

ORIGINAL ARTICLE

Antidepressant prescriptions have not fully reflected evolving evidence from cumulative network meta-analyses and guideline recommendations

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Accepted 17 December 2020; Published online 6 January 2021

Abstract

Objectives: 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 United States, regarding antidepressant treatments of major depression over the past 3 decades.

Study Design and Setting: We conducted network meta-analyses (NMAs) of antidepressants every 5 years up to 2016 based on a comprehensive data set of double-blind randomized controlled trials. We identified CPGs and extracted their recommendations. We surveyed the prescriptions in the United States at 5-year 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, whereas 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 United States were recommended by CPGs. However, changes in prescriptions did not correspond to alterations in CPGs or to apparent changes in the effects indicated by NMAs. Many factors including marketing efforts, regulations, or patient values may have played a role.

Conclusion: Enhancements including accelerating CPG updates and monitoring the impact of marketing on prescriptions should be considered in future EBM implementation. © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Evidence-based medicine; Network meta-analysis; Clinical practice guideline; Antidepressant

Funding: This study was supported in part by JSPS Grant-in-Aid for Scientific Research (Grant number 17k19808) to TAF and by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre (grant BRC-1215-20,005) to ACi and EGO. The funder has no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication.

Competing interests: T.A.F. reports personal fees from Mitsubishi-Tanabe, MSD, and Shionogi and a grant from Mitsubishi-Tanabe, outside the submitted work; T.A.F. has a patent 2018-177688 (pending). A.Ci. 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/>.

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<https://doi.org/10.1016/j.jclinepi.2020.12.023>

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What is new?

- 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 antidepressants.

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 because of 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 because of 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 the 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 3 decades (Fig. 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 United States, 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 (Fig. 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 data set included published and unpublished double-

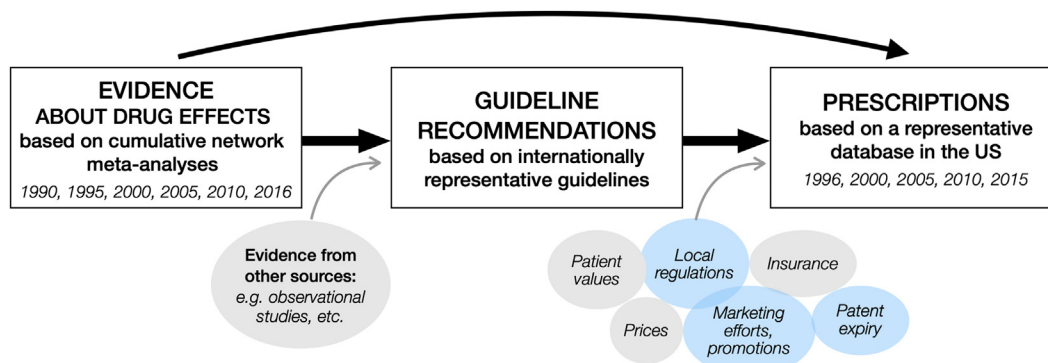


Fig. 1. Three elements of the evidence-based medicine process and their relationship evaluated in the present study. Rectangles indicate the three elements studied: a) cumulative evidence about drug effects, b) clinical practice guidelines, and c) prescription patterns. Bubbles indicate important factors which may influence the process, but we do not have accurate and sufficient data. Blue bubbles indicate factors we explored, although indirectly: we studied the impact of patent expiry year and safety warnings from the regulatory agency and compared the share of drugs marketed by the same company. Factors in gray bubbles are unobserved in this study. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

blind RCTs of new generation antidepressant treatment for adult patients (≥ 18 years old) with acute phase MDD [18]. The primary outcomes were as follows: efficacy (response rate, measured as the proportion of patients who achieved a reduction of at least 50% on any validated depression severity scales compared with 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 present study because having a placebo arm among the comparisons changed the nature of the trials [26,27].

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 1 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 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 the study by Luo et al.[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 (Y.L. and E.G.O.) 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 United States based on a population-representative database

The real-world prescription patterns were depicted based on the Medical Expenditure Panel Survey (MEPS) database in the United States [40]. Briefly, the MEPS comprises yearly large-scale surveys since 1996. A total of 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 patients with MDD being prescribed that antidepressant monotherapy among all the patients with MDD 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 the study by Luo et al.[23].

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

First, 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, 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.

Second, we compared CPGs and prescriptions in the United States. 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 (Fig. 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. Because 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 the 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. Although 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, whereas 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, although always as a drug category.

3.2. Comparison between cumulative NMA and CPG recommendations

As an illustration, Figure 2A compares the NMA as of 2000 with the recommendations in CPGs published between 2000 and 2005, whereas 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

Table 1. Summary of recommendations extracted from representative clinical practice guidelines

Date of publication	Organization	Country	Recommended drugs ^a			
			TCA	SSRI	SNRI	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	-	Trazodone 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	^b	-
2008	BAP	UK	-	SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Venlafaxine, duloxetine	Mirtazapine
2009	NICE	UK	-	SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	^b	-
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 ^c
2018 ^d	NICE	UK	-	SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	-	Mirtazapine

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.

