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Economic impact of medication nonadherence by disease groups: a systematic review

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Title Page

Title: Economic impact of medication nonadherence by disease groups: a systematic review

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Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A literature search was conducted in PubMed and Scopus in March 2017 where neither publication date nor language restriction filters were used. Seventy four individual studies assessing the cost of medication nonadherence were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Individual studies reported a wide range of costs, calculated using different methods. Disease groups assessed were cardiovascular disease, mental health, diabetes mellitus, osteoporosis, respiratory disease, gastrointestinal disease, epilepsy, HIV/AIDS, Parkinson's disease, musculoskeletal conditions, cancer, addiction, metabolic conditions and blood related conditions. Medication possession ratio was the metric most utilized to calculate patient adherence, but the cut-off points chosen to define nonadherence varied. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (81% of studies), pharmacy costs (72%), inpatient costs (51%), outpatient costs (51%), emergency department visit costs (30%), medical costs (27%) and hospitalization costs (18%). Lower levels of adherence were generally associated with higher total costs. The annual adjusted disease state specific economic cost of nonadherence per person ranged from \$949-\$53,504 (in 2015 US dollars). Costs attributed to "all causes" nonadherence ranged from \$5,271 to \$52,341.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. However, current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy and change due to significant variations in costs and their economic implications. Differences in methods make the comparison amongst studies challenging and make an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338

Strengths and Limitations of this study:

- This is the first systematic review assessing the economic impact of medication nonadherence across all disease groups.
- The findings of this review build on current literature and present the first comprehensive analysis of the cost ranges of medication nonadherence within and amongst disease groups whilst simultaneously analyzing the range of outcomes used to estimate costs.
- A large proportion of studies provided insufficient statistical data and considerable heterogeneity to perform a meta-analysis according to outcome/indicators.
- Owing to heterogeneous research design, examination of the economic impact of medication nonadherence was restricted due to the lack of full economic evaluations available.

1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources. [2]. Medications are a cost-effective treatment modality, but intentional and unintentional inappropriate medication use by patients is common, mostly through differing degrees of adherence termed medication nonadherence. Medication adherence is defined as ‘the extent to which the patients’ behavior matches agreed recommendations from the prescriber’, emphasising the importance on the patients’ decisions and highlighting the modifiable aspect of nonadherence[3].

With estimates of 50% nonadherence to long term therapy for chronic illnesses[4], efforts to improve medication adherence represent an opportunity to improve health outcomes and health system efficiency. The clinical, economic and human consequences of medication nonadherence pose significant burdens. Estimates of the costs range from US\$100-\$290 billion[5] in the United States, €1.25 billion[6] in Europe and approximately A\$7 billion[7 8] in Australia. As well as substantially increasing healthcare costs, nonadherence compromises the effective use of medicines, can decrease patients’ quality of life, increases the risk of medication misadventures, can lead to poor health outcomes, and can result in preventable hospitalizations[9]. Nonadherence is thus a critical clinical and economic problem [4].

An understanding of the economic impact of medication nonadherence on the healthcare system can influence health policy. While the cost of nonadherence for some disease groups has already been analyzed with varying findings, no systematic reviews provide a holistic and comparative picture across disease groups. The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.

2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[10].

2.1 Search strategy and selection criteria

A literature search was conducted in March 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB])) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases. Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[11] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-

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3 group analysis and statistical significance), conclusions and miscellaneous (funding source,
4 references to other relevant studies, limitations and reviewers comments).
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7 All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group -
8 Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [12],
9 allowing meaningful comparisons between nonadherence cost data. This online tool uses a two
10 stage computation process to adjust estimates of costs for currency and/or price year utilizing a
11 Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic
12 Product[12]. The PPP values given by the International Monetary Fund were chosen. If details of the
13 original price year could not be ascertained from a study the mid-point year of the study period was
14 used for calculations. The mean cost was calculated and reported where studies separated out costs
15 for different confounding factors within the one outcome measure in a disease state. Annual costs
16 were extrapolated from the original study data if results were not presented in this manner.
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24 The cost analysis of studies (figures 2 and 3) reported annual medication nonadherence costs
25 incurred by the patient from a healthcare provider perspective. The definition of medication
26 nonadherence was derived from the included studies; with nonadherence referring to differing
27 degrees of adherence based on the studies metric of estimation. The most utilized methods were
28 medication possession ratio (MPR) and proportion of days covered (PDC). Multiple nonadherence
29 costs from individual studies may have been included where further sub-classification of
30 nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups,
31 with disease group and cost classification derived from the study. Total healthcare costs included
32 direct costs to the healthcare system while total costs incorporated direct and indirect costs.
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39 **2.3 Quality criteria and economic evaluation classification**

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41 Economic evaluation requires a comparison of two or more alternative courses of action, while
42 considering both the inputs and outputs associated with each [13]. All studies were classified in
43 accordance with Drummond's distinguishing characteristics of healthcare evaluations as either
44 partial evaluations (outcome description, cost description, cost-outcome description, efficacy or
45 effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility
46 analysis, cost effectiveness analysis, cost minimization analysis).
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52 The Drummond checklist [14] for economic evaluation was used to assess the quality of studies. The
53 original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full
54 economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the
55 required item and zero if it did not with a maximum potential score of 28. The study was classified as
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3 high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were
4 satisfied and low quality if 50% of the criteria or less were satisfied.
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9 **2.4 Meta-Analysis**

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11 Outcome/indicator costs were independently extracted utilising predesigned data extraction forms
12 (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs,
13 emergency department costs, and hospitalisation costs) for the purpose of integrating the findings
14 on the cost of medication nonadherence to pool data and increase the power of analysis.
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3 Results

3.1 Study Selection

Search strategies retrieved 2691 potential articles after duplicates were removed. Two hundred and sixty six articles were selected for full text review. Seventy four studies were included in the review (Figure 1).

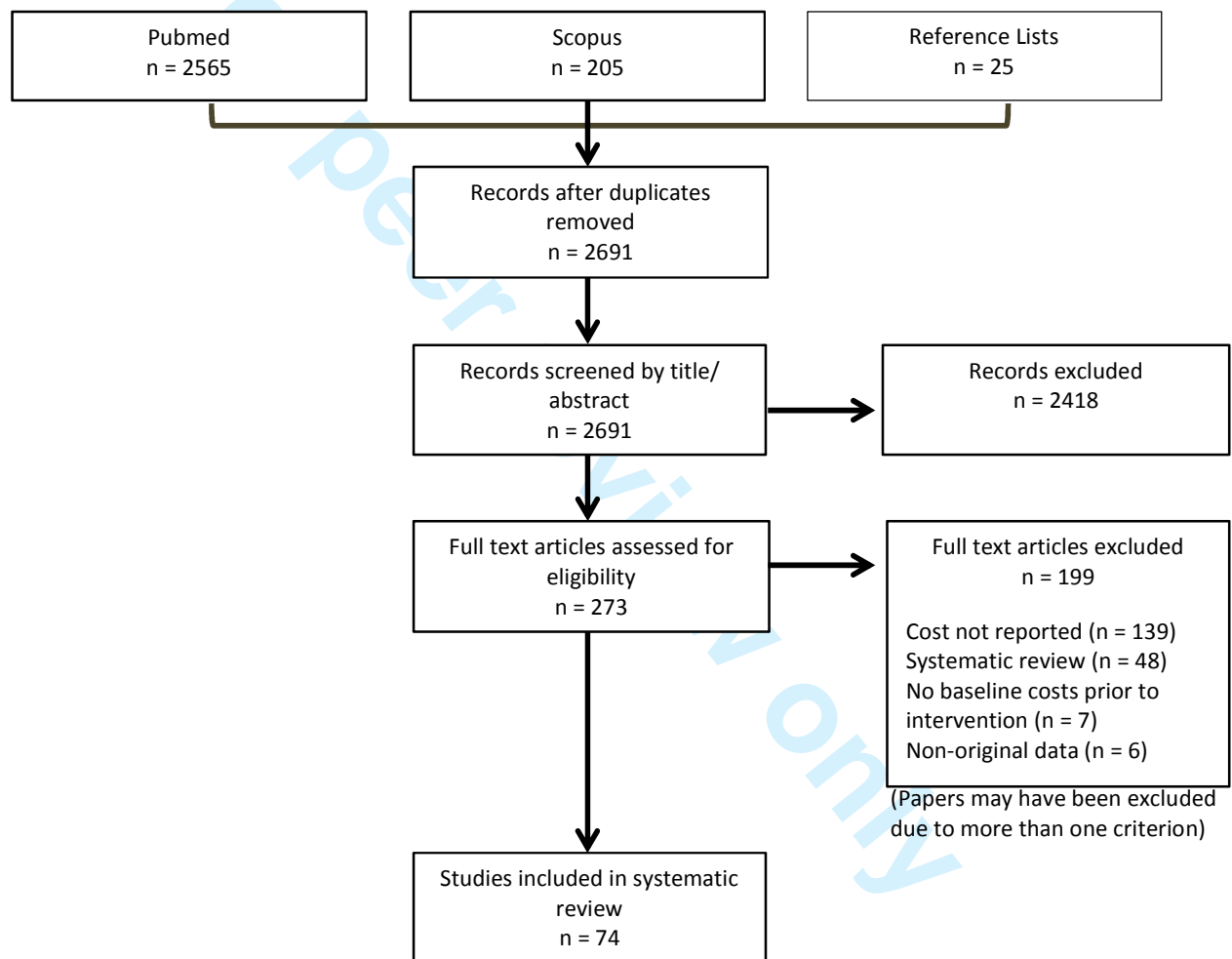


Figure 1: Flow diagram of references identified, retrieved and included in the systematic review

3.2 Characteristics of individual studies

Sixty-one studies (82%) were conducted in the United States[15-75], four in Europe[76-79], four in Asia[80-83], three in Canada[84-86], one in the United Kingdom[87] and one across multiple countries throughout Europe and the United Kingdom[88]. Publication years ranged from 1997 to 2016. Individual studies reported a large variety of costs, calculated by varying means. Forty-one studies (55%) reported unadjusted costs[15 19 20 23 25-29 31-36 39 41-43 45-49 51 56-59 61 62 66 69 75 77-79 81-83 88], 19 (25%) adjusted costs[16-18 22 24 37 44 50 52-54 60 65 67 70-72 76 80], 11 a combination of adjusted and unadjusted[21 30 38 40 55 63 64 68 73 74 86], two unadjusted and predicted[84 85] and one predicted costs[87]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy claims data (87%)[15-22 24-45 48 50 52-77 81-86]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data, disease state specific recommended guidelines and health claims data. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 48 studies (64%) reporting nonadherence based on this measure[17 18 21 22 25-29 33-37 39 40 42-44 48 50 51 53-57 61-72 75-77 81-86]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g. 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (9%)[24 30 38 41 45 73 74], with all other studies utilizing an array of measures including self-report[87], urine testing[49], observational assessment[88], time to discontinuation[52], cumulative possession ratio[16], disease specific medication management guidelines[59 78], Morisky 4-Item scale[46], medication gaps[31], prescription refill rates[15 20] and medication supplies[60]. The main characteristics of the included studies are summarised in eTable 1.

3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high [26 30 33 43 44 50 65 69 76 82], 55 of medium [15-19 21-25 27-29 31 32 34-41 46-49 51 52 54-57 59-61 63 64 66 67 70-75 77 78 80 83-88] and nine of low quality [20 42 53 58 62 68 79 81]. Scores ranged from 26.1% to 87.5% (mean 62.9%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [65]. The item 'the choice of discount rate is stated and justified' was applicable only to studies covering a time period of more than one year; all studies that cover more than one year failed to identify or explain why costs had not been discounted. Details of the analysis and interpretation of results were lacking in the majority of studies resulting in medium or low quality scores.

Through utilisation of Drummond's distinguishing characteristics of healthcare evaluations criteria [13] it is apparent that no full economic evaluation was conducted in any of the included studies. All studies performed partial economic evaluations of varying extents. The classification of economic evaluations resulted in 54 cost description studies (72% of those included), 15 cost outcome descriptions and five cost analysis studies (eTable 1).

3.4 Medication nonadherence and costs

The adjusted total cost of nonadherence across all disease groups ranged from \$949 to \$53,504, while the unadjusted total cost ranged from \$669 to \$162,699. Figures 2 and 3 highlight the minimum, maximum and interquartile range of annual costs incurred by patients across disease groups where three or more studies were included for review. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

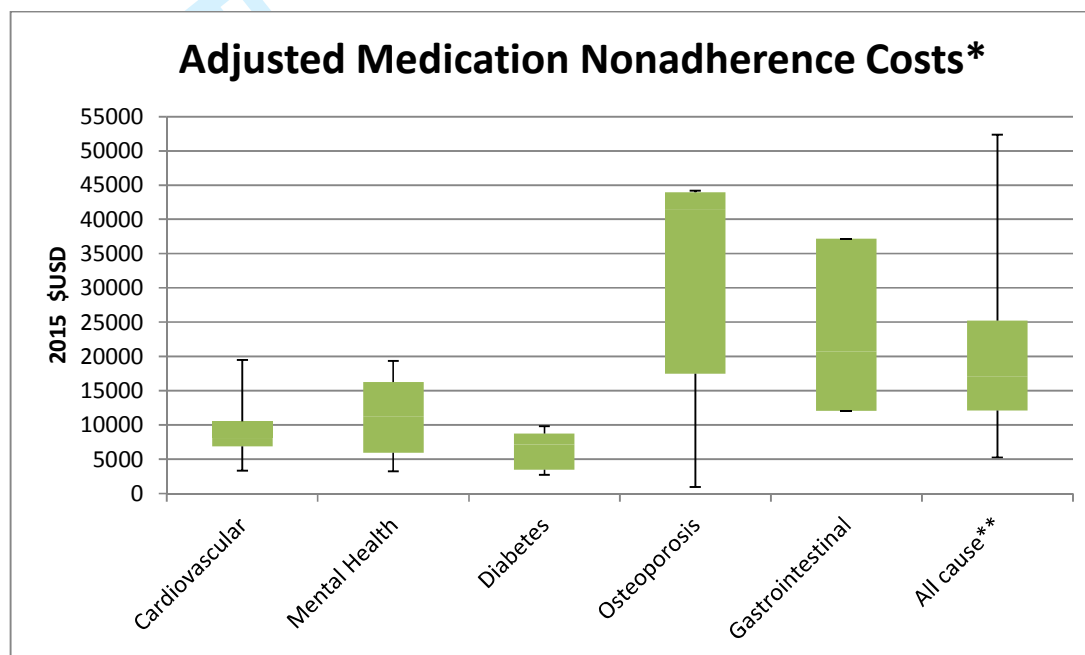


Figure 2: Annual Adjusted Medication Nonadherence Costs

*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.

** All cause costs: mixed disease state studies

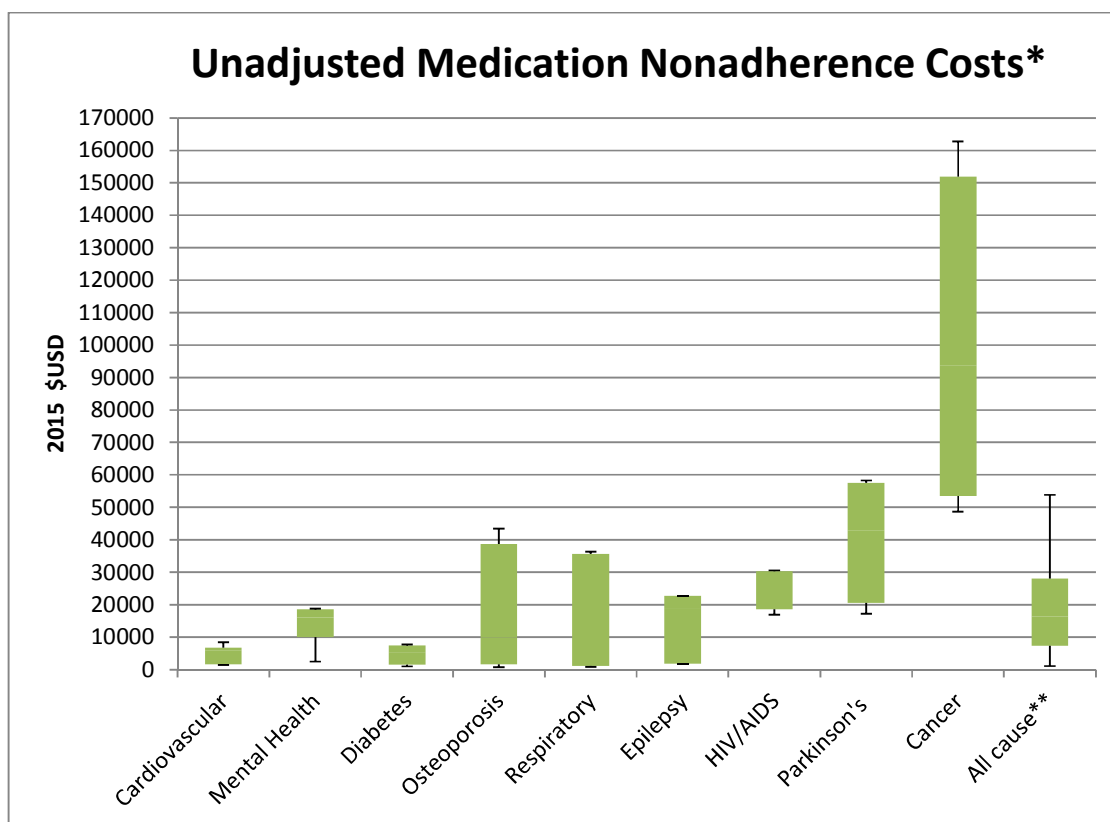


Figure 3: Annual Unadjusted Medication Nonadherence Costs

*Disease groups with three or more studies were included. Epilepsy only included three studies limiting the range of costs.

** All cause costs: mixed disease state studies

Many different indicators were used to estimate medication nonadherence costs. The main ones were total cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs (47%), , medical costs (29%) , emergency department costs (28%), and hospitalization costs (18%) (eTable 1).

Lower levels of adherence across all measures (*e.g.* MPR, PDC) were generally associated with higher total costs. From those that reported total or total healthcare costs, 37 studies (50%) reported nonadherence costs to be greater than adherence costs[17 18 20 22 24 25 27 30-32 35 36 40 42 43 48 49 51 54-58 64-72 76 85-88] and 11 studies (15%) reported nonadherence costs to be less than adherence costs[16 19 29 37 52 56 59 75 81 83 84]. Four reported fluctuating findings based on varying nonadherence cost subcategories[26 41 61 82] and two studies reported conflicting findings between adjusted and unadjusted costs [73 74]. Sunyecz et al[62], Eisenberg et al[34] and Joe et al[80] reported all cause total nonadherence costs to be higher (\$28,395 vs. \$24,134, \$7,551 vs. \$7,051 and \$5,271 vs. \$4,375)) but disease group specific nonadherence costs to be lower (\$1923 vs. \$3273, \$703 vs. \$1012 and \$3,252 vs. \$4,151) whereas Hansen et al[40] reported all cause total

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3 nonadherence costs to be lower (\$18540 vs. \$52302) but disease group specific nonadherence total
4 costs to be higher (\$3,879 vs. \$2,954).
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7 The association between nonadherence and cost was determined through use of a variety of scaling
8 systems. The most utilized methods were MPR and PDC. These measures could then further be sub-
9 categorized based on the percentage of adherence/nonadherence. The 80-100% category was
10 classified as the most adherent group across both scales, with the most common definition of
11 nonadherence being <80% MPR or PDC.
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15 **Cardiovascular Disease**

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18 Twelve studies measured the economic impact of medication nonadherence in cardiovascular
19 disease [17 24 54 55 58 60 61 70 75 82 84 85]. Six studies reported adjusted costs [17 24 54 55 60
20 70] with annual costs being extrapolated for two of these[24 54]. Total healthcare costs and/or total
21 costs were assessed in all of the studies with the major indicators measured including pharmacy
22 costs^{16,20,21,23,25}, medical costs^{15,16,20, 23,25} and outpatient costs^{16, 21}. The annual economic cost of
23 nonadherence ranged from \$3,347 to \$19,472. Sokol et al[60] evaluated the economic impact of
24 medication nonadherence across three cardiovascular conditions; hypertension,
25 hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined,
26 pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups.
27 Total costs and medical costs were lower for the adherent groups of hypertension and
28 hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical
29 costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.
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40 Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total
41 costs of nonadherence ranging from \$1,433 to \$8,377 [58 61 75 82 84 85]. Rizzo et al[58] reported
42 cost findings through subgroup analysis of five conditions. For all conditions the total healthcare
43 costs were higher for nonadherent groups compared with adherent. While Zhao et al[75],
44 categorized participants into adherence subgroups; finding that total healthcare costs were lower
45 for the nonadherent population. The remaining studies used five key indicators to determine the
46 economic impact: inpatient costs[61 82], outpatient costs[61 82], pharmacy costs[61 84 85], medical
47 costs[84 85] and hospitalization costs[84 85].
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53 **Mental Health**

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56 The analyses used to report the economic impact of medication nonadherence in mental health
57 varied widely. Ten of 13 studies provided a total nonadherence cost estimate in mental health[16 18
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3 20 45 52 59 67 80 87 88], with annual cost data being extrapolated for three of these[20 59 88]. Six
4 studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged
5 from \$3,252 to \$19,363 [16 18 52 53 67 80]. Bagalman et al[18] focused primarily on the indirect
6 costs associated with nonadherence – short-term disability, workers compensation and paid time off
7 costs – while all other studies addressed direct costs. The main indicators used to measure the direct
8 economic impact of medication nonadherence were pharmacy costs[16 32 45 52 53 59 67 88],
9 inpatient costs[32 53 59 87 88], outpatient costs[16 32 52 59 88] and hospitalization costs[15 16 52
10 88].

