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Title

Antidepressant Prescriptions Have Not Fully Reflected Evolving Evidence from Cumulative Network Meta-analyses and Guideline Recommendations

Authors

Yan Luo[1], Edoardo G. Ostinelli[2], Ethan Sahker[1,3], Anna Chaimani[4], Yuki Kataoka[5], Yusuke Ogawa[6], Andrea Cipriani[2], Georgia Salanti[7], Toshi A Furukawa[1*]

Affiliations

[1] Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto 606-8501, Japan

[2] Department of Psychiatry, University of Oxford, Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford OX3 7JX, UK

[3] Japanese Society for the Promotion of Science (JSPS), Overseas Fellowship Division, Tokyo 102-0083, Japan

[4] Université de Paris, Research Center of Epidemiology and Statistics (CRESS-UMR1153), INSERM, INRA, Paris F-75004, France

[5] Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center, Hyogo 660-8550, Japan

[6] Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto 606-8501, Japan

[7] Institute of Social and Preventive Medicine, University of Bern, Bern CH-3012, Switzerland

Email addresses

Yan Luo[1], lilacluo@gmail.com

Edoardo G. Ostinelli[2], edoardo.ostinelli@psych.ox.ac.uk

Ethan Sahker[1,3], sahker.ethan.2e@kyoto-u.ac.jp

Anna Chaimani[4], anna.chaimani@parisdescartes.fr

Yuki Kataoka[5], youkiti@gmail.com

Yusuke Ogawa[6], ogawa.yusuke.2u@kyoto-u.ac.jp

Andrea Cipriani[2], andrea.cipriani@psych.ox.ac.uk

Georgia Salanti[7], georgia.salanti@ispm.unibe.ch

Toshi A Furukawa[1*], furukawa@kuhp.kyoto-u.ac.jp

Corresponding author

Toshi A Furukawa, MD, PhD

Department of Health Promotion and Human Behavior, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Phone: +81-75-753-9491; Fax: +81-75-753-4641; Email: furukawa@kuhp.kyoto-u.ac.jp

Abstract

Objective

This study compares three major elements of evidence-based medicine (EBM) practices, namely evidence synthesis, clinical practice guidelines (CPGs) and real-world prescriptions in the US, regarding antidepressant treatments of major depression over the past three decades.

Study design and setting

We conducted network meta-analyses (NMAs) of antidepressants every 5 years up to 2016 based on a comprehensive dataset of double-blind randomized controlled trials. We identified CPGs and extracted their recommendations. We surveyed the prescriptions in the US at 5-yearly intervals up to 2015.

Results

Most drugs recommended by CPGs presented favorable performance in efficacy and acceptability in NMAs. However, CPG recommendations were often in terms of drug classes rather than individual drugs, while NMAs suggested distinctive difference between drugs within the same class. The update intervals of all CPGs were longer than 5 years. All the antidepressants prescribed frequently in the US were recommended by CPGs. However, changes in prescriptions did not correspond to alterations in CPGs nor to apparent changes in the effects indicated by NMAs. Many factors including marketing efforts, regulations or patient values may have played a role.

Conclusions

Enhancements including accelerating CPG updates and monitoring the impact of marketing on prescriptions should be considered in future EBM implementation.

Keywords

Evidence-based medicine, network meta-analysis, clinical practice guideline, antidepressant

Running title

Antidepressant Prescriptions Have Not Fully Reflected Evidence and Guidelines

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What is new (HIGHLIGHTS)

- Ideally synthesized evidence, guidelines and prescriptions were compared dynamically
- Network meta-analysis helps earlier detection of discriminable effect of antidepressants
- Guidelines' infrequent updates failed to capture all the changes in the evidence
- Fluctuations in real-world prescriptions could not be explained by changes in guidelines
- Marketing efforts might have played a critical role in prescriptions of antidepressant

1 INTRODUCTION

Evidence-based medicine (EBM) provides the principle for decision-making in medical practice [1]. Ideally, systematic reviews (SRs) synthesize evidence from clinical trials. Clinical practice guidelines (CPGs) then interpret the evidence and make concrete recommendations. Eventually, physicians should update their knowledge with new evidence and guidelines, and share the information with patients so that they can discuss and agree on a final decision [2].

However, previous studies have revealed potential problems in this ideal EBM process. Evidence itself may be biased due to unpublished data [3]. SRs may be out-of-date at the time of publication [4, 5]. Similarly, CPGs may not be updated in a timely manner [6], or fail to reflect valid evidence due to methodological flaws [7, 8]. When it comes to clinical decision-making, physicians may not follow the recommendations or evidence because of personal experiences and beliefs, or they are too busy to access the updated knowledge [9-11]. Further aggravating the problem, both physicians and patients can be influenced by pharmaceutical industry's marketing strategies [12, 13].

