A systematic review and meta-analysis on impact of suboptimal use of antidepressants, bisphosphonates, and statins on healthcare resource utilisation and healthcare cost

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Abstract

Background
Depression, osteoporosis, and cardiovascular disease impose a heavy economic burden on society. Understanding economic impacts of suboptimal use of medication due to nonadherence and non-persistence (non-MAP) for these conditions is important for clinical practice and health policy-making.

Objective
This systematic literature review aims to assess the impact of non-MAP to antidepressants, bisphosphonates and statins on healthcare resource utilisation and healthcare cost (HRUHC), and to assess how these impacts differ across medication classes.

Methods
A systematic literature review and an aggregate meta-analysis were performed. Using the search protocol developed, PubMed, Cochrane Library, ClinicalTrials.gov, JSTOR and EconLit were searched for articles that explored the relationship between non-MAP and HRUHC (i.e., use of hospital, visit to healthcare service providers other than hospital, and healthcare cost components including medical cost and pharmacy cost) published from November 2004 to April 2021. Inverse-variance meta-analysis was used to assess the relationship between non-MAP and HRUHC when reported for at least two different populations.

Results
Screening 1,123 articles left 10, seven and 13 articles on antidepressants, bisphosphonates, and statins, respectively. Of those, 27 were rated of good quality, three fair and none poor using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. In general, non-MAP was positively associated with HRUHC for all three...
medication classes and most prominently for bisphosphonates, although the relationships differed across HRUHC components and medication classes. The meta-analysis found that non-MAP was associated with increased hospital cost (26%, \( p = 0.02 \)), outpatient cost (10%, \( p = 0.01 \)), and total medical cost excluding pharmacy cost (12%, \( p < 0.00001 \)) for antidepressants, and increased total healthcare cost (3%, \( p = 0.07 \)) for bisphosphonates.

Conclusions

This systematic literature review is the first to compare the impact of non-MAP on HRUHC across medications for three prevalent conditions, depression, osteoporosis and cardiovascular disease. Positive relationships between non-MAP and HRUHC highlight inefficiencies within the healthcare system related to non-MAP, suggesting a need to reduce non-MAP in a cost-effective way.

Introduction

Poor medication adherence or persistence (MAP) is related to increased morbidity and mortality [1–4] and greater healthcare resource utilisation and healthcare cost (HRUHC) [5–7]. Interventions to improve MAP are reported to give positive effects on morbidity, HRUHC and patient satisfaction [8, 9].

Suboptimal use of medication due to nonadherence and non-persistence (non-MAP) is prevalent in chronic conditions [10–12] because a long-term therapy is often interrupted by undesirable medication use, including erratic use, under-use and premature discontinuation of therapy. The prevalence of non-MAP across all chronic conditions has been estimated at approximately 50% by the World Health Organisation [10]. The annual cost of non-MAP to the US healthcare system has been estimated at between USD 100 billion and USD 289 billion [11, 13, 14].

Depression, osteoporosis, and cardiovascular disease (CVD) are among the most prevalent conditions in developed countries [15–17] and impose a large health and economic burden on society [18–21]. For example, in the US, the total annual economic burden of major depressive disorder was estimated at $210 billion [20]; total annual healthcare spending associated with osteoporosis fractures among Medicare beneficiaries at $57 billion [22]; and total annual healthcare system cost for heart disease or stroke at $214 billion [23]. In 2015 in Australia, the three disease groups, CVD, musculoskeletal conditions and mental and substance use disorders, accounted for around 39% of the total burden of disease as measured using disability-adjusted life year (DALY) [21]. Although MAP for these conditions is important in achieving clinical goals [16, 24, 25], reported MAP is relatively low [16, 26, 27].

Antidepressants, bisphosphonates, and statins are medications used for the chronic conditions depression, osteoporosis, and CVD, respectively. Antidepressants aim to correct chemical imbalances of neurotransmitters in the brain responsible for changes in mood and behaviour, bisphosphonates are used to prevent loss of bone density, and statins are used to lower cholesterol. While the minimum recommended length of antidepressant and bisphosphonate therapy is six months [24, 28] and three to five years [29], respectively, discontinuation of statins is generally not recommended [30].

Understanding how and to what extent non-MAP impacts health outcomes, leads to premature death, and exhausts valuable healthcare resources is important for improving clinical practice, developing health policies and prioritising research. Awareness of MAP patterns can
help clinicians improve clinical practice and better manage health outcomes by regularly checking MAP, identifying reasons for non-MAP, and implementing interventions to improve MAP including better patient and clinician communication and shared decision making, better support from other health system stakeholders such as community care nurses, better medication packaging, and patient education. More accurate and informative MAP measures enable healthcare policymakers to better evaluate costs and benefits of MAP policies and interventions. In addition, better understanding of the link between MAP and HRUHC provides insights into prioritisation of future research.

This systematic literature review and meta-analysis aims to provide a comprehensive summary of the impact of non-MAP to three medication classes, antidepressants, bisphosphonates and statins, on HRUHC as measured by hospitalisation, emergency department (ED) presentation, visit to other healthcare service providers, healthcare cost and pharmacy cost. Evaluation of the three different medication classes under one systematic literature review permits understanding of whether different medication classes used with different patterns have different impacts on HRUHC using the same evaluation criteria.

Methods

This review was conducted in accordance with a protocol (see dx.doi.org/10.17504/protocols.io.b4m4qu8w) developed using the process recommended by the Centre for Reviews and Dissemination [31] and written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [32]. The abstraction and analysis of data were conducted by the first author based on the methods developed by all authors, and reviewed by all authors.

Selection criteria

The scope of the systematic review was studies assessing the impact of non-MAP on HRUHC in antidepressants, bisphosphonates or statins. There was no restriction on the definition of MAP while HRUHC for the review included use of hospital, visit to healthcare service providers other than hospital, and healthcare cost components including medical cost and pharmacy cost. Studies were required to address the distinct impact of MAP to one of the three classes of medications on HRUHC, to be peer-reviewed, to be available as full articles, to be written in English, and to include quantitative analysis of the impact. The eligibility criteria are summarised in Table 1.

Search strategy

We used five search engines or registries: PubMed, Cochrane Library, ClinicalTrials.gov, JSTOR and EconLit. The period over which the search was conducted was 1 November 2004 to 30 April 2021. The period was set to achieve a balance between the number of studies included and focusing on a more recent period to ensure relevance of the findings. The search strategy was developed based on preliminary reviews of literature aiming at comprehensively including internationally used terminologies. Subsequent reviews of reference lists were conducted using the snowballing technique [33] to identify additional publications. The search strategy used with PubMed and Cochrane Library is displayed by item 38 in Table 2. For ClinicalTrials.gov, JSTOR and EconLit, due to the restriction on the length or form of search terms, we broadened our search specification to find studies having keywords (in their abstract for JSTOR and EconLit) showing the names of medications including statin, antidepressant, bisphosphonate or disphosphonate, and MAP or non-MAP using several words including adherence, compliance, nonadherence, noncompliance or persistence.
After removing duplicates, abstracts were screened to arrive at the eligible or possibly eligi-
ble studies for a full-text review. The full-text review was conducted to exclude articles not
meeting the eligibility criteria, and to extract data.

Data extraction
Extracted information for the review includes authors, country, year of publication, study type
(e.g., retrospective cohort study), medications studied, data period, characteristics of cohort,
statistical method of analysis, measure of MAP, reported MAP of cohort, and summary of
impact of non-MAP on HRUHC. In cases where both adjusted estimates (incorporating
covariates) and unadjusted estimates (not incorporating covariates) for the relationship
between MAP and HRUHC were reported, we summarise the adjusted estimates only because
the inclusion of covariates facilitates meaningful interpretation and comparison. We report
statistically significant or insignificant coefficients showing the relationships between MAP
and HRUHC rather than absolute amounts of change in HRUHC where possible. This is to
account for different baseline levels of HRUHC and different contexts (e.g., time frame, coun-
try). Other supporting information (e.g., covariates, reported conflicts of interest) was also col-
lected to support quality assessments.

Quality criteria
Quality of study and risk of bias were evaluated using the Quality Assessment Tool for
Observational Cohort and Cross-Sectional Studies [34]. This tool is used to assess the qual-
ity of observational cohort or cross-sectional studies [e.g., 35, 36] and was considered
appropriate for the review because all included studies were observational cohort studies.
The tool rates a study quality as good, fair or poor based on 14 questions about study objec-
tives, sample selection, definition and use of exposure and outcome, analysis method and
risk of bias.

Aggregate data meta-analysis
A meta-analysis was conducted for a certain relationship between MAP and HRUHC when
reported for at least two different cohorts of population. Note that “different cohorts” here
refers to both cohorts in different studies and different cohorts within a single study. For mul-
tiple results to be synthesised, the measure of MAP (e.g., adherence defined by amount of

Table 1. Selection criteria.

| Language | English |
|----------|---------|
| Publication | Peer-reviewed, full articles |
| Type of study | Review, correspondence (i.e., letters), editorial, expert opinion, discussion or commentary |
| Year | From November 2004 to April 2021 |
| Method | Quantitative analysis showing direct and clear impact of MAP on HRUHC * |
| Exposure measure | MAP to antidepressants, statins or bisphosphonates (either as a whole class of medication or as any individual medication from each class) |
| Outcome measure | Combined MAP to multiple medications including a medication of interest |
| Use of hospital; visits to other healthcare service providers; or healthcare cost components (e.g., medical cost, pharmacy cost) |

HRUHC = healthcare resource utilisation and healthcare cost; and MAP = medication adherence or persistence
a. The term, “direct and clear impact” is used to highlight that we exclude studies in which the impact of MAP on HRUHC can be implied from an analysis that does not measure the impact. For example, we exclude a study that describes MAP characteristics of a treatment group and measures the impact of the treatment on HRUHC.

