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論文題目	Evidence Synthesis, Practice Guidelines and Real-World Prescriptions of New Generation Antidepressants in the Treatment of Major Depressive Disorder: A Meta-epidemiological Study (大うつ病に対する第2世代抗うつ薬に関するエビデンス統合と診療ガイドラインと実際の処方の比較研究)		
(論文内容の要旨)			
<p>Background: Evidence-based medicine (EBM) is widely considered the guiding principle in today's clinical practice. However, gaps may exist in evidence synthesis and implementation process. Evidence synthesis may not have been conducted in an unbiased and timely manner; 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.</p> <p>Objectives: The study aims to present the evolution in three major elements in the process of practicing EBM, namely evidence synthesis, clinical practice guideline (CPG) recommendations and real-world clinical practice, and to describe their concordance or discordance, regarding the prescription of new generation antidepressants for major depressive disorder (MDD) through the past three decades.</p> <p>Methods: First, cumulative network meta-analyses (NMAs) based on a comprehensive dataset of double-blind randomized controlled trials (RCTs) of the acute phase antidepressant treatment for MDD were conducted to represent ideally synthesized evidence over the years (up to 2016). The primary outcomes of the NMAs were efficacy (treatment response) and acceptability (all-cause discontinuation). The confidence in evidence was assessed using the CINeMA (Confidence in Network Meta-Analysis) framework. A Shiny web application was built to perform and present NMAs interactively. Second, recommendations from several representative practice guidelines published from 1990 until 2018 regarding the antidepressant treatment of MDD were extracted. Next, the real-world prescription patterns of antidepressant monotherapy for MDD were estimated every 5 years from 1990 to 2015, using the Medical Expenditure Panel Survey, a nationally representative database in the US. Finally, the evidence based on cumulative NMAs, the CPG recommendations, and the prescription patterns were compared, in order to find possible discrepancies. Potential reasons and factors that may cause deviations, such as patent expiry, local regulations, and marketing efforts, were also investigated.</p> <p>Results: Evidence evolution based on cumulative NMAs was shown on the Shiny web, indicating a dramatic change of drugs with relative superiority, and the potentially exaggerated performance of newly approved drugs. CPGs developed by different groups had unique features, and most of them based recommendations primarily on published RCTs and their pairwise meta-analyses. In general, the development of the CPGs followed a rigorously reported methodology which improved over time. The prescription data suggested that sertraline and fluoxetine were among the most frequently prescribed antidepressants throughout the 20 years in the US, while the trend for some new drugs changed dramatically. Comparison between the three elements indicated that most of the drugs recommended by CPGs presented relatively superior performance in efficacy and acceptability with moderate confidence in the evidence. However, the CPG recommendations were</p>			

<p>often in terms of drug classes rather than particular drugs and the update intervals of all CPGs were longer than 5 years, thus lagging behind the most up-to-date evidence. 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 cumulative NMAs. For example, escitalopram achieved large prescription volume before formal recommendation, but then gradually lost its market share after being recommended. Many factors including marketing efforts, regulations or patient values may play a role.</p> <p>Conclusions: The study provides an overview of how accumulating evidence may have influenced CPG recommendations and led to real-world prescriptions regarding antidepressant treatment of MDD in the past three decades. Though CPGs appeared to reflect the evidence, enhancements including accelerating CPG updates, monitoring the impact of marketing on prescriptions, and educating clinicians to actively seek evidence in order to avoid excessive influence from the pharmaceutical companies, should be considered in future EBM implementation.</p>			
<p>(論文審査の結果の要旨)</p> <p>本研究は、大うつ病に対する抗うつ薬治療に関して、過去30年間にわたりエビデンスに基づく医療（EBM）がどのように実践されてきたかを研究し、EBMの改善すべき方向性を明らかにするメタ疫学研究である。</p> <p>まず21種の抗うつ薬の臨床試験を網羅的に収集したデータセットに基づき、累積ネットワークメタ解析を実施し、薬の効果に関するエビデンスの経年変化を示した。次に大うつ病について世界の代表的な診療ガイドラインを選び、治療の推奨の変遷をレビューした。最後に、米国の国民を代表するデータベースを使い抗うつ薬のリアルワールドでの処方を経年的に推定した。</p> <p>エビデンス・診療ガイドライン・実際の処方を比較した結果、エビデンスが時代とともに変化していた。ガイドラインの推奨はエビデンスから大きな乖離がないが、エビデンス更新の速度に追いついていない懸念があった。実際の処方には複数の因子が関与し、うち製薬会社のマーケティング戦略の影響が大きいことが明らかとなった。よって、今後のEBMの実践においては、有力なエビデンス統合手法によりエビデンスを構築し、ガイドラインを効率的に更新し、さらにマーケティングの診療への影響をモニタリングする必要があると示唆された。</p> <p>以上の研究は、EBMの実世界での実践過程を系統的に検討する世界初の研究であり、医療の原則となるEBMに関する今後の改善点を示し、より良質な医療を提供することに重要な糸口となる。</p> <p>したがって、本論文は博士（医学）の学位論文として価値あるものと認める。</p> <p>なお、本学位授与申請者は、令和3年10月18日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。</p>			
<p>要旨公開可能日： 年 月 日 以降</p>			