Major depressive disorder (MDD) is one of the most common mental disorders across cultures [14, 15]. Antidepressants have long been recommended as the first-line treatment for MDD, although their absolute effectiveness has been debated to date [16]. Selecting the optimal medication from an overwhelming array of options is not straightforward. Earlier evidence based on randomized controlled trials (RCTs) and pairwise meta-analyses (MAs) suggested that antidepressants had indistinguishable efficacy. With the advent of new evidence synthesis methods, some antidepressants emerged as being more efficacious and acceptable than others [17, 18]. The new body of evidence comprised a large amount of unpublished data to minimize publication bias, and was synthesized by network meta-analyses (NMAs), a method that compares multiple treatments simultaneously. NMA can detect the difference between treatments earlier, and with greater power than conventional pairwise MAs [19], hence provide the highest level of evidence [20, 21].

It remains unclear in the past decades, whether CPG recommendations duly reflected the evidence, and how the real-world prescriptions followed the evidence and CPGs. The aim of this study is to compare the three elements in this process, namely synthesized evidence, CPG recommendations, and real-world prescriptions, for new generation antidepressants in treating acute phase MDD through the past three decades (Figure 1). As some of the evidence was not available in early years (e.g. unpublished trial reports could not be retrieved from regulatory agencies until 2000), it was impossible to identify evidence as was available in those days, presumably in a deficient and biased manner. Rather, we have shown the evolution of evidence via a series of consecutively conducted NMAs using the largest network of RCTs to date [18, 22]. Therefore, we use this ideally synthesized evidence as the benchmark, to reveal what should have been in the CPGs had we been able to perform the best evidence synthesis, which could indicate advantages of implementing NMA. We have also described

real-world prescription patterns of antidepressants in the past 20 years in the US, based on a population representative database [23]. In the present study we selected several internationally representative CPGs for the pharmacological treatment of MDD, examined how they were developed and updated, and extracted their recommendations. We then compared the ideal evidence based on cumulative NMAs, the CPG recommendations, and the prescriptions. We described the discrepancies over time if there were any, and investigated some factors that may have caused the deviations. Understanding potential barriers in the process of practicing EBM will help us identify future direction of improvement.

2 METHODS

The protocol for this study has been published [24]. This study did not require approval by an institutional review board because only group-level data and deidentified data were used. It was registered at UMIN Clinical Trials Registry (identifier: UMIN000031898).

2.1 Three elements of the EBM process

We have previously published and described the first and the third elements in the EBM process (Figure 1) [22, 23]. Here we provide brief summaries of the methods for these two elements, and describe the second element.

2.1.1 Evidence based on cumulative network meta-analyses

The evidence synthesized in this study was supposed to reflect the ideal evidence which should have been available at each retrospective time point. Briefly, the dataset included published and unpublished double-blind RCTs of new generation antidepressant treatment for acute phase MDD adult patients (≥18 years old) [18]. The primary outcomes were: *efficacy* (response rate, measured as the proportion of patients who achieved a reduction of at least 50% on any validated depression severity scales compared to baseline at 8 weeks) and *acceptability* (all cause discontinuation rate, measured as the proportion of patients who withdrew early due to any reasons) [25]. We included only head-to-head trials (n=190) in the current study, because having a placebo arm among the comparisons changed the nature of the trials [26, 27].

In order to track the evidence evolution, we conducted a series of cumulative NMAs every 5 years since 1990 (i.e., at 1990, 1995, 2000, 2005, 2010 and 2016 respectively), each of which included all the RCTs completed up to one year before that date. For each NMA, a random-effects model was used to estimate the odds ratios (ORs) for both efficacy and acceptability. Then we assessed the confidence in the evidence using the CINeMA (Confidence in Network Meta-Analysis) framework [28, 29], rating the evidence for each estimate at four levels: high, moderate, low and very low confidence (details of assessment are described in the Appendix 1 (p.3-4)). We presented the results in a two-dimensional plot at each time point. Each node represented an antidepressant, with x-axis indicating the efficacy

while y-axis indicating the acceptability compared with citalopram, a drug that was consistently prescribed through the decades. We use a pie chart for each node to illustrate the level of confidence in the evidence for each drug. Further information is provided in [22].