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medication used relative to total amount recommended greater than 80% over six months) was required to be comparable in terms of the length of measuring period and which aspect of MAP is measured (e.g., adherence, adherence rate, persistence). In addition, medication class (e.g., antidepressants) and type of HRUHC (e.g., hospitalisation cost) were required to be the same. When the requirements were met, the combined result was estimated using the inverse-variance method which allocates each study a weight equal to the inverse of the variance of the

| Table 2. Search strategy. |
|---------------------------|
| 1. Medication Adherence (as MeSH Terms) |
| 2. Patient Compliance (as MeSH Terms) |
| 3. non-adherence (in either title or abstract) |
| 4. Drug Therapy (as MeSH Terms) |
| 5. medication (in either title or abstract) |
| 6. (2 OR 3) AND (4 OR 5) |
| 7. 1 OR 6 |
| 8. hmg coa statins (as MeSH Terms) |
| 9. antidepressants (as MeSH Terms) |
| 10. bisphosphonates (as MeSH Terms) |
| 11. 8 OR 9 OR 10 |
| 12. Hospitalizations (as MeSH Terms) |
| 13. hospital’ (in either title or abstract) |
| 14. Emergency Departments (as MeSH Terms) |
| 15. emergency (in either title or abstract) |
| 16. Practice, General (as MeSH Terms) |
| 17. general practice” (in either title or abstract) |
| 18. gp (in either title or abstract) |
| 19. primary care (in either title or abstract) |
| 20. visit” (in either title or abstract) |
| 21. Costs and Cost Analysis (as MeSH Terms) |
| 22. cost (in either title or abstract) |
| 23. costs (in either title or abstract) |
| 24. burden” (in either title or abstract) |
| 25. accident and emergency (in either title or abstract) |
| 26. A&E (in either title or abstract) |
| 27. emergencies (in either title or abstract) |
| 28. urgent medical aid service (in either title or abstract) |
| 29. casualty department” (in either title or abstract) |
| 30. secondary care (in either title or abstract) |
| 31. specialist” (in either title or abstract) |
| 32. outpatient’ (in either title or abstract) |
| 33. day patient” (in either title or abstract) |
| 34. medical consultation” (in either title or abstract) |
| 35. resource use” (in either title or abstract) |
| 36. physician” (in either title or abstract) |
| 37. 12 OR 13 OR …… OR 36 |
| 38. 7 AND 11 AND 37 |

MeSH = Medical Subject Headings
Note: Asterisks were used to include plurals.

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effect estimate \[37\], i.e. 

\[
\text{inverse \text{–} variance weighted average} = \frac{\sum Y_i (1/SE_i^2)}{\sum (1/SE_i^2)}
\]

where \(Y_i\) is the effect estimated in the \(i\)th study, \(SE_i\) is the standard error of the estimate, and the summation is across all studies. When the standard error was not reported, it was approximated from the confidence interval or \(p\)-value \[38\]. Analysis was implemented using RevMan v5.4 \[39\].

**Results**

**Study selection**

As shown by the PRISMA flow diagram in Fig 1, the initial search, abstract screening and full-text review have left 30 articles for the review. The characteristics of individual studies on antidepressants, bisphosphonates and statins are summarised in Tables 3–5, respectively. Study findings of the impacts of MAP to antidepressants, bisphosphonates and statins on several different types of HRUHC are summarised in Tables 6–8, respectively. A summary of the directions of the impact of MAP on HRUHC based on the study findings is presented in Table 9.

**Quality assessment**

We used the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies \[34\] to assign each study a grade of either good, fair or poor. Of the 30 studies, 27 achieved a good rating while three studies achieved a fair rating primarily due to not reporting detailed statistical results for the total healthcare cost including pharmacy costs \[40\], not reporting detailed statistical results for hospitalisations and outpatient visits \[41\], and not reporting clear definitions of MAP and HRUHC measures \[42\]. The assessments are summarised in Table 10.

**Descriptive results**

**Study characteristics.** *Antidepressants.* Ten studies reviewed considered the impact of MAP to antidepressants on HRUHC. These were all retrospective cohort studies using health research or claims database. Eight studies were conducted in the US. The studies were conducted with the data covering 3.6 years on average with standard deviation (SD) of 1.3 years, between 1999 and 2014. Three studies \[43–45\] were on all classes of antidepressants, two studies \[46, 47\] were on all selective serotonin reuptake inhibitors (SSRIs) medications, and other studies were on selected classes of antidepressants.

Seven studies broke down the examination period into three periods, commonly used in MAP research. The three periods are the baseline period in which patient characteristics are measured, the MAP period in which MAP is measured, and the follow-up period in which outcomes are measured. While lengths of each period are the same for each individual within a study, the date at which each period starts or ends depended on an individual date for the start of therapy, or index, which is screened in a pre-specified index period.

Cohort sizes ranged from 1,361 to 79,642 with an average of 31,659 (SD 25,382). All studies included both genders. Most studies targeted adult patients aged at least 18 years while one study was without age restriction \[45\], one study was for seniors aged 66 years or greater \[48\], and one study was for working-age patients aged between 16 and 65 \[47\]. Seven studies targeted patients with depression, and three other studies targeted patients with specified diseases other than depression but taking antidepressants: type-2 diabetes \[44\]; coronary artery disease, dyslipidaemia or diabetes \[49\]; and chronic obstructive pulmonary disease \[45\].
Bisphosphonates. Seven studies reviewed considered the impact of MAP to bisphosphonates on HRUHC: all were retrospective cohort studies using health research or claims database. Four studies were conducted in the US. The studies were conducted with the data covering 8.0 years on average (SD 1.8 years), between 1999 and 2013. Five studies broke down the examination period into baseline, MAP, and follow-up period. All studies considered alendronate and risedronate either exclusively [41, 50, 51] or as part of a wider medication range. Cohort sizes ranged between 17,770 and 38,234 with an average of 29,544 (SD 7,974). Most studies targeted female patients except two studies that considered both male and female [50, 52]. All studies set a minimum age to be included in the study cohort, the most common being 55 years [51–
| Paper                  | Country | Study type                          | Medication                                                                                                                                   | Data period and breakdown of the period                        | Size, age and gender of cohort | Description of cohort                                      |
|-----------------------|---------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------|-----------------------------------------------------------|
| Eaddy et al. (2005)   | US      | Retrospective cross-sectional using health research/ claims database | All SSRI medications including citalopram, fluoxetine, paroxetine immediate-release, paroxetine controlled-release, and sertraline | Data period: Jan 2001—Jun 2003. Index period: Jun 2001—Jun 2002 Baseline period: 6 months to index MAP and follow-up period: 12 months from index | 56,753                       | Patients diagnosed with depression and newly prescribed SSRIs |
| Katon et al. (2005)   | US      | Retrospective cross-sectional using health research/ claims database | Bupropion hydrochloride, bupropion hydrochloride sustained-release, citalopram hydrobromide, escitalopram oxalate, fluoxetine hydrochloride, mirtazapine, nefazodone hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride controlled release, sertraline hydrochloride, venlafaxine hydrochloride, and venlafaxine hydrochloride extended-release | Data period: 2001–2003 Index period: Jul 2001—Dec 2002 Baseline period: 6 months to index MAP period: 6 months from index Follow-up period: 12 months from index | 8,040                        | Coronary artery disease, dyslipidaemia or diabetes patients newly prescribed antidepressants |
| Cantrell et al. (2006)| US      | Retrospective cohort using health research/ claims database | SSRIs including fluoxetine, sertraline, citalopram, escitalopram, paroxetine immediate-release, and paroxetine controlled-release | Data period: Jan 2001—Jun 2003 Index period: Jul 2001—Jun 2002 Baseline period: 6 months to index MAP period: 6 months from index Follow-up period: 1 year from index | 22,947                       | Patients diagnosed with depression and newly prescribed SSRIs |
| Robinson et al. (2006)| US      | Retrospective cohort using health research/ claims database | All classes of antidepressants                                                                                                               | Data period: Jan 2001—Sep 2004 Follow-up period: 6 months from index | 60,386                       | Patients newly diagnosed with depression and prescribed antidepressants |
| Stein et al. (2006)   | US      | Retrospective cohort using health research/ claims database | Venlafaxine, venlafaxine extended-release, fluoxetine, sertraline, paroxetine, paroxetine controlled-release, citalopram, escitalopram, and fluvoxamine | Data period: 2001–2003 Index period: Jul 2001—Dec 2002 Baseline period: 6 months to index MAP and follow-up period: 12 months from index | 13,085                       | Patients prescribed antidepressants and newly diagnosed with anxiety or anxiety and comorbid depression |
| Tournier et al. (2009)| Canada  | Retrospective cohort using health research/ claims database | Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, nefazodone, trazodone, and venlafaxine | Data period: 1999–2001 Index period: 2000 Baseline period: 1 year to index MAP period: 180 days from index Follow-up period: 1 year from index | 12,825                       | Patients newly prescribed antidepressants                 |

(Continued)
There were 13 studies reviewed that considered the impact of MAP to statins on HRUHC. These studies were retrospective cohort studies using health research or claims data except for a prospective observational study, a longitudinal study using a survey, and a secondary analysis using a randomised clinical trial. Ten studies were conducted in the US. The studies were conducted with data covering 4.3 years on average (SD 2.6 years) between 1997 and 2015. Four studies divided the examination period into baseline, MAP and follow-up period.

Five studies were on all classes of statins, three studies were on selected classes of statins, and five studies were on several medications including statins. All studies were conducted with relatively large cohort sizes of over 500 individuals (between 682 and 381,422), except Cheng, Chan, which included 83 individuals. The average sample size was 44,744 (SD 101,804). Five studies targeted all adult patients and four did not specify an age range, while other studies were on different age ranges, as seen in Table 5. Six studies were for patients with baseline diseases including osteoporosis.

53. No studies limited the cohort to those with specific underlying diseases other than osteoporosis.

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| Paper               | Country | Study type                                      | Medication                                      | Data period and breakdown of the period | Size, age and gender of cohort | Description of cohort                                                                 |
|---------------------|---------|------------------------------------------------|------------------------------------------------|----------------------------------------|--------------------------------|--------------------------------------------------------------------------------------|
| Ereshefsky et al.  | US      | Retrospective cohort using health research/   | Citalopram, escitalopram, fluoxetine,           | Data period: Jan 2002 – Jun 2006        | 45,481                         | Patients newly diagnosed with depression and prescribed antidepressants             |
| et al. [66]         |         | claims database                                 | paroxetine, and sertraline                     | Index period: 2003–2004                 |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Baseline period: 12 months to index    |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | MAP period: 6 months to index          | 18+, All                       |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Follow-up period: 18 months from index |                                |--------------------------------------------------------------------------------------|
| Albrecht et al.     | US      | Retrospective cohort using health research/   | All classes of antidepressants                  | Data period: 2006–2012                  | 16,075                         | Patients diagnosed with depression and chronic obstructive pulmonary disease         |
| (2017) [45]         |         | claims database                                 |                                                 | Index period: Jul 2012—Jun 2013       |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Baseline period: 6 months to index    | 18+, All                       |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | MAP period: 180 days from index        |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Follow-up period: 12 months from end of |                                |--------------------------------------------------------------------------------------|
| Vega et al.         | US      | Retrospective cohort using health research/   | All classes of antidepressants                  | Data period: Jan 2012—Jun 2014         | 1,361                          | Type-2 diabetes patients newly diagnosed with major depression                       |
| et al. (2017) [44]  |         | claims database                                 |                                                 | Index period: Jul 2012—Jun 2013       |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Baseline period: 6 months to index    | 18+, All                       |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | MAP period: 180 days from index        |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Follow-up period: 12 months from end of |                                |--------------------------------------------------------------------------------------|
| Aznar-Lou et al.    | Spain   | Longitudinal retrospective cohort study using  | All SSRI medications                            | Data period: 2011–2014                  | 79,642                         | Patients newly prescribed SSRI and diagnosed with depressive disorder                |
| (2018) [47]         |         | health research/ claims database                |                                                 | Index period: 2011–2014                |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Baseline period: 6 months to index    |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | MAP period: 180 days from index        |                                |--------------------------------------------------------------------------------------|
|                     |         |                                                 |                                                 | Follow-up period: 12 months from end of |                                |--------------------------------------------------------------------------------------|

SSRI = selective serotonin reuptake inhibitor

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diabetes [42, 58, 63], coronary heart disease [54], and acute myocardial infarction [55, 65]; the remaining studies were for any patients newly prescribed statins.

