumulative ranking curve (SUCRA) to estimate ranking probabilities for each intervention with regard to the two primary outcomes. We will show ranked forest plots of ORs with 95% CI in comparison with a common comparator as a sensitivity analysis: we will use fluoxetine as the common comparator as it is the most frequently used drug in the trials network.[24]

We will use STATA (Stata Corp 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp) to conduct cNMA. [38 39]

Identification and extraction of recommendations in guidelines

We will use a series of CPGs as our benchmark in comparisons. English written guidelines proposed by government agencies (such as National Institute for Health and Care Excellence), or professional academic societies (such as American Psychiatric Association) will be included. Due to the ambiguity and subjectivity associated with the Appraisal of Guidelines Research and Evaluation II (AGREE II) instrument for quality assessment of guidelines[40], we will not apply AGREE instrument in the appraisal of guidelines, but we will describe the methodology of each guideline development in supplementary materials. As a result, we will extract recommendations for specific antidepressants or for specific classes of antidepressants from internationally representative guidelines listed below:

1) Practice guidelines for the treatment of patients with major depressive disorder published by American Psychiatric Association (APA), in 1993, 2000, 2010 respectively.[7 41 42]
2) Guidelines for management of depression proposed by National Institute for Health and Care Excellence (NICE), in 2004, 2009 and 2018.[10 43 44]
3) Guidelines for treating depressive disorders with antidepressants proposed by British Association for Psychopharmacology (BAP), in 1993, 2000, 2008 and 2015. [8 45-47]
4) Clinical practice guidelines for treatment of major depression proposed by Agency for Health Care Policy and Research (AHCPR) in 1993. [9]

We will extract recommendations with respect to acute phase treatment for adult patients with a primary diagnosis of unipolar non-psychotic major depression. We define recommendations as statements used in CPGs involving the words like “recommend”, “must”, “necessary”, “should”, “appropriate” or other words indicating instructions from guidelines. Basic information of the guideline (institution, year, targeted patients, diagnostic criteria, etc.), pharmacotherapy recommendations as acute phase treatment (particular drugs and categories recommended and least recommended, severity of the disease, etc.), pharmacotherapy recommendations for patients who have no satisfactory response to initial treatment will be recorded in detail, in order to be compared with results from cNMA and real world. We will also collect the quality of evidence and strength of

recommendations backing extracted recommendations. Two researchers will independently identify recommendations and extract information from CPGs. Any disagreement will be resolved through discussion or in consultation with a third researcher.

Real-world prescriptions data extraction

We will extract real-world prescription data from the Medical Expenditure Panel Survey (MEPS) database. [30]MEPS is a database composed of large-scale surveys of families and individuals and their medical providers, collecting data on the use of specific health services, the cost, and the health insurance in the United States. The survey started in 1996. MEPS has two major components, the household component and the insurance component, both of which provide data on a yearly basis. In the household component a representative sample of families and individuals are interviewed every year and detailed information including demographic characteristics, health status, use of medical services, specific medications, cost for each person is collected. Each annual MEPS household sample size is about 15,000 households. This set of households is a subsample of households participating in the previous year's National Health Interview Survey (NHIS) led by the National Center for Health Statistics. The NHIS sampling frame gives a nationally representative sample of the non-institutionalized population in the US, and oversamples of Blacks and Hispanics. In 2006, after implementing a new sample design, Asian population has been included in order to deal with the oversampling issues. To correct for oversampling and for non-response, each participant is given a weight adjusting for nonresponse over time and some poststratification variables (region, race/ethnicity, sex, age, poverty status and etc.), in order to produce national estimates.[30] MEPS database has been used for the analysis of health expenditures and real-world prescriptions of specific drugs in several studies.[48-50]

Participants

We will include those who have been classified as “Depressive disorders” in the category of “657 Mood disorder”, of either sex and aged 18 years or older. The corresponding ICD-10 numbers are: 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 311. MEPS database only code the diagnosis for the first 3 digits using ICD numbers (296, 311).