2.1.2 Guideline recommendations in the internationally representative CPGs

As described in the protocol, we have identified all the published versions of the following English written, representative CPGs concerning the acute phase pharmacological treatment for adult patients diagnosed with MDD proposed by these professional institutions (government agencies or professional academic societies): (1) American Psychiatric Association (APA) [30-32]; (2) Agency for Health Care Policy and Research (AHCPR) [33]; (3) British Association for Psychopharmacology (BAP) [34-37]; (4) National Institute for Health and Care Excellence (NICE) [38, 39].

Two researchers (YL and EGO) independently extracted the information about the methodology of guideline development: (1) search strategies; (2) types of publication primarily used to produce recommendations; (3) the latest SRs referenced; (4) whether the panel conducted additional evidence synthesis, and the method of synthesis. We also extracted specific recommendations. We considered a drug being recommended if the statement used 'recommend', 'must', 'necessary', 'should', 'appropriate' or other similar words to express instructions. Merely mentioned in the explanatory paragraph without explicit suggestions was not considered a recommendation. If the recommendation was in terms of drug category, we searched the definition in that guideline to identify corresponding drugs. Recommendations regarding particular subgroups such as elderly, severe, hospitalized, or pregnant patients were excluded.

2.1.3 Antidepressant prescriptions in the US based on a population-representative database

The real-world prescription patterns were depicted based on the Medical Expenditure Panel Survey (MEPS) database in the US [40]. Briefly, the MEPS comprises yearly large-scale surveys since 1996. 20,000 to 40,000 participants from a nationally representative sample of families and individuals and their medical providers were involved every year. We included patients diagnosed with MDD, and excluded those with bipolar disorder and psychotic depression. Our target medications were antidepressants being approved for MDD by the US Food and Drug Administration (FDA). We focused on antidepressant monotherapy, defined as patients who were prescribed only one antidepressant within the whole year.

To be consistent with evidence synthesis, the proportion of a particular antidepressant was estimated by the number of MDD patients being prescribed that antidepressant monotherapy among all the MDD patients on monotherapy in the years 1996, 2000, 2005, 2010 and 2015. The calculation was based on the national estimates using sampling weights. We drew a plot to show the prescription proportions for each antidepressant over the years. Further details are available in [23].

2.2 Comparison between cumulative NMAs, CPGs, and real-world prescriptions

Firstly, we compared the ideal evidence based on cumulative NMAs and CPG recommendations. We marked on the plot of each NMA the drugs recommended by CPGs published within 5 years of that NMA, in order to visually examine the relative effect indicated by evidence behind the drugs. We used distinct colors to label drugs that were commonly recommended by more than two CPGs, and those only recommended by a specific CPG.

Secondly, we compared CPGs and prescriptions in the US. We first examined whether frequently prescribed antidepressants were recommended by CPGs, and whether the time of recommendation matched the growth in prescription. Conversely, we examined the prescription proportions for drugs that were recommended by CPGs. Then, as we anticipated many potential factors might influence real-world prescriptions (Figure 1), we investigated the following: (1) changes in relative efficacy and acceptability based on NMAs; (2) patent expiry; (3) FDA safety warnings; (4) marketing promotions. For (1), we identified visually noticeable rises and falls in the prescription trend, and checked whether they were accompanied by apparent changes in the effect indicated by NMAs. (2) ~ (4) were examined graphically on the prescription plot. We marked the year of patent expiry. We searched for FDA safety warnings on critical side effects after approval for specific antidepressants. Warnings concerning all antidepressants (e.g. the black-box warning of suicidal risk), or only to specific patient groups (e.g. pregnancy use) were excluded. We tagged the year of warning on the plot. Since we did not have precise data on marketing investment, we explored relationship of the market share between drugs from the same company. We matched the antidepressants by company that marketed the branded products to visualize their relations.

3 RESULTS

3.1 CPG recommendations

3.1.1 Update frequency

The update of all the guidelines took more than 5 years, ranging from 5 to 10 years, with a median interval of 7 years (Table 1).

3.1.2 Methodology used in developing CPGs

Most CPGs reported the methodology with details. Improvement was observed over time: databases searched were increasing, and new evidence synthesis methods such as NMAs were adopted gradually. Though all CPGs conducted extensive literature searches on main medical databases, NICE's was the most comprehensive, including trial registries and unpublished data. All the CPGs based their recommendations primarily on published SRs and RCTs. The newest SRs referenced in the guidelines were usually published a year before or even in the same year as the publication of guideline. Pairwise MAs were the most frequent sources of evidence, except for NICE-2009, BAP-2015, and NICE-2018,

in which NMAs were taken into consideration. BAP considered the indirect comparisons in NMAs produced weaker evidence, while NICE fully addressed the interpretations of referenced NMAs. AHCPR and NICE also conducted MAs and/or NMAs on their own. BAP-2008 and BAP-2015 also referenced previously published guidelines.