Medication adherence or persistence. Antidepressants. While various methods were used to measure MAP to antidepressants, the most common measure was persistence, defined as the duration of time from initiation to discontinuation of therapy. Five studies used it as a single method [48, 66], as one of several methods [40, 44], or in combination with another method. Table 4. Characteristics of reviewed studies on bisphosphonates.

| Paper            | Country | Study type                                      | Medication                                      | Data period and breakdown of the period | Sample size | Age and gender of cohort | Description of cohort                                                                 |
|------------------|---------|------------------------------------------------|------------------------------------------------|----------------------------------------|-------------|--------------------------|--------------------------------------------------------------------------------------|
| Briesacher et al. (2007) [50] | US      | Retrospective cohort using health research/claims database | Alendronate, and risedronate                    | Data period: 2000–2004 Baseline period: 1 year to index MAP and follow-up period: 31 Dec 2004 from index | 17,988      | 40+, All                | Patients diagnosed with osteoporosis and newly prescribed bisphosphonates          |
| Sunnyecz et al. (2008) [41]   | US      | Retrospective cohort using health research/claims database | Alendronate, and risedronate                    | Data period: Jan 1999—Jun 2005 Index period: Jan 2000—Jun 2002 Baseline period: 1 year to index MAP and follow-up period: 3 or more years from index | 32,944      | 45+, Female             | Patients newly prescribed bisphosphonates                                          |
| Eisenberg et al. (2015) [52]  | US      | Retrospective cohort using health research/claims database | Alendronate, risedronate, and ibandronate      | Data period: Jan 2006—Sep 2012 Index period: Jan 2007—Sep 2010 Baseline period: 1 year to index MAP period: 1 year from end of MAP period Follow-up period: 1 year from end of MAP period | 27,905      | 55+, All                | Patients diagnosed with osteoporosis and prescribed bisphosphonates               |
| LaFleur et al. (2015) [70]    | US      | Retrospective cohort using health research/claims database | Oral alendronate, oral or injectable ibandronate, oral risedronate, and injectable zoledronic acid | Data period: Jan 2003—Dec 2011 | 35,650      | 50+, Female             | Veterans newly or continually prescribed bisphosphonates                            |
| Ferguson et al. (2016) [49]   | UK      | Retrospective cohort using health research/claims database | Alendronate, risedronate, ibandronate, and etidronate | Data period: 1999–2008 Index period: 2000–2007 | 36,320      | 50+, Female             | Patients diagnosed with postmenopausal osteoporosis and newly prescribed bisphosphonates |
| Kjellberg et al. (2016) [53]  | Denmark | Retrospective cohort using health research/claims database | Alendronate, risedronate, and ibandronate      | Data period: 2002–2010 Index period: 2003–2008 Baseline period: 1 year to index MAP period: 1 year from index Follow-up period: 1 year from end of MAP period | 38,234      | 55+, Female             | Patients newly prescribed bisphosphonates                                          |
| Sharman Moser et al. (2016) [51] | Israel | Retrospective cohort using health research/claims database | Alendronate, and risedronate                    | Data period: 2004–2013 Index period: 2005–2011 Baseline period: 1 year to index MAP period: 1 year from index Follow-up period: 1 year from end of MAP period | 17,770      | 55+, Female             | Patients newly prescribed bisphosphonates                                          |

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| Paper                  | Country     | Study type                                      | Medication                                      | Data period and breakdown of the period         | Size, age and gender of cohort | Description of cohort                                                                 |
|------------------------|-------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------|
| Cheng et al. (2006)    | Hong Kong   | Prospective observational cohort study         | Simvastatin and atorvastatin                    | Index period: Jan 2003—Jun 2003                  | 83                            | Coronary heart disease patients prescribed statins for less than 12 months           |
|                        |             |                                                |                                                | MAP and follow-up period: Jul 2003—Dec 2003     | 18+, All                       |                                                                                      |
| Gibson et al. (2006)   | US          | Retrospective cohort using health research/claims database | All classes of statins                          | Data period: 2000–2003                         | 117,366                       | New or incident, continuing or prevalent statin users                                   |
|                        |             |                                                |                                                | MAP period: Jul 2001—Dec 2002                   |                               |                                                                                      |
|                        |             |                                                |                                                | Follow-up period: 2003                         | 18+, All                       |                                                                                      |
| Stuart et al. (2009)   | US          | Retrospective cohort using health research/claims database | All classes of statins, oral anti-diabetes agents and Angiotensin converting enzyme inhibitors | Data period: 1997–2004 (4,641)”                | 7,441 (4,641)”                 | Diabetes patients                                                                     |
|                        |             |                                                |                                                |                                                | All, All                      |                                                                                      |
| Aubert et al. (2010)   | US          | Retrospective cohort using health research/claims database | All classes of statins                          | Data period: Jan 2000—Jun 2004                  | 10,227                        | Patient newly prescribed statins                                                     |
|                        |             |                                                |                                                | Index period: Jul 2001—Jun 2002                 |                               |                                                                                      |
|                        |             |                                                |                                                | Baseline period: 6 months to index              |                               |                                                                                      |
|                        |             |                                                |                                                | MAP period: 2 years from index                  | 18+, All                       |                                                                                      |
|                        |             |                                                |                                                | Outcome period: 1 year from end of MAP period   |                               |                                                                                      |
| Pittman et al. (2011)  | US          | Retrospective cohort using health research/claims database | Atorvastatin, fluvastatin, lovastatin, pravastatin, rosvastatin, simvastatin, and simvastatin/ezetimibe | Data period: Jan 2007—Jun 2009                 | 381,422                       | Statin users not including those newly prescribed statins                            |
|                        |             |                                                |                                                | Index period: Jan 2008—Jun 2008                 |                               |                                                                                      |
|                        |             |                                                |                                                | Baseline period: Jan 2007—Dec 2007              | 18–61, All                     |                                                                                      |
|                        |             |                                                |                                                | MAP period: 1 year to index                     |                               |                                                                                      |
|                        |             |                                                |                                                | Follow-up period: Jan 2008—Jun 2009             |                               |                                                                                      |
| Stuart et al. (2011)   | US          | Longitudinal study using survey data           | Statins and renin–angiotensin–aldosterone system inhibitors | Data period: 1997–2005                          | 3,765 (1,139)                 | Diabetes patients using studied medications                                          |
|                        |             |                                                |                                                | Follow-up period: until participants completed their survey tenure, were lost to follow-up, were admitted to long-term care facility, or died | All, All                       |                                                                                      |
| Wu et al. (2011)       | US          | Retrospective cohort using health research/claims database | All classes of statins                          | Data period: 2004–2006                          | 1,705                         | Diabetes patients newly prescribed statins                                          |
|                        |             |                                                |                                                | Index period: 2005                              | 18+, All                       |                                                                                      |
|                        |             |                                                |                                                | Baseline period: 1 year to index                |                               |                                                                                      |
|                        |             |                                                |                                                | MAP and follow-up period: 1 year from index     |                               |                                                                                      |
| Chen et al. (2012)     | US          | Retrospective cohort using health research/claims database | All classes of statins                          | Data period: Dec 2009—Dec 2010                  | 30,139                        | Patients discharged from the acute inpatient setting with diabetes                   |
|                        |             |                                                |                                                | Index period: Dec 2009—Nov 2010                 |                               |                                                                                      |
|                        |             |                                                |                                                | Follow-up period: 30 days from end of MAP period | 19+, All                       |                                                                                      |

(Continued)
Discontinuation was defined by having a treatment gap greater than 15 days \[40, 44, 49\], or greater than 30 days \[48, 66\].

Medication possession ratio (MPR), calculated by adding the days' supply for all medications and then dividing over a set period \[67\], was used by four studies, either as a single measure \[68\], as one of several measures \[40, 44\] or in combination with a persistence measure \[49\]. Proportion of days covered (PDC), the proportion of days a patient has a drug administered in a study interval \[67\], was used by one study \[45\]. For MPR and PDC measures, the measured adherence was categorised to form an independent variable in the studies, the most common method being categorising MPR or PDC of at least 80% as adherent \[40, 44, 49, 68\]. Other methods used include nonadherence for the first prescription \[47\] and customised rules \[43, 46\].

Nine studies measured MAP for a fixed duration of six months or 180 days \[40, 44, 48, 49, 66\], of one year \[46, 68\], of one month \[47\] and of 214 days \[43\]. One study measured MAP during the available follow-up period for each patient \[45\].