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17 The total unadjusted cost for medication nonadherence ranged from \$2,512 to \$18,811 as reported
18 in three studies[45 59 88]. Becker et al[20] used a subgroup analysis to classify patients based on
19 their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%,
20 <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual
21 costs that were \$3,018 more than those of the maximal adherence group (75-100%).

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26 Knapp et al[87] outlined the predicted cost of nonadherence with reference to relative impact and
27 other factors associated with resource use and costs in patients with schizophrenia. Total costs
28 (\$116,434) were substantially higher than the other two indicators, which were inpatient costs
29 (\$13,577) and external services costs (\$3,241).

30 31 32 33 **Diabetes mellitus:**

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Nine studies reported some cost measurement of the impact of medication nonadherence with
reference to the health system and the individual[33 38 40 44 68 70 81 83 86]. One study estimated
that the total US cost attributable to nonadherence in diabetes was slightly over \$5 billion[44]. Five
studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient
ranging from \$2,741 to \$9,819 [40 44 68 70 86]. One study reported total costs in relation to
subgroup analysis based on MPR level[68], and another reported total healthcare costs through
subgroup analysis of commercially insured and Medicare supplemental patients[70].

A further three studies reported unadjusted cost findings[33 81 83] and four studies reported
unadjusted costs in addition to adjusted values[38 40 68 86]. Unadjusted total healthcare costs
and/or total costs ranged from \$1,142 to \$7,951. Extrapolated annual costs were determined for
two studies based on cost data presented [33 83].

The most prominent indicators used to determine costs were pharmacy costs[33 38 40 68 70 86],
outpatient costs[33 40 70 83 86], inpatient costs[40 70 86] and hospitalization costs[44 81 83]. All
studies assessed the direct costs associated with medication nonadherence. One study evaluated

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3 the relationship between nonadherence and short term disability costs in addition to assessing
4 direct costs[38].
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7 **Osteoporosis:**

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9 The cost of medication nonadherence in relation to osteoporosis was predominately examined
10 through analysis of the direct costs associated with nonadherence using total healthcare costs
11 and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department
12 costs. Two studies further assessed the economic impact of nonadherence through evaluation of
13 fracture related costs [41 77]. Four out of 11 studies reported the adjusted cost of medication
14 nonadherence in addition to reporting unadjusted costs [21 73 74 76]. Three studies further
15 classified nonadherence through subgroup analysis, with Briesacher et al[21] using MPR 20% interval
16 increases and the two studies conducted by Zhao et al[73 74] using PDC, with ≥80% classified as high
17 adherence, 50-79% medium adherence and <50% low adherence . In the studies conducted by Zhao
18 et al[73 74], total healthcare costs were highest for the medium adherence group (\$41,402 and
19 \$44,190) followed by the highest adherence group (\$37,553 and \$43,863), and lowest for the low
20 adherence group (\$34,019 and \$43,771). These annual costs were extrapolated from study data. In
21 contrast, Briesacher et al[21] modelled the subgroup analyses against the lowest adherence group
22 (<20% MPR), finding that costs decreased as adherence increased.
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33 Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from \$669
34 to \$43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In
35 the three studies that reported the lowest level of nonadherence to be PDC <50%, the cost of this
36 category ranged from \$16,938 to \$43,404 [41 73 74].
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40 One study examined only the medical costs of nonadherence through MPR subgroup analysis in
41 commercial and Medicare supplemental populations. The findings were that, for all levels of
42 nonadherence, costs of nonadherence were higher for Medicare supplemental patients [39].
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46 **Respiratory Disease:**

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48 All five studies reported the unadjusted cost of medication nonadherence. The methods of
49 classifying adherence levels varied greatly among them[29 31 46 57 78]. Two studies used MPR[29
50 57], one the Morisky 4-Item scale[46], one the Global Initiative for Chronic Obstructive Lung Disease
51 (GOLD) 2007 Guidelines[78] and one a 37 day gap in claims data[31]. Joshi et al[46] reported on the
52 indirect costs of medication nonadherence through consideration of losses in total productivity
53 costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs.
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55 Delea et al[29] reported a direct relationship between decreases in medication nonadherence level
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3 and total costs, whereas Quittner et al[57] reported an inverse relationship between decreases in
4 medication nonadherence level and total healthcare cost. The total expenses associated with the
5 lowest subgroup of adherence across all measures ranged from \$804 to \$36,259.
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8 **Gastrointestinal Disease:**

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10 Three of five studies reported the adjusted annual cost of medication nonadherence per patient
11 utilizing the MPR method [37 50 65]. Of these, two reported the total cost (\$12,085 and \$37,151)[37
12 65] with the main contributors to the overall total cost being inpatient costs (22% and 37%),
13 outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).
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16 The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the
17 total cost nor total healthcare costs[23 47]. Carter et al[23] reported hospitalization costs to be
18 \$42,854 while Kane et al[47] reported a significantly lower cost at \$5,566 in addition to other direct
19 cost contributors.
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22 **Epilepsy:**

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24 Three studies reported the economic impact of medication nonadherence in epilepsy. They all
25 reported unadjusted costs using an MPR cut off of <80%[28 35 36]. The main economic indicators
26 used to assess total costs were inpatient costs (\$2,289 to \$6,874), emergency department visit costs
27 (\$331 to \$669) and pharmacy costs (\$442 to \$1,067). Davis et al[28] modelled the costs of the
28 nonadherent group against the adherent group. The annual costs reported by Faught et al[36] were
29 extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from \$1,866
30 to \$22,673.
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33 **HIV/AIDS:**

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35 The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all
36 three studies was similar [19 25 56]. Two of the three studies examined the costs only for HIV[19
37 25], while Pruitt et al[56] assessed the cost in AIDS as well as HIV. The total unadjusted costs for
38 nonadherent HIV patients ranged from \$16,957 to \$30,068 with one study further categorizing
39 patients with HIV as having either a high viral load or low viral load[19]. The total cost of
40 nonadherence in AIDS was \$30,523[56]. All studies used comparable indicators (total cost, inpatient
41 cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.
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Parkinson's Disease:

The direct costs associated with Parkinson's disease were assessed in all three studies. The unadjusted total cost ranged from \$10,988 to \$52,023 [27 30 66]. Wei et al[66] further sub-grouped patients into MPR adherence percentage categories, and found that costs increased on all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with nonadherence. One study additionally reported the adjusted cost, estimating that \$10,290 could be attributed to medication nonadherence annually[30].

Musculoskeletal Conditions:

Differing subgroup analyses was used to measure the impact of medication nonadherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of nonadherence[43], one assessed only the medical costs[63] and one examined the direct costs in commercial and Medicare supplemental patient populations[72]. Zhao et al[72] reported the adjusted annual cost in the commercial population to be \$22,609, and in the Medicare supplemental group, \$28,126. Ivanova et al[43] reported only unadjusted costs and the annual total cost of \$3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

Cancer:

Two studies evaluated the effects of medication nonadherence in cancer[26 69]. One study reported total annual costs of \$119,416[69], while the other gave a subgroup analysis based on classified adherence levels[26]. In general the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs (\$162,699 and \$67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

Addiction:

The adjusted annual total healthcare cost of medication nonadherence was reported as \$53,504[49] while the unadjusted cost ranged from \$29,406 to \$52,213 [49 64]. Leider et al[49] reported the main contributors to this cost to be outpatient costs (\$10,829) and pharmacy costs (\$8,855), whereas Tkacz et al[64] reported them to be inpatient costs (\$28,873 and \$28,407) and outpatient costs (\$15,893 and \$15,460).

Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication nonadherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of \$138,525[48]. The economic indicators used to derive this cost were inpatient costs (\$16,192), outpatient costs (\$111,100), emergency department visit costs (\$801) and pharmacy costs (\$3,538).

Blood conditions:

Only Candrilli et al[22] reported cost findings on the relationship between nonadherence and healthcare costs, giving an adjusted total cost estimate of \$13,458 for nonadherence classified as MPR <80%.

All causes:

In addition to disease-specific studies of the economic impact of medication nonadherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of these studies, annual costs were extrapolated from the original data[24 40 43 54 57 59 88]. Ten studies reported on economic indicators without giving total cost or total healthcare cost[15 38 39 47 48 50 53 75 79 88], and one study reported on costs per episode of nonadherence[79] .

The adjusted cost of medication nonadherence was reported in 10 studies with an estimated range of \$7,808 to \$52,341 [22 24 30 40 52 54 60 65 70 71]. Sokol et al[60] reported the all-cause cost of nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[54] reported only using MPR level breakdown.

Fourteen studies reported the unadjusted economic impact of medication nonadherence with an estimated range of \$1,037 to \$53,793 [15 34 39 43 47 48 51 57-59 62 75 79 88]. A further four studies reported adjusted and unadjusted costs[30 38 40 86]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).

3.5 Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication nonadherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of required statistical parameters in particular standard deviation[89]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.

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4 Discussion

To our knowledge, this is the first systematic review analyzing the economic impact of medication nonadherence across different disease groups. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, Emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesise costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g. mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g. cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to medication nonadherence thus enabling greater planning in terms of health policy to help counteract costs.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [90], who compared six key adherence measures on the same study participants, found that the measures produced similar adherence values for all participants, although PDC and continuous measure of medication gaps produced slightly lower values. While this highlights the comparability of the measures of

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3 medication nonadherence, it further justifies the need to agree on consistent methods for
4 estimating nonadherence through use of pharmacy claims data.
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7 MPR was the most commonly used measure to estimate medication nonadherence. MPR was used
8 in 64% of studies, followed by PDC, which was used in 9%. These percentages were consistent with
9 those found recently by Sattler et al [91]. Even though the measures of medication nonadherence
10 may be comparable, the definition of MPR and the cut-off points to define nonadherence differed
11 significantly. Dragomir et al[84] defined MPR as the total days' supply of medication dispensed in the
12 period, divided by the follow up period, with the assumption of 100% adherence during
13 hospitalization; Wu et al[70] removed the number of hospitalized days from the calculation; and
14 Pittman et al[54] calculated the total number of days between the dates of the last filling of a
15 prescription in the first six months in a given year and the first filling of a prescription in the 365 days
16 before the last filling. Nonadherence could also be further classified into subcategories within MPR
17 and PDC based on percentages. Twenty-eight studies defined nonadherence as MPR < 80%, and 19
18 studies categorized nonadherence into varying percentage subgroups. While Karve et al[92]
19 validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting
20 subsequent hospitalizations in patients across a broad array of chronic diseases, 71 of the 74 studies
21 included in this review examined more than just hospitalization costs as an indicator metric. Further
22 research is required to identify and standardise nonadherence thresholds using other outcomes such
23 as laboratory, productivity and pharmacy measures.
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35 Within the 74 studies covered, 30 different indicators were used to measure the cost of
36 nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a
37 meta-analysis was impossible. It is imperative that a standardized approach be established to
38 measure and report the economic impact of medication nonadherence. The core outcome set must
39 take into consideration the perspective of the intended audience and the proportion of
40 nonadherence cost that is attributable to each outcome to determine an appropriate model[93]. The
41 critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient
42 costs, outpatient costs, emergency department visit costs, medical costs and hospitalization costs for
43 analysis based on direct costs. For indirect analysis the core outcomes include short term disability
44 costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs.
45 We suggest that further analysis of the contribution of each outcome to the overall cost of
46 nonadherence be undertaken to help develop a tool that can be utilized for future research.
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55 Many studies have examined the relationship between nonadherence and economic outcomes using
56 a cross-sectional analysis[44]. The implications of this are that potentially crucial confounders such
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3 as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for
4 example, did greater adherence result in reduced costs and improved health outcomes, or was the
5 patient healthier initially and more capable of being adherent? A longitudinal design is needed to
6 overcome this limitation.
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10 None of the studies included a full economic evaluation. An economic evaluation requires a
11 comparison of two or more alternative courses of action, while considering both the inputs and
12 outputs associated with each[13]. While none of the studies taken separately could inform a choice
13 between alternative courses of action, they did provide key evidence for decision makers about
14 costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority
15 of studies to model cost estimates. Three-quarters of the studies were classified as cost
16 descriptions, providing a cost or outcome overview of the health consequences associated with
17 nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall
18 conclusions that are able to be drawn and emphasised the need for future study design to
19 incorporate elements allowing full economic evaluations to be conducted. Hughes et al[94]
20 highlighted the need for more information on the consequences of nonadherence, so that economic
21 evaluations could reflect the potential long-term effect of this growing problem.
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30 Due to the advances in technology available to record and assess medication nonadherence, the
31 inclusion of studies undertaken in the late 1990s and early 2000s may have affected the
32 comparability of results, despite the fact that these studies met the inclusion criteria[15 16 58 67 68
33 87]. The quality of data presents a limitation. Information on disease groups with fewer included
34 studies may be less reliable than information on those with more. However, our findings affirm the
35 pattern of association between nonadherence and increasing healthcare costs.
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5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilisation of existing data could help to better define costs and provide valuable input into the development of an economic model to standardise the economic impact of medication nonadherence.

6 Footnotes

Contributors: RC, VGC, SB, FFL and MF conceived the paper. RC and VGC performed all the data extraction and quality assessment. RC drafted the initial form and all revisions of this manuscript. All other authors (RC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

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Table 1: Studies identified with costs reported by adherence level and disease state

Author, Year, Country	Objective	Study Characteristics	Adherence (as reported in paper)	Outcomes/ Indicators	Results (USD, 2015)	Quality
Cardiovascular Disease						
<i>Aubert et al</i> [1] 2010 US	To investigate whether compliance during the first 2 years of statin therapy is associated with reduced hospitalization rates and direct medical costs during year 3.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 10227 (A:3512, NA:6715)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = non-compliant <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence:</u> THC:\$5289.61 (\$6865.90), MC:\$4908.09 (\$6370.60)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Casciano et al</i> [2] 2013 US	To assess the economic burden of underuse and nonadherence of warfarin therapy among patients with non-valvular atrial fibrillation in a commercially insured population.	<u>Design:</u> Retrospective, observational, quasi-experimental study <u>Follow Up:</u> 18months <u>Sample Size:</u> 13289 (A:2852, NA:4184, NE:6253)	<u>Measure:</u> PDC <u>Classification:</u> PDC <80 = low adherence , 0 = no warfarin exposure <u>Method of Assessment:</u> pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence*:</u> TC:\$16612.44(\$19936.70), IC:\$9382.56 (\$11260.10), OC:\$8605.92 (\$10328), PC:\$2388.24 (\$2866.20), MC:\$15235.80(\$18285)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Dilokthornsakul et al</i> [3] 2012 Thailand	To determine the effects of medication supplies on healthcare costs and hospitalizations in patients with chronic heart failure receiving angiotensin converting enzyme inhibitors or	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 393 (A:168, NA:219, OA:6)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = undersupply, MPR >120 = oversupply <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> THC:\$1157 (\$1433.06), IC:\$1019 (\$1262.13), OC:\$138 (\$170.93)	<u>Quality:</u> high <u>Classification:</u> cost description

angiotensin receptor blockers.

Dragomir et al[4]
2010
Canada

To evaluate the impact of low adherence to antihypertensive agents on cardiovascular outcomes and hospitalization costs.

Design: Retrospective cohort study
Follow Up: 3 years
Sample Size: 56896 (A:38217, NA:18679)

Measure: MPR
Classification: MPR≥80 = adherent, MPR < 80 = nonadherent
Method of Assessment: pharmacy claims data

Total Healthcare Costs
Pharmacy Costs
Medical Costs
Hospitalization Costs

Type of Costs: unadjusted and predicted
Classification: disease state specific and hospitalised patients
Currency Year: CAD, 2006
Cost of Nonadherence: Unadjusted Disease state specific: THC:\$7165 (\$6900.87), PC: \$1800 (\$1733.64), MC: \$1370 (\$1319.50), HC: \$3995 (\$3847.73)

Quality: medium
Classification: cost description

Unadjusted Hospitalised patients:
THC: \$17397 (\$16755.67), PC:\$2685 (\$2586.02), MC:\$2608 (\$2511.86), HC: \$12104 (\$11657.79)
Predicted disease state specific:
HC:\$3877 (\$3734.08)
Predicted hospitalised patient:
HC:\$11715 (\$11283.13)

Dragomir et al[5]
2010
Canada

To evaluate the impact of low adherence to statins on clinical issues and direct healthcare costs.

Design: Retrospective cohort study
Follow Up: 3 years
Sample Size: 55134 (A:28549, NA:26585)

Measure: MPR
Classification: MPR≥80 = adherent, MPR < 80 = nonadherent
Method of Assessment: pharmacy claims data

Total Healthcare Costs
Pharmacy Costs
Medical Costs
Hospitalization Costs

Type of Costs: unadjusted and predicted
Classification: disease state specific and hospitalised patients
Currency Year: CAD, 2005
Cost of Nonadherence: Unadjusted Disease state specific:
THC:\$6243 (\$6175.76), PC:\$2506 (\$2479.01), MC:\$1241 (\$1227.63), HC:\$2496 (\$2469.12)

Quality: medium
Classification: cost description

Unadjusted Hospitalised patients:
THC:\$14725 (\$14566.40), PC:\$3374 (\$3337.66), MC:\$2475 (\$2448.34), HC:\$8876 (\$8780.40)
Predicted disease state specific:

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6					HC:\$2669 (\$2640.25)		
7					Predicted hospitalised patient: HC\$9214		
8					(\$9114.76)		
9	<i>Pittman et al</i> [6]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted	<u>Quality:</u> medium
10	2011	relation among statin	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
11	US	adherence, subsequent	<u>Follow Up:</u> 18 months	MPR ≥ 80 =	Costs	state specific	description
12		hospitalizations and	<u>Sample Size:</u> 381422	>60<79% =	Pharmacy	<u>Currency Year:</u> USD, 2009	
13		healthcare costs.	(A:258013, MA:65795,	moderate	Costs	<u>Cost of Nonadherence</u> *: all cause:	
14			LA:57614)	adherence, MPR	Medical Costs	THC(>80):\$6798.67 (\$7505.66),	
15				<59 =low		THC(60-79):\$7072.67 (\$7808.16),	
16				adherence		THC(<59):\$7401.33 (\$8170.99),	
17				<u>Method of</u>		PC(>80):\$1767.33 (\$1951.11),	
18				<u>Assessment:</u>		PC(60-79):\$1789.33 (\$1975.40),	
19				pharmacy claims		PC(<59):\$1937.33 (\$2138.79),	
20				data		MC(>80):\$4472.67 (\$4937.78),	
21						MC(60-79):\$4840.67 (\$5344.05),	
22						MC(<59):\$5138.67 (\$5673.04)	
23						Disease state specific:	
24						PC(>80):\$558.67 (\$616.77),	
25						PC(60-79):\$442.67 (\$488.70),	
26						PC(<59):\$325.33 (\$359.16),	
27						MC(>80):\$1596.67 (\$1762.71),	
28						MC(60-79):\$1722 (\$1901.07),	
29						MC(<59):\$1792.67 (\$1979.09)	
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31	<i>Pittman et al</i> [7]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted and unadjusted	<u>Quality:</u> medium
32	2010	relationship between	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
33	US	adherence to	<u>Follow Up:</u> 2 years	MPR ≥ 80 =	Costs	<u>Currency Year:</u> USD, 2008	description
34		antihypertensive	<u>Sample Size:</u>	>60<79% =	Outpatient	<u>Cost of Nonadherence:</u> Adjusted:	
35		medications and	625620(A:467006,	moderate	Costs	THC(>80):\$7261 (\$8077.79),	
36		subsequent	MA:96226, LA:62388)	adherence, MPR	ED Costs	THC(60-79):\$7530 (\$8377.05),	
37		hospitalizations,		<59 =low	Pharmacy	THC(<59):\$7370 (\$8199.05),	
38		emergency		adherence	Costs	OC(>80):\$3390 (\$3771.34),	
39		department visits and			Hospitalization	OC(60-79):\$3705 (\$4121.77),	
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costs of care.

Method of Assessment:
pharmacy claims data

Costs

OC(<59):\$3776 (\$4200.76),
EDC(>80):\$101 (\$112.36),
EDC(60-79):\$134 (\$149.07),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2383 (\$2651.06),
PC(60-79):\$1932 (\$2149.33),
PC(<59):\$1509 (\$1678.75),
HC(>80):\$1386 (\$1541.91),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$1913 (\$2128.19)
Unadjusted:
THC(>80):\$7182 (\$7989.90),
THC(60-79):\$7560 (\$8410.42),
THC(<59):\$7995 (\$8894.35),
OC(>80):\$3396 (\$3778.01),
OC(60-79):\$3635 (\$4043.90),
OC(<59):\$3887 (\$4324.25),
EDC(>80):\$102 (\$113.47),
EDC(60-79):\$131 (\$145.74),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2317 (\$2577.64),
PC(60-79):\$2034 (\$2262.80),
PC(<59):\$1880 (\$2091.48),
HC(>80):\$1366 (\$1519.66),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$2057 (\$2288.39)

For peer review

Rizzo et al[8]
1997
US

To investigate variations in compliance with four classes of antihypertensive agents- diuretics, ACEIs, CCBs and β -

Design: Retrospective cohort study
Follow Up: 12 months
Sample Size: 7211(P:2668, NC:3101, NP:649, T:793)

Measure: ordinary least square regression analysis
Classification: >80% = persistent, \geq 30<80% = non-compliance, <30%

Total Healthcare Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 1994
Cost of Nonadherence: All cause:
THC(>80):\$341 (\$509.66),
THC(30-80):\$694 (\$1037.26),

Quality: low
Classification: cost description

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blockers and the health care costs associated with various degrees of compliance.