3.1.3 Recommendations

We summarized the recommendations in Table 1. Antidepressants were recommended as the first-line treatment for patients with MDD above threshold severity, especially with persistent symptoms, in all CPGs. Most CPGs claimed they prioritized drugs with better safety profiles, as most antidepressants had comparable efficacy. All the CPGs recommended some particular antidepressants, usually with unspecified or weaker strength of evidence than the general statements. Selective serotonin reuptake inhibitors (SSRIs) were recommended by all the CPGs, though always as a drug category.

Table 1. Summary of Recommendations Extracted from Representative Clinical Practice Guidelines

Date of publication	Organization	Country	Recommended drugs*			
			TCAs	SSRIs	SNRIs	Others
1993	AHCPR	US	secondary TCA: *nortriptyline, desipramine*	SSRIs: *fluoxetine, paroxetine, sertraline*	-	trazodone bupropion
1993	APA	US	acceptable	SSRIs: *fluoxetine, paroxetine, sertraline*	-	trazodone bupropion
1993	BAP	UK	lofepramine	SSRIs: *fluoxetine, fluvoxamine, paroxetine, sertraline*	-	trazadone mianserin
2000	APA	US	nortriptyline, desipramine	SSRIs: *citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	venlafaxine	bupropion
2000	BAP	UK	lofepramine	SSRIs: *citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	venlafaxine	nefazodone mirtazapine, reboxetine
2004	NICE	UK	-	SSRIs: *citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	#	-
2008	BAP	UK	-	SSRIs: *citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	venlafaxine, duloxetine	mirtazapine
2009	NICE	UK	-	SSRIs: *citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	#	-
2010	APA	US	-	SSRIs: *citalopram, escitalopram, fluoxetine, paroxetine, sertraline*	venlafaxine, desvenlafaxine, duloxetine	bupropion, mirtazapine
2015	BAP	UK	-	SSRIs: *citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	-	agomelatine, vortioxetine mirtazapine[§]
2018[¶]	NICE	UK	-	SSRIs: *citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	-	mirtazapine

*Drug categories are based on National Drug Code Directory of the US Food and Drug Administration. If recommendations were in the form of drug category rather than a particular drug, all the drugs belonging to that category according to that guideline's definition are presented.
#NICE-2004 stated that *venlafaxine* was not appropriate in primary care due to safety concerns. And NICE-2009 stated that both *venlafaxine* and *duloxetine* might not be considered as an initial treatment due to safety issues.
§BAP-2015 did not recommend *mirtazapine* explicitly in the main statements, but suggested it could be considered due to efficacy. The reason why it was not in the main recommendations was that the evidence for mirtazapine came from indirect comparisons in a network meta-analysis, which was considered less strong than direct comparisons.
¶NICE started the update in 2015, but now it is still ongoing and the formal update has not yet published. The newest draft was updated in May, 2018 and was open online (https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0725/documents, https://www.nice.org.uk/guidance/gid-cgwave0725/documents/full-guideline-updated).
Abbreviations: APA-American Psychiatric Association; NICE-National Institute for Health and Care Excellence; BAP-British Association for Psychopharmacology; AHCPR-Agency for Health Care Policy and Research. TCA=tricyclic antidepressant; SSRI=serotonin reuptake inhibitor; SNRI=serotonin and norepinephrine reuptake inhibitor.