Reported average values of MAP ranged between 19% and 85%. However, heterogeneity in the length of MAP period and type of MAP measure used did not allow an estimation of an aggregate average.
### Table 6. Impact of adherence or persistence to antidepressants on healthcare resource utilisation and healthcare costs.

| Paper                     | Method of analysis                | Measure of MAP                                                                 | Reported MAP of cohort                                                                 | Impact of MAP on HRUHC                                                                 |
|---------------------------|-----------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Eaddy et al. (2005) [46]  | Analysis of covariance            | 1-year adherence is categorised into five mutually exclusive groups:           | 36%, 16%, 13%, 12% and 23% were in <90 days, ≥90 days, Partial, Titration and Change category, respectively. | (Annual average per-patient provider submitted charge for <90 Days, ≥90 Days, Partial, Titration and Change with statistical significance reported as compared to ≥90-day category) |
|                           |                                   | 1. <90 days: not having at least 90 days of continuous therapy without 15-day gap. |                                                                                        |                                                                                      |
|                           |                                   | 2. ≥90 days: having 90 days or more of continuous therapy without 15-day gap, titration in dose and evidence of receiving another antidepressant. |                                                                                        |                                                                                      |
|                           |                                   | 3. Partial: having at least 90 days of continuous therapy with at least one 15-day gap after 90 days and without titration in dose and evidence of receiving another antidepressant. |                                                                                        |                                                                                      |
|                           |                                   | 4. Titration: having at least 90 days of continuous therapy with an increase in dosage and without 15-day gap and evidence of receiving another antidepressant. |                                                                                        |                                                                                      |
|                           |                                   | 5. Change: having at least 90 days of continuous therapy with evidence of receiving another antidepressant and without 15-day gap. |                                                                                        |                                                                                      |
| Katon et al. (2005) [40]  | Multivariate log-linear regression | Adherence is defined as 6-month MPR ≥ 80% and absence of 15-day gap in first 90 days. | 38% were adherent.                                                                    | (Reporting figures for adherent vs non-adherent patients)                             |
|                           |                                   |                                                                                |                                                                                        |                                                                                      |
|                           |                                   |                                                                                |                                                                                        |                                                                                      |
| Cantrell et al. (2006) [10]| Analysis of covariance            | Three methods to measure 180-day MAP are compared:                           | MPR method: 43% were adherent.                                                        |                                                                                      |
|                           |                                   | 1. MPR method: adherence is defined as 180-day MPR ≥ 80%.                      | LOT method: 45% were adherent.                                                        |                                                                                      |
|                           |                                   | 2. Length of Therapy (LOT) method: adherence is defined as no 15-day gap in 180 days. | MPR/LOT method: 43% were adherent.                                                  |                                                                                      |
|                           |                                   | 3. MPR/LOT method: adherence is defined as 180-day MPR ≥ 80% and no 15-day gap in at least 90 days in 180 days. |                                                                                        |                                                                                      |

(Continued)
### Table 6. (Continued)

| Paper                           | Method of analysis                      | Measure of MAP                                                                 | Reported MAP of cohort | Impact of MAP on HRUHC                                                                 |
|---------------------------------|----------------------------------------|-------------------------------------------------------------------------------|------------------------|----------------------------------------------------------------------------------------|
| Robinson et al. (2006) [43]      | Multivariate exponential conditional mean regression | A patient is adherent when:                                                   | 19% were adherent.     | Extra total healthcare cost of $806 (p < 0.001) for adherent patients.                |
|                                 |                                        | (1) at least 84 days’ supply during first 114 days;                          |                        | Extra mental-health specific healthcare cost of $644 (p < 0.001) for adherent patients. |
|                                 |                                        | (2) at least 180 days’ supply during first 214 days;                         |                        | Additional information*                                                                  |
|                                 |                                        | (3) at least three contacts with healthcare providers including at least one contact with a practitioner licensed to prescribe. |                        | Median unadjusted total healthcare cost: $5,169 (adherent patients) $2,734 (nonadherent patients). |
| Stein et al. (2006) [68]         | Inferential analyses, analysis of covariance | Adherence is defined as 1-year MPR ≥ 80% and patients are categorised into four groups including: nonadherent; adherent, no change; adherent, dosage was titrated; and adherent, change in medication. | 15% were adherent.     | (Reporting figures for adherent vs non-adherent patients)                             |
|                                 |                                        | 57% were non-adherent.                                                       |                        | 1. Patients with anxiety disorders alone                                                |
|                                 |                                        | Lower medical care cost at $2,640 (SD 5,341) vs $3,070 (SD 5,932), at p < 0.05. |                        |                                                                                       |
|                                 |                                        | 19% were adherent, dosage titrated.                                           |                        | Greater anxiety medication cost at $700 (SD 261) vs $277 (SD 259), at p < 0.05.        |
|                                 |                                        | 10% were adherent, change in medication.                                      |                        | Greater other medication cost at $909 (SD 2,129) vs $771 (SD 1,329), at p < 0.05.     |
|                                 |                                        | 2. Patients with anxiety and depressive disorders                             |                        | Greater total cost at $4,248 (SD 6,001) vs $4,119 (SD 5,366), at p < 0.05.            |
|                                 |                                        | Lower medical care cost at $3,220 (SD 5,323) vs $3,807 (SD 5,932), at p < 0.05. |                        | Greater other medication cost at $892 (SD 2,243) vs $801 (SD 1,358), at p < 0.05.     |
|                                 |                                        | Greater anxiety medication cost at $691 (SD 272) vs $338 (SD 281), at p < 0.05. |                        | Greater total cost at $4,803 (SD 6,942) vs $4,946 (SD 6,394), at p < 0.05.           |
| Tournier et al. (2009) [18]     | Multivariate logistic regression model  | Non-persistence is defined as a treatment duration of less than 180 days without a 30-day gap. | Percentages of non-persistent treatment by antidepressant class | (Reporting figures for persistent vs non-persistent patients)                         |
|                                 |                                        | 1. SSRI: 53%                                                                 |                        | Greater cost of initial antidepressants ($321 [316, 326] vs $102 [98, 107]).           |
|                                 |                                        | 2. Serotonin noradrenergic reuptake inhibitors: 53%                           |                        | Greater cost of other medications ($1,444 [1,417, 1,472] vs $1,193 [1,163, 1,224]). |
|                                 |                                        | Lower cost of psychiatric visits ($37 [31, 42] vs $42 [38, 47]).              |                        | Greater cost of other specialty visits ($420 [404, 436] vs $462 [444, 480]).          |
|                                 |                                        | Lower non-psychiatric hospitalisation costs ($1,768 [1,632, 1,908] vs $2,200 [2,44, 2,356]). |                        | No significant difference in psychiatric hospitalisation costs ($64 [4, 80] vs $52 [32, 72]). |
| Ereshefsky et al. (2010) [66]    | Multivariate GLM with gamma distribution and log link | Persistence is defined as treatment gap not greater than 30 days during 180 days. | 19% were persistent.     | Higher healthcare costs in non-persistent patients (RR 1.054 [0.999; 1.112], p = 0.055). |
| Albrecht et al. (2017) [15]      | GLM with binomial distribution and complementary log-log link | Rolling 3-month average from 30-day PDCs, then categorised using two methods: | 55% achieved average PDC ≥ 80%. | (Reporting figures for the second categorisation of MAP)                               |
|                                 |                                        | 1. 0%, <20%, ≥20% and <40%, ≥40% and <60%, ≥60% and <80%, and ≥80%.          |                        | Lower ED visits (HR 0.74 [0.70, 0.78], insignificant) and all-cause hospitalisations (HR 0.77 [0.73, 0.81], insignificant) for adherence ≥80%, compared to adherence = 0%. |
|                                 |                                        | 2. 0%, >0% and <80%, and ≥80%.                                              |                        | Lower ED visits (HR 0.72 [0.68, 0.76], insignificant) and all-cause hospitalisations (HR 0.77 [0.72, 0.82], insignificant) for adherence >0% and <80%, compared to adherence = 0%. |

*Continued*
Bisphosphonates. For bisphosphonate studies, MPR was used to measure MAP by six studies, as a single measure [50, 52, 53], in combination with a persistence measure [51, 69], or in addition to a persistence measure [41].

Of those, four studies defined adherence as MPR at least either 70% [51–53] or 80% [41]. One study categorised MPR into several groups by threshold [50] and one study did not form categories but reported a proportion of patients who achieved at least 80% of MPR [69]. The studies using persistence measures defined discontinuation as a treatment gap greater than 30 days [41], 60 days [51], or three months [69]. One study that did not use MPR categorised longitudinal quarterly MAP into four categories: non-switching, switching, discontinuing, and reinitiating [70].

Three studies measured MAP for a one-year period [51–53]. Other studies measured MAP during the available period for each patient. The wide range of reported average values of MAP between 20% and 85% could not be summarised further because of the heterogeneity in the length of MAP period and type of MAP measure used.

Statins. Seven statin studies used MPR as a single measure of MAP by defining MAP as an MPR of at least 80% [56–58, 62], by having multiple categories of MAP using the MPR [60, 61], or by using the MPR as a numerical variable [63]. Three studies used PDC by using the threshold at 80% to define MAP for multiple medications [64], as a numerical variable [65], and as a numerical variable along with GlowCap adherence measure, the number of days the electronic pill bottle was opened divided by the total number of days followed [55]. Other methods include assessment based on percentage of doses taken within the suggested time.

Table 6. (Continued)

| Paper | Method of analysis | Measure of MAP | Reported MAP of cohort | Impact of MAP on HRUHC |
|-------|-------------------|----------------|------------------------|------------------------|
| Vega et al. (2017) [44] | Multivariate GLM with gamma distribution and log link with bootstrapping | 1. Adherence is defined as 180-day MPR ≥ 80%. 2. Persistence is defined as absence of a 15-day gap in 180 days. 3. Adherence and persistence is defined as 180-day MPR 80% and absence of a 15-gap in first 90 days. | 36% were adherent. 32% were persistent. 31% were adherent and persistent. | Marginal total cost of -$350 [-$462, -$247], $493 [-$1,165, $1,060] for adherent, persistent and adherent/persistent patients, respectively. | |
| Aznar-Lou et al. (2018) [47] | Multivariate logistic regression | Initial non-adherence is defined as not filling prescription for newly prescribed SSRI in the month of prescription or the following month. | 15% were initially non-adherent. | Marginal medical cost of $2,290 [-$2,430, -$2,162], $183 [-$195, -$173] and -$2,152 [-$2,283, -$2,031] for adherent, persistent and adherent/persistent patients, respectively. Marginal pharmacy cost of $1,940 [$1,870, $2,007], $676 [$592, $700] and $987 [$952, $1,021] for adherent, persistent and adherent/persistent patients, respectively. Less general practice visits (OR of 0.82 [0.79, 0.84], p<0.05) for initially non-adherent patients. No significant difference in specialist visits (OR of 1.04 [0.99, 1.08], p>0.05). | |

a. Additional information is provided for comparison purpose when the reported figures are not in relative terms.