= non-persistence
Method of Assessment:
pharmacy claims data

THC(<30):\$735 (\$1098.53)
Disease state specific:
Renal:
THC(>80):\$2135 (\$3190.98),
THC(30-80):\$2488 (\$3718.58),
THC(<30):\$2529 (\$3779.86),
Acute MI:
THC(>80):\$1358 (\$2029.67),
THC(30-80):\$1711 (\$2557.27),
THC(<30):\$1752 (\$2618.55), Diabetes:
THC(>80):\$770 (\$1150.85),
THC(30-80):\$1123 (\$1678.44),
THC(<30):\$1164 (\$1739.72),
CHF:
THC(>80):\$698 (\$1043.23),
THC(30-80):\$1051 (\$1570.83),
THC(<30):\$1092 (\$1632.11),
Angina:
THC(>80):\$702 (\$1049.21),
THC(30-80):\$1055 (\$1576.81),
THC(<30):\$1096 (\$1638.09)

For peer review

Sokol et al[9]
2005
US

To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Design: Retrospective cohort observational study
Follow Up: 12 months
Sample Size: 137277
Diabetes:(≥80: 1801, 60-79: 599, 40-59: 419, 20-39: 259, <19: 182)
Hypertension:(≥80: 5804, 60-79: 921, 40-59: 562, 20-39: 344, <19: 350)

Measure:
medication supply
Classification: 1-19%, 20-39%, 40-59%, 60-79%, 80-100%
Method of Assessment:
pharmacy claims data

Total Costs
Pharmacy Costs
Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 1998
Cost of Nonadherence: All cause:
Diabetes:
TC(1-19):\$16498 (\$23071.58),
TC(20-39):\$13077 (\$18287.49),
TC(40-59):\$12978 (\$18149.05),
TC(60-79):\$11484 (\$16059.77),
TC(80-100):\$8886 (\$12426.60),
PC(1-19):\$1312 (\$1834.76),

Quality: medium
Classification: cost description

Hypercholesterolemia:
(≥80: 1754, 60-79: 520,
40-59: 324, 20-39: 216,
<19: 167)

CHF: (≥80: 518, 60-79:
107, 40-59: 82, 20-39:
70, <19: 86)

PC(20-39):\$1877 (\$2624.89),
PC(40-59):\$1970 (\$2754.94),
PC(60-79):\$2121 (\$2966.11),
PC(80-100):\$2510 (\$3510.10),
MC(1-19):\$15186 (\$21236.82),
MC(20-39):\$11200 (\$15662.61),
MC(40-59):\$11008 (\$15394.10),
MC(60-79):\$9363 (\$13093.66),
MC(80-100):\$6377 (\$8917.90),

Hypertension:

TC(1-19):\$9747 (\$13630.66),
TC(20-39):\$11238 (\$15715.75),
TC(40-59):\$9491 (\$13272.66),
TC(60-79):\$8929 (\$12486.73),
TC(80-100):\$8386 (\$11272.38),
PC(1-19):\$916 (\$1280.98),
PC(20-39):\$952 (\$1331.32),
PC(40-59):\$1123 (\$1570.46),
PC(60-79):\$1271 (\$1777.43),
PC(80-100):\$1817 (\$2540.98),
MC(1-19):\$8831 (\$12349.69),
MC(20-39):\$10286 (\$14384.43),
MC(40-59):\$8368 (\$11702.20),
MC(60-79):\$7658 (\$10709.31),
MC(80-100):\$6570 (\$9187.80),

Hypercholesterolemia:

TC(1-19):\$10916 (\$15265.45),
TC(20-39):\$7982 (\$11162.40),
TC(40-59):\$6756 (\$9447.91),
TC(60-79):\$8412 (\$11763.74),
TC(80-100):\$6752 (\$9442.31),
PC(1-19):\$1067 (\$1492.14),
PC(20-39):\$1152 (\$1611.01),

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PC(40-59):\$1247 (\$1743.86),
PC(60-79):\$1736 (\$2427.70),
PC(80-100):\$1972 (\$2757.74),
MC(1-19):\$9849(\$13773.30),
MC(20-39):\$6830 (\$9551.39),
MC(40-59):\$5509 (\$7704.04),
MC(60-79):\$6676 (\$9336.03),
MC(80-100):\$4780 (\$6684.58),
CHF:
TC(1-19):\$23964 (\$33512.38),
TC(20-39):\$19188 (\$26833.40),
TC(40-59):\$26311 (\$36794.54),
TC(60-79):\$29785 (\$41652.74),
TC(80-100):\$22164 (\$30995.18),
PC(1-19):\$1961 (\$2742.35),
PC(20-39):\$2055 (\$2873.81),
PC(40-59):\$2208 (\$3087.77),
PC(60-79):\$3412 (\$4771.50),
PC(80-100):\$3107 (\$4344.97),
MC(1-19):\$22003 (\$30770.03),
MC(20-39):\$17133 (\$23959.59),
MC(40-59):\$24103 (\$33706.77),
MC(60-79):\$26373 (\$36881.24),
MC(80-100):\$19056 (\$26648.81)
Disease state specific: Diabetes:
TC(1-19):\$8867 (\$12400.03),
TC(20-39):\$4124 (\$5767.20),
TC(40-59):\$6522 (\$9120.67),
TC(60-79):\$6291 (\$8797.63),
TC(80-100):\$4570 (\$6390.90),
PC(1-19):\$55 (\$76.91),
PC(20-39):\$165 (\$230.74),
PC(40-59):\$285 (\$398.56),

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PC(60-79):\$404 (\$564.97),
PC(80-100):\$763 (\$1067.02),
MC(1-19):\$8812 (\$12323.11),
MC(20-39):\$6959 (\$9731.79),
MC(40-59):\$6237 (\$8722.11),
MC(60-79):\$5887 (\$8232.66),
MC(80-100):\$3808 (\$5325.29),
Hypertension:
TC(1-19):\$4878 (\$6821.62),
TC(20-39):\$6062 (\$8477.39),
TC(40-59):\$5297 (\$7407.57),
TC(60-79):\$5262 (\$7358.63),
TC(80-100):\$4871 (\$6811.84),
PC(1-19):\$31 (\$43.35),
PC(20-39):\$89(\$124.46),
PC(40-59):\$184 (\$257.31),
PC(60-79):\$285 (\$398.56),
PC(80-100):\$489 (\$683.84),
MC(1-19):\$4847 (\$6778.27),
MC(20-39):\$5973 (\$8352.92),
MC(40-59):\$5113 (\$7150.26),
MC(60-79):\$4977 (\$6960.07),
MC(80-100):\$4383 (\$6129.39),
Hypercholesterolemia:
TC(1-19):\$6888 (\$9632.50),
TC(20-39):\$4999 (\$6990.84),
TC(40-59):\$3825 (\$5349.06),
TC(60-79):\$5541 (\$7748.79),
TC(80-100):\$3924(\$5487.51),
PC(1-19):\$78 (\$109.08),
PC(20-39):\$213 (\$297.87),
PC(40-59):\$373 (\$521.62),
PC(60-79):\$603 (\$843.26),

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For peer review

PC(80-100):\$801 (\$1120.16),
MC(1-19):\$6810 (\$9523.42),
MC(20-39):\$4786 (\$6692.97),
MC(40-59):\$3452 (\$4827.44),
MC(60-79):\$4938 (\$6905.53),
MC(80-100):\$3124 (\$4368.75),
CHF:
TC(1-19):\$9841 (\$13762.12),
TC(20-39):\$7733 (\$10814.19),
TC(40-59):\$11378 (\$15911.53),
TC(60-79):\$13924 (\$19471.98),
TC(80-100):\$12698 (\$17787.48),
PC(1-19):\$15 (\$20.98),
PC(20-39):\$90 (\$125.86),
PC(40-59):\$134 (\$187.39),
PC(60-79):\$158 (\$220.95),
PC(80-100):\$437 (\$611.12),
MC(1-19):\$9826 (\$13741.14),
MC(20-39):\$7643 (\$10688.33),
MC(40-59):\$11244 (\$15724.14),
MC(60-79):\$13766 (\$19251.02),
MC(80-100):\$12261 (\$17146.36)

Stroupe et al[10]
2006
US

To determine the rates of undersupply, appropriate supply, and oversupply of antihypertensive drugs as measured by refill adherence, among patient with complicated and uncomplicated hypertension and to

Design: Retrospective cohort study
Follow Up: 3.3 years
Sample Size: 15206 (not specified)

Measure: MPR
Classification:
MPR<80 = undersupply, MPR >120 = oversupply
Method of Assessment:
pharmacy claims data

Total Healthcare Costs
Inpatient Costs
Outpatient Costs
Pharmacy Costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002
Cost of Nonadherence**: THC:\$6032.5 (\$7830.11), IC:\$2067 (\$2682.94), OC:\$3965 (\$5146.52), PC:\$130 (\$1683.74)

Quality: medium
Classification: cost description

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examine the association of refill adherence with hospitalization and healthcare costs among these patients.

Wu et al[11]
2011
US

To study statin adherence and assess associated medical utilisation and healthcare costs in patients with type 2 diabetes, based on national Medicaid database.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 1705 (A:624, NA:1081)

Measure: MPR
Classification: MPR≥80 = adherent, MPR <80 = nonadherent
Method of Assessment: pharmacy claims data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2005
Cost of Nonadherence: all cause: THC:\$17807 (\$21370.30), PC:\$4915 (\$5898.52) MC:\$12892 (\$15471.77)
Disease state specific: THC:\$2789 (\$3347.10), PC:\$489(\$586.85) MC:\$2300 (\$2760.25)

Quality: medium
Classification: cost description

Zhao et al[12]
2014
US

To evaluate the associations between statin adherence level, healthcare costs, hospital admissions and emergency room visits after statin therapy is taken for 1 year.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 10312 (96-100: 2453, 90-95: 1496, 85-89: 584, 80-84: 768, 70-79: 960, 60-69: 777, 40-59: 1687, <40:1587)

Measure: MPR
Classification: <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100%
Method of Assessment: pharmacy claims data, census data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2010
Cost of Nonadherence: all cause: PC(96-100):\$2976.80 (\$3247.04), PC(90-95):\$2826.99 (\$3083.63), PC(85-89):\$2795.39 (\$3049.16), PC(80-84):\$2690.89 (\$2935.17), PC(70-79):\$2192.83 (\$2391.90), PC(60-69):\$2323.27 (\$2534.18), PC(40-59):\$2153.93 (\$2349.47), PC(<40):\$1749.18 (\$1907.97)
Disease state specific: THC(96-100):\$6536.05 (\$7129.40), THC(90-95):\$6493.80 (\$7083.31),

Quality: medium
Classification: cost description

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THC(85-89):\$6459.40 (\$7045.79),
THC(80-84):\$6227.47 (\$6792.80),
THC(70-79):\$5713.47 (\$6232.14),
THC(60-69):\$5875.26 (\$6408.62),
THC(40-59):\$5817.58 (\$6345.70),
THC(<40):\$5249.12 (\$5725.64),
PC(96-100):\$449.86 (\$490.70), PC(90-95):\$439.74 (\$479.66),
PC(85-89):\$458.83 (\$500.48),
PC(80-84):\$423.15 (\$461.56),
PC(70-79):\$356.74 (\$389.13),
PC(60-69):\$371.30 (\$405.01),
PC(40-59):\$279.21 (\$304.56),
PC(<40):\$133.92 (\$146.08),
MC(96-100):\$3559.25 (\$3882.36),
MC(90-95):\$3666.81 (\$3999.69),
MC(85-89):\$3664 (\$3996.62), MC(80-84):\$3586.58 (\$3912.17), MC(70-79):\$3520.64 (\$3840.25), MC(60-69):\$3551.99 (\$3874.44), MC(40-59):\$3663.65 (\$3996.24),
MC(<40):\$3499.95 (\$3817.68)

Mental Health

Bagalman et al[13]
2010
US

To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 1258 (A:444, NA:814)

Measure: MPR
Classification: MPR≥80 = adherent, MPR <80 = nonadherent
Method of Assessment: pharmacy claims data

Total Costs
Short term disability cost
Workers compensation cost
Paid time off cost

Type of Costs: adjusted
Classification: disease state specific
Currency Year: USD, 2005
Cost of Nonadherence: TC:\$6894 (\$8273.53), STDC:\$2134 (\$2561.03), WCC:\$762 (\$914.48), PTOC:\$3998 (\$4798.03)

Quality: medium
Classification: cost description

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49	<p><i>Becker et al</i>[14] 2007 US</p>	<p>Examine treatment outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505)</p>	<p><u>Measure:</u> prescription refill rate <u>Classification:</u> 75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, <25% = negligible adherence <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Total Costs</p>	<p><u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2006 <u>Cost of Nonadherence*:</u> TC(75-100):\$13564 (\$15792.91), TC(50-74):\$13772 (\$16035.09), TC(25-49):\$15792 (\$18387.03), TC(<25):\$16156 (\$18810.84)</p>	<p><u>Quality:</u> low <u>Classification:</u> cost description</p>
	<p><i>Eaddy et al</i>[15] 2005 US</p>	<p>To evaluate the effect of partial compliance of patients with prescribed oral atypical and conventional antipsychotic agents and the corresponding impact on resource utilisation.</p>	<p><u>Design:</u> Retrospective database analysis <u>Follow Up:</u> 1 year <u>Sample Size:</u> 7864 (<80%:2655, 80-125%:5065, >125%:144)</p>	<p><u>Measure:</u> continuous multiple interval medications available <u>Classification:</u> <80% = partially compliant, 80-125% = compliant, >125% = overly compliant <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Inpatient costs Outpatient costs Pharmacy costs Medical costs Physician office visit costs Other costs</p>	<p><u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence*:</u> IC:\$37380 (\$4906.39), OC:\$504 (\$654.19), PC:\$1872 (\$2429.83), MC:\$6228 (\$8083.86), POC:\$1944 (\$2523.29) OtC:\$12 (\$15.58)</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost description</p>
	<p><i>Gilmer et al</i>[16] 2004</p>	<p>To evaluate the relationship between</p>	<p><u>Design:</u> Retrospective database analysis</p>	<p><u>Measure:</u> cumulative</p>	<p>Total costs Outpatient</p>	<p><u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost</p>

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US	adherence to treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.	<u>Follow Up:</u> 1 year <u>Sample Size:</u> 1619 (<49%:388, 50-79%:259, 80-100%:664, >110%:308)	<u>possession ratio Classification:</u> <49% = nonadherent, 50-79% = partially adherent, 80-100% = adherent, >110% = excess medication fillers <u>Method of Assessment:</u> pharmacy claims data	costs Pharmacy costs Hospitalization costs	<u>Currency Year:</u> USD, 1999 <u>Cost of Nonadherence:</u> TC:\$8168 (\$11261.74), OC:\$3464 (\$4776.04), PC:\$1542 (\$2126.05), HC:\$3413 (\$4705.72)	description
Hong et al[17] 2011 UK	To investigate clinical and economic consequences of medication non-adherence in the treatment of bipolar disorder following a manic or mixed episode.	<u>Design:</u> Prospective observational study <u>Follow Up:</u> 21 months <u>Sample Size:</u> 1341(A:1024, NA:317)	<u>Measure:</u> assessed by treating psychiatrist <u>Classification:</u> adherent vs. nonadherent <u>Method of Assessment:</u> observational assessment	Total costs Inpatient costs Outpatient costs Pharmacy costs Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> GBP, 2008 <u>Cost of Nonadherence*:</u> all cause: PC:£55.43 (\$94.47) Disease state specific: TC:£5846.29 (\$9964.10) IC:£2740.57 (\$4670.88), OC:£1082.86 (\$1845.57), PC:£1630.29 (\$2778.58), HC:£337.14 (\$574.60)	<u>Quality:</u> medium <u>Classification:</u> cost description
Jiang et al[18] 2015 US	To estimate the impact of adherence to and persistence with atypical antipsychotics on healthcare costs and risk of hospitalization by controlling potential	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 32374 (A:11642, NA:20732)	<u>Measure:</u> PDC <u>Classification:</u> (PDC>80% = adherent, PDC<80% = nonadherent) <u>Method of Assessment:</u>	Total costs Pharmacy costs Medical services costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence:</u> Disease state specific: TC:\$14141 (\$14517.37) PC:\$3971 (\$4076.69), MSC:\$10170 (\$10440.68)	<u>Quality:</u> low <u>Classification:</u> cost description

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5		sources of endogeneity		medical and		
6				pharmacy claims		
7				data		
8	<i>Joe et al</i> [19]	To investigate the	<u>Design:</u> Retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> adjusted
9	2016	association between	cohort study	percentage of		<u>Classification:</u> all cause and disease
10	South Korea	psychiatric medication	<u>Follow Up:</u> 1 year	days of psychiatric		state specific
11		non-compliance and	<u>Sample Size:</u> 7848	prescription (PDP)		<u>Currency Year:</u> USD, 2011
12		psychiatric and non-	(A:2774, NA:2774,	<u>Classification:</u>		<u>Cost of Nonadherence:</u> all cause:
13		psychiatric service	P:1956, NP:1956)	PDP≥80% =		TC:\$4961 (\$5271.40)
14		utilisation and costs.		adherent,		Disease state specific:
15				PDP<80% =		TC:\$3061 (\$3252.50)
16				nonadherent;		
17				persistent =		
18				continued		
19				medication		
20				without		
21				interruption ≥ 56		
22				day, non-		
23				persistent = at		
24				least one		
25				medication		
26				interruption > 56		
27				days		
28				<u>Method of</u>		
29				<u>Assessment:</u>		
30				health insurance		
31				data		
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34	<i>Knapp et al</i> [20]	To assess the relative	<u>Design:</u> Retrospective	<u>Measure:</u> self-	Total costs	<u>Type of Costs:</u> predicted
35	2004	impact of non-	cohort study	report	Inpatient costs	<u>Classification:</u> disease state specific
36	UK	adherence and other	<u>Follow Up:</u> 1 year	<u>Classification:</u>	External	<u>Currency Year:</u> GBP, 2001
37		factors associated with	<u>Sample Size:</u> 658	adherent vs.	services costs	<u>Cost of Nonadherence:</u>
38		resource use and costs	(A:549, NA:109)	nonadherent		TC:£57580 (\$116434.12)
39		incurred by people		<u>Method of</u>		IC:£6714 (\$13576.57),
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5		with schizophrenia.	<u>Assessment:</u>		ESC:£1603 (\$3241.47)	
6			survey			
7	<i>Offord et al</i> [21]	To quantify early	<u>Design:</u> Retrospective	<u>Measure:</u> time to	Total costs	<u>Type of Costs:</u> adjusted
8	2013	nonadherence to	cohort study	discontinuation	Outpatient	<u>Classification:</u> all cause and disease
9	US	antipsychotic	<u>Follow Up:</u> 1 year	<u>Classification:</u>	costs	state specific
10		medications in patients	<u>Sample Size:</u> 1462	adherent vs.	Pharmacy	<u>Currency Year:</u> USD, 2008
11		with schizophrenia and	(A:589, NA:873)	nonadherent	costs	<u>Cost of Nonadherence:</u> all cause:
12		its impact on short-		<u>Method of</u>	Hospitalization	TC:\$15400 (\$17132.34)
13		term antipsychotic		<u>Assessment:</u>	costs	OC:\$5773 (\$6422.40),
14		adherence, healthcare		pharmacy claims		PC:\$3777 (\$4201.87),
15		utilisation and costs.		data		HC:\$5850 (\$6508.06)
16						Disease state specific:
17						TC:\$5358 (\$5960.72)
18						OC:\$858 (\$954.52),
19						PC:\$1549 (\$1723.25),
20						HC:\$2952 (\$3284.07)
21						
22	<i>Offord et al</i> [22]	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Inpatient	<u>Type of Costs:</u> adjusted
23	2013	of medication	cohort study	<u>Classification:</u>	costs	<u>Classification:</u> all cause and disease
24	US	adherence on	<u>Follow Up:</u> 1 year	MPR ≥ 70= high	Pharmacy	state specific
25		healthcare utilisation	<u>Sample Size:</u> 354	adherence, MPR <	costs	<u>Currency Year:</u> USD, 2008
26		among Medicare	(A:126, NA:228)	70 = low		<u>Cost of Nonadherence:</u> all cause:
27		insured schizophrenia		adherence		IC:\$9053 (\$10071.37),
28		patients.		<u>Method of</u>		PC:\$4267 (\$4746.99),
29				<u>Assessment:</u>		Disease state specific:
30				pharmacy claims		IC:\$2468 (\$2745.62),
31				data		PC:\$1085 (\$1207.05)
32						
33	<i>Robinson et al</i> [23]	To determine if the	<u>Design:</u> Retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> unadjusted
34	2006	type of antidepressant	claims analysis	Antidepressant	Inpatient	<u>Classification:</u> all cause and disease
35	US	drug is related to	<u>Follow Up:</u> 6 months	medication	costs	state specific
36		adherence and assess	<u>Sample Size:</u> 60386	management	Outpatient	<u>Currency Year:</u> USD, 2004
37		the 6 month health	(A:11526, NA:8860)	measures	costs	<u>Cost of Nonadherence</u> †: all cause:
38		care costs among		<u>Classification:</u>	ED visit costs	TC:\$12658 (\$15678.21)
39		newly diagnosed		meeting less than	Pharmacy	IC:\$3006 (\$3723.24),
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patients.

<3 medication management measures = nonadherent

costs Physician office visit costs

OC:\$6118 (\$7577.76),
EDC:\$334 (\$413.69)
PC:\$3200 (\$3963.52),
POC:\$178 (\$220.47)
Disease state specific:
TC:\$2028 (\$2511.88)
IC:\$102 (\$126.34),
OC:\$734 (\$909.13),
EDC:\$18 (\$22.29)
PC:\$1174 (\$1454.12),
POC:\$120 (\$148.63)

Svarstad et al[24]
2001
US

To examine the relationship of medication non-adherence to hospital use and costs among severely mentally ill clients.