3.2 Comparison between cumulative NMAs and CPGs recommendations

As an illustration, Figure 2A compares the NMA as of 2000 with the recommendations in CPGs published between 2000 and 2005, while Figure 2B compares the NMA as of 2005 with CPGs published between 2005 and 2010 (details in the legend). Most of the commonly recommended drugs had slightly to moderately better efficacy than citalopram except fluvoxamine (ORs of response rate except fluvoxamine: 1.00-1.55 in 2000, 1.00-1.26 in 2005; ORs≥1 favor the drug other than citalopram), and comparable or slightly worse acceptability than citalopram except duloxetine (ORs of discontinuation rate 0.98-1.41 in 2000, 1.08-1.34 except duloxetine in 2005; ORs≥1 favor citalopram). Compared to other SSRIs, fluvoxamine was less favorable in efficacy (OR 0.92 in 2000 and 0.94 in 2005), acceptability (OR 1.37 in 2000 and 1.34 in 2005), and evidence credibility (moderate or high confidence accounted for only 3.8% in 2000, and 15.6% in 2005). It was still commonly recommended by CPGs as one of SSRIs, and no attempt was made to distinguish between individual SSRIs. Duloxetine, despite the low acceptability estimated in 2005 in NMA (OR 2.02), was recommended by both APA and BAP, whereas NICE was against its use as an initial treatment due to concerns about tolerability. Bupropion was recommended only by APA, since it was not approved to treat MDD in the UK. In 2000, three relatively new drugs, nefazodone, reboxetine and mirtazapine were recommended only by BAP. In 2008 BAP stopped recommending nefazodone and reboxetine, which is justified by our NMA, as in 2005 both presented low acceptability and low certainty in the evidence. Additionally, unlike the positive attitude towards venlafaxine in the contemporary APA and BAP CPGs, NICE stated that venlafaxine should only be initiated and monitored by mental health specialists, because of its increased risk of intolerability, overdose toxicity and withdrawal symptoms.

The plots at other time points are provided in eFigure1 in the Appendix 2.1 (p.5-8). In general, the relative efficacy, acceptability, and confidence in the evidence of drugs changed every 5 years, as new products were launched into the market. In addition, eFigure 1 again indicates that BAP was more open to new drugs, since it recommended agomelatine and vortioxetine in 2015 while other contemporary CPGs did not.

3.3 Comparison between CPGs recommendations and prescriptions

Figure 3 shows the prescription patterns of eight most frequently prescribed antidepressants as monotherapy in treating MDD in the US during the past 20 years. eFigure 2 in the Appendix 2.2 (p.9) shows it for all available drugs. Since APA is the only CPG proposed by a US organization with updates, we could only compare the prescription patterns with the APA recommendations. All the eight antidepressants in Figure 3 were recommended by APA. However, escitalopram was not formally recommended until 2010, despite high volume prescriptions beginning in 2005. Conversely, eFigure 2 shows that most recommended drugs were relatively frequently prescribed, except for mirtazapine, which was prescribed persistently at low levels.

Figure 3 displays the influence of several factors on prescriptions. First, due to infrequent updating of the guideline, changes in APA recommendations (marked by drugs being newly recommended) could not explain the fluctuations in prescription. Second, a reduction in the share after patent expired can be seen in sertraline, fluoxetine, paroxetine, venlafaxine and escitalopram. Third, the FDA liver side effect warning for duloxetine in 2005 seems not to have caused a prescription decrease. However, the risk of causing QT prolongation followed a fall for both escitalopram and citalopram. Finally, it exhibits a shift pattern in prescription proportions of the drugs whose branded products are marketed by the same company. A reduction in one drug was accompanied by an increasing tendency for another. The shift between citalopram and escitalopram pair was around 2005, when citalopram just lost its patent. Citalopram experienced a drop while escitalopram soon achieved a very large prescription volume when it was quite new. There is a slight shift in the prescription proportions of fluoxetine and duloxetine pair after fluoxetine lost its patent. The shift between two longstanding drugs sertraline and venlafaxine was not obvious. It should be mentioned that venlafaxine was marketed by Wyeth before Pfizer completed acquisition of Wyeth in 2009. For paroxetine and bupropion, paroxetine's share continued to go down after patent expiry; while bupropion whose patent has expired for long, achieved a slight increase in the share, which may be related to the approval of a new once-daily sustained-release formulation in 2003.

We also explored the relationship between effect changes in NMAs and prescription fluctuations. We identified a visually prominent growth in citalopram and duloxetine share between 2005 and 2010, and a loss of share in fluoxetine and paroxetine after 2000 (Figure 3). After comparing NMA at 2005 and 2010, as well as NMA at 2010 and 2016 (eFigure 1), no corresponding leap or drop in relative efficacy or acceptability was noticed. In fact, duloxetine sustained relatively low efficacy (ORs 1.02-1.13) and acceptability (ORs 1.61-2.02) in both 2005 and 2010. Moreover, citalopram and escitalopram were frequently prescribed immediately upon entering the market, where evidence had not yet been sufficient.

4 DISCUSSION

Cumulative NMAs suggested that the efficacy, acceptability, and confidence in the evidence for certain drugs were distinguishable and changed dynamically through the decades. CPGs developed by different groups had unique features: NICE expressed more concerns on safety; whereas BAP seemed more open to new drugs and committed more amendments in their updates. CPGs were developed following a rigorously reported methodology which improved over time. Even in comparison with ideally synthesized evidence, no obvious inappropriateness was found in CPG recommendations. However, NMA could have helped us differentiate the effect of individual drugs earlier and detect the changes in the effect. Real-world prescriptions were not against CPG recommendations; however, the fluctuations could not be fully explained by either CPGs or cumulative NMAs, and many factors may have played a role.