CR = cost ratio; ED = emergency department; GLM = generalized linear model; HR = hazard ratio; HRUHC = healthcare resource utilisations and healthcare costs; MAP = medication adherence or persistence; MPR = medication possession ratio; OR = odd ratio; PDC = proportion of days covered; RR = relative risk; SD = standard deviation; SE = standard error; and SSRI = selective serotonin reuptake inhibitor

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Table 7. Impact of adherence or persistence to bisphosphonates on healthcare resource utilizations and healthcare costs.

| Paper                  | Method of analysis                             | Measure of MAP                                                                 | Reported MAP of cohort | Impact of MAP on HRUHHC                                      |
|------------------------|------------------------------------------------|-------------------------------------------------------------------------------|------------------------|-------------------------------------------------------------|
| Briesacher et al. (2007) [50] | Multivariate regression                       | Five categories of each follow-up year’s MPR, 0–19%, 20–39%, 40–59%, 60–79%, and 80–100%. | (For the five MAP categories) | (Compared to MPR of 0–19%, below findings significant at p < 0.1) |
|                        |                                               | Year 1: 43%, 13%, 10%, 14%, and 20%.                                         | Year 1: 35%, 11%, 8%, 8%, and 39%. | Marginal total costs are -$859, -$474, -$366 and $151 for MPR 80–100%, 60–79%, 40–59%, and 20–39%, respectively. |
|                        |                                               | Year 2: 31%, 10%, 7%, 8%, and 44%.                                          | Year 3: 31%, 10%, 7%, 8%, and 44%. | Marginal prescription costs are $997, $923, $402 and $160 for MPR 80–100%, 60–79%, 40–59%, and 20–39%, respectively. |
| Sunyez et al. (2008) [41] | GLM and logistic multivariate regression        | Persistence is defined as no gap ≥ 30 days for follow-up period.             | 21% were persistent.      | 8.9% [-0.122, -0.056] at p < 0.001 and 3.5% [-0.064, -0.007] at p = 0.014 lower total cost for persistent and compliant patients, respectively. |
|                        |                                               | Compliance is defined as 3-year MPR ≥ 0.80.                                  | 37% were compliant.       | Almost 50% lower risk of hospitalisation and 1.6 times greater likelihood of outpatient visits for persistent patients. |
| Eisenberg et al. (2015) [52] | GLM with gamma distribution and log link              | Adherence is defined as 1-year MPR ≥ 70%.                                    | 41% were adherent.        | (Reporting for adherent vs non-adherent patients) |
|                        |                                               | (Not mutually exclusive)                                                     | 19% were non-switching.   | 9% (SE 1.04 at p = 0.007) lower osteoporosis-related costs. |
|                        |                                               | 1% were switching.                                                           | 1% were switching.        | 3% (SE 1.03 at p = 0.298) lower total costs insignificantly. |
| LaFleur et al. (2015) [70] | Generalized estimating equations (GEE) with gamma distribution and log link | Longitudinal quarterly MAP (starting from the first prescription filled at least 6 months after the first outpatient encounter) is categorised into four types: | (Not mutually exclusive) | (Continued) |
|                        |                                               | 1. Non-switching: continuing on index bisphosphonate.                        | 80% were discontinuing.   | 14% [-0.29, 0], 106% [-1.14, 0.98] and 17% [0.13, 0.20] greater total cost for switchers, discontinuers and reininitiators, respectively. |
|                        |                                               | 2. Switching: switching from index bisphosphonate to a different bisphosphonate. | 4% were reinitiating.     | 66% [-0.78, -0.54], 234% [-2.37, -2.31] and 58% [-0.61, -0.56] less osteoporosis-related pharmacy cost for switchers, discontinuers and reininitiators, respectively. |
|                        |                                               | 3. Discontinuing: presence of gap ≥ 90 days.                                 |                        | |
|                        |                                               | 4. Reinitiating: restarting index bisphosphonate after discontinuation or switch. |                        | |

Additional information:
- Full costs (e.g., total outpatient cost) were not reported.

(Continued)
Ten studies measured MAP for fixed duration of one year [55, 58, 60, 61, 65], of six months [54, 59, 64], and of 18 months to two years [56, 57]. Other studies measured MAP for the available period for each patient. The wide range of reported average values of MAP between 17% and without time constraint [54], statin supply for at least 90 days in the year prior to hospitalisation [59], and annual number of prescription fills [42].
Table 8. Impact of adherence or persistence to statins on healthcare resource utilizations and healthcare costs.

| Paper            | Method of analysis                          | Measure of MAP                                      | Reported MAP of cohort | Impact of MAP on HRUHC                                                                 |
|------------------|---------------------------------------------|----------------------------------------------------|------------------------|----------------------------------------------------------------------------------------|
| Cheng et al. (2006) [54] | Backward multiple regression analysis       | Adherence was monitored with two follow-up visits scheduled at 3 and 6 months and also using the statin prescription dispensed in a bottle with the Medication Event Monitoring System. | Median dose-count adherence: 96.4%                                                   | No statistically significant relationship found at p<0.05 regarding total direct medical cost per member per month involving clinic visits, statin medications, laboratory tests on lipids and management of CHD events. |

Adherence was assessed by dose-count defined as the percentage of doses taken, and dose-time was defined as the percentage of doses taken within the suggested time interval.  
Median dose-time adherence: 88.1%

| Gibson et al. (2006) [56] | Logit model and GLM with gamma distribution and log link | Adherence is defined as 18-month MPR ≥ 80%. | Mean MPR for new users: 28% (Reporting figures for adherent vs non-adherent patients) | New users  
Higher physician office visits (OR of 2.526 [SE 0.930], p<0.01) and lower CHD hospitalisations (OR of 0.414 [SE 0.203], p<0.1).  
No significant difference in ED visits, hospitalisations and all types of cost (p>0.1).  
Mean MPR for continuing users: 59%  
Lower ED visits (OR of 0.220 [SE 0.057], p<0.01), lower hospitalisation (OR of 0.0568 [SE 0.177], p<0.1) and lower CHD hospitalisations (OR of 0.18 [SE 0.09], p<0.01).  
No significant difference in physician office visits (p>0.1).  
Higher prescription drug spending (coefficient estimate of 0.703 [SE 0.069], p<0.1).  
No significant difference in other costs (p>0.1). |

| Stuart et al. (2009) [42] | GLM with gamma distribution and log link, poisson model and logistic regression model | Annual number of prescription fills per class per year | Not reported. (With one additional prescription fill)  
0.5% [-0.9, -0.04] at p<0.05 lower hospitalization risk.  
0.05 [-0.09, -0.02] at p<0.01 fewer inpatient days.  
$107 [-193, -21] at p<0.05 less Medicare spending in 2006 USD. |

| Aubert et al. (2010) [57] | GLM and logistic regression model            | Adherence is defined as 2-year MPR ≥ 80%.          | 34% were adherent. (Reporting for adherent vs non-adherent patients) | Lower percentage of patients hospitalized (16% vs 19%, p <0.01) and fewer hospitalizations (25 vs 33 per 100 patients, p <0.01).  
Lower total medical cost excluding cost of statin therapy ($4,040 [$3,601, $4,478] vs $4,908 [$4,594, $5,222], p <0.01).  
Lower total medical cost including cost of statin therapy ($4,909 [$4,470, $5,347] vs $5,290 [$4,976, $5,604], p <0.01). |

(Continued)
### Table 8. (Continued)

| Paper                  | Method of analysis                                        | Measure of MAP                                                                 | Reported MAP of cohort | Impact of MAP on HRUHC (95% CI is in square brackets) |
|------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------|------------------------|------------------------------------------------------|
| Pittman et al. (2011)  | Logistic regression and GLM                               | Three categories of 365-day MPR, 80%-100%, 60%-79% and 0%-59%.               | 15.1%, 17.3% and 67.6% of patients achieved MPR of 0–59%, 60–79% and 80% or more, respectively. | Compared to MPR of 80% or more, greater cardiovascular hospitalisation for MPR of 0–59% (OR of 1.26 [1.21, 1.31] at p < 0.05) and MPR of 60–79% (OR of 1.12 [1.08, 1.16] at p < 0.05). |
|                        |                                                           |                                                                               |                        | All-cause total healthcare costs of $11,101 (SE 84.3, p < 0.001), $10,609 (SE 77.7, p < 0.001) and $10,198 (SE 39.4) for MPR of 0–59%, 60–79% and 80% or more, respectively. |
|                        |                                                           |                                                                               |                        | Cardiovascular medical costs of $2,689 (SE 43.9, p < 0.001), $2,583 (SE 40.4, p < 0.001) and $2,395 (SE 20.5) for MPR of 0–59%, 60–79% and 80% or more, respectively. |
|                        |                                                           |                                                                               |                        | All-cause medical costs of $7,708 (SE 81.9, p < 0.001), $7,261 (SE 75.5, p < 0.001) and $6,709 (SE 38.3) for MPR of 0–59%, 60–79% and 80% or more, respectively. |
|                        |                                                           |                                                                               |                        | All other prescription costs of $2,906 (SE 14.9, p < 0.001), $2,684 (SE 13.7, not significant) and $2,651 (SE 7.0) for MPR of 0–59%, 60–79% and 80% or more, respectively. |
| Stuart et al. (2011)   | GLM with gamma distribution and log link                 | Adherence is measured using pill counts during entire follow-up period, and defined as a variant of MPR—the number of pills aggregated into 30-pill fills, divided by the number of months observed for each study subject (up to 36 months). | Median 3-year adherence was 77%. | $832 (SE 219, p < 0.01) or 2.1% lower annual Medicare expenditure for 10% more adherent patients. |
| Wu et al. (2011) [58]  | Logistic regression model and multiple-linear regression model with natural logarithm | Adherence is defined as 1-year MPR ≥ 80%.                                     | 37% were adherent.     | Lower ED visits (OR 0.71 [0.519, 0.812], p < 0.01). |
|                        |                                                           |                                                                               |                        | Lower hospitalisations (OR 0.80 [0.636, 0.966], p < 0.05). |
|                        |                                                           |                                                                               |                        | Lower all-cause medical cost (estimated coefficient -0.14 with SE 0.0638, p < 0.05). |
|                        |                                                           |                                                                               |                        | Lower hyperlipidaemia-related cost (estimated coefficient -0.11 with SE 0.07, p < 0.05). |
| Chen et al. (2012) [59]| Logistic regression model                                | Adherence is defined as supply for statins ≥ 90 days in the year prior to hospitalisation. | 45% were adherent.     | Lower risk of hospital readmission (OR 0.91 [0.85, 0.97], p < 0.01) for adherent patients. |
| Paper                        | Method of analysis                                                                 | Measure of MAP                                      | Reported MAP of cohort | Impact of MAP on HRUHC                                                                 |
|------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------|------------------------|------------------------------------------------------------------------------------------|
| Roberts et al. (2014) [64]   | Logistic regression model                                                         | 6-month PDC ≥ 80%                                  | 61% were adherent.                                                                 | (Reporting figures for adherent vs non-adherent patients) Less likelihood ED visit (OR of 0.86 [0.51, 1.43] at p>0.05) and less likelihood of hospitalisation (OR of 0.85 [0.48, 1.52] at p>0.05). |
| Zhao et al. (2014) [60]      | GLM with gamma distribution and log link function and logistic regression model    | Eight categories of 12-month MPR, <40%, 40%-59%, 60%-69%, 70%-79%, 80%-84%, 85%-89%, 90%-95%, and 96%-100%. | 6%, 69%, 3%, 4%, 3%, 2%, 6% and 6% were in adherence categories of <40%, 40%-59%, 60%-69%, 70%-79%, 80%-84%, 85%-89%, 90%-95%, and 96%-100%, respectively. | Greater healthcare costs as much as CR 1.074 [1.011, 1.140] at p = 0.02, CR 1.140 [1.057, 1.229] at p = 0.001, CR 1.112 [1.031, 1.199] at p = 0.006, CR 1.186 [1.091, 1.288] at p = 0.001, CR 1.209 [1.136, 1.286] at p<0.001 and CR 1.188 [1.123, 1.256] at p<0.001 for the adherence categories of 40%-59%, 60%-69%, 80%-84%, 85%-89%, 90%-95%, and 96%-100%, respectively (No significant difference for adherence 70%-79% at p = 0.199). |
| Li and Huang (2015) [62]     | Logistic and linear regression models                                             | Adherence is defined as MPR during entire follow-up period ≥ 80%. | 59% were adherent.                                                                 | No significant difference in all-cause hospitalisations (p>0.05). Lower ED visits as much as ED visit ratio of 0.656 [0.524, 0.821] at p<0.001, 0.643 [0.512, 0.807] at p<0.001, 0.722 [0.569, 0.916] at p = 0.007, 0.651 [0.544, 0.779] at p<0.001 and 0.637 [0.544, 0.747] at p<0.001 for the adherence categories of 60%-69%, 80%-84%, 85%-89%, 90%-95%, and 96%-100%, respectively (No significant difference for adherence categories 40%-59% and 70%-79% at p>0.2). |
| Mehta et al. (2019) [55]     | Cox proportional hazards model                                                    | 1. 12-month PDC.                                   | Average PDC: 72–83%                                                          | Statin PDC was associated, not significantly, with lower risk of all-cause readmission (HR 0.832 [0.568, 1.219], p=0.41). |
|                             | 2. GlowCap adherence (GC), the number of days the pill bottle was opened divided by the total number of days followed. | Average GC: 68–89%                                  | Statin GC was associated with lower risk of all-cause readmission (HR 0.663 [0.467, 0.940], p<0.05). |