Design: Retrospective database analysis
Follow Up: 1 year
Sample Size: 619 (A:413, NA:206)

Measure: quarter pharmacy claims
Classification: one or more quarters without a claim = nonadherent
Method of Assessment: pharmacy claims data, previous study data

Hospitalization costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 1990
Cost of Nonadherence: all cause:
HC:\$3992 (\$6593.06)
Disease state specific:
Schizophrenia/schizo affective disorder:
HC:\$3421 (\$5650.01)
Bipolar disorder:
HC:\$9701 (\$16021.85),
Other severe mental illness:
HCD:\$3024 (\$4994.34)

Quality: medium
Classification: cost description

White et al[25]
2003
US

To evaluate the economic impact of antidepressant treatment adherence among patients treated for depression

Design: Retrospective database analysis
Follow Up: 6 months
Sample Size: 14190 (A:5638, NA:8552)

Measure: MPR
Classification: MPR≥70% = adherent, MPR<70% = nonadherent
Method of Assessment: pharmacy claims

Total costs
Pharmacy costs
Medical costs

Type of Costs: adjusted
Classification: disease state specific
Currency Year: USD, 1999
Cost of Nonadherence:
TC:\$11815 (\$16290.09)
PC:\$1123 (\$1548.35),
MC:\$10692 (\$14741.74)

Quality: medium
Classification: cost description

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5			data			
6	Diabetes					
7	<i>An et al</i> [26]	This study evaluated	<u>Design:</u> Prospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
8	2014	the association	cohort study	<u>Classification:</u>	Outpatient	<u>Classification:</u> disease state specific
9	Korea	between medication	<u>Follow Up:</u> 3 years	MPR≥90% =	costs	<u>Currency Year:</u> USD, 2007
10		adherence and	<u>Sample Size:</u> 608	adherent,	Hospitalization	<u>Cost of Nonadherence*:</u>
11		clinical/economic	(A:472, NA:136)	MPR<90% =	costs	TC:\$1657.11 (\$1884.14)
12		outcomes in patients		nonadherent		OC: \$1413.99 (\$1608.20),
13		with type II diabetes		<u>Method of</u>		HC: \$243.11 (\$276.12)
14		mellitus in the republic		<u>Assessment:</u>		
15		of Korea over 3 year		pharmacy claims		
16		period.		data		
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18	<i>Egede et al</i> [27]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Inpatient costs	<u>Type of Costs:</u> unadjusted
19	2012	longitudinal effects of	cohort study	<u>Classification:</u>	Outpatient	<u>Classification:</u> disease state specific
20	US	medication	<u>Follow Up:</u> 5 years	MPR≥80% =	costs	<u>Currency Year:</u> USD, 2006
21		nonadherence on key	<u>Sample Size:</u> 740195	adherent,	Pharmacy	<u>Cost of Nonadherence*:</u>
22		costs and estimate	(A:427390, NA:312805)	MPR<80% =	costs	IC:\$14515.24 (\$17886.40)
23		potential savings from		nonadherent		OC: \$3599.27 (\$4434.16),
24		increased adherence		<u>Method of</u>		PC: \$1073.12 (\$1322.42)
25		using novel		<u>Assessment:</u>		
26		methodology that		pharmacy claims		
27		accounts for shared		data		
28		correlation among cost				
29		categories.				
30						
31	<i>Gentil et al</i> [28]	To examine healthcare	<u>Design:</u> Retrospective,	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted and unadjusted
32	2015	costs associated with	observational cohort	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease
33	Canada	adherence to oral	analysis	MPR≥80% =	Outpatient	state specific
34		antihyperglycemic	<u>Follow Up:</u> 1 year	adherent,	costs	<u>Currency Year:</u> CAD, 2010
35		agents and the effects	<u>Sample Size:</u> 301	MPR<80% =	Pharmacy	<u>Cost of Nonadherence:</u>
36		of depression and	(A:224, NA:77)	nonadherent	costs	Adjusted all cause:
37		anxiety disorders on		<u>Method of</u>	Physician	TC:\$11124 (\$9818.67),
38		these in older adults		<u>Assessment:</u>	office visit	IC:\$7419 (\$6548.43)
39		with type 2 diabetes		pharmacy claims	costs	OC: \$2687 (\$2371.70),
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For peer review

Hagen et al[29]
2014
US

To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/ short term disability costs

Design: Retrospective, observational cohort analysis
Follow Up: 1 year
Sample Size: 4978 (A:2820, NA:2158)

Measure: PDC
Classification: PDC≥80% = compliant, PDC<80% = noncompliant
Method of Assessment: pharmacy claims data

Healthcare costs
Pharmacy costs
Medical costs
Short term disability costs

data
PC: \$504 (\$444.86),
POC:\$513 (\$452.80)
Adjusted disease state specific:
TC:\$4477 (\$3951.65),
IC:\$2836 (\$2503.21)
OC: \$1518 (\$1339.87),
PC^{###}: \$-444 (\$-391.90),
POC:\$568 (\$517.24)
Unadjusted all cause:
TC:\$14979 (\$13221.30),
IC:\$6351 (\$5605.75)
OC: \$4058 (\$3581.82),
PC: \$3503 (\$3091.94),
POC:\$1066 (\$940.91)
Unadjusted disease state specific:
TC:\$9008 (\$7950.97),
IC:\$2854 (\$2519.10)
OC: \$2654 (\$2342.57),
PC: \$2498 (\$2204.87),
POC:\$1002 (\$884.42)
Type of Costs: adjusted and unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2003
Cost of Nonadherence: Adjusted all cause:
PC: \$1668 (\$2065.99),
Adjusted disease state specific:
HC:\$7642 (\$9465.39), PC:\$614 (\$760.50), MC:\$5974 (\$7399.40),
STDC:\$1840 (\$2279.03)
Unadjusted all cause:
PC:\$1727 (\$2139.06)

Quality: medium
Classification: cost description

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6					Unadjusted disease state specific:	
7					HC:\$6919 (\$8569.88), PC:\$785	
8					(\$972.30), MC:\$5192 (\$6430.82),	
9					STDC:\$1717 (\$2126.68)	
10	<i>Hansen et al</i> [30]	To compare all cause	<u>Design:</u> Retrospective,	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted and unadjusted
11	2010	total health care costs	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> all cause and disease
12	US	and diabetes mellitus	<u>Follow Up:</u> 2 years	MPR≥80% =	costs	state specific
13		specific health care	<u>Sample Size:</u> 108592	adherent,	Inpatient costs	<u>Currency Year:</u> USD, 2005
14		costs between patients	(A:63830, NA:44762)	MPR<80% =	Outpatient	<u>Cost of Nonadherence[#]:</u> Adjusted all
15		who were adherent or		nonadherent	costs	cause:
16		non-adherent to		<u>Method of</u>	Pharmacy	THC:\$13258 (\$15911.01)
17		monotherapy with		<u>Assessment:</u>	costs	Adjusted disease state specific:
18		metformin,		pharmacy claims		THC:\$2284 (\$2741.04)
19		pioglitazone or a		data		Unadjusted all cause:
20		sulfonylurea and to				THC:\$15448.50 (\$18539.90),
21		examine whether cost				IC:\$4242.33 (\$5091.25),
22		differences varied				OC:\$ 7377.83, PC:\$3828 (\$4594.01)
23		among patients using				Unadjusted disease state specific:
24		these oral antidiabetic				THC:\$3232.33 (\$3879.15), IC:\$873.50
25		drugs.				(\$1048.29), OC:\$1545.67(\$1854.96),
26						PC:\$812.67 (\$975.29)
27						
28	<i>Hong et al</i> [31]	To assess the	<u>Design:</u> Retrospective,	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
29	2011	relationship between	cohort study	<u>Classification:</u>	Hospitalization	<u>Classification:</u> disease state specific
30	South Korea	initial adherence to	<u>Follow Up:</u> 3 years	MPR≥80% =	costs	<u>Currency Year:</u> KRW, 2007
31		oral antihyperglycemic	<u>Sample Size:</u> 40082	adherent,		<u>Cost of Nonadherence:</u>
32		medications and	(A:11800, NA:28282)	MPR<80% =		TC:₩765453 (\$1142.31),
33		subsequent health		nonadherent		HC:₩397549 (\$593.28)
34		outcomes.		<u>Method of</u>		
35				<u>Assessment:</u>		
36				pharmacy claims		
37				data		
38						
39	<i>Jha et al</i> [32]	How often do	<u>Design:</u> Retrospective,	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
40	2012	previously non-	observational claims	<u>Classification:</u>	ED costs	<u>Classification:</u> disease state specific
41						<u>Quality:</u> high
42						<u>Classification:</u> cost
43						description
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5	US	adherent patients	analysis	MPR≥80% =	Hospitalization	<u>Currency Year:</u> USD, 2011	outcome
6		become adherent and	<u>Follow Up:</u> unclear	adherent,	costs	<u>Cost of Nonadherence***:</u>	description
7		vice versa?	<u>Sample Size:</u> 135639	MPR<80% =		TC:\$4680000000 (\$5006563305.49),	
8		Are changes in	(A:99976, NA:36553)	nonadherent		EDC:\$735000000 (\$786287185.80),	
9		adherence associated		<u>Method of</u>		HC:\$3950000000 (\$4225625012.11)	
10		with increased or		<u>Assessment:</u>			
11		decreased		pharmacy claims			
12		hospitalizations or		data			
13		emergency					
14		department visits?					
15		Are there certain					
16		subgroups of					
17		populations that seem					
18		to benefit more than					
19		others when they					
20		adhere to their					
21		medication?					
22		What are the financial					
23		implications of changes					
24		in adherence for the					
25		nation at large and for					
26		Medicare?					
27							
28							
29	White et al[33]	To assess the	<u>Design:</u> Retrospective,	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted and unadjusted	<u>Quality:</u> low
30	2004	relationship between	database analysis	<u>Classification:</u>	Pharmacy	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
31	US	diabetic medication	<u>Follow Up:</u> 1 year	MPR≥95%,	costs	<u>Currency Year:</u> USD, 2000	analysis
32		adherence, total	<u>Sample Size:</u> 67029	MPR>75%<95%,	Non-pharmacy	<u>Cost of Nonadherence:</u> adjusted:	
33		healthcare costs and	(>95:20170, 75-95:	MPR<75%	costs	TC(≥95):\$4835 (\$6518.17),	
34		utilisation with	14074, <75:16713)	<u>Method of</u>		TC(75-95):\$5314 (\$7163.92),	
35		patients with type 2		<u>Assessment:</u>		TC(<75):\$5706 (\$7692.38),	
36		diabetes mellitus and		pharmacy claims		PC(≥95):\$1429 (\$1926.47),	
37		concomitant diabetes		data		PC(75-95):\$1157 (\$1559.78),	
38		and cardiovascular				PC(<75):\$762 (\$1027.27),	
39		disease.				NPC(≥95):\$3406 (\$4591.70),	
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For peer review only

Wu et al[34]
2009
US

To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

Design: Retrospective, cohort study
Follow Up: 1 year
Sample Size: 2354 (A:830, NA:1524)

Measure: MPR
Classification: MPR≥80%= high compliance, MPR<80% = low compliance
Subgroup
Analysis: commercial and Medicare supplemental
Method of Assessment: pharmacy claims data

Total healthcare costs
Inpatient costs
Outpatient costs
Pharmacy costs

NPC(75-95):\$4157 (\$5604.14),
NPC(<75):\$4944 (\$6665.11)
Unadjusted:
TC(≥95):\$4809 (\$6483.12),
TC(75-95):\$5333 (\$7189.53),
TC(<75):\$5605 (\$7556.22),
PC(≥95):\$1402 (\$1890.07),
PC(75-95):\$1153 (\$1554.38),
PC(<75):\$766 (\$1032.66),
NPC(≥95):\$3407 (\$4593.05),
NPC(75-95):\$4180 (\$5635.15),
NPC(<75):\$4839 (\$6523.56)
Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2006
Cost of Nonadherence: adjusted all cause:
THC(com):\$32407 (\$37732.29),
THC(med):\$24622 (\$28668.02),
IC(com):\$ 12851(\$14692.74),
IC(med):\$ 6754 (\$7863.85),
OC(com):\$11888 (\$13841.50),
OC(med):\$10598 (\$12339.52),
PC(com):\$7667 (\$8926.88),
PC(med):\$7270 (\$8464.65)
Adjusted disease state specific:
Diabetes:
THC(com):\$10024 (\$11671.20),
THC(med):\$5015 (\$5839.09),
IC(com):\$2232 (\$2598.77),
IC(med):\$2606 (\$3034.23),
OC(com):\$1989 (\$2315.84),

Quality: medium
Classification: cost description

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OC(med):\$1231 (\$1433.28),
PC(com):\$1451 (\$1689.44),
PC(med):\$1179 (\$1372.74)
DPNP:
THC(com):\$3565 (\$4150.82),
THC(med):\$2384 (\$2775.75),
IC(com):\$1739 (\$2024.76),
IC(med):\$1048 (\$1220.21),
OC(com):\$362 (\$421.49),
OC(med):\$181 (\$210.74),
PC(com):\$1464 (\$1704.57)
PC(med):\$1155 (\$1344.80)

Osteoporosis

<p><i>Briesacher et al</i>[35] 2007 US</p>	<p>To assess rates of osteoporotic fractures and health care utilisation as a function of bisphosphonate compliance in usual clinical practice.</p>	<p><u>Design:</u> Retrospective, cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 17988 (not specified)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Total costs Inpatient costs Outpatient costs Pharmacy costs</p>	<p><u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence ****:</u> adjusted: TC(80-100):-\$859 (-\$1063.96), TC(60-79):-\$474 (-\$587.10), TC(40-59):-\$366 (-\$453.33), TC(20-39):\$151 (\$187.03), IC(80-100):-\$3233 (-\$4004.40), IC(60-79):-\$856(-\$1060.24), IC(40-59):-\$6221 (-\$7705.34), IC(20-39):-\$585 (-\$724.58), OC(80-100):-\$445 (-\$551.18), OC(60-79):-\$538 (-\$666.37), OC(40-59):-\$236 (-\$292.31), OC(20-39):\$60 (\$74.32), PC(80-100):\$997 (\$1234.89), PC(60-79):\$923 (\$1143.23), PC(40-59):\$402 (\$497.92), PC(20-39):\$160(\$198.18)</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost description</p>
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For peer review only

Eisenberg et al[36]
2015
US

To determine healthcare outcomes associated with compliance and noncompliance to bisphosphonate therapy in women diagnosed with osteoporosis

Design: Retrospective claims study
Follow Up: 2 years
Sample Size: 27905 (A:11368, NA:16537)

Measure: MPR
Classification: (≥70% = compliant, <70% = noncompliant)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Physician office visit costs

Unadjusted:
TC(80-100):-\$1273 (-\$1576.74),
TC(60-79):-\$294 (-\$364.15),
TC(40-59):-\$573 (-\$709.72),
TC(20-39):\$101 (\$125.10),
IC(80-100):-\$883 (-\$1093.68),
IC(60-79):-\$384 (-\$475.62),
IC(40-59):-\$597 (-\$739.44),
IC(20-39):-\$93 (-\$115.19),
OC(80-100):-\$774 (-\$958.68),
OC(60-79):-\$193 (-\$239.05),
OC(40-59):-\$145 (-\$179.60),
OC(20-39):\$148 (\$183.31),
PC(80-100):\$384 (\$475.62),
PC(60-79):\$284 (\$351.76),
PC(40-59):\$170 (\$210.56),
PC(20-39):\$48 (\$59.45)

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2012
Cost of Nonadherence: all cause:
TC:\$7237 (\$7550.72),
IC:\$1986 (\$2072.09),
OC:\$2057 (\$2146.17),
EDC:\$258 (\$269.18),
PC:\$2197 (\$2292.24),
POC:\$738 (\$769.99)
Disease state specific:
TC:\$674 (\$703.22),
IC:\$334 (\$348.48),
OC:\$77 (\$80.34),
EDC:\$5 (\$5.22),

Quality: medium
Classification: cost description

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6					PC:\$213 (\$222.23),		
7					POC:\$44 (\$45.91)		
8	<i>Halpern et al</i> [37]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Medical costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
9	2011	associations of	analysis	<u>Classification:</u>		<u>Classification:</u> all cause	<u>Classification:</u> cost
10	US	adherence to	<u>Follow Up:</u> 540 days	(≥80% = high		<u>Currency Year:</u> USD, 2006	outcome
11		osteoporosis therapies	<u>Sample Size:</u> 21655	adherence,		<u>Cost of Nonadherence:</u> commercial:	description
12		with occurrence of	(≥80%:8759,	≥50<80% =		MC(≥80):\$4295 (\$5000.78),	
13		closed fracture, all	≥50<80%:5237,	moderate		MC(50-80):\$4697 (\$5468.84),	
14		cause medical costs	<50%:7659)	adherence, <50%		MC(<50):\$5596 (\$6515.56)	
15		and all cause		= low adherence		Medicare:	
16		hospitalizations.		<u>Method of</u>		MC(≥80):\$4590 (\$5344.25),	
17				<u>Assessment:</u>		MC(50-80):\$5536 (\$6445.71),	
18				pharmacy claims		MC(<50):\$5801 (\$6754.25)	
19				data			
20	<i>Hazel-Fernandez et al</i> [38]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
21	2013	healthcare utilisation	cohort study	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific and	<u>Classification:</u> cost
22	US	patterns of medicare	<u>Follow Up:</u> 12 months	(≥80% = high	costs	fracture related	outcome
23		part D beneficiaries	<u>Sample Size:</u> 761	adherence,	Inpatient costs	<u>Currency Year:</u> USD, 2010	description
24		newly initiating	(≥80%:163,	≥50<80% =	Outpatient	<u>Cost of Nonadherence</u> *:	
25		teriparatide and to	≥50<80%:57,	moderate	costs	Disease state specific:	
26		assess the association	<50%:541)	adherence, <50%	ED costs	THC(≥80):\$21033 (\$22942.39),	
27		of medication		= low adherence	Pharmacy	THC(50-80):\$25574 (\$27895.62),	
28		adherence and		<u>Method of</u>	costs	THC(<50):\$15528 (\$16937.64),	
29		persistence with bone		<u>Assessment:</u>		IC(≥80):\$2198 (\$2397.54),	
30		fracture.		pharmacy claims		IC(50-80):\$8448 (\$9214.91),	
31				data		IC(<50):\$4897 (\$5341.55),	
32						OC(≥80):\$5151 (\$5618.61),	
33						OC(50-80):\$6439 (\$7023.54),	
34						OC(<50):\$5806 (\$6333.07),	
35						EDC(≥80):\$211 (\$230.15),	
36						EDC(50-80):\$330 (\$359.96),	
37						EDC(<50):\$465 (\$507.21),	
38						PC(≥80):\$13472 (\$14695),	
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PC(50-80):\$10358 (\$11298.31),
PC(<50):\$4361 (\$4756.89)
Fracture related:
THC(≥80):\$12670 (\$13820.19),
THC(50-80):\$9292 (\$10135.53),
THC(<50):\$4419 (\$4820.16),
IC(≥80):\$366 (\$399.23),
IC(50-80):\$830 (\$905.35),
IC(<50):\$1325 (\$1445.28),
OC(≥80):\$1048 (\$1143.14),
OC(50-80):\$955 (\$1041.70),
OC(<50):\$767 (\$836.63),
EDC(≥80):\$6 (\$6.54),
EDC(50-80):\$9 (\$9.82),
EDC(<50):\$44 (\$47.99),
PC(≥80):\$10810 (\$11791.34),
PC(50-80):\$7420 (\$8093.59),
PC(<50):\$2068 (\$2255.73)

<p><i>Huybrechts et al[39]</i> 2006 US</p>	<p>To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 5 years <u>Sample Size:</u> 38120 (A:9530, NA:28590)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> (≥80% = compliant, <50% = noncompliant) <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Total costs Medical costs Institutional costs</p>	<p><u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2000 <u>Cost of Nonadherence:</u> TC:\$7200 (\$9706.44), MC:\$1476 (\$1989.84), InstC:\$5736 (\$7732.80)</p>	<p><u>Quality:</u> low <u>Classification:</u> cost description</p>
<p><i>Kjellberget al[40]</i> 2016 Denmark</p>	<p>To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 38234 (A:26806, NA:11428)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> (≥70% = compliant, <70% = noncompliant) <u>Method of</u></p>	<p>Total costs Medical costs</p>	<p><u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> Euro, 2011 <u>Cost of Nonadherence:</u> all cause: TC:€4933 (\$6209.58),</p>	<p><u>Quality:</u> high <u>Classification:</u> cost outcome description</p>

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	noncompliance with health care resource use and cost.		<u>Assessment:</u> pharmacy claims data		MC:€3471 (\$4369.20), Disease state specific: TC:€754 (\$949.12), MC:€426 (\$536.24), <u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence:</u> all cause: TC:\$11749 (\$12484.12), IC:\$8768 (\$9316.60), OC:\$3945 (\$4191.83), EDC:\$104 (\$110.51), PC:\$2981 (\$3167.52), MC:\$8768 (\$9316.60), OtC:\$997 (\$1059.38) Disease state specific: TC:\$630 (\$669.42), IC:\$443 (\$470.72), OC:\$158 (\$167.89), EDC:\$3 (\$3.19), PC:\$325 (\$345.33), OtC:\$26 (\$27.63)	<u>Quality:</u> medium <u>Classification:</u> cost outcome description
Modi et al[41] 2015 US	To evaluate compliance with osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 27913 (A:23430, NA:34483)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = compliant, <80% = noncompliant) <u>Method of Assessment:</u> healthcare claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other costs		
Olsen et al[42] 2013 Denmark	To assess the association between refill compliance and all cause health care costs.	<u>Design:</u> Retrospective observational study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 47176 (not specified)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = optimal compliance, >50<80% = suboptimal compliance, <50% = low compliance) <u>Method of Assessment:</u>	Fracture costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> fracture site specific <u>Currency Year:</u> DKK, 2010 <u>Cost of Nonadherence:</u> Hip fracture: FC(50-80):kr817575.50 (\$74531.41), FC(<50):kr4454954 (\$549987.04) Spine fracture: FC(50-80):kr174700 (\$21568.12), FC(<50):kr226472 (\$27959.14)	<u>Quality:</u> medium <u>Classification:</u> cost analysis