Interventions

Of the 21 antidepressants included in the GRISELDA network, the following drugs will not be included among the drugs prescribed for depressive disorders in MEPS: agomelatine and reboxetine have not been approved by FDA for marketing in USA, fluvoxamine has an indication for obsessive-compulsive disorder but not for depression, and milnacipran for fibromyalgia only. On the other hand, there are many antidepressants, other than new generation antidepressants, which may have been prescribed especially in older days, such as imipramine, desipramine, doxepin or nortriptyline. Although our focus of comparison is new generation antidepressants, we will extract

the frequency of prescription of all antidepressants in the MEPS study. Using the National Drug Code Directory[51], which included all registered drugs in FDA, we identified all antidepressants ever used in the USA as the following: 1) Tricyclic Antidepressants [EPC]: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine; 2) Serotonin Reuptake Inhibitor [EPC]: citalopram, escitalopram, fluoxetine, nefazodone, paroxetine, sertraline, trazodone; 3) Serotonin and Norepinephrine Reuptake Inhibitor [EPC]: desvenlafaxine, duloxetine, venlafaxine, levomilnacipran; 4) No Pharm Class: bupropion, mirtazapine, vilazodone, vortioxetine. All the 24 listed antidepressants will be searched in MEPS during data extraction.

Data extraction

We will extract prescription data for antidepressants listed above in the year 1996, 2000, 2005, 2010 and 2015 (Table 1). Since diagnostic labels available MEPS data cannot distinguish unipolar depression from bipolar depression and psychotic depression, both of which require different drug treatments than unipolar depression, we will exclude those patients who are concomitantly taking mood stabilizers or any antipsychotics. According to the National Drug Code Directory [51], Mood Stabilizer [EPC] include: carbamazepine, divalproex, lamotrigine, lithium, valproate, valproic acid; and Phenothiazine [EPC], Typical Antipsychotics [EPC] and Atypical Antipsychotics [EPC] include: aripiprazole, asenapine, brexipiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperido, iloperidone, loxapine, lurasidone, molindone, olanzapine, paliperidone, perphenazine, pimavanserin, quetiapine, risperidone, thioridazine, thiothixene, ziprasidone. We will exclude all participants taking any of these drugs concomitantly with an antidepressant.

Every participant in one MEPS cohort (called 'panel' in MEPS) is interviewed five times (called 'rounds') for 2 years. For example, the file of 2015 contains the 2015 portion of Round 3 and Rounds 4 and 5 for Panel 19, as well as Rounds 1, 2 and the 2015 portion of Round 3 for Panel 20 (see Figure 1).[30] We will check the prescription of antidepressants at round 2 from panel 20 and round 4 from panel 19 (similar patterns in other given years), because each participant, either from panel 19 or 20, must have this intermediate round of interview within 2015, and we will use it as a cross-sectional investigation. We will use the total number of patients with the diagnosis of depression and who are on antidepressant monotherapy but not taking mood stabilizers and antipsychotics (listed above) concomitantly at this round as denominator, and the prescription for a particular drug as monotherapy as numerator. Given lack of precise information for medication schedule (e.g. start time of diagnosis, primary medication, time of start and change of medication), we will not be able to restrict the prescriptions to inception prescriptions in the acute phase treatment of MDD, and the results will include both incident and prevalent uses. As MEPS data set give each participant a sample weight according to nonresponse and poststratification variables, we will use the sample weights to estimate the nationally representative number of patients on a specific therapy. Finally the ranking of the of prescriptions will then be based on the estimated numbers of prescriptions in the general US population.

We will use Python 3.6 to extract data from MEPS dataset.

Comparison between cNMA, CPGs, and real-world prescriptions

We propose that a cNMA at a specific time point (e.g. 2000) should be taken as a reference for any guidelines that are going to be published in the next five years (e.g. 2000 through 2004), and then inform real world prescriptions afterwards (e.g. 2005 and after). We will therefore compare the results of NMA, CPG recommendations and real-world practice in these corresponding years, and the trend between these time points will also be taken into considerations. Table 1 shows the time periods for comparisons. We will assess if the recommendable sets estimated from cNMA (i.e. drugs which have good balance between efficacy and acceptability) are reflected in the drugs recommended by guidelines, which then will be compared with the rankings in actual clinical practice. Moreover, as MEPS is a database from the US, we will attempt to compare results from MEPS with the US guidelines APA. We will describe the possible differences and explore the time lag from the ideally available evidence to guideline recommendations and from guideline recommendations to the real world practices. We will also investigate the potential factors which may influence the actual prescriptions including side-effects profiles of specific drugs, year of FDA approval, the price of the drug while on patent, and the year of patent expiration of each drug.

Table 1. Time periods for comparisons in our study.

Trials (completion year*)	Cumulative NMAs	CPGs (publication year)	Real world prescriptions (MEPS data file year)
~present	present	2016~present	-
~2009	2010	2010~2014	2015
~2004	2005	2005~2009	2010
~1999	2000	2000~2004	2005
~1994	1995	1995~1999	2000
~1989	1990	1990~1994	1996**

* For trials whose completion year is not available, publication date will be used; when neither is known, the date of approval of the drug by regulatory agencies will be used as its completion date.