(Continued)
and 96% could not be summarised further because of the heterogeneity in the length of MAP period and type of MAP measure used.

**Impact of MAP on HRUHC.** *Antidepressants.* Among the ten studies on antidepressants, six reported significantly increased HRUHC by non-MAP, including total healthcare cost [44, 66], medical cost excluding pharmacy cost [40, 44, 49], hospitalisation cost [49], outpatient cost [49], cost of non-psychiatric hospitalisation [48], psychiatric and other specialty visits [48] and general practice (GP) visits [47].

Three studies reported reduced pharmacy costs [44, 48, 68]. Some studies also found reduced total and mental health specific healthcare costs [43], reduced cost of GP services [48], mixed results for total healthcare cost and medical cost excluding pharmacy cost [46], and mixed results for medical cost excluding pharmacy cost [68] over several categories of MAP. Insignificant impacts were reported on total healthcare cost [68], mental health specific hospitalisation cost [48], hospitalisations [45], ED visits [45] and specialty visits [47]. In addition, insignificant impacts of MAP on hospitalisation cost, ED cost, outpatient cost, GP service cost, and antidepressant and other pharmacy costs were reported [46].

* Bisphosphonates. All seven studies on bisphosphonates reported significantly increased utilisation or cost of at least one type of health resource following non-MAP, including total healthcare cost [41, 50, 51, 53, 70], osteoporosis-related healthcare cost [52, 53], all-cause combined and osteoporosis-related medical cost excluding pharmacy cost [53], hospitalisation cost [50], outpatient cost [50], outpatient visits and use of ED services [53], hospitalisations [41, 53], osteoporosis-related hospitalisations and outpatient services [53], and combined HRUHC [69].

### Table 8. (Continued)

| Paper                       | Method of analysis                  | Measure of MAP                                                                 | Reported MAP of cohort                                                                 | Impact of MAP on HRUHC                                                                 |
|-----------------------------|------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Kirsch et al. (2020) [65]   | Generalized additive mixed model   | 1-year PDC for each year in follow-up period                                   | (For the first, second and third year)                                                | The impacts of PDC on several cost outcomes were graphically shown in the study, separately for male and female patients. |
| Studies on antidepressants | Studies on bisphosphonates | Studies on statins |
|---------------------------|---------------------------|-------------------|
| Eaddy et al. (2005)       | Katon et al. (2005)       | Cantrell et al. (2006) |
| Ereshefsky et al. (2010)  | Albrecht et al. (2017)    | Robinson et al. (2006) |
| Vega et al. (2017)        | Eizenberg et al. (2015)   | Stein et al. (2006) |
| Tournier et al. (2009)    | LaFleur et al. (2015)     | Tournier et al. (2009) |
| Sunyecz et al. (2008)     | Sharman et al. (2016)     | Eadsen-Lou et al. (2018) |
| Briesacher et al. (2007)  | Aponte et al. (2014)      | Kirsch et al. (2020) |
| Gibson et al. (2006)      | Chen et al. (2012)        | Li and Huang (2015) |
| Stuart et al. (2009)      | Pittman et al. (2011)     | Mehta et al. (2019) |
| Wu et al. (2011)          | Roberts et al. (2014)     | Zhao et al. (2014) |
| Ursan et al. (2014)       | Chen et al. (2018)        | Kjellberg et al. (2016) |
| Briesacher et al. (2007)  | Albrecht et al. (2017)    | Stuart et al. (2011) |
| Chen et al. (2012)        | Chen et al. (2018)        | Wu et al. (2011) |
| Roberts et al. (2014)     | Zhao et al. (2014)        | Li and Huang (2015) |
| Mehta et al. (2019)       | Zhao et al. (2014)        | Kjellberg et al. (2016) |

| Total healthcare cost | + | - | X | + | + | + | X | + | + | - | - | X |
|----------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| DS healthcare cost   | - |  | - | - |  |  | - | - | - | - | - | - |
| Medical cost         | + | + | - | + | + | + | + | + | + | + | + | + |
| Hospitalisation cost | X | + | - | - |  |  | - | - | - | - | - | - |
| Hospitalisation cost (non-DS) | - | - | - | - | - | - | - | - | - | - | - | - |
| ED cost              | - | - | - | - | - | - | - | - | - | - | - | - |
| Outpatient care      | X | + | - | - |  |  | - | - | - | - | - | - |
| General practice care cost | - | - | - | - | - | - | - | - | - | - | - | - |
| Rehabilitation cost  | - | - | - | - | - | - | - | - | - | - | - | - |
| Pharmacy cost        | - | - | - | - | - | - | - | - | - | - | - | - |
| DS Pharmacy cost     | X | + | - | - |  |  | - | - | - | - | - | - |
| Hospitalisation cost | X | + | - | - |  |  | - | - | - | - | - | - |
| Hospitalisation cost (non-DS) | - | - | - | - | - | - | - | - | - | - | - | - |
| DS hospitalisation   | - | - | - | - | - | - | - | - | - | - | - | - |
| ED visits            | X | + | - | - |  |  | - | - | - | - | - | - |
| DS ED-only visits    | - | - | - | - | - | - | - | - | - | - | - | - |
| Outpatient visits    | - | - | - | - | - | - | - | - | - | - | - | - |
| DS Outpatient visits | - | - | - | - | - | - | - | - | - | - | - | - |
| General practice visits | - | - | - | - | - | - | - | - | - | - | - | - |
| Specialty visits     | X | + | - | - |  |  | - | - | - | - | - | - |
| DS specialty visits  | - | - | - | - | - | - | - | - | - | - | - | - |
| Non-DS specialty visits | - | - | - | - | - | - | - | - | - | - | - | - |
| Combined HRUHC       | - | - | - | - | - | - | - | - | - | - | - | - |

**Notes:**
- +: Greater for nonadherent or nonpersistent patients
- -: Lower for nonadherent or nonpersistent patients
- X: Not significant result (using measure of significance as defined in the paper)
- + -: Mixed results from use of multiple measures of MAP

ED: Emergency department
DS: Disease-specific i.e., depression-related, osteoporosis-related and cardiovascular disease-related for antidepressants, bisphosphonates and statins, respectively

Medical cost: Healthcare cost not including pharmacy cost

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### Table 10. Quality assessment of reviewed studies using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

| Studies on antidepressants | Studies on bisphosphonates | Studies on statins |
|----------------------------|----------------------------|-------------------|
| Eaddy et al. (2005)        | Rhee et al. (2005)         | Suen et al. (2005) |
| Katon et al. (2005)        | Liao et al. (2005)         | Tournier et al. (2009) |
| Cantrell et al. (2006)     | Elliott et al. (2006)      | Ereshefsky et al. (2010) |
| Robinson et al. (2006)     | Simpley et al. (2006)      | Albrecht et al. (2017) |
| Stein et al. (2006)        | Bentham et al. (2006)      | Vega et al. (2017) |
| Cantrell et al. (2006)     | Farquhar et al. (2006)     | Aznar-Lou et al. (2018) |
| Briesacher et al. (2007)   | Kjellberg et al. (2007)   | Sharman et al. (2016) |
| Sunyecz et al. (2008)      | Gibson et al. (2006)       | Chen et al. (2006) |
| Eisenberg et al. (2015)    | Stuart et al. (2015)       | Pittman et al. (2011) |
| LaFleur et al. (2015)      | Wu et al. (2015)           | Zhao et al. (2015) |
| Ferguson et al. (2016)     | Stuart et al. (2016)       | Muller et al. (2013) |
| Kirsch et al. (2020)       | Li and Huang (2015)        | Reshi et al. (2020) |

1. Was the research question or objective in this paper clearly stated?  
2. Was the study population clearly specified and defined?  
3. Was the participation rate of eligible participants at least 50%?  
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified, and applied uniformly to all participants?  
5. Was a sample size justification, power description, or variance and effect estimates provided?  
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?  
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if one existed?  