Although CPG were developed based on valid methodology, using NMA conducted on a comprehensive dataset as benchmark let us see how it may have facilitated EBM process. First, consistent with previous studies [19, 41], NMA could have promoted earlier detection of individual drug difference in effect. SSRIs were recommended as a group without further distinguishing within the category by CPGs, whereas our evidence suggested fluvoxamine was less favorable in efficacy, acceptability and evidence certainty compared with other SSRIs. Second, our cumulative NMAs indicates a rapid change in evidence, implying that CPGs may need to speed up their updates in order to catch up with evidence. Recently, living systematic reviews, based on prospectively designed consecutive NMA, were suggested to be able to shorten the time of SR update [42-44]. It can further contribute to a living guideline, which updates as soon as new evidence becomes available, making timely recommendations possible [45, 46]. Therefore, high quality NMAs based on exhaustive data to minimize publication bias [3], if being utilized properly, may increase the precision and update speed of future CPGs.

Similar to previous studies, our study implies that factors other than CPG recommendations and evidence may shape the real-world prescription patterns [47]. Marketing efforts may be especially worthy of note. We observed a shift in the prescription share between citalopram and escitalopram and between fluoxetine and duloxetine, both shortly after the patent expiry of the older product, which may be explained by a switch of promotional resources from the old drug in favor of the novel product marketed by the same company. Especially duloxetine's growth was before formal recommendation, regardless of its comparably unfavorable efficacy and acceptability indicated in the NMAs and by FDA's safety warning. This shift pattern was also observed among paroxetine and bupropion, right when bupropion's new formulation was approved in 2003. Furthermore, the fact that citalopram and escitalopram achieved large market shares when they were just launched, also implicitly implies a remarkable role of promotions. It may be dangerous, especially in the US, where direct-to-consumer advertising is legal, the influence was on not only physicians but also patients [48, 49]. How EBM

should be properly implemented under the impact of marketing needs more attention. In addition, we found that patient values might also play a role. Mirtazapine appeared an example of an interplay between side-effect profiles and unique cultural values. It was recommended by APA, though the prescription volume remained at low level. This might be due to its side effect of gaining weight and increasing serum lipid level, which possibly caused more worries to American physicians and patients than it did in other countries [50].

There are some limitations in our study. First, we did not use any statistical tests to evaluate the associations. Statistical tests such as correlation test needs assumptions and thus may lose clinical relevancy. Due to the descriptive nature, we could not draw firm conclusions. Second, owing to difficulties in acquiring truly available evidence in early years, we used NMAs to illustrate the evidence. It makes the comparison not straightforward, because NMA was not applicable in the past. However, comparing to this ideal evidence help us realize how NMA could have facilitated evidence synthesis and how our future practice can be improved. Besides, our NMAs did not reflect long-term beneficial and harmful effect, which should have been valued in CPG development. Nevertheless, it could still be useful for drug selections. Third, due to lack of some sufficient and precise information in the MEPS database and for factors like marketing investment, the explanations concerning changes in prescription are generating hypotheses rather than proving associations. In fact, marketing strategies are not always explicit, like interactions between representatives from companies and clinicians or advertisements [51, 52], they can take more implicit forms, such as via scientific publications [53, 54], which are even more dangerous while their influence is hard to be quantified. Future studies, based on richer and more accurate data, and from other countries worldwide, are warranted to validate those hypotheses.

5 CONCLUSIONS

To our knowledge, this is the first study to describe and compare the evolutions of the three main elements in EBM process: ideally synthesized evidence about treatment effects, CPGs, and prescriptions simultaneously, with regard to antidepressants in treating MDD patients over the past three decades. The findings indicate that there is still good room for improvement. CPGs appeared to reflect the evidence base, but NMA could have helped us detect distinctions between individual drugs and changes in the effect earlier. By contrast, the real-world prescription patterns showed larger fluctuations which were not fully explicable either in terms of CPG recommendations or cumulative NMA results. We suggest enhancements should include accelerating guideline updates, involving advanced evidence synthesis methods for guideline development, and monitoring the impact of marketing on prescriptions.

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Competing interests

TAF reports personal fees from Mitsubishi-Tanabe, MSD and Shionogi and a grant from Mitsubishi-Tanabe, outside the submitted work; TAF has a patent 2018-177688 (pending). ACi has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma. All the other authors report no competing interests to declare.