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			pharmacy claims data		Humerus fracture: FC(50-80):kr117776.50 (\$14540.12), FC(<50):kr795217.50 (\$98173.70) Forearm fracture: FC(50-80):-kr463024 (-\$57162.70), FC(<50):kr45072.50 (\$8665.81) Other fracture: FC(50-80):-kr19261.50 (-\$2377.93), FC(<50):kr684067.50 (\$84451.66)	
<i>Sunycz et al</i> [43] 2008 US	To examine the relationship between persistence and compliance with bisphosphonate therapy and total and osteoporosis related costs and healthcare resource utilisation in a cohort of female bisphosphonate naïve users.	<u>Design</u> : Retrospective observational study <u>Follow Up</u> : 3 years <u>Sample Size</u> : 32944 (A:12186, NA:20758)	<u>Measure</u> : MPR <u>Classification</u> : (≥80% = compliant, <80% = noncompliant) <u>Method of Assessment</u> : pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Radiology costs	<u>Type of Costs</u> : unadjusted <u>Classification</u> : all cause and disease state specific <u>Currency Year</u> : USD, 2005 <u>Cost of Nonadherence</u> : All cause: THC:\$23660 (\$28394.52), IC:\$18839 (\$22608.81), OC:\$10061 (\$12074.27), EDC:\$832 (\$988.49), PC:\$6941 (\$8329.94), RC:\$1079 (\$1294.91) Disease state specific: THC:\$1602 (\$1922.57), IC:\$14074 (\$16890.30), OC:\$501 (\$601.25), EDC:\$452 (\$542.45), PC:\$918 (\$1101.70), RC:\$184 (\$220.82)	<u>Quality</u> : low <u>Classification</u> : cost description
<i>Zhao et al</i> [44] 2014 US	To examine the association between teriparatide adherence and healthcare utilisation and costs	<u>Design</u> : Retrospective cohort study <u>Follow Up</u> : 36 months <u>Sample Size</u> : 824 (≥80:362, 50-80%:219,	<u>Measure</u> : PDC <u>Classification</u> : (≥80% = high, 50-80% = medium, <50% = low)	Total healthcare costs Inpatient costs Outpatient	<u>Type of Costs</u> : adjusted and unadjusted <u>Classification</u> : disease state specific <u>Currency Year</u> : USD, 2010 <u>Cost of Nonadherence</u> : Adjusted:	<u>Quality</u> : medium <u>Classification</u> : cost description

among hip fracture patients. <50%:243)

Method of Assessment: pharmacy claims data

costs Pharmacy costs

THC(≥80):\$34428 (\$37553.4),
 THC(50-80):\$37956 (\$41401.68),
 THC(<50):\$31188 (\$34019.28),
 IC(≥80):\$7548 (\$8233.20),
 IC(50-80):\$11520 (\$1256.80),
 IC(<50):\$11556 (\$12605.04),
 OC(≥80):\$9312 (\$10157.40),
 OC(50-80):\$12816 (\$13979.40),
 OC(<50):\$13044 (\$14228.16),
 PC(≥80):\$18864 (\$20576.52),
 PC(50-80):\$13116 (\$14306.64),
 PC(<50):\$7452 (\$8128.44)

Unadjusted:
 THC(≥80):\$37464 (\$40865.04),
 THC(50-80):\$35076 (\$38260.20),
 THC(<50):\$29484 (\$32160.60),
 IC(≥80):\$7092 (\$7735.80),
 IC(50-80):\$11100 (\$12107.64),
 IC(<50):\$10632 (\$11597.16),
 OC(≥80):\$9900 (\$10798.68),
 OC(50-80):\$11352 (\$12382.56),
 OC(<50):\$11988 (\$13076.28),
 PC(≥80):\$20484 (\$22343.52),
 PC(50-80):\$12624 (\$13770),
 PC(<50):\$6864 (\$7487.16)

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2010

Quality: medium
Classification: cost description

Cost of Nonadherence*:
 Adjusted:
 THC(≥80):\$40212 (\$43862.52),
 THC(50-80):\$40512 (\$44189.76),
 THC(<50):\$40128 (\$43770.84),

Zhao et al[45]
 2013
 US

To examine the association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty

Design: Retrospective observational cohort study
Follow Up: 36 months
Sample Size: 1568 (≥80: 783, 50-80%: 382, <50%: 403)

Measure: PDC
Classification: (≥80% = high, 50-80% = medium, <50% = low)
Method of Assessment: pharmacy claims

Total healthcare costs
 Inpatient costs
 Outpatient costs
 Pharmacy costs

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lasty (KV) patients.

data

IC(≥80):\$8136 (\$8874.60),
IC(50-80):\$12060 (\$13154.76),
IC(<50):\$15444 (\$43404.36),
OC(≥80):\$12924 (\$14097.24),
OC(50-80):\$14928 (\$16283.16),
OC(<50):\$17568 (\$19162.80),
PC(≥80):\$19392 (\$21152.40),
PC(50-80):\$13908 (\$15170.52),
PC(<50):\$8700 (\$9843.24)
Unadjusted:
THC(≥80):\$42768 (\$46650.48),
THC(50-80):\$36780 (\$40118.88),
THC(<50):\$39792 (\$43404.36),
IC(≥80):\$7620 (\$8311.80),
IC(50-80):\$12228 (\$13338.12),
IC(<50):\$15768 (\$17199.48),
OC(≥80):\$14580 (\$15903.60),
OC(50-80):\$12108 (\$13207.20),
OC(<50):\$15324 (\$16715.16),
PC(≥80):\$20568 (\$22435.20),
PC(50-80):\$12444 (\$13573.68),
PC(<50):\$8700 (\$9489.84)

For peer review only

Respiratory Disease

Delea et al[46]
2008
US

To assess the association between adherence with fluticasone propionate/salmeterol combination product in a single inhaler and asthma care utilisation and costs in asthma

Design: Retrospective longitudinal cohort study
Follow Up: 24 months
Sample Size: 12907 (≥75: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652)

Measure: MPR
Classification: (≥75, 50-75%, 25-50%, <25%)
Method of Assessment: pharmacy claims data

Total costs
Outpatient costs
ED costs
Other costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence*:
TC(≥75):\$1564 (\$1990.27),
TC(50-75):\$1128 (\$1435.44),
TC(25-50):\$900 (\$1145.30),
TC(<25):\$632 (\$804.25),
OC(≥75):\$1272 (\$1618.69),

Quality: medium
Classification: cost description

patients in typical US clinical practice

OC(50-75):\$852 (\$1084.21),
 OC(25-50):\$600 (\$763.53),
 OC(<25):\$388 (\$493.75),
 EDC(≥75):\$32 (\$40.72),
 EDC(50-75):\$36 (\$45.81),
 EDC(25-50):\$60 (\$76.35),
 EDC(<25):\$48 (\$61.08),
 OtC(≥75):\$292 (\$371.59),
 OtC(50-75):\$276 (\$351.22),
 OtC(25-50):\$300 (\$381.77),
 OtC(<25):\$240 (\$305.41)

17 *Diehl et al*[47]
 18 2010
 19 US

To evaluate respiratory-related medical outcomes and cost for infants who were prescribed and received palivizumab in accordance with the dosing schedule recommended by the American Academy of Paediatrics in 2006 versus those who did not.

Design: Retrospective claims analysis
Follow Up: 7 months
Sample Size: 245 (A:73, NA:172)

Measure: 37 day gap in claims
Classification: (>37 day gap in claims = noncompliant)
Method of Assessment: pharmacy claims data

Total costs
 Pharmacy costs
 Services costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2007
Cost of Nonadherence:
 TC:\$19093.46 (\$21656.12),
 PC:\$7647.40 (\$8673.81),
 SC**:\$11604.03 (\$13161.45)

Quality: medium
Classification: cost description

31 *Joshi et al*[48]
 32 2006
 33 US

Examine the association of medication adherence with workplace productivity and health related quality of life in asthma patients.

Design: quantitative analysis
Follow Up:
Sample Size: 385 (high:150, medium:73, low: 162)

Measure: Morisky scale
Classification: (0= high adherence, 1-2 = medium adherence, >2 = low adherence)
Method of Assessment:

Total productivity cost
 Absenteeism costs
 Presenteeism costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002
Cost of Nonadherence^{##}:
 TPC(0):\$1210.90 (\$1571.73),
 TPC(1-2):\$1428.50 (\$1854.17),
 TPC(>2):\$1073.10 (\$1392.87),
 AbC(0):\$633.70 (\$822.53),
 AbC(1-2):\$608.90 (\$790.34),

Quality: medium
Classification: cost outcome description

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6			questionnaire		AbC(>2):\$474.80 (\$616.28),	
7					PrC(0):\$577.20 (\$749.20),	
8					PrC(1-2):\$819.60 (\$1063.83),	
9					PrC(>2):\$598.30 (\$776.59)	
10	<i>Miravittles et</i>	To analyse the	<u>Design:</u> multicentre,	<u>Measure:</u> GOLD	ED costs	<u>Quality:</u> medium
11	<i>al[49]</i>	economic impact of	retrospective,	2007 Guidelines	Pharmacy	<u>Classification:</u> cost
12	2013	non-adherence to the	observational study	<u>Classification:</u>	costs	<u>Classification:</u> cost
13	Spain	global initiative for	<u>Follow Up:</u> 18 months	(adherent,	Physician	<u>Cost of Nonadherence:</u>
14		obstructive lung	<u>Sample Size:</u> 1365	nonadherent)	office visit	EDC:€40.83 (\$57.91),
15		disease (GOLD)	(A:246, NA:1119)	<u>Method of</u>	costs	PC:€771.50 (\$1094.27),
16		guidelines in patients		<u>Assessment:</u> GOLD	Hospitalization	POC:€106.29 (\$150.76),
17		with chronic		guidelines	costs	HC:€101.61 (\$144.12)
18		obstructive pulmonary			Primary care	PCC:€123.84 (\$175.65),
19		disease (COPD).			costs	IntC:€321.44 (\$455.92),
20					Interdisciplinary	MTC:€36.66 (\$51.99),
21					y visit costs	RC:€24.24 (\$34.38),
22					Medical test	LC:€17.35 (\$24.61)
23					costs	
24					Radiology	
25					costs	
26					Laboratory	
27					costs	
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30	<i>Quittner et al[50]</i>	To evaluate	<u>Design:</u> retrospective,	<u>Measure:</u> MPR	Total	<u>Quality:</u> medium
31	2014	associations of	cohort study	<u>Classification:</u>	healthcare	<u>Classification:</u> cost
32	US	adherence to	<u>Follow Up:</u> 2 years	(≥80% = high	costs	<u>Classification:</u> cost
33		pulmonary	<u>Sample Size:</u> 3287	adherence, 50-		<u>Cost of Nonadherence*:</u>
34		medications, age,	(≥80%: 663, 50-80%:	80% = moderate		All cause:
35		healthcare use and	949, <50%: 1675)	adherence, <50%		THC(≥80):\$35749.50 (\$38244.05),
36		cost among cystic		= low adherence)		THC(50-80):\$45031.50 (\$48173.73),
37		fibrosis patients.		<u>Method of</u>		THC(<50):\$50284.50 (\$53793.28)
38				<u>Assessment:</u>		Disease state specific:
39				pharmacy claims		
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			data		THC(≥80):\$23764 (\$25422.22), THC(50-80):\$33132.50 (\$35444.44), THC(<50):\$33894 (\$36259.07)		
	Gastrointestinal Disease						
11	<i>Carter et al</i> [51]	To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.	<u>Design:</u> retrospective, observational cohort claims analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 638 (A:466, NA:172)	<u>Measure:</u> number of infusions in 12 month period <u>Classification:</u> (7-9 infusions = adherent, <7 infusions = nonadherent) <u>Method of Assessment:</u> health claims data	Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2007 <u>Cost of Nonadherence:</u> HC:\$37783 (\$42854.12)	<u>Quality:</u> medium <u>Classification:</u> cost outcome description
12	2011						
13	US						
23	<i>Gosselin et al</i> [52]	To examine the effects of gastroesophageal reflux disease (GERD) patients compliance with PPI therapy on health care resource utilisation and costs.	<u>Design:</u> retrospective cohort study <u>Follow Up:</u> <u>Sample Size:</u> 41837 (A:28321, NA:13516)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Medical costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2003 <u>Cost of Nonadherence:</u> TC:\$9497 (\$12085.43), IC:\$2116 (\$2692.72), OC:\$5458 (\$6945.59), PC:\$1922 (\$2445.85), MC:\$7575 (\$9639.58)	<u>Quality:</u> medium <u>Classification:</u> cost description
24	2009						
25	US						
34	<i>Kane et al</i> [53]	To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 571 (A:375, NA:196)	<u>Measure:</u> number of infusions in 12 month period <u>Classification:</u> (≥8 infusions = adherent, <7 infusions =	Outpatient costs ED costs Pharmacy costs Medical costs Hospitalization	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> All cause: OC:\$6679 (\$8272.62),	<u>Quality:</u> medium <u>Classification:</u> cost outcome description
35	2009						
36	US						

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	patients.		nonadherent)	costs	EDC:\$314 (\$388.92), MC:\$16129 (\$19977.40), HC:\$6893 (\$8537.68) Disease state specific: OC:\$3931 (\$4868.94), EDC:\$91 (\$112.71), PC:\$18751 (\$23225.01), MC:\$10243 (\$12686.99), HC:\$4494 (\$5566.27)	
			<u>Method of</u>			
			<u>Assessment:</u>			
			health claims data			
Mitra et al[54]	To assess the association between adherence to oral 5-aminosalicylates (5-ASAs) and all cause costs and health care utilisation among patients with active ulcerative colitis.	<u>Design:</u> retrospective, observational cohort study <u>Follow Up:</u> 12 months <u>Sample Size:</u> 1693 (A:476, NA:1216)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of</u>	Inpatient costs Outpatient costs ED costs Pharmacy costs Ancillary costs Non-pharmacy costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2010 <u>Cost of Nonadherence:</u> All cause: PC:\$1541.60 (\$1681.55) Disease state specific: IC:\$28726.65 (\$31334.47), OC:\$1145.67 (\$1249.67), EDC:\$635.95 (\$693.68), AC:\$4923.29 (\$5370.23), NPC:\$14226.32 (\$15517.79)	<u>Quality:</u> high <u>Classification:</u> cost description
Wan et al[55]	To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 360 days <u>Sample Size:</u> 1646 (A:674, NA:972)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of</u>	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2009 <u>Cost of Nonadherence:</u> All cause: TC:\$47411 (\$52341.27), THC:\$32522 (\$35903.96), IC:\$17634 (\$19467.76), OC:\$10909 (\$12043.43), EDC:\$458 (\$505.63),	<u>Quality:</u> high <u>Classification:</u> cost description
			<u>Assessment:</u>			
			pharmacy claims data			

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					PC:\$18410 (\$20324.46) Disease state specific: TC:\$33652 (\$37151.47), THC:\$18764 (\$20715.27), IC:\$12564 (\$13870.53), OC:\$5890 (\$6502.50), EDC:\$48 (\$52.99), PC:\$15150 (\$16725.45)	
Epilepsy						
<i>Davis et al</i> [56]	To assess the extent of refill non-adherence with antiepileptic drugs (AEDs) and the potential association between AED non-adherence and healthcare costs in an adult managed care population.	<u>Design:</u> retrospective claims analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 10892 (A:6644, NA:4248)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs ED costs Pharmacy costs Other pharmacy costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2003 <u>Cost of Nonadherence</u> ^{###} : TC:\$1466 (\$1865.56), IC:\$1799 (\$2289.32), EDC:\$260 (\$330.86), PC:-\$71 (-\$90.35), OtPC:-\$358 (-\$455.57)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Ettinger et al</i> [57]	To assess the extent to which elderly patients diagnosed with epilepsy are non-adherent to antiepileptic drugs (AEDs) and the potential association between AED non-adherence and seizure recurrence, resource utilisation and annual direct medical costs.	<u>Design:</u> retrospective claims analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 1278 (A:758, NA:520)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs ED costs Pharmacy costs Physician Office visit costs Ancillary costs Other pharmacy costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2003 <u>Cost of Nonadherence:</u> TC:\$17817 (\$22673.06), IC:\$2714 (\$3453.71), EDC:\$526 (\$669.36), PC:\$347 (\$441.58), POC:\$3063 (\$3897.83), AC:\$8344 (\$10618.18), OtPC:\$2822 (\$3591.14)	<u>Quality:</u> medium <u>Classification:</u> cost outcome description
<i>Faught et al</i> [58]	To study the impact of	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium

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5	2009	non-adherence to	observational open	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
6	US	antiepileptic drugs	cohort design	(≥80% = adherent,	Outpatient	<u>Currency Year:</u> USD, 2002
7		(AEDs) on healthcare	<u>Follow Up:</u> 4.65 years	<80% =	costs	<u>Cost of Nonadherence</u> *:
8		utilisation and direct	<u>Sample Size:</u> 33658	nonadherent)	ED costs	TC:\$14417.64 (\$18713.91),
9		medical costs in a	(A:24907, NA:8751)	<u>Method of</u>	Pharmacy	IC:\$6682.28 (\$6873.51),
10		Medicaid population.		<u>Assessment:</u>	costs	OC:\$2172.40 (\$2819.75),
11				pharmacy claims	Other	EDC:\$405.96 (\$526.93),
12				data	pharmacy	PC:\$822.40 (\$1067.46),
13					costs	OtPC:\$4334.60 (\$5626.26)
14						
15	HIV/AIDS					
16	<i>Barnett et al</i> [59]	To characterise the	<u>Design:</u> retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> unadjusted
17	2011	cost of HIV care	observational cohort	antiretroviral		<u>Classification:</u> disease state specific;
18	US	including combination	study	taking behaviour		viral load count
19		antiretroviral	<u>Follow Up:</u> 1 year	<u>Classification:</u>		<u>Currency Year:</u> USD, 2006
20		treatment.	<u>Sample Size:</u> 1896	(85% adherence		<u>Cost of Nonadherence</u> **:
21			(not specified)	with 3		High viral load:
22				antiretroviral		TC:\$25824 (\$30067.54)
23				therapy regimen =		Low viral load:
24				adherent, all other		TC:\$20509.67 (\$23879.92)
25				use =		
26				nonadherent)		
27				<u>Method of</u>		
28				<u>Assessment:</u>		
29				pharmacy claims		
30				data		
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32	<i>Cooke et al</i> [60]	To measure adherence	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted
33	2014	to antiretroviral	claims analysis	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
34	US	therapy regimens in	<u>Follow Up:</u> 1 year	(≥90% = adherent,	costs	<u>Currency Year:</u> USD, 2011
35		commercially insured	<u>Sample Size:</u> 3528	<90% =	Inpatient costs	<u>Cost of Nonadherence:</u>
36		patients with HIV	(A:1737, NA:640)	nonadherent)	Outpatient	THC:\$18868 (\$20184.58),
37		infection and analyse		<u>Method of</u>	costs	IC:\$2700 (\$2888.40),
38		the clinical and		<u>Assessment:</u>	Pharmacy	OC:\$915 (\$978.85),
39		demographic factors		pharmacy claims	costs	PC:\$15253 (\$16317.33)
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5		associated with $\geq 90\%$		data		
6		adherence.				
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8	<i>Pruitt et al</i> [61]	To examine Medicaid	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
9	2015	insured HIV positive	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
10	US	and AIDS diagnosed	<u>Follow Up:</u> 2 years	($\geq 90\%$ = adherent,	Outpatient	<u>Currency Year:</u> USD, 2009
11		patient groups	<u>Sample Size:</u> 502 (A:56,	<90% =	costs	<u>Cost of Nonadherence</u> * :
12		separately to	NA:176)	nonadherent)	Pharmacy	HIV:
13		determine association		<u>Method of</u>	costs	TC:\$15360 (\$16957.32),
14		of ART adherence to		<u>Assessment:</u>	Other	IC:\$3864 (\$4265.76),
15		mean monthly total		pharmacy claims	pharmacy	OC:\$3948 (\$4358.52),
16		healthcare		data	costs	PC:\$4956 (\$5471.40),
17		expenditures in the 24			Behavioural	OtPC:\$1764 (\$1947.48),
18		month measurement			health	BHIC:\$840 (\$927.36)
19		period.			inpatient costs	AIDS:
20						TC:\$27648 (\$30523.08),
21						IC:\$13008 (\$14360.76),
22						OC:\$5880 (\$6491.52),
23						PC:\$5640 (\$6226.56),
24						OtPC:\$2580 (\$2848.32),
25						BHIC:\$528 (\$582.96)
26						
27	Parkinson's					
28	Disease					
29	<i>Davis et al</i> [62]	To assess the extent to	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
30	2010	which patients	administrative claims	<u>Classification:</u>	Pharmacy	<u>Classification:</u> disease state specific
31	US	diagnosed with	study	($\geq 80\%$ = adherent,	costs	<u>Currency Year:</u> USD, 2001
32		Parkinson's disease are	<u>Follow Up:</u> 12 months	<80% =	Medical costs	<u>Cost of Nonadherence:</u>
33		non-adherent with	<u>Sample Size:</u> 3119	nonadherent)		TC:\$18511 (\$24262.36),
34		antiparkinson therapy	(A:1211, NA:1908)	<u>Method of</u>		PC:\$2684 (\$3537.36),
35		and the potential		<u>Assessment:</u>		MC:\$15827 (\$20859.12)
36		association between		pharmacy claims		
37		non-adherence and all		data		
38		cause medical costs.				
39						
40	<i>Delea et al</i> [63]	To assess the	<u>Design:</u> retrospective	<u>Measure:</u> PDC	Total costs	<u>Type of Costs:</u> adjusted and unadjusted
41						<u>Quality:</u> high
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5	2011	associations between	historical cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease
6	US	adherence to	<u>Follow Up:</u> 12 months	(≥80% =	Pharmacy	state specific
7		levodopa/carbidopa/e	<u>Sample Size:</u> 1215	satisfactory, <80%	costs	<u>Currency Year:</u> USD, 2005
8		ntacapone therapy and	(A:617, NA:598)	= unsatisfactory)	Other costs	<u>Cost of Nonadherence:</u>
9		healthcare utilisation		<u>Method of</u>		Adjusted all cause:
10		and costs.		<u>Assessment:</u>		TC:\$19686 (\$23625.30),
11				pharmacy claims		IC:\$5954 (\$7145.43),
12				data		PC:\$6391 (\$7669.88),
13						OC:\$8795 (\$10554.94)
14						Adjusted disease state specific:
15						TC:\$8574 (\$10289.71),
16						IC:\$3705 (\$4446.39),
17						PC:\$3850 (\$4620.41),
18						OC:\$1884 (\$2261)
19						Unadjusted all cause:
20						TC:\$19362 (\$23236.46),
21						IC:\$5463 (\$6556.18),
22						PC:\$6158 (\$7390.26),
23						OC:\$7740 (\$9288.82)
24						Unadjusted disease state specific:
25						TC:\$9156 (\$10988.18),
26						IC:\$3238 (\$3885.94),
27						PC:\$3789 (\$4547.20),
28						OC:\$2129 (\$2555.03)
29						
30						
31	<i>Wei et al</i> [64]	To examine the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
32	2014	associations of	cross-sectional study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
33	US	adherence to	<u>Follow Up:</u> 19 months	(>90<100% = high,	Outpatient	<u>Currency Year:</u> USD, 2007
34		antiparkinson drugs	<u>Sample Size:</u> 7583 (90-	>80<89% =	costs	<u>Cost of Nonadherence:</u>
35		with healthcare	100%:3948, 80-	moderate, ≤79% =	Pharmacy	TC(90-100):\$36407 (\$41293.43),
36		utilisation and	89%:1456, ≤79%:2179)	low)	costs	TC(80-89):\$43417 (\$49244.29),
37		economic outcomes.		<u>Method of</u>		TC(≤79):\$45867 (\$52023.13),
38				<u>Assessment:</u>		IC(90-100):\$15294 (\$17346.71),
39				pharmacy claims		IC(80-89):\$21603 (\$24502.49),
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			data		IC(≤79):\$24727 (\$28045.78), OC(90-100):\$10155 (\$11517.97), OC(80-89):\$11838 (\$13426.86), OC(≤79):\$12889 (\$14618.92), PC(90-100):\$10957 (\$12427.61), PC(80-89):\$9976 (\$11314.95), PC(≤79):\$8251 (\$9358.42)	
Musculoskeletal						
<i>Ivanova et al</i> [65] 2012 US	To compare the rates of severe relapse and total direct and indirect costs over a 2 year period between US based employees with MS who were adherent and non-adherent to disease modifying drugs.	<u>Design:</u> retrospective cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 648 (A:448, NA:200)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Short term disability costs Absenteeism cost	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause, disease state specific and indirect <u>Currency Year:</u> USD, 2007 <u>Cost of Nonadherence</u> *: All cause: TC:\$8079 (\$9276.76), THC:\$6022 (\$6830.25), IC:\$1030.50 (\$1168.81), OC:\$3231 (\$3664.65), EDC:\$143.50 (\$162.76), PC:\$1617 (\$1834.03), MC:\$4405.50 (\$4996.79) Disease state specific: TC:\$3005 (\$3408.32), IC:\$505 (\$572.78), OC:\$1710 (\$1939.51), EDC:\$37 (\$41.97), PC:\$753 (\$854.07), MC:\$2252 (\$2554.26) Indirect: STDC:\$1231 (\$1396.22), AbC:\$826 (\$936.86)	<u>Quality:</u> high <u>Classification:</u> cost outcome description
<i>Tan et al</i> [66] 2011	To assess the impact of treatment adherence	<u>Design:</u> retrospective cohort study	<u>Measure:</u> MPR <u>Classification:</u>	Medical costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> disease state specific	<u>Quality:</u> medium <u>Classification:</u> cost

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5	US	on MS related	<u>Follow Up:</u> 12 months	(≥80% = adherent,	<u>Currency Year:</u> USD, 2007	description
6		hospitalizations	<u>Sample Size:</u> 2446	<80% =	<u>Cost of Nonadherence:</u>	
7		(inpatient), ER visits,	(A:1459, NA:987)	nonadherent)	Adjusted:	
8		MS relapses and		<u>Method of</u>	MC:\$4348 (\$5062.49)	
9		medical costs.		<u>Assessment:</u>	Unadjusted:	
10				pharmacy claims	MC:\$5179 (\$6030.04)	
11				data		
12						
13	<i>Zhao et al[67]</i>	To examine predictors	<u>Design:</u> retrospective	<u>Measure:</u> MPR	<u>Type of Costs:</u> adjusted	<u>Quality:</u> medium
14	2011	associated with	cohort analysis	<u>Classification:</u>	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
15	US	duloxetine adherence	<u>Follow Up:</u> 12 months	(≥80% = adherent,	<u>Currency Year:</u> USD, 2008	analysis
16		and its association with	<u>Sample Size:</u> 5435	<80% =	<u>Cost of Nonadherence:</u> commercial:	
17		healthcare costs	(A:1744, NA:3691)	nonadherent)	TC:\$20323 (\$22609.12),	
18		among fibromyalgia		<u>Method of</u>	IC:\$4808 (\$5348.85),	
19		patients.		<u>Assessment:</u>	OC:\$9822 (\$10926.87),	
20				pharmacy claims	PC:\$5693 (\$6333.40)	
21				data	<u>Medicare:</u>	
22					TC:\$25282 (\$28125.96),	
23					IC:\$8604 (\$9571.86),	
24					OC:\$10068 (\$11200.54),	
25					PC:\$6611 (\$7354.67)	
26						
27	Cancer					
28	<i>Darkow et al[68]</i>	Estimate the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> high
29	2007	association between	observational cohort	<u>Classification:</u>	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
30	US	treatment	analysis	(≥95% = very high,	<u>Currency Year:</u> USD, 2004	description
31		interruptions and non-	<u>Follow Up:</u> 12 months	>90<95% = high,	<u>Cost of Nonadherence:</u>	
32		adherence with	<u>Sample Size:</u> 267	>50<90% =	THC(≥95):\$42250 (\$52330.90),	
33		imatinib and	(≥95%:120, 90-95%:25,	intermediate,	THC(90-95):\$39236 (\$48597.76),	
34		healthcare costs for US	50-90%:69, <50%:53)	<50% = low)	THC(50-90):\$54770 (\$67838.19),	
35		managed care patients.		<u>Method of</u>	THC(<50):\$131357 (\$162698.93),	
36				<u>Assessment:</u>	IC(≥95):\$1156 (\$1431.82),	
37				pharmacy claims	IC(90-95):\$1362 (\$1686.97),	
38				data	IC(50-90):\$19096 (\$23652.33),	
39					IC(<50):\$81572 (\$101035.18),	
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For peer review

costs
 Other costs
 OC(≥95):\$9299 (\$11517.75),
 OC(90-95):\$11148 (\$13807.93),
 OC(50-90):\$14631 (\$18121.97),
 OC(<50):\$33956 (\$42057.94),
 EDC(≥95):\$36 (\$44.59),
 EDC(90-95):\$568 (\$703.53),
 EDC(50-90):\$104 (\$128.81),
 EDC(<50):\$183 (\$226.66),
 PC(≥95):\$29056 (\$35988.80),
 PC(90-95):\$23693 (\$29346.18),
 PC(50-90):\$18330 (\$22703.56),
 PC(<50):\$8733 (\$10816.70),
 OtPC(≥95):\$2462 (\$3049.44),
 OtPC(90-95):\$2091 (\$2589.92),
 OtPC(50-90):\$2238 (\$2771.99),
 OtPC(<50):\$5732 (\$7099.66),
 OtC(≥95):\$241 (\$298.50),
 OtC(90-95):\$374 (\$463.24),
 OtC(50-90):\$371 (\$459.52),
 OtC(<50):\$1181 (\$1462.79)

27	<i>Wu et al</i> [69]	To examine the association between adherence with imatinib and direct healthcare costs and resource utilisation	<u>Design:</u> retrospective observational cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 592 (A:350, NA:242)	<u>Measure:</u> MPR <u>Classification:</u> (≥85% = high adherence, <85% = low adherence) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Other pharmacy costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2008 <u>Cost of Nonadherence:</u> TC:\$107341 (\$119415.73), IC:\$44498 (\$49503.55), OC:\$34097 (\$37932.55), EDC:\$248 (\$275.90), PC:\$22846 (\$25415.93), OtPC:\$5652 (\$6287.79)	<u>Quality:</u> medium <u>Classification:</u> cost description
38	Addiction <i>Leider et al</i> [70]	To assess the economic burden of chronic	<u>Design:</u> retrospective claims based analysis	<u>Measure:</u> urine testing	Total healthcare	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific	<u>Quality:</u> medium <u>Classification:</u> cost

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5	US	opioid users and to	<u>Follow Up:</u> 12 months	<u>Classification:</u>	costs	<u>Currency Year:</u> USD, 2008	analysis
6		determine whether	<u>Sample Size:</u> 2100	(positive test =	Inpatient costs	<u>Cost of Nonadherence:</u>	
7		opioid regimen non-	(A:442, NA:1658)	nonadherent,	Outpatient	THC:\$26433 (\$29406.43),	
8		adherence contributes		negative test =	costs	IC:\$6361 (\$7076.55),	
9		to increased		adherent)	ED costs	OC:\$9734 (\$10828.97),	
10		healthcare costs.		<u>Method of</u>	Pharmacy	EDC:\$421 (\$468.36),	
11				<u>Assessment:</u>	costs	PC:\$7960 (\$8855.42),	
12				health claims data	Medical costs	MC:\$1957 (\$2177.14)	
13				<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted and unadjusted	<u>Quality:</u> medium
14	<i>Tkacz et al</i> [71]	To estimate the	<u>Design:</u> retrospective	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
15	2014	healthcare service	cohort analysis	(≥80% = adherent,	costs	<u>Currency Year:</u> USD, 2010	description
16	US	utilisation and costs	<u>Follow Up:</u> 12 months	<80% =	Inpatient costs	<u>Cost of Nonadherence:</u>	
17		associated with	<u>Sample Size:</u> 455	nonadherent)	Outpatient	Adjusted:	
18		buprenorphine	(A:146, NA:309)	<u>Method of</u>	costs	THC:\$49051 (\$53503.88),	
19		medication assisted		<u>Assessment:</u>	ED costs	IC:\$26470 (\$28872.96),	
20		therapy adherence		pharmacy claims	Pharmacy	OC:\$14570 (\$15892.67),	
21		among a sample of		data	costs	EDC:\$4439 (\$4841.98),	
22		opioid dependent				PC:\$3581 (\$3906.09)	
23		members.				Unadjusted:	
24						THC:\$47868 (\$52213.49),	
25						IC:\$26043 (\$28407.20),	
26						OC:\$14173 (\$15459.63),	
27						EDC:\$4058 (\$4426.39),	
28						PC:\$3557 (\$3879.91)	
29							
30							
31	Metabolic						
32	conditions other						
33	than diabetes						
34	mellitus						
35	<i>Lee et al</i> [72]	To assess the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
36	2011	relationship between	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
37	US	medication adherence	<u>Follow Up:</u> 12 months	(≥80% = high	Outpatient	state specific	description
38		and healthcare costs	<u>Sample Size:</u> 4923	adherent, <80% =	costs	<u>Currency Year:</u> USD, 2010	
39		among US patients on	(A:1372, NA:1304)	low adherent)	ED costs	<u>Cost of Nonadherence:</u>	
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dialysis given
cinacalcet to manage
secondary
hypoparathyroidism.

Method of
Assessment:
pharmacy claims
data

Pharmacy
costs
Other
pharmacy
costs

All cause:
PC:\$5556 (\$6060.38)
Disease state specific:
TC:\$126996 (\$138524.78),
IC:\$14844 (\$16191.55),
OC:\$101854 (\$111100.37),
EDC:\$734 (\$800.63),
PC:\$3244 (\$3538.49),
OtPC:\$9564 (\$10432.23)

Blood

Candrilli et al[73]
2011
US

To investigate the
relationships among
hydroxyurea
adherence, healthcare
utilisation and
healthcare costs.

Design: retrospective
longitudinal study
Follow Up: 12 months
Sample Size: 312
(A:110, NA:202)

Measure: MPR
Classification:
(≥80% = adherent,
<80% =
nonadherent)
Method of
Assessment:
pharmacy claims
data

Total costs
Inpatient costs
ED costs
Pharmacy
costs
Physician
office visit
costs
Ancillary costs

Type of Costs: adjusted
Classification: all cause and disease
state specific
Currency Year: USD, 2008
Cost of Nonadherence:
All cause:
TC:\$ 20436 (\$22734.83),
IC:\$9780 (\$10880.15),
EDC:\$837 (\$931.15),
PC:\$2579 (\$2869.11),
POC:\$3483 (\$3874.80),
AC:\$3911 (\$4350.95)
Disease state specific:
TC:\$12097 (\$13457.78),
IC:\$7315 (\$8137.86),
EDC:\$552 (\$614.09),
PC:\$158 (\$175.77),
POC:\$1865 (\$2074.79),
AC:\$2466 (\$2743.40)

Quality: medium
Classification: cost
description

All

*Alvarez Payero et
al*[74]
2014

To determine the
profile of patients who
are admitted to

Design: retrospective
observational study
Follow Up: 1527 days

Measure:
pharmacy records
Classification:

Hospitalization
costs

Type of Costs: unadjusted
Classification: all cause
Currency Year: EUR, 2012

Quality: low
Classification: cost
outcome

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Spain	hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.	<u>Sample Size:</u> 87 (A:21, NA:66)	(>75% = adherent, ≤75% = nonadherent) <u>Method of Assessment:</u> pharmacy and hospital claims data	<u>Cost of Nonadherence^{####}:</u> All cause: HC:€6275.80 (\$8893.94)	description
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A: adherent, NA: nonadherent, MA: moderate adherence, LA: low adherence, NC: noncompliance, NP: nonpersistent, P: persistent, T: turbulent, NE: no exposure, CHF: chronic heart failure, THC: total healthcare costs, TC: total costs, IC: inpatient costs, OC: outpatient costs, EDC: emergency department visit costs, PC: pharmacy costs, MC: medical costs, HC: hospitalization costs, POC: physician office visit costs, NPC: non-pharmacy costs, AC: ancillary costs, OtPC: other pharmacy costs, RC: radiology costs, SC: services costs, InstC: institutional costs, ESC: external services costs, MSC: medical services costs, PCC: primary care costs, MTC: medical test costs, FC: fracture costs, LC: laboratory costs, IntC: interdisciplinary costs, BHIC: behavioural health inpatient costs, STDC: short term disability costs, WCC: workers compensation costs, PTOC: paid time off costs, TPC: total productivity costs, AbC: absenteeism costs, PrC: presenteeism costs, OtC: other costs, com: commercial patients, med: Medicare supplemental patients, USD: United States dollar, GBP: Great British Pound, EUR: Euro, DKK: Danish krone, CAD: Canadian dollar, KRW: South Korean won

*: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group; #: extrapolated annual cost and subgroups averaged; ##: cost represents losses in workplace productivity; ###: negative value as costs modelled against adherent group; ####: cost per episode of nonadherence

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	supp
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	supp
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

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Economic impact of medication nonadherence by disease groups: a systematic review

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Title Page

Title: Economic impact of medication nonadherence by disease groups: a systematic review

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Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A comprehensive literature search was conducted in PubMed and Scopus in March 2017. Studies quantifying the cost of medication nonadherence in relation to economic impact were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Seventy five individual studies assessing the cost of medication nonadherence across fourteen disease groups were included. Wide scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease specific economic cost of nonadherence per person ranged from \$949-\$53,504 (in 2015 US dollars). Costs attributed to “all causes” nonadherence ranged from \$5,271 to \$52,341. Medication possession ratio was the metric most utilized to calculate patient adherence, with varying cut-off points defining nonadherence. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (81% of studies), pharmacy costs (72%), inpatient costs (51%), outpatient costs (51%), emergency department visit costs (30%), medical costs (27%) and hospitalization costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. Current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system. Differences in methods make the comparison amongst studies challenging and an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338

Strengths and Limitations of this study:

- This is a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of medication nonadherence via quantifying the cost of medication nonadherence across different disease groups.
- A large comprehensive review – 2,692 citations identified, 75 studies included.
- Inability to perform a meaningful meta-analysis- insufficient statistical data and considerable heterogeneity according to outcome/indicators.
- Robust application of adapted Drummond checklist to evaluate the quality of economic evaluations.

1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources. [2]. Medications are a cost-effective treatment modality[3], but intentional and unintentional inappropriate medication use by patients is common, mostly through differing degrees of adherence termed medication nonadherence. Medication adherence is defined as ‘the extent to which the patients’ behavior matches agreed recommendations from the prescriber’, emphasising the importance on the patients’ decisions and highlighting the modifiable aspect of nonadherence[4].

With estimates of 50% nonadherence to long term therapy for chronic illnesses[5], efforts to improve medication adherence represent an opportunity to improve health outcomes and health system efficiency. The clinical, economic and human consequences of medication nonadherence pose significant burdens. Estimates of the costs range from US\$100-\$290 billion[6] in the United States, €1.25 billion[7] in Europe and approximately A\$7 billion[8 9] in Australia. As well as substantially increasing healthcare costs, nonadherence compromises the effective use of medicines, can decrease patients’ quality of life, increases the risk of medication misadventures, can lead to poor health outcomes, and can result in preventable hospitalizations[10]. Ten percent of hospitalizations in older adults are attributed to medication nonadherence [11 12] with the typical nonadherent patient requiring three extra medical visits per year leading to \$2000 increased treatment costs per annum[13]. In diabetes the estimated costs savings associated with improving medication nonadherence range from \$661 million to \$1.16 billion [14]. Nonadherence is thus a critical clinical and economic problem[5] .

An understanding of the economic impact of medication nonadherence on the healthcare system can influence health policy. While the cost of nonadherence for some disease groups has already been analyzed with varying findings, no systematic reviews provide a holistic and comparative picture across disease groups. Policymakers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[15]. However there is still a budgetary problem that needs to be considered. Quantifying the cost of medication nonadherence is a necessary element to allow valuable correlation between healthcare resource use associated with higher disease prevalence and costs associated with medication nonadherence to be drawn. The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the

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literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.

For peer review only

2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[16].

2.1 Search strategy and selection criteria

A literature search was conducted in March 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB])) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases (eTable 1). Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[17] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-

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3 group analysis and statistical significance), conclusions and miscellaneous (funding source,
4 references to other relevant studies, limitations and reviewers comments).
5

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7 Costs were defined as any indicator associated with medication nonadherence that was quantified
8 with a monetary value in the original study. This included direct costs (those costs borne by the
9 healthcare system, community and patients' families in addressing the illness), indirect costs (mainly
10 productivity losses to society caused by the health problem or disease) and avoidable costs (those
11 costs incurred for patients suffering complications, resulting from suboptimal medicines use, and
12 patients with the same disease who experienced no complications). The indicators were grouped for
13 analysis based on the original studies classification of the cost. All costs were converted to US
14 dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and
15 Practice Information and Coordinating -Centre Cost Converter tool [18], allowing meaningful
16 comparisons between nonadherence cost data. This online tool uses a two stage computation
17 process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product
18 deflator index and Purchasing Power Parities for Gross Domestic Product[18]. The PPP values given
19 by the International Monetary Fund were chosen. If details of the original price year could not be
20 ascertained from a study the mid-point year of the study period was used for calculations. The mean
21 cost was calculated and reported where studies separated out costs for different confounding
22 factors within the one outcome measure in a disease state. Annual costs were extrapolated from the
23 original study data if results were not presented in this manner.
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34 The definition of medication nonadherence was derived from the included studies; with
35 nonadherence referring to differing degrees of adherence based on the studies metric of estimation.
36 Multiple nonadherence costs from individual studies may have been included where further sub-
37 classification of nonadherence levels was defined. The analysis assessed nonadherence costs within
38 disease groups, with disease group and cost classification derived from the study. Total healthcare
39 costs included direct costs to the healthcare system while total costs incorporated direct and indirect
40 costs.
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49 **2.3 Quality criteria and economic evaluation classification**

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51 Economic evaluation requires a comparison of two or more alternative courses of action, while
52 considering both the inputs and outputs associated with each [19]. All studies were classified in
53 accordance with Drummond's distinguishing characteristics of healthcare evaluations as either
54 partial evaluations (outcome description, cost description, cost-outcome description, efficacy or
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3 effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility
4 analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).
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7 The Drummond checklist [20] for economic evaluation was used to assess the quality of studies. The
8 original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full
9 economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the
10 required item and zero if it did not with a maximum potential score of 28. The study was classified as
11 high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were
12 satisfied and low quality if 50% of the criteria or less were satisfied.
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16 17 18 19 **2.4 Meta-Analysis**

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21 Outcome/indicator costs were independently extracted utilising predesigned data extraction forms
22 (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs,
23 emergency department costs, and hospitalisation costs) for the purpose of integrating the findings
24 on the cost of medication nonadherence to pool data and increase the power of analysis.
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3 Results

3.1 Study Selection

Search strategies retrieved 2692 potential articles after duplicates were removed. Two hundred and seventy four articles were selected for full text review. Seventy five studies were included in the review (Figure 1).