(Continued)
| Studies on antidepressants | Studies on bisphosphonates | Studies on statins |
|-----------------------------|---------------------------|---------------------|
| Eaddy et al. (2005) [46]   | Robinson et al. (2006)    | Mehta et al. (2019) [55] |
| Katon et al. (2005) [49]   | Cheng et al. (2006)       | Kirsch et al. (2020) [65] |
| Cantrell et al. (2006) [40]| Tournier et al. (2009)    | Wu et al. (2011) [58] |
| Robinson et al. (2006) [43]| Stein et al. (2006)       | Sharman Moser et al. (2016) [51] |
| Ereshefsky et al. (2010) [66]| Albrecht et al. (2017) [45]| Chen et al. (2012) [54] |
| Sunyecz et al. (2008) [41]| Vega et al. (2017) [44]   | Roberts et al. (2014) [64] |
| Aznar-Lou et al. (2018) [47]| Eisenberg et al. (2015) [52]| Zhao et al. (2014) [60] |
| Briesacher et al. (2007) [50]| LaFleur et al. (2015) [70]| Li and Huang (2015) [62] |
| Sunyecz et al. (2008) [41]| Eisenberg et al. (2015) [52]| Briesacher et al. (2007) [50] |

8. For exposures that vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

9. Were the exposure measures (independent variable(s) clearly defined, valid, reliable, and implemented consistently across all study participants)?

10. Was the exposure(s) assessed more than once over time?

11. Were the outcome measures (dependent variable(s) clearly defined, valid, reliable, and implemented consistently across all study participants)?

12. Were the exposure assessors blinded to the exposure status of participants?

13. Was the outcome assessed more than once over time?

14. Was loss to follow-up after baseline 20% or less?

Number of N or NR

(Continued)
Table 10. (Continued)

| Studies on antidepressants | Studies on bisphosphonates | Studies on statins |
|----------------------------|----------------------------|-------------------|
| Eaddy et al. (2005)        | Robinson et al. (2006)     | Albrecht et al. (2017) |
| Katon et al. (2005)        | Vega et al. (2010)         | Ereshefsky et al. (2010) |
| Cantrell et al. (2006)     | Amor et al. (2007)         | Briesacher et al. (2007) |
| Stein et al. (2006)        | Robinson et al. (2008)     | Sunyecz et al. (2008) |
| Tournier et al. (2009)     | Mraz et al. (2007)         | Vega et al. (2017) |
| Ereshefsky et al. (2010)   | Ruhoff et al. (2011)       | Ereshefsky et al. (2010) |
| Ferguson et al. (2016)      | Holfberg et al. (2016)     | Albrecht et al. (2017) |
| Sharman et al. (2016)       | Morse et al. (2016)        | Albrecht et al. (2017) |
| Albrecht et al. (2017)      | Giannousis et al. (2016)   | Albrecht et al. (2017) |
| Albrecht et al. (2018)      | Li et al. (2018)           | Albrecht et al. (2017) |
| Liu et al. (2018)           | Yi et al. (2018)           | Albrecht et al. (2017) |
| Wu et al. (2018)            | Zhao et al. (2018)         | Albrecht et al. (2017) |
| Li and Huang (2018)         | Mehta et al. (2019)        | Albrecht et al. (2017) |
| Stuart et al. (2019)        | Kirsch et al. (2020)       | Albrecht et al. (2017) |

Quality rating:
- **G**: Good
- **F**: Fair
- **P**: Poor

Y: Yes; N: No; NR: Not reported; -: NA

a. Rating is done by giving good for 0–2 N or NR, fair for 3–4 N or NR and poor for greater than 4 N or NR.

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Four studies reported reduced utilisation or cost of several types of resource, including pharmacy cost [50, 53], cost of bisphosphonates [53, 70], osteoporosis-related healthcare cost [70], and outpatient visits [41].

**Statins.** Nine of 13 statin studies reported that at least one type of HRUHC significantly increased following non-MAP. The increased HRUHCs include total healthcare cost [57, 61, 63], CVD-related healthcare cost [58], medical cost excluding pharmacy cost [42, 57, 58, 61], CVD-related medical cost excluding pharmacy cost [61], pharmacy cost other than statins [61], hospitalisation cost [62], ED visits [58, 60], hospitalisations [42, 57–59, 62], hospital days [42], and CVD hospitalisations [56, 61]. In contrast, Zhao, Zabriski [60] found decreased total healthcare costs for nonadherent patients. Pittman, Chen [61] found lower statin prescription cost for nonadherent patients.

Several studies found insignificant impacts of MAP to statins on total healthcare cost [54, 56, 65], hospitalisation cost [65], outpatient cost [65], remedy and aid cost [65], hospitalisations [60, 64], CVD hospitalisations [62], and ED visits [62, 64]. Gibson, Mark [56] divided patients into two groups–new users and continuing users–and found mixed results for pharmacy cost, GP visits, ED visits, and hospitalisations. Kirsch, Becker [65] found non-linear impact on pharmacy cost only for female patients and positive impact on rehabilitation cost only for male patients. Mehta, Asch [55] used multiple measures of MAP and found mixed results on hospitalisation.

**Aggregate data meta-analysis.** We conducted a meta-analysis to estimate the impact of MAP on HRUHC when reported for at least two different population cohorts using comparable measures of MAP to the same medication class and the same type of HRUHC. Of 30 studies, only eight were used in the meta-analysis to obtain five synthesised results. Further findings were not possible due to the heterogenous types of MAP and HRUHC examined by the reviewed studies.

Table 11 summarises the averaged impacts of MAP on HRUHC from the meta-analysis. Forest plots and more detailed figures are found in S2 File. For antidepressants, having greater than 80% adherence by either medication possession ratio (MPR) or proportion of days covered (PDC) during a six-month or 180-day period was found to reduce the total medical cost not including pharmacy cost by 12% [-16%, -8%], the hospitalisation cost by 26% [-48%, 4%].

| Type of HRUHC                        | Measure of MAP                                          | Number of cohorts \(a\) | N       | Difference in cost    | p-value |
|-------------------------------------|--------------------------------------------------------|--------------------------|---------|-----------------------|---------|
| **Antidepressants**                 |                                                        |                          |         | % [95% CI]            |         |
| Total medical cost excluding pharmacy cost | MPR or PDC ≥ 80% during 6-month or 180-day period       | 5                        | 34,074  | -12% [-16%, -8%]      | < 0.00001 |
| Hospitalisation cost               | 6-month MPR ≥ 80%                                       | 3                        | 9,766   | -26% [-48%, -4%]      | 0.02    |
| Outpatient cost                    | 6-month MPR ≥ 80%                                       | 3                        | 9,766   | -10% [-17%, -2%]      | 0.01    |
| Total healthcare cost              | Absence of 15-day gap during 180-day period            | 2                        | 46,842  | -1% [-6%, 0%]         | 0.80    |
| **Bisphosphonates**                |                                                        |                          |         |                       |         |
| Total healthcare cost              | MPR ≥ 70% during 1-year period                          | 3                        | 83,909  | -3% [-6%, 0%]         | 0.07    |

\(a\) Note three cohorts from a single study (Katon et al., [49]) were used for the calculation of impact of MAP to antidepressants on total medical cost excluding pharmacy cost, hospitalisation cost and outpatient cost.

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and outpatient cost by 10% [-17%, -2%]. The impact of persistence in using antidepressants for a 180-day period without 15-day gap on total healthcare cost was found insignificant. For bisphosphonates, having greater than 70% or 80% adherence by one-year MPR was found to reduce the total healthcare cost by 3% [-6%, 0%]. For statins, no meta-analysis could be performed mainly due to inconsistency in the measures of MAP within studies.

Discussion

This review provides a comprehensive view on the impact of MAP to antidepressants, bisphosphonates and statins on HRUHC. It is the first to provide an integrated understanding of the impact of MAP to three medication classes on HRUHC using a broad array of HRUHC measures including total healthcare cost, disease-specific healthcare cost, medical cost excluding pharmacy cost, pharmacy cost, cost of medication, hospitalisation, outpatient service use, ED visits, GP visits and specialty visits. Previous reviews on the impact of MAP to these three medication classes on HRUHC did not address diverse measures of MAP or HRUHC, or did not make comparisons with other medication classes used for prevalent conditions [e.g., 6, 71, 72].

MAP varies by medication class, MAP measure, length of follow-up period and study design, limiting scope for comparison. Nevertheless, the review found broad consistency in reported MAP to antidepressants, with the percentage of patients with MPR or PDC at least 80% during a 180 day or six month period ranging between 36% and 43% [40, 44, 49, 68] and percentages of persistent patients as measured by continued use in 180 days without a 30-day gap of 19% [66] and 35% to 47% [48]. These findings are comparable with a previous review (on studies not limited to those on the impact of MAP on HRUHC) indicating that 35% to 55% of patients remain adherent or persistent to antidepressant therapy at six months [73].

The proportion of patients adherent to bisphosphonates were between 20% and 70% in the studies that measured MAP as a MPR or PDC of at least 70% or 80% during a one year period [50–53]. The mean persistence of oral bisphosphonates for one year similarly ranged between 18% and 75% in a systematic review by Fatoye, Smith [74]. The wide range of MAP could be partly due to variance between studies in factors related to non-MAP including younger age [74] and more frequent dosing [74, 75]. Of the four studies compared above [50–53], the lower bound of the range (i.e., 20%) was found from Briesacher, Andrade [50] on patients aged at least 40, compared with the other three studies which were all on patients aged at least 55.

Among statin users, 17% to 68% were found to have a MPR at least 80% during a one year period [58, 60, 61]. These findings are comparable with a previous review showing that patients with a MPR for statins at least 80% ranged between 18% and 92% for different lengths of MAP period [76]. Consistent with previous studies that found lower MAP for new statin users compared to continuous users [56, 76], Wu, Seiber [58] and Zhao, Zabriski [60] reported a lower percentage of adherence for new statin users than Pittman, Chen [61] for continuous users.

The MPR and PDC were the most frequently used methods to summarise MAP. While they both measure the percentage of the time that a patient has medication available, the PDC was introduced to mitigate the overestimation problem of the MPR in which early refill (i.e. refill when the medication is still available) is included in the amount of medication available in the measuring period [77]. We found the tendency that the PDC measure was used for studies published later.