**As MEPS database started with 1996, so we will use data from 1996 for the analysis of prescriptions.

Patient and public involvement

This research protocol was written without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not expected to contribute to conducting this study and to the writing of this document for readability or accuracy.

DISCUSSION

We have presented the study protocol for investigating the gaps between ideally synthesized evidence, guideline recommendations and real-world clinical practices in the prescriptions of new generation antidepressants for unipolar major depressive disorders.

Our study has several strengths. It is one of the first studies to make comparisons between pooled evidence derived from cumulative network meta-analyses, recommendations from guidelines, and real-world clinical practices. In the cNMA, we will use the comprehensive dataset from our previous study [24], which included both published and unpublished trials. And we will use MEPS database, which collect detailed information of health status and specific medications from a representative sample in the US, as a reflection of real world prescription profile. We expect this study to show the gaps between evidence and practice, and our findings will inform future developments of evidence-based medicine. For instance, the cNMA used in this study may eventually evolve into prospectively designed sequential network meta-analysis which can be used to continuously update evidence and contribute to living guidelines, which is a guideline that is updated as soon as new evidence becomes available, so that it can provide timely and trustworthy suggestions for decision-makers.[15 52 53]

There are some limitations to our study. First, MEPS does not allow us to extract very precise information, including whether the antidepressant is being used as first-line or later treatments. This may lower the comparability between the cNMA of acute phase treatment studies of unipolar depression and the real world practices, as patients on continuation/maintenance treatment may continue using the same antidepressants after guideline recommendations for acute phase treatment change. However, it must be noted that three quarters of patients who initiate antidepressant treatment discontinue the drug within 90 days[54], suggesting that the majority of the patients in MEPS database represent initial prescriptions. Second, MEPS is a US database so we will not be able to make comparisons between guideline recommendations and actual practices in other countries. Lastly, the reasons behind the differences between evidence and practice may be very complicated and we will need to factor in various potential confounding factors such as the side-effects, marketing efforts of pharmaceutical companies and local regulations such as price or patent status of a particular drug.[15 55 56]

In conclusion, our study represents a unique inquiry into gaps from evidence to real-world practices, and may provide valuable insights into future developments of EBM.

Ethics and dissemination

This study does not require institutional review board approval. We have registered it in the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR): UMIN000031898.

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Competing interests

TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has received research support from Mitsubishi-Tanabe and Mochida. ACi is supported by the NIHR Oxford Cognitive Health Clinical Research Facility, and was expert witness for Accord Healthcare for a patent issue about quetiapine extended release. All the other authors report no competing interests to declare.

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Contributors

YL and TAF conceived the study and drafted the protocol. ACh, YK, EGO, YO, ACi and GS assisted in the study design and critically revised the protocol. All authors gave final approval of the version to be published.

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Figure legend: **Figure 1**. Survey structure of 2015 file in MEPS.[30]

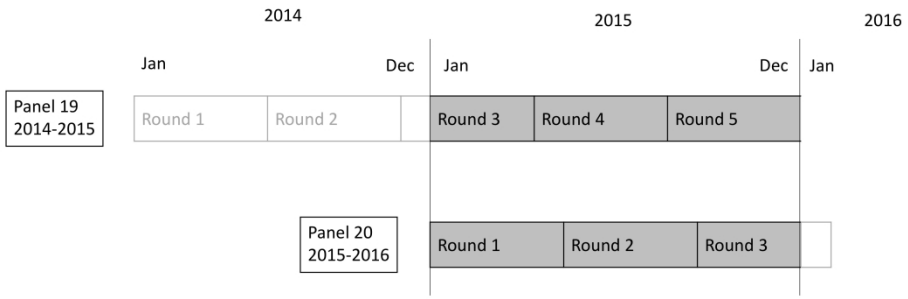

Figure 1. Survey structure of 2015 file in MEPS.[30]

338x190mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (UMIN000031898, see Main document Page 2)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (see Main document Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (see Main document Page 11)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review (see Main document Page 11)
Sponsor	5b	Provide name for the review funder and/or sponsor (see Main document Page 11)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (see Main document Page 4)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (see Main document Page 4)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (see Main document Page 5)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (see Main document Page 5)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (see Main document Page 6)
Study records:		

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (see Main document Page 6)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (see Main document Page 6)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (see Main document Page 6)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (see Main document Page 5-6)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (see Main document Page 6)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (see Main document Page 6)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (see Main document Page 6-7)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (see Main document Page 6-7)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (see Main document Page 6-7)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (see Main document Page 6-7)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (see Main document Page 5-6)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (see Main document Page 6-7)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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