3.2 Characteristics of individual studies

Sixty-two studies (82%) were conducted in the United States[11 21-81], four in Europe[82-85], four in Asia[86-89], three in Canada[90-92], one in the United Kingdom[93] and one across multiple countries throughout Europe and the United Kingdom[94]. Publication years ranged from 1997 to 2016. Individual studies reported a large variety of costs, calculated by varying means. Forty-two studies (56%) reported unadjusted costs[21 25 26 29 31-35 37-42 45 47-49 51-55 57 62-67 71 74 80 81 83-85 87-89 94], 19 (25%) adjusted costs[11 22-24 28 30 43 50 56 58-60 70 72 75-77 82 86], 11 a combination of adjusted and unadjusted[27 36 44 46 61 68 69 73 78 79 92], two unadjusted and predicted[90 91] and one predicted costs[93]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy claims data (87%)[11 21-28 30-51 54 56 58-83 87-92]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data, disease state specific recommended guidelines and health claims data. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 49 studies (65%) reporting nonadherence based on this measure[23 24 27 28 31-35 39-43 45 46 48-50 54 56 57 59-63 66-77 80-83 87-92]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g., 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (9%)[30 36 44 47 51 78 79], with all other studies utilizing an array of measures including self-report[93], urine testing[55], observational assessment[94], time to discontinuation[58], cumulative possession ratio[22], disease specific medication management guidelines[65 84], Morisky 4-Item scale[52], medication gaps[37], prescription refill rates[21 26] and medication supplies[11]. The main characteristics of the included studies are summarised in eTable 2.

3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high[32 36 39 49 50 56 70 74 82 88], 56 of medium[11 21-25 27-31 33-35 37 38 40-47 52-55 57 58 60-63 65 66 68 69 71 72 75-81 83 84 86 89-94] and nine of low quality[26 48 59 64 67 73 85 87]. Scores ranged from 26.1% to 87.5% (mean 62.9%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [70]. The item 'the choice of discount rate is stated and justified' was applicable only to studies covering a time period of more than one year; all studies that cover more than one year failed to identify or explain why costs had not been discounted. Details of the analysis and interpretation of results were lacking in the majority of studies resulting in medium or low quality scores.

Through utilisation of Drummond's distinguishing characteristics of healthcare evaluations criteria[19] it is apparent that no full economic evaluation was conducted in any of the included studies. All studies performed partial economic evaluations of varying extents. The classification of economic evaluations resulted in 55 cost description studies (73% of those included), 15 cost outcome descriptions and five cost analysis studies (eTable 2).

3.4 Medication nonadherence and costs

The cost analysis of studies (figure 2 and figure 3) reported annual medication nonadherence costs incurred by the patient per year. The adjusted total cost of nonadherence across all disease groups ranged from \$949 to \$53,504, while the unadjusted total cost ranged from \$669 to \$162,699. Figure 2 and figure 3 highlight the minimum, maximum and interquartile range of annual costs incurred by patients across disease groups where three or more studies were included for review. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Many different indicators were used to estimate medication nonadherence costs with no clear definition of what was incorporated in each cost component. The composition of included costs to estimate total cost or total healthcare cost varied significantly between studies thus indicators were grouped for analysis based on the original studies classification of the cost. The main ones were total cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs (47%), medical costs (29%), emergency department costs (28%), and hospitalization costs (18%) (eTable 2). Avoidable costs (e.g., unnecessary hospitalisations, physician office visits and healthcare resource utilization) were not well defined with majority of studies failing to quantify these costs.

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3 Lower levels of adherence across all measures (*e.g.*, MPR, PDC) were generally associated with
4 higher total costs. From those that reported total or total healthcare costs, 37 studies (50%)
5 reported nonadherence costs to be greater than adherence costs[23 24 26 28 30 31 33 36-38 41 42
6 46 48 49 54 55 57 60-64 69-77 82 91-94] and 11 studies (15%) reported nonadherence costs to be
7 less than adherence costs[22 25 35 43 58 62 65 80 87 89 90]. Four reported fluctuating findings
8 based on varying nonadherence cost subcategories[32 47 66 88] and two studies reported
9 conflicting findings between adjusted and unadjusted costs [78 79]. Sunyecz et al[67], Eisenberg et
10 al[40] and Joe et al[86] reported all cause total nonadherence costs to be higher (\$28,395 vs.
11 \$24,134, \$7,551 vs. \$7,051 and \$5,271 vs. \$4,375)) but disease group specific nonadherence costs to
12 be lower (\$1923 vs. \$3273, \$703 vs. \$1012 and \$3,252 vs. \$4,151) whereas Hansen et al[46]
13 reported all cause total nonadherence costs to be lower (\$18540 vs. \$52302) but disease group
14 specific nonadherence total costs to be higher (\$3,879 vs. \$2,954).

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22 The association between nonadherence and cost was determined through use of a variety of scaling
23 systems. The most utilized methods were MPR and PDC. These measures could then further be sub-
24 categorized based on the percentage of adherence/nonadherence. The 80-100% category was
25 classified as the most adherent group across both scales, with the most common definition of
26 nonadherence being <80% MPR or PDC.
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34 **3.5 Cost of medication nonadherence via disease group**

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36 Cancer exhibited more than double the cost variation of all other disease groups (\$114,101).
37 Osteoporosis (\$43,240 vs. \$42,734), diabetes mellitus (\$7,077 vs. \$6,808) and mental health
38 (\$16,110 vs. \$23,408) cost variations were similar between adjusted and unadjusted costs while
39 cardiovascular disease adjusted costs were more than double unadjusted costs (\$16,124 vs. \$6,943).
40 Inpatient costs represented the greatest proportion of costs contributing to total costs and/or total
41 healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy
42 and parkinson's disease. HIV/AIDS, cancer and gastrointestinal disease groups highest proportion of
43 costs were attributed to pharmacy costs while outpatient costs were greatest in musculoskeletal
44 conditions. Direct costs had greater economic bearing than indirect costs across all disease groups.
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50 **3.5.1 Cardiovascular Disease**

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53 Twelve studies measured the economic impact of medication nonadherence in cardiovascular
54 disease [11 23 30 60 61 64 66 75 80 88 90 91]. Six studies reported adjusted costs [11 23 30 60 61
55 75] with annual costs being extrapolated for two of these[30 60]. Total healthcare costs and/or total
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3 costs were assessed in all of the studies with the major indicators measured including pharmacy
4 costs[11 30 60 61 75], medical costs[11 23 30 60 75] and outpatient costs[30 61]. The annual
5 economic cost of nonadherence ranged from \$3,347 to \$19,472. Sokol et al[11] evaluated the
6 economic impact of medication nonadherence across three cardiovascular conditions; hypertension,
7 hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined,
8 pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups.
9 Total costs and medical costs were lower for the adherent groups of hypertension and
10 hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical
11 costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.

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18 Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total
19 costs of nonadherence ranging from \$1,433 to \$8,377 [64 66 80 88 90 91]. Rizzo et al[64] reported
20 cost findings through subgroup analysis of five conditions. For all conditions the total healthcare
21 costs were higher for nonadherent groups compared with adherent. While Zhao et al[80],
22 categorized participants into adherence subgroups; finding that total healthcare costs were lower
23 for the nonadherent population. The remaining studies used five key indicators to determine the
24 economic impact: inpatient costs[66 88], outpatient costs[66 88], pharmacy costs[66 90 91], medical
25 costs[90 91] and hospitalization costs[90 91].

31 **3.5.2 Mental Health**

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33 The analyses used to report the economic impact of medication nonadherence in mental health
34 varied widely. Eleven of 14 studies provided a total nonadherence cost estimate in mental health[22
35 24 26 51 58 65 72 81 86 93 94], with annual cost data being extrapolated for four of these[26 65 81
36 94]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient
37 ranged from \$3,252 to \$19,363 [22 24 58 59 72 86]. Bagalman et al[24] focused primarily on the
38 indirect costs associated with nonadherence – short-term disability, workers compensation and paid
39 time off costs while Robertson et al[81] highlighted the association between medication
40 nonadherence and incarceration, with findings indicating incarceration and arrest costs are higher
41 for worsening degrees of nonadherence. All other studies addressed direct costs. The main
42 indicators used to measure the direct economic impact of medication nonadherence were pharmacy
43 costs[22 38 51 58 59 65 72 94], inpatient costs[38 59 65 93 94], outpatient costs[22 38 58 65 94] and
44 hospitalization costs[21 22 58 94].

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53 The total unadjusted cost for medication nonadherence ranged from \$2,512 to \$25,920 as reported
54 in four studies [51 65 81 94]. Becker et al[26] used a subgroup analysis to classify patients based on
55 their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%,
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3 <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual
4 costs that were \$3,018 more than those of the maximal adherence group (75-100%).
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7 Knapp et al[93] outlined the predicted cost of nonadherence with reference to relative impact and
8 other factors associated with resource use and costs in patients with schizophrenia. Total costs
9 (\$116,434) were substantially higher than the other two indicators, which were inpatient costs
10 (\$13,577) and external services costs (\$3,241).
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13 14 **3.5.3 Diabetes mellitus:**

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16 Nine studies reported some cost measurement of the impact of medication nonadherence with
17 reference to the health system and the individual[39 44 46 50 73 75 87 89 92]. One study estimated
18 that the total US cost attributable to nonadherence in diabetes was slightly over \$5 billion[50]. Five
19 studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient
20 ranging from \$2,741 to \$9,819 [46 50 73 75 92]. One study reported total costs in relation to
21 subgroup analysis based on MPR level[73], and another reported total healthcare costs through
22 subgroup analysis of commercially insured and Medicare supplemental patients[75].
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26 A further three studies reported unadjusted cost findings[39 87 89] and four studies reported
27 unadjusted costs in addition to adjusted values[44 46 73 92]. Unadjusted total healthcare costs
28 and/or total costs ranged from \$1,142 to \$7,951. Extrapolated annual costs were determined for
29 two studies based on cost data presented [39 89].
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33 The most prominent indicators used to determine costs were pharmacy costs[39 44 46 73 75 92],
34 outpatient costs[39 46 75 89 92], inpatient costs[46 75 92] and hospitalization costs[50 87 89]. All
35 studies assessed the direct costs associated with medication nonadherence. One study evaluated
36 the relationship between nonadherence and short term disability costs in addition to assessing
37 direct costs[44].
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40 41 42 43 **3.5.4 Osteoporosis:**

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45 The cost of medication nonadherence in relation to osteoporosis was predominately examined
46 through analysis of the direct costs associated with nonadherence using total healthcare costs
47 and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department
48 costs. Two studies further assessed the economic impact of nonadherence through evaluation of
49 fracture related costs [47 83]. Four out of 11 studies reported the adjusted cost of medication
50 nonadherence in addition to reporting unadjusted costs [27 78 79 82]. Three studies further
51 classified nonadherence through subgroup analysis, with Briesacher et al[27] using MPR 20% interval
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3 increases and the two studies conducted by Zhao et al[78 79] using PDC, with $\geq 80\%$ classified as high
4 adherence, 50-79% medium adherence and $< 50\%$ low adherence . In the studies conducted by Zhao
5 et al[78 79], total healthcare costs were highest for the medium adherence group (\$41,402 and
6 \$44,190) followed by the highest adherence group (\$37,553 and \$43,863), and lowest for the low
7 adherence group (\$34,019 and \$43,771). These annual costs were extrapolated from study data. In
8 contrast, Briesacher et al[27] modelled the subgroup analyses against the lowest adherence group
9 ($< 20\%$ MPR), finding that costs decreased as adherence increased.
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14 Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from \$669
15 to \$43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In
16 the three studies that reported the lowest level of nonadherence to be PDC $< 50\%$, the cost of this
17 category ranged from \$16,938 to \$43,404 [47 78 79].
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22 One study examined only the medical costs of nonadherence through MPR subgroup analysis in
23 commercial and Medicare supplemental populations. The findings were that, for all levels of
24 nonadherence, costs of nonadherence were higher for Medicare supplemental patients [45].
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27 **3.5.5 Respiratory Disease:**

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29 All five studies reported the unadjusted cost of medication nonadherence. The methods of
30 classifying adherence levels varied greatly among them[35 37 52 63 84]. Two studies used MPR[35
31 63], one the Morisky 4-Item scale[52], one the Global Initiative for Chronic Obstructive Lung Disease
32 (GOLD) 2007 Guidelines[84] and one a 37 day gap in claims data[37]. Joshi et al[52] reported on the
33 indirect costs of medication nonadherence through consideration of losses in total productivity
34 costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs.
35 Delea et al[35] reported a direct relationship between decreases in medication nonadherence level
36 and total costs, whereas Quittner et al[63] reported an inverse relationship between decreases in
37 medication nonadherence level and total healthcare cost. The total expenses associated with the
38 lowest subgroup of adherence across all measures ranged from \$804 to \$36,259.
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46 **3.5.6 Gastrointestinal Disease:**

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48 Three of five studies reported the adjusted annual cost of medication nonadherence per patient
49 utilizing the MPR method [43 56 70]. Of these, two reported the total cost (\$12,085 and \$37,151)[43
50 70] with the main contributors to the overall total cost being inpatient costs (22% and 37%),
51 outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).
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3 The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the
4 total cost nor total healthcare costs[29 53]. Carter et al[29] reported hospitalization costs to be
5 \$42,854 while Kane et al[53] reported a significantly lower cost at \$5,566 in addition to other direct
6 cost contributors.
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9 10 **3.5.7 Epilepsy:**

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12 Three studies reported the economic impact of medication nonadherence in epilepsy. They all
13 reported unadjusted costs using an MPR cut off of <80%[34 41 42]. The main economic indicators
14 used to assess total costs were inpatient costs (\$2,289 to \$6,874), emergency department visit costs
15 (\$331 to \$669) and pharmacy costs (\$442 to \$1,067). Davis et al[34] modelled the costs of the
16 nonadherent group against the adherent group. The annual costs reported by Faught et al[42] were
17 extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from \$1,866
18 to \$22,673.
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23 24 **3.5.8 HIV/AIDS:**

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26 The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all
27 three studies was similar [25 31 62]. Two of the three studies examined the costs only for HIV[25
28 31], while Pruitt et al[62] assessed the cost in AIDS as well as HIV. The total unadjusted costs for
29 nonadherent HIV patients ranged from \$16,957 to \$30,068 with one study further categorizing
30 patients with HIV as having either a high viral load or low viral load[25]. The total cost of
31 nonadherence in AIDS was \$30,523[62]. All studies used comparable indicators (total cost, inpatient
32 cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.
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38 39 **3.5.9 Parkinson's Disease:**

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41 The direct costs associated with Parkinson's disease were assessed in all three studies. The
42 unadjusted total cost ranged from \$10,988 to \$52,023 [33 36 71]. Wei et al[71] further sub-grouped
43 patients into MPR adherence percentage categories, and found that costs increased on all economic
44 indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs
45 which decreased with nonadherence. One study additionally reported the adjusted cost, estimating
46 that \$10,290 could be attributed to medication nonadherence annually[36].
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50 51 **3.5.10 Musculoskeletal Conditions:**

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53 Differing subgroup analyses was used to measure the impact of medication nonadherence on the
54 annual cost incurred by patients. One study assessed both the direct and indirect costs of
55 nonadherence[49], one assessed only the medical costs[68] and one examined the direct costs in
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3 commercial and Medicare supplemental patient populations[77]. Zhao et al[77] reported the
4 adjusted annual cost in the commercial population to be \$22,609, and in the Medicare supplemental
5 group, \$28,126. Ivanova et al[49] reported only unadjusted costs and the annual total cost of
6 \$3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate
7 the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and
8 medical costs. Outpatient costs made the largest contribution to the overall total.
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12 **3.5.11 Cancer:**

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15 Two studies evaluated the effects of medication nonadherence in cancer[32 74]. One study reported
16 total annual costs of \$119,416[74], while the other gave a subgroup analysis based on classified
17 adherence levels[32]. In general the lowest two adherence subgroups (<50% and 50-90%) reported
18 the highest total healthcare costs (\$162,699 and \$67,838). This trend followed for inpatient costs,
19 outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.
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24 **3.5.12 Addiction:**

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26 The adjusted annual total healthcare cost of medication nonadherence was reported as \$53,504[55]
27 while the unadjusted cost ranged from \$29,406 to \$52,213 [55 69]. Leider et al[55] reported the
28 main contributors to this cost to be outpatient costs (\$10,829) and pharmacy costs (\$8,855),
29 whereas Tkacz et al[69] reported them to be inpatient costs (\$28,873 and \$28,407) and outpatient
30 costs (\$15,893 and \$15,460).
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35 **3.5.13 Metabolic conditions other than diabetes mellitus:**

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37 One study measured the influence of medication nonadherence on direct healthcare costs in
38 metabolic conditions, reporting an unadjusted attributable total cost of \$138,525[54]. The economic
39 indicators used to derive this cost were inpatient costs (\$16,192), outpatient costs (\$111,100),
40 emergency department visit costs (\$801) and pharmacy costs (\$3,538).
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45 **3.5.14 Blood conditions:**

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47 Only Candrilli et al[28] reported cost findings on the relationship between nonadherence and
48 healthcare costs, giving an adjusted total cost estimate of \$13,458 for nonadherence classified as
49 MPR <80%.
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52 **3.5.15 All causes:**

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54 In addition to disease-specific studies of the economic impact of medication nonadherence, 28
55 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of
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3 these studies, annual costs were extrapolated from the original data[30 46 49 60 63 65 94]. Ten
4 studies reported on economic indicators without giving total cost or total healthcare cost[21 44 45
5 53 54 56 59 80 85 94], and one study reported on costs per episode of nonadherence[85] .
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8 The adjusted cost of medication nonadherence was reported in 10 studies with an estimated range
9 of \$7,808 to \$52,341 [11 28 30 36 46 58 60 70 75 76]. Sokol et al[11] reported the all-cause cost of
10 nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[60]
11 reported only using MPR level breakdown.
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15 Fourteen studies reported the unadjusted economic impact of medication nonadherence with an
16 estimated range of \$1,037 to \$53,793 [21 40 45 49 53 54 57 63-65 67 80 85 94]. A further four
17 studies reported adjusted and unadjusted costs[36 44 46 92]. The most frequent indicators used to
18 measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs
19 (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency
20 department visit costs (25%).
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28 **3.6 Meta-Analysis**

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30 Statistical analysis was attempted to collate the large collection of results from individual studies for
31 the purpose of integrating the findings on the cost of medication nonadherence. However, the
32 criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of
33 required statistical parameters in particular standard deviation[95]. Combining studies that differ
34 substantially in design and other factors would have yielded meaningless summary results.
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4 Discussion

This systemic review broadens the scope of knowledge associated with the economic impact of medication nonadherence across different disease groups while building upon previous reviews where greater focus was on targeting overall risk factors or conceptual issues associated with medication nonadherence. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, Emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence with studies failing to quantify avoidable costs separately to direct and indirect costs possibly due to coding restraints in healthcare claims databases. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesise costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g., mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g., cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty. Given the complexity of medication nonadherence in terms of varying study designs, methods of estimation and adherence definitions there is a limitation as to the ability to truly estimate costs attributed to nonadherence until further streamlined processes are defined.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, with few studies defining exactly what that cost category incorporated, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to