Several studies [40, 41, 44, 45, 54, 55] reported results that allow comparison among multiple methods of measuring MAP. For example, Mehta, Asch [55] compared MAP as measured by PDC based on pharmacy claims as well as GlowCap adherence using electronic pill bottles. They found that the significantly lower risk of all-cause readmission of patients previously
discharged with a diagnosis of acute myocardial infarction was found only when the GlowCap adherence was used, highlighting the importance of measurement method for MAP.

In general, non-MAP was found to be associated with increased HRUHC. Of the 30 papers included, 25 found a significant positive association between non-MAP and one or more measures of HRUHC, although in some cases negative or mixed associations were found for other HRUHC measures. This generally positive association between non-MAP and HRUHC has also been found in previous reviews [e.g. 6, 78].

This review revealed that the association between non-MAP and increased healthcare costs is most definitive for medical costs excluding pharmacy costs. Of 10 papers that assessed total healthcare costs net of pharmacy costs, eight reported a positive association with non-MAP, the remaining two reporting mixed results. Non-MAP was found to be negatively associated with total pharmacy costs for five of the seven papers that assessed this, reflecting higher pharmacy costs for patients that are adhering to, and therefore consuming more of, their medication. Of the 18 papers that assessed total healthcare costs, 10 reported a positive association between total healthcare costs and non-MAP, and a further six found no significant association or mixed results across multiple MAP categories. This result is a combination of generally lower pharmacy costs and generally higher medical costs excluding pharmacy costs for non-MAP patients. These findings related to healthcare and pharmacy costs apply across all three medications considered.

Increase in hospitalisations and ED visits associated with non-MAP was frequently reported. Of 12 studies that measured the impact of non-MAP on hospitalisation, seven found a positive impact while the rest found either mixed or insignificant results. Of seven studies that assessed the impact of non-MAP on ED visits, three found a positive impact while four found insignificant results or mixed results across multiple patient categories. Several HRUHC measures were reported by too few papers to enable comparison; for example, the impact on specialty visits was reported by only one study [47].

While general patterns of resource use were similar across the three medication classes, some differences exist. First, the pattern of increased healthcare cost following non-MAP was the most apparent in bisphosphonate studies. All seven studies on bisphosphonates found an increase in at least one type of HRUHC. Of six studies that assessed the total healthcare cost, five found a positive association with non-MAP, while one found no significant association. The clearer pattern found could be related to the tendency that studies on bisphosphonates used longer data periods (average 8.0 years compared to average 3.6 and 4.3 years for the studies on antidepressants and statins, respectively) and less heterogeneous cohorts (typically females aged at least 55 compared to all adult patients in the studies on antidepressants and statins).

Second, the impacts of non-MAP on hospitalisation and ED visits were more frequently studied on statins and were found to be generally positively associated. Third, the associations between non-MAP and total pharmacy costs were negative for all studies on antidepressants and bisphosphonates that assessed this, but were heterogeneous for the studies on statins; negative for continuing users [36], non-linear for female patients [65] and insignificant for others. This shows that non-MAP to statins does not necessarily imply non-MAP to other medications. Future studies to examine such selective non-MAPs will be useful to further understand the reasons for non-MAP to statins.

Last, in the studies on antidepressants and statins compared to bisphosphonates, notwithstanding the general finding of positive associations, there were greater numbers of reported insignificant impacts of non-MAP on HRUHC. The impacts of non-MAP may not be sufficiently captured with a short follow-up period given that nine [45–48, 54, 60, 64, 65, 68] of 11 studies that reported insignificant associations measured MAP and HRUHC for the same (i.e.,
overlapping) six-month to one-year period. There could also be idiosyncratic healthcare system factors. Li and Huang [62] found an insignificant impact on ED visits and discussed that the finding may not accurately show the impact on the occurrence of emergency situations that are potentially costly due to frequent non-emergency use of emergency care services in Taiwan.

Comparing the directions of impact on different types of HRUHC within an individual study can suggest underlying mechanisms linking MAP and HRUHC. For example, Tournier, Moride [48] found that persistence to antidepressants increases GP service costs and pharmacy costs but decreases specialty visits and non-psychiatric hospitalisation costs. This shows that spending on primary care to maintain mental health can reduce the costs associated with adverse health outcomes. Another similar pattern was found by Sunyecz, Mucha [41] reporting that persistence to bisphosphonates reduces total healthcare cost and hospitalisations but increases outpatient visits.

The meta-analysis found positive associations between non-MAP and HRUHC for total medical cost excluding pharmacy cost, hospital cost and outpatient cost for antidepressants all at 5% significance level, and total healthcare cost for bisphosphonates at 10% significance. The average magnitude of the impact of non-MAP to antidepressants on hospitalisation cost was estimated at 26%.

Heterogeneities in study location, data type, cost calculation method, HRUHC measure, analysis method and other characteristics limited the extent to which further meta-analysis could be conducted and overall conclusions drawn. This meant we could not conduct a meta-analysis on statins and a meta-analysis on other HRUHC components, and it limited the number of studies included in the meta-analyses that were conducted. Study characteristics will also influence the meta-analysis results. For example, more costly healthcare in the US than the UK [79] along with the preponderance of US studies included in the meta-analysis is expected to result in higher estimates of impact of non-MAP on HRUHC which may not be generalisable to non-US locations.

Comparisons across studies having different characteristics were not possible primarily due a limited number of studies having certain characteristics different to the majority. For example, a comparison by location was limited because the review included at most one study conducted in a non-US country for each medication class; a comparison by analysis method was limited because most studies used generalized linear models; and a comparison by data type was limited because most studies used an administrative dataset with limited use of other (e.g., survey data) types.

The quality assessments in Table 10 show that all included studies meet the majority of assessment criteria related to study objectives, selection criteria for study populations, justification of sample selection and size, measurement of MAP, study timeframes and quality of analysis. While 28 of 30 studies reviewed did not assess MAP more than once, a single MAP figure comprises multiple observations on medication use over time and hence any inaccuracy that may arise from assessing an exposure once only would be small. There was no evident difference in quality across the studies on the three medication classes.

Of the 30 reviewed studies, 27 studies used a large administrative dataset allowing for a sample size greater than 1,000 and measured MAP using administrative records of filling prescriptions (e.g., pharmacy claims). This approach to measuring MAP is standard and has the advantages that MAP is passively measured and easy to track for large populations [80] and does not influence participant behaviour. However, limitations include that filled medications are not necessarily taken; a diagnosis for which medications are prescribed is mostly unavailable; the reason for non-MAP is not known; a case of discontinuation recommended by health service provider is not identified (e.g., side effects); and data does not capture all medications
used by a patient (e.g., data extracted from an insurance plan does not capture medications funded from other means). In addition, the measure of MAP can be sensitive to modelling decisions in preparing pharmacy data sets [81], and most reviewed studies did not provide details of these decisions.

Not measuring MAP prior to HRUHC was a common problem, most prominent in the studies on antidepressants. Although 22 studies set separate measurement periods for MAP and HRUHC, only eight clearly showed that MAP was measured strictly prior to HRUHC. As MAP could be affected directly by HRUHC (e.g., GP visits to get prescriptions) or indirectly by health conditions suggested by HRUHC (e.g., reassuring the need for medication at ED visit), measuring MAP prior to HRUHC would avoid potential reverse causality problems. The findings within these eight studies were generally consistent with the overall findings of this review.

Limited generalisability was found for several studies. For example, results within Gibson, Mark [56] may be only applicable for an insured population as it was based on patients covered by employer-sponsored health insurance. The patient population of Ferguson, Feudjo Tepie [69] is atypical in that a significant proportion had a high level of glucocorticoid use.

Many studies did not clearly specify the payer and recipient for the measured healthcare costs although such specification will be useful when study findings are used for developing health policy. Only a few studies specifically stated from whose perspective the costs are measured. For example, Cheng, Chan [54] reported that the costs were calculated for each patient from the perspective of a public health provider. Considering the type of data used by the majority (i.e., administrative claim data), most studies that assessed healthcare costs are likely to have measured the cost paid by an insurance company or the public healthcare system to healthcare service providers.

There are several limitations of this systematic review. First, only a limited meta-analysis could be undertaken due to heterogeneous types of MAP and HRUHC within the studies. There is a need for agreement on consistent methods to be applied to measure MAP and more studies on each type of HRUHC to improve comparability. Second, the review does not attempt to directly evaluate individual patient factors that may influence the impact of MAP on HRUHC (e.g., age, sex, comorbidity, severity of disease); such factors were highly heterogeneous across different studies and could not be meaningfully incorporated. However, 28 of 30 studies did measure these and other potentially confounding variables and made statistical adjustments accordingly in measuring the impact of MAP on HRUHC, enabling valid comparison without a need for direct evaluation of these factors in this review.

Third, 22 of the studies were conducted in the US and therefore results may fail to reflect experience in other countries; this is due partly to the exclusion of non-English articles as well as to the preponderance of US studies. Several studies have found that exclusion of non-English articles is unlikely to result in bias [82, 83]. Among English articles, the strict search protocol limits bias in study selection and ensures that the US dominance is due to dominance of research. Additional research conducted outside the US will permit greater understanding of the impact of MAP on HRUHC dependent on healthcare systems.

Last, the review focuses only on HRUHC from a healthcare system perspective and does not address other non-healthcare burdens such as loss of productivity, absence from work, loss of quality of life and costs of home care or informal care. Several previous studies examined such burdens following non-MAP [84–87]. These aspects are outside the scope of our review however it should be acknowledged that total economic impact of non-MAP will be greater than that indicated by HRUHC within this review.
Conclusions
This systematic literature review is the first to compare the impact of non-MAP to medications for three prevalent conditions—depression, osteoporosis and cardiovascular disease—on healthcare resource utilisation and cost. While previous reviews generally focused on finding the impact of MAP on particular healthcare costs or clinical outcomes, this review considered a wide range of measures and three different medication classes. From 30 included studies assessed to be of good or fair quality, we found generally positive associations between non-MAP and healthcare resource utilisation and cost for all three medication classes but most prominently for bisphosphonates. Notwithstanding this general finding, the significance and direction of associations was heterogeneous across alternative HRUHC measures and medication classes. In some cases, non-MAP reduced healthcare resource utilisation or cost, particularly for pharmacy. The ability to quantitatively summarise the impact of non-MAP on healthcare resource utilisation and cost was challenged by a small number of studies reporting comparable results; the development of more consistent measures would enable more meaningful analysis. The study highlights the need to understand how and to what extent poor MAP exhausts healthcare resources to inform clinical practice, health policy and research.

Supporting information
S1 Checklist. PRISMA checklist.
(DOCX)
S1 Fig. Forest plots for aggregate meta-analysis.
(DOCX)

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