Ethical standards

This study does not require institutional review board approval and participant consent, because only group-level data and deidentified data were used.

Availability of data and materials

The data for evidence synthesis are openly available in https://github.com/y-luo06/cNMA_of_antidepressant. The prescription data used in this study are publicly available in the Medical Expenditure Panel Survey (MEPS), https://meps.ahrq.gov/mepsweb/.

Authors' contributions

YL and TAF designed the study. Regarding evidence synthesis, YO managed the original data, YL and ACh conducted statistical analyses, TAF and GS gave suggestions for analytical plans. YL and EGO extracted the guideline recommendations. YL conducted analysis for prescription data, and YK helped the analysis. YL, ES, EGO, ACi and TAF participated in interpretation of the results. YL drafted the manuscript and all authors critically

revised the manuscript and approved the final version. All authors gave final approval of the version to be published.

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Figures

Figure 1. **Three elements of the evidence-based medicine process and their relationship evaluated in the present study.** Rectangles indicate the three elements studied: a) cumulative evidence about drug effects, b) clinical practice guidelines, and c) prescription patterns. Bubbles indicate important factors which may influence the process, but we do not have accurate and sufficient data. Blue bubbles indicate factors we explored, though indirectly: we studied the impact of patent expiry year, safety warnings from the regulatory agency and compared the share of drugs marketed by the same company. Factors in grey bubbles are unobserved in this study.

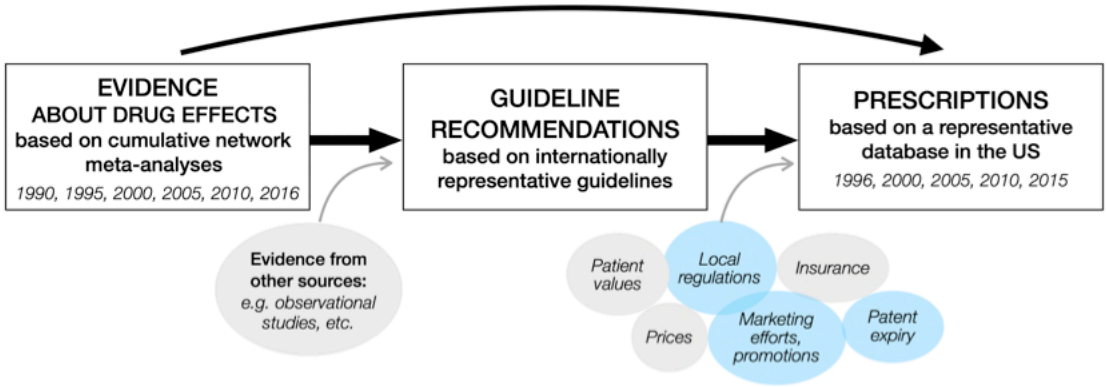

Figure 2. **Comparison between network meta-analyses and guideline recommendations in 2000 (A) and 2005 (B)**. Results are presented as ORs compared with *citalopram*. Efficacy is shown in x-axis, with ORs≥1 favoring the specific drug, while acceptability is shown in y-axis, with ORs≥1 favoring citalopram. Therefore, the drugs in the right upper corner should be better in both efficacy and acceptability.

The node for each drug is shown in terms of a pie chart, which indicates the composition of 4-level confidence of evidence among all comparisons with that drug, for both efficacy and acceptability. Green■: high, blue■: moderate, yellow■: low, and red■: very low confidence. The size of each node is proportionate to the inverse of the width of confidence interval regarding efficacy. *Bigger nodes indicate better precision in efficacy*.

Drug names labeled in *green* indicate that they were *commonly recommended by more than two guidelines* published *within 5 years* from the time of network meta-analyses. Names in *orange* indicate that they were recommended by *British Association for Psychopharmacology (BAP)* only (BAP-2000, BAP-2008), whereas those in *purple* indicate that they were recommended only by *American Psychiatric Association (APA)* (APA-2000, APA-2010). The ★ label indicates a *relatively new drug*.