^a 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 in accordance with that guideline's definition are presented.

^b NICE-2004 stated that *venlafaxine* was not appropriate in primary care because of safety concerns. In addition NICE-2009 stated that both *venlafaxine* and *duloxetine* might not be considered as an initial treatment because of safety issues.

^c BAP-2015 did not recommend *mirtazapine* explicitly in the main statements, but suggested it could be considered because of 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.

^d 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>).

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 with 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 because of concerns about tolerability. Bupropion was recommended only by APA because 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. In addition, unlike the positive attitude toward venlafaxine

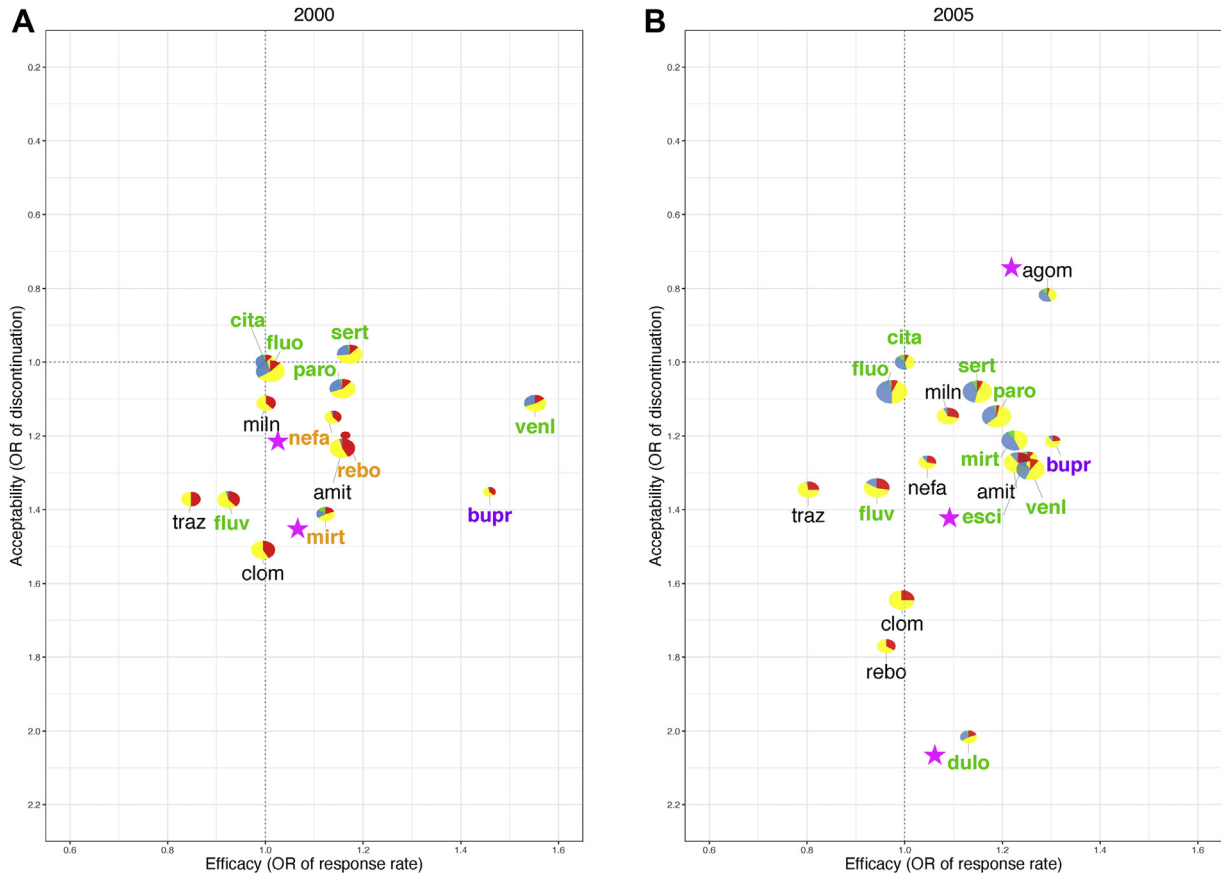


Fig. 2. Comparison between network meta-analyses and guideline recommendations in 2000 (A) and 2005 (B). Results are presented as ORs compared with *citalopram*. Efficacy is shown in x-axis, with ORs ≥ 1 favoring the specific drug, whereas acceptability is shown in y-axis, with ORs ≥ 1 favoring *citalopram*. 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. ORs, odds ratios. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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 eFigure 1 in 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 because it recommended agomelatine and vortioxetine in 2015 while other contemporary CPGs did not.