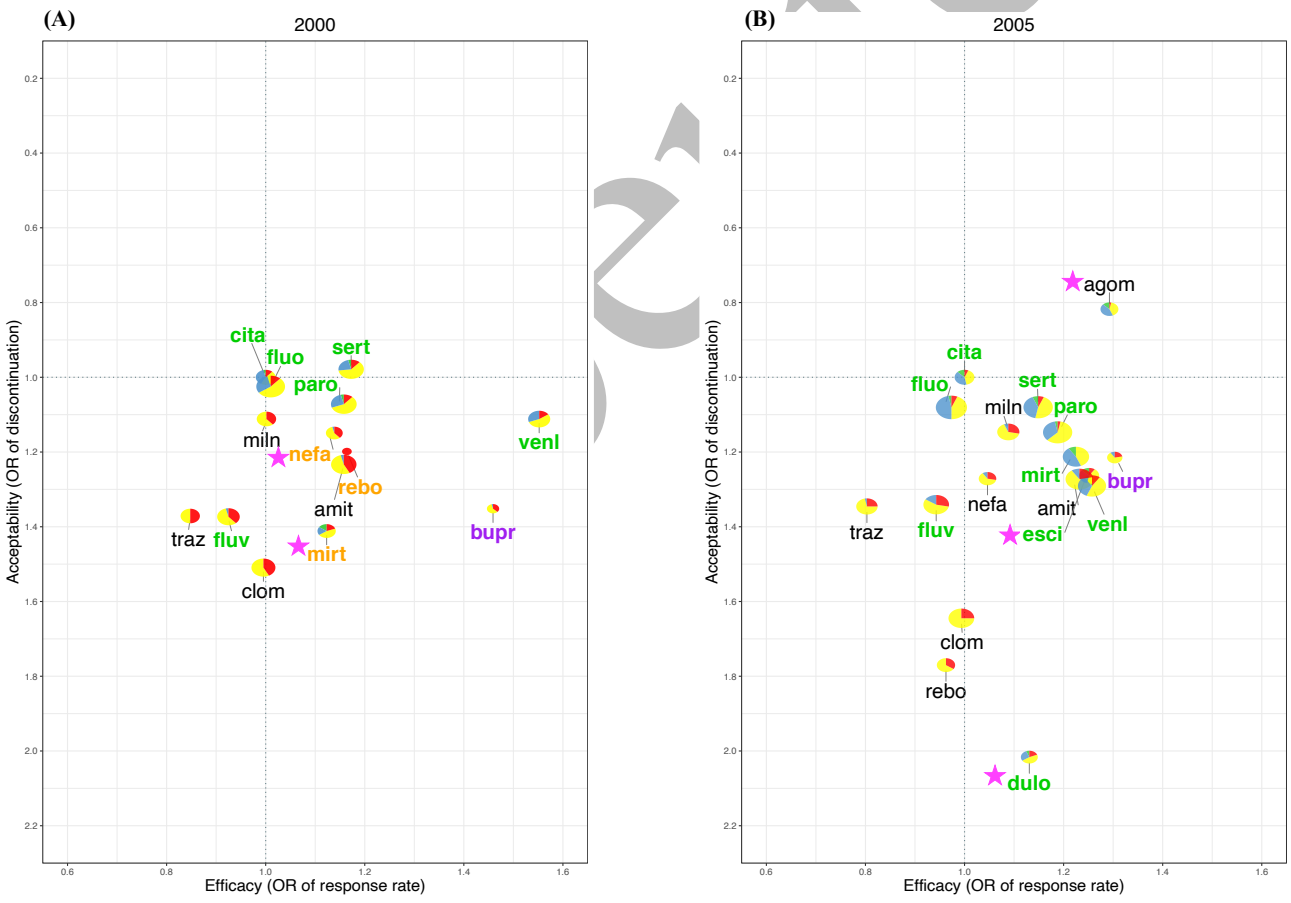

Figure 3. Prescriptions of the eight most frequently prescribed antidepressants (as monotherapy) **for major depression patients over the years** (proportions). Drugs whose branded products are marketed by the same company are labeled in the same color, one by a solid line and another a dotted line.

Circles mark the drug and the year when it was first recommended in the APA guideline. *Triangles* indicate the year of patent expiry for a specific drug. *Crosses* label the safety warning issued by FDA, locating the year and the drug. Note that FDA only published the warning of QT prolongation for citalopram, while the Medicines and Healthcare Products Regulatory Agency in the UK issued it for both citalopram and escitalopram. For all the labels, the color also matches the drug.

*Patent expiration of paroxetine (GSK): the patent was expired in 1999 in the EU and UK, while in the US, it was still protected (until 2006). However, since several generic companies attained abbreviated new drug application (ANDA) before 2006, legal actions were taken by GSK. In 2003, the US District Court of Illinois ruled that one generic version of paroxetine did not infringe GSK's original patent, and then the generic drug was launched in 2003. (Reference: Generic Depression: Can Paxil Avoid Prozac's Fate? Journal of Generic Medicines. 2004, 1(2), 181–184. https://doi.org/10.1057/palgrave.jgm.4940010)