3.3. Comparison between CPG recommendations and prescriptions

Figure 3 shows the prescription patterns of eight most frequently prescribed antidepressants as monotherapy in

treating MDD in the United States during the past 20 years. eFigure 2 in Appendix 2.2 (p.9) shows it for all available drugs. Because 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, because of 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

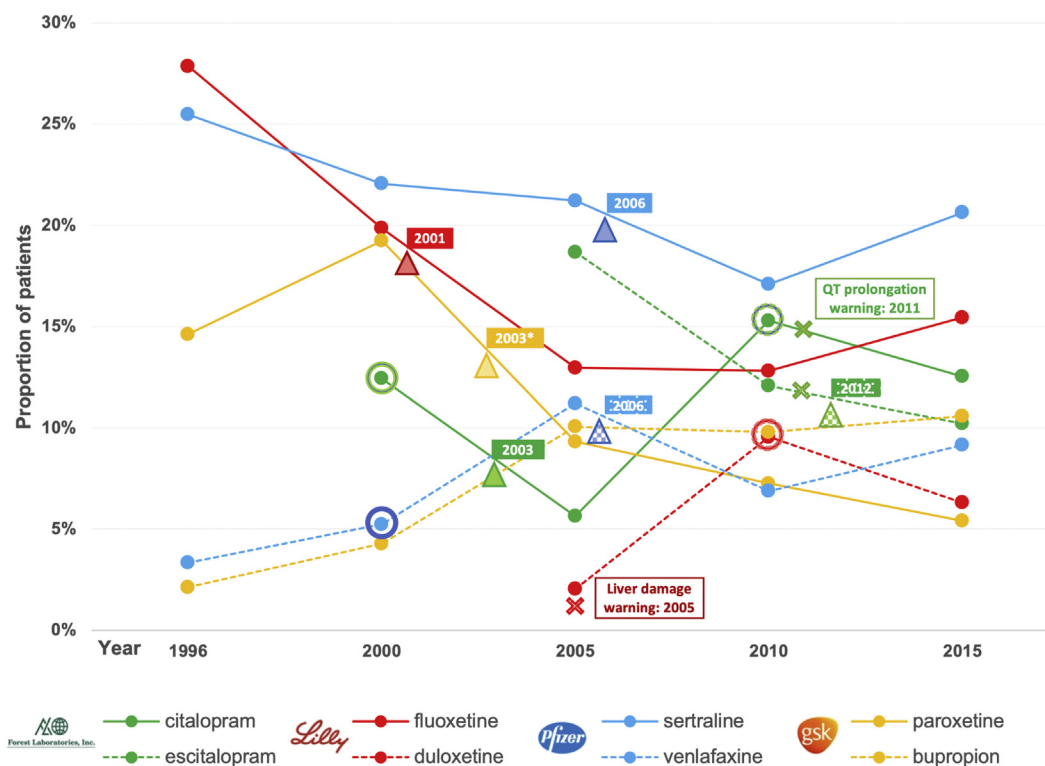


Fig. 3. Prescriptions of the eight most frequently prescribed antidepressants (as monotherapy) for patients with major depression over the years (proportions). Drugs whose branded products are marketed by the same company are labeled in the same color, one by a solid line and another by a dotted line. *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, whereas 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, whereas in the United States, it was still protected (until 2006). However, because 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.) (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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 the 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 the 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 (Fig. 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 on 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 CPGs were developed based on valid methodology, using NMA conducted on a comprehensive data set 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 indicate a rapid change in evidence, implying that CPGs may need to speed up their updates to catch up with evidence. Recently, living SRs, 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 used 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 United States, 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 interplay between side effect profiles and unique cultural values. It was recommended by APA, although 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 the correlation test need assumptions and thus may lose clinical relevancy. Because of 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 with this ideal evidence helps 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, because of 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 patients with MDD over the past 3 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.

Acknowledgments

A.Ci. and E.G.O. are supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility, and A.Ci. is also supported by an NIHR Research Professorship (grant RP-2017-08-ST2-006) and by the NIHR Oxford and Thames Valley Applied Research Collaboration. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the UK Department of Health. G.S. has received funding from the Swiss National Science Foundation (Grant no. 179158).

The analysis regarding the prescription pattern in this article was conducted at the CFACT Data Center, and the support of AHRQ is acknowledged. The results and conclusions in this article are those of the authors and do not indicate concurrence by AHRQ or the Department of Health and Human Services.

Authors' contributions: Y.L. and T.A.F. designed the study. Regarding evidence synthesis, Y.O. managed the original data, Y.L. and A.Ch. conducted statistical analyses, and T.A.F. and G.S. gave suggestions for analytical plans. Y.L. and E.G.O. extracted the guideline recommendations. Y.L. conducted analysis for prescription data, and Y.K. helped for the analysis. Y.L., E.S., E.G.O., A.Ci., and T.A.F. participated in interpretation of the results. Y.L. 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.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinepi.2020.12.023>.

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