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3 medication nonadherence thus enabling greater planning in terms of health policy to help
4 counteract costs.
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7 The economic, clinical and humanistic consequences of medication nonadherence will continue to
8 grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to
9 adequately address the determinants of adherence through utilization of effective health
10 interventions. Haynes et al [96] highlights that “increasing the effectiveness of adherence
11 interventions may have a far greater impact on the health of the population than any improvement
12 in specific medical treatments”. Improving medication adherence provides an opportunity for major
13 cost savings to healthcare systems. Moving forward health policy needs to recognize the link
14 between adherence and health system efficacy and the opportunity it presents to allocate health
15 budget spending more appropriately. Predictions of population health outcomes through utilization
16 of treatment efficacy data need to be used in conjunction with adherence rates to inform planning
17 and project evaluation[5]. The correlation between increased nonadherence and higher disease
18 prevalence should be used to inform policy makers to help circumvent avoidable costs to the
19 healthcare system.
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28 The metric of adherence estimation varied substantially within and across disease groups; likely
29 affecting the comparisons between studies. However, Hess et al [97], who compared six key
30 adherence measures on the same study participants, found that the measures produced similar
31 adherence values for all participants, although PDC and continuous measure of medication gaps
32 produced slightly lower values. While this highlights the comparability of the measures of
33 medication nonadherence, it further justifies the need to agree on consistent methods for
34 estimating nonadherence through use of pharmacy claims data.
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40 MPR was the most commonly used measure to estimate medication nonadherence. MPR was used
41 in 65% of studies, followed by PDC, which was used in 9%. These percentages were consistent with
42 those found recently by Sattler et al [98]. Even though the measures of medication nonadherence
43 may be comparable, the definition of MPR and the cut-off points to define nonadherence differed
44 significantly. Dragomir et al[90] defined MPR as the total days' supply of medication dispensed in the
45 period, divided by the follow up period, with the assumption of 100% adherence during
46 hospitalization; Wu et al[75] removed the number of hospitalized days from the calculation; and
47 Pittman et al[60] calculated the total number of days between the dates of the last filling of a
48 prescription in the first six months in a given year and the first filling of a prescription in the 365 days
49 before the last filling. Nonadherence could also be further classified into subcategories within MPR
50 and PDC based on percentages. Twenty-eight studies defined nonadherence as $MPR < 80\%$, and 19
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3 studies categorized nonadherence into varying percentage subgroups. While Karve et al[99]
4 validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting
5 subsequent hospitalizations in patients across a broad array of chronic diseases, 72 of the 75 studies
6 included in this review examined more than just hospitalization costs as an indicator metric. Further
7 research is required to identify and standardise nonadherence thresholds using other outcomes such
8 as laboratory, productivity and pharmacy measures.
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13 Within the 75 studies covered, 34 different indicators were used to measure the cost of
14 nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a
15 meta-analysis was impossible. It is imperative that a standardized approach be established to
16 measure and report the economic impact of medication nonadherence. The core outcome set must
17 take into consideration the perspective of the intended audience and the proportion of
18 nonadherence cost that is attributable to each outcome to determine an appropriate model[100].
19 The critical indicators based on the findings of this review include total costs, pharmacy costs,
20 inpatient costs, outpatient costs, emergency department visit costs, medical costs and
21 hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes
22 include short term disability costs, workers compensation costs, paid time off costs, absenteeism
23 costs and productivity costs. We suggest that further analysis of the contribution of each outcome to
24 the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future
25 research.
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34 Many studies have examined the relationship between nonadherence and economic outcomes using
35 a cross-sectional analysis[50]. The implications of this are that potentially crucial confounders such
36 as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for
37 example, did greater adherence result in reduced costs and improved health outcomes, or was the
38 patient healthier initially and more capable of being adherent? A longitudinal design is needed to
39 overcome this limitation.
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44 None of the studies included a full economic evaluation. An economic evaluation requires a
45 comparison of two or more alternative courses of action, while considering both the inputs and
46 outputs associated with each[19]. While none of the studies taken separately could inform a choice
47 between alternative courses of action, they did provide key evidence for decision makers about
48 costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority
49 of studies to model cost estimates. Three-quarters of the studies were classified as cost
50 descriptions, providing a cost or outcome overview of the health consequences associated with
51 nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall
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3 conclusions that are able to be drawn and emphasised the need for future study design to
4 incorporate elements allowing full economic evaluations to be conducted. Hughes et al[101]
5 highlighted the need for more information on the consequences of nonadherence, so that economic
6 evaluations could reflect the potential long-term effect of this growing problem.
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10 Of the seventy five included studies, sixty two of the studies were conducted in the United States.
11 Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and
12 disease states. Comparison of costs between healthcare systems is difficult as no two are the same
13 and as healthcare is generally more expensive in the United States cost estimates may not reflect
14 average values. Thus caution needs to be taken when interpreting results however findings help to
15 represent the significance of the economic burden medication nonadherence plays. Analysis of
16 studies not conducted in the United States support the finding that generally medication
17 nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.
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23 Due to the advances in technology available to record and assess medication nonadherence, the
24 inclusion of studies undertaken in the late 1990s and early 2000s may have affected the
25 comparability of results, despite the fact that these studies met the inclusion criteria[21 22 64 72 73
26 93]. The quality of data presents a limitation. Information on disease groups with fewer included
27 studies may be less reliable than information on those with more. However, our findings affirm the
28 pattern of association between nonadherence and increasing healthcare costs.
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5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilisation of existing data could help to better define costs and provide valuable input into the development of an economic model to standardise the economic impact of medication nonadherence.

6 Footnotes

Contributors: RC, VGC, SB, FFL and MF conceived the paper. RC and VGC performed all the data extraction and quality assessment. RC drafted the initial form and all revisions of this manuscript. All other authors (RC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

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Figure Legends

Figure 1: PRISMA Flow Diagram

The PRISMA diagram details the search and selection process applied during the overview. The search yielded a total of 2692 citations. Studies were selected based on the inclusion criteria; studies reporting the cost of medication nonadherence using original cost data. Intervention studies were required to report baseline data. Seventy five original studies met the inclusion criteria.

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year

Encompass the minimum, maximum and interquartile range of adjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Gastrointestinal only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Figure 1: Annual Unadjusted Medication Nonadherence Costs per patient per year

Encompass the minimum, maximum and interquartile range of unadjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Epilepsy only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

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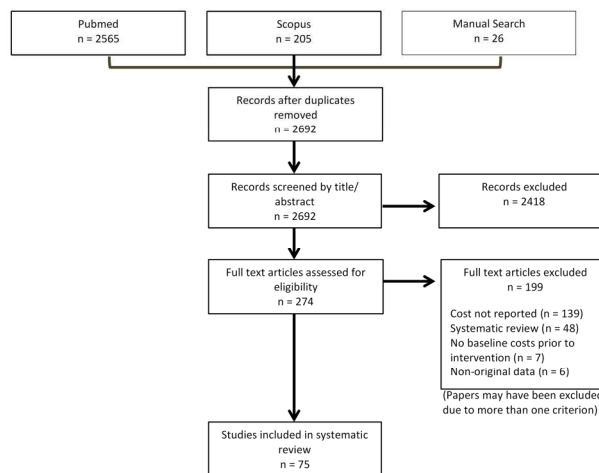


Figure 1: PRISMA Flow Diagram

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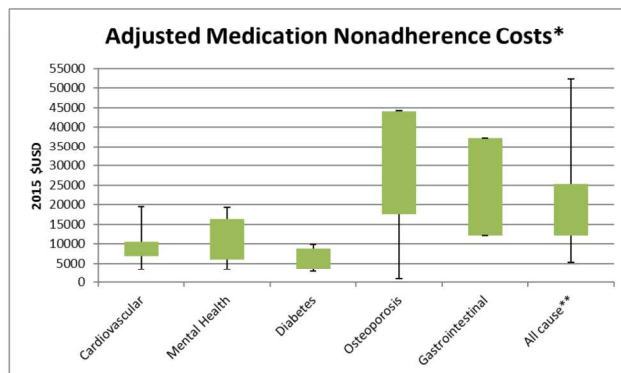
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Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year *Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.** All cause costs: mixed disease state studies

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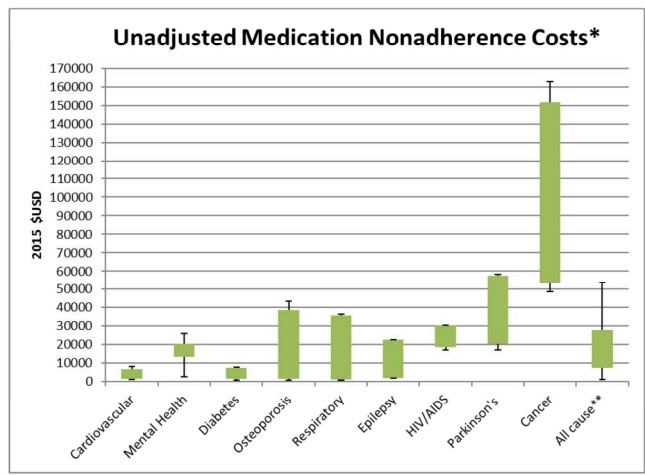


Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year *Disease groups with three or more studies were included. Epilepsy only included three studies limiting the range of costs.** All cause costs: mixed disease state studies

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eTable 1 Search Strategy

Database	Search Strategy
PubMed	((costs[TIAB] OR "Costs and Cost Analysis"[MH] OR burden[TIAB]) AND (nonadherence[TIAB] OR ("Patient Compliance"[MH] AND ("Drug Therapy"[MH] OR medication[TIAB]))) OR "Medication adherence"[MH]))
Scopus	(TITLE-ABS-KEY (medication AND compliance OR patient AND compliance)) AND (TITLE-ABS-KEY (statistical AND model)) AND (TITLE-ABS-KEY (health AND care AND cost))

eTable 2: Studies identified with costs reported by adherence level and disease state

Author, Year, Country	Objective	Study Characteristics	Adherence (as reported in paper)	Outcomes/ Indicators	Results (USD, 2015)	Quality
Cardiovascular Disease						
<i>Aubert et al</i> [1] 2010 US	To investigate whether compliance during the first 2 years of statin therapy is associated with reduced hospitalization rates and direct medical costs during year 3.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 10227 (A:3512, NA:6715)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = non-compliant <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence:</u> THC:\$5289.61 (\$6865.90), MC:\$4908.09 (\$6370.60)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Casciano et al</i> [2] 2013 US	To assess the economic burden of underuse and nonadherence of warfarin therapy among patients with non-valvular atrial fibrillation in a commercially insured population.	<u>Design:</u> Retrospective, observational, quasi-experimental study <u>Follow Up:</u> 18months <u>Sample Size:</u> 13289 (A:2852, NA:4184, NE:6253)	<u>Measure:</u> PDC <u>Classification:</u> PDC <80 = low adherence, 0 = no warfarin exposure <u>Method of Assessment:</u> pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence*:</u> TC:\$16612.44(\$19936.70), IC:\$9382.56 (\$11260.10), OC:\$8605.92 (\$10328), PC:\$2388.24 (\$2866.20), MC:\$15235.80(\$18285)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Dilokthornsakul et al</i> [3] 2012 Thailand	To determine the effects of medication supplies on healthcare costs and hospitalizations in patients with chronic heart failure receiving angiotensin converting enzyme inhibitors or	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 393 (A:168, NA:219, OA:6)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = undersupply, MPR >120 = oversupply <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> THC:\$1157 (\$1433.06), IC:\$1019 (\$1262.13), OC:\$138 (\$170.93)	<u>Quality:</u> high <u>Classification:</u> cost description

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<i>Dragomir et al</i> [4] 2010 Canada	angiotensin receptor blockers. To evaluate the impact of low adherence to antihypertensive agents on cardiovascular outcomes and hospitalization costs.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 56896 (A:38217, NA:18679)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥80 = adherent, MPR < 80 = nonadherent <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare Costs Pharmacy Costs Medical Costs Hospitalization Costs	<u>Type of Costs:</u> unadjusted and predicted <u>Classification:</u> disease state specific and hospitalised patients <u>Currency Year:</u> CAD, 2006 <u>Cost of Nonadherence:</u> Unadjusted Disease state specific: THC:\$7165 (\$6900.87), PC: \$1800 (\$1733.64), MC: \$1370 (\$1319.50), HC: \$3995 (\$3847.73) Unadjusted Hospitalised patients: THC: \$17397 (\$16755.67), PC:\$2685 (\$2586.02), MC:\$2608 (\$2511.86), HC: \$12104 (\$11657.79) Predicted disease state specific: HC:\$3877 (\$3734.08) Predicted hospitalised patient: HC:\$11715 (\$11283.13)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Dragomir et al</i> [5] 2010 Canada	To evaluate the impact of low adherence to statins on clinical issues and direct healthcare costs.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 55134 (A:28549, NA:26585)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥80 = adherent, MPR < 80 = nonadherent <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare Costs Pharmacy Costs Medical Costs Hospitalization Costs	<u>Type of Costs:</u> unadjusted and predicted <u>Classification:</u> disease state specific and hospitalised patients <u>Currency Year:</u> CAD, 2005 <u>Cost of Nonadherence:</u> Unadjusted Disease state specific: THC:\$6243 (\$6175.76), PC:\$2506 (\$2479.01), MC:\$1241 (\$1227.63), HC:\$2496 (\$2469.12) Unadjusted Hospitalised patients: THC:\$14725 (\$14566.40), PC:\$3374 (\$3337.66), MC:\$2475 (\$2448.34), HC:\$8876 (\$8780.40) Predicted disease state specific:	<u>Quality:</u> medium <u>Classification:</u> cost description

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4					HC:\$2669 (\$2640.25)	
5					Predicted hospitalised patient: HC\$9214	
6					(\$9114.76)	
7	<i>Pittman et al</i> [6]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted
8	2011	relation among statin	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> all cause and disease
9	US	adherence, subsequent	<u>Follow Up:</u> 18 months	MPR \geq 80 =	Costs	state specific
10		hospitalizations and	<u>Sample Size:</u> 381422	adherent, MPR	Pharmacy	<u>Currency Year:</u> USD, 2009
11		healthcare costs.	(A:258013, MA:65795,	>60<79% =	Costs	<u>Cost of Nonadherence*:</u> all cause:
12			LA:57614)	moderate	Medical Costs	THC(>80):\$6798.67 (\$7505.66),
13				adherence, MPR		THC(60-79):\$7072.67 (\$7808.16),
14				<59 =low		THC(<59):\$7401.33 (\$8170.99),
15				adherence		PC(>80):\$1767.33 (\$1951.11),
16				<u>Method of</u>		PC(60-79):\$1789.33 (\$1975.40),
17				<u>Assessment:</u>		PC(<59):\$1937.33 (\$2138.79),
18				pharmacy claims		MC(>80):\$4472.67 (\$4937.78),
19				data		MC(60-79):\$4840.67 (\$5344.05),
20						MC(<59):\$5138.67 (\$5673.04)
21						Disease state specific:
22						PC(>80):\$558.67 (\$616.77),
23						PC(60-79):\$442.67 (\$488.70),
24						PC(<59):\$325.33 (\$359.16),
25						MC(>80):\$1596.67 (\$1762.71),
26						MC(60-79):\$1722 (\$1901.07),
27						MC(<59):\$1792.67 (\$1979.09)
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30	<i>Pittman et al</i> [7]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted and unadjusted
31	2010	relationship between	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific
32	US	adherence to	<u>Follow Up:</u> 2 years	MPR \geq 80 =	Costs	<u>Currency Year:</u> USD, 2008
33		antihypertensive	<u>Sample Size:</u>	adherent, MPR	Outpatient	<u>Cost of Nonadherence:</u> Adjusted:
34		medications and	625620(A:467006,	>60<79% =	Costs	THC(>80):\$7261 (\$8077.79),
35		subsequent	MA:96226, LA:62388)	moderate	ED Costs	THC(60-79):\$7530 (\$8377.05),
36		hospitalizations,		adherence, MPR	Pharmacy	THC(<59):\$7370 (\$8199.05),
37		emergency		<59 =low	Costs	OC(>80):\$3390 (\$3771.34),
38		department visits and		adherence	Hospitalization	OC(60-79):\$3705 (\$4121.77),
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costs of care.

Method of Assessment:
pharmacy claims data

Costs

OC(<59):\$3776 (\$4200.76),
EDC(>80):\$101 (\$112.36),
EDC(60-79):\$134 (\$149.07),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2383 (\$2651.06),
PC(60-79):\$1932 (\$2149.33),
PC(<59):\$1509 (\$1678.75),
HC(>80):\$1386 (\$1541.91),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$1913 (\$2128.19)
Unadjusted:
THC(>80):\$7182 (\$7989.90),
THC(60-79):\$7560 (\$8410.42),
THC(<59):\$7995 (\$8894.35),
OC(>80):\$3396 (\$3778.01),
OC(60-79):\$3635 (\$4043.90),
OC(<59):\$3887 (\$4324.25),
EDC(>80):\$102 (\$113.47),
EDC(60-79):\$131 (\$145.74),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2317 (\$2577.64),
PC(60-79):\$2034 (\$2262.80),
PC(<59):\$1880 (\$2091.48),
HC(>80):\$1366 (\$1519.66),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$2057 (\$2288.39)*Rizzo et al*[8]
1997
USTo investigate variations in compliance with four classes of antihypertensive agents- diuretics, ACEIs, CCBs and β -Design: Retrospective cohort studyFollow Up: 12 monthsSample Size:

7211(P:2668, NC:3101, NP:649, T:793)

Measure: ordinary least square

regression analysis

Classification:>80% = persistent, \geq 30<80% = non-compliance, <30%

Total Healthcare Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 1994
Cost of Nonadherence: All cause:
THC(>80):\$341 (\$509.66),
THC(30-80):\$694 (\$1037.26),Quality: low
Classification: cost description

blockers and the health care costs associated with various degrees of compliance.

= non-persistence
Method of Assessment:
 pharmacy claims data

THC(<30):\$735 (\$1098.53)
 Disease state specific:
 Renal:
 THC(>80):\$2135 (\$3190.98),
 THC(30-80):\$2488 (\$3718.58),
 THC(<30):\$2529 (\$3779.86),
 Acute MI:
 THC(>80):\$1358 (\$2029.67),
 THC(30-80):\$1711 (\$2557.27),
 THC(<30):\$1752 (\$2618.55), Diabetes:
 THC(>80):\$770 (\$1150.85),
 THC(30-80):\$1123 (\$1678.44),
 THC(<30):\$1164 (\$1739.72),
 CHF:
 THC(>80):\$698 (\$1043.23),
 THC(30-80):\$1051 (\$1570.83),
 THC(<30):\$1092 (\$1632.11),
 Angina:
 THC(>80):\$702 (\$1049.21),
 THC(30-80):\$1055 (\$1576.81),
 THC(<30):\$1096 (\$1638.09)

Sokol et al[9]
 2005
 US

To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Design: Retrospective cohort observational study
Follow Up: 12 months
Sample Size: 137277
 Diabetes:(≥80: 1801, 60-79: 599, 40-59: 419, 20-39: 259, <19: 182)
 Hypertension:(≥80: 5804, 60-79: 921, 40-59: 562, 20-39: 344, <19: 350)

Measure:
 medication supply
Classification: 1-19%, 20-39%, 40-59%, 60-79%, 80-100%
Method of Assessment:
 pharmacy claims data

Total Costs
 Pharmacy Costs
 Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 1998
Cost of Nonadherence: All cause:
 Diabetes:
 TC(1-19):\$16498 (\$23071.58),
 TC(20-39):\$13077 (\$18287.49),
 TC(40-59):\$12978 (\$18149.05),
 TC(60-79):\$11484 (\$16059.77),
 TC(80-100):\$8886 (\$12426.60),
 PC(1-19):\$1312 (\$1834.76),

Quality: medium
Classification: cost description

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Hypercholesterolemia:
(≥80: 1754, 60-79: 520,
40-59: 324, 20-39: 216,
<19: 167)
CHF: (≥80: 518, 60-79:
107, 40-59: 82, 20-39:
70, <19: 86)

PC(20-39):\$1877 (\$2624.89),
PC(40-59):\$1970 (\$2754.94),
PC(60-79):\$2121 (\$2966.11),
PC(80-100):\$2510 (\$3510.10),
MC(1-19):\$15186 (\$21236.82),
MC(20-39):\$11200 (\$15662.61),
MC(40-59):\$11008 (\$15394.10),
MC(60-79):\$9363 (\$13093.66),
MC(80-100):\$6377 (\$8917.90),
Hypertension:
TC(1-19):\$9747 (\$13630.66),
TC(20-39):\$11238 (\$15715.75),
TC(40-59):\$9491 (\$13272.66),
TC(60-79):\$8929 (\$12486.73),
TC(80-100):\$8386 (\$11272.38),
PC(1-19):\$916 (\$1280.98),
PC(20-39):\$952 (\$1331.32),
PC(40-59):\$1123 (\$1570.46),
PC(60-79):\$1271 (\$1777.43),
PC(80-100):\$1817 (\$2540.98),
MC(1-19):\$8831 (\$12349.69),
MC(20-39):\$10286 (\$14384.43),
MC(40-59):\$8368 (\$11702.20),
MC(60-79):\$7658 (\$10709.31),
MC(80-100):\$6570 (\$9187.80),
Hypercholesterolemia:
TC(1-19):\$10916 (\$15265.45),
TC(20-39):\$7982 (\$11162.40),
TC(40-59):\$6756 (\$9447.91),
TC(60-79):\$8412 (\$11763.74),
TC(80-100):\$6752 (\$9442.31),
PC(1-19):\$1067 (\$1492.14),
PC(20-39):\$1152 (\$1611.01),

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PC(40-59):\$1247 (\$1743.86),
PC(60-79):\$1736 (\$2427.70),
PC(80-100):\$1972 (\$2757.74),
MC(1-19):\$9849(\$13773.30),
MC(20-39):\$6830 (\$9551.39),
MC(40-59):\$5509 (\$7704.04),
MC(60-79):\$6676 (\$9336.03),
MC(80-100):\$4780 (\$6684.58),
CHF:
TC(1-19):\$23964 (\$33512.38),
TC(20-39):\$19188 (\$26833.40),
TC(40-59):\$26311 (\$36794.54),
TC(60-79):\$29785 (\$41652.74),
TC(80-100):\$22164 (\$30995.18),
PC(1-19):\$1961 (\$2742.35),
PC(20-39):\$2055 (\$2873.81),
PC(40-59):\$2208 (\$3087.77),
PC(60-79):\$3412 (\$4771.50),
PC(80-100):\$3107 (\$4344.97),
MC(1-19):\$22003 (\$30770.03),
MC(20-39):\$17133 (\$23959.59),
MC(40-59):\$24103 (\$33706.77),
MC(60-79):\$26373 (\$36881.24),
MC(80-100):\$19056 (\$26648.81)
Disease state specific: Diabetes:
TC(1-19):\$8867 (\$12400.03),
TC(20-39):\$7124 (\$9916.90),
TC(40-59):\$6522 (\$9120.67),
TC(60-79):\$6291 (\$8797.63),
TC(80-100):\$4570 (\$6390.90),
PC(1-19):\$55 (\$76.91),
PC(20-39):\$165 (\$230.74),
PC(40-59):\$285 (\$398.56),

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PC(60-79):\$404 (\$564.97),
PC(80-100):\$763 (\$1067.02),
MC(1-19):\$8812 (\$12323.11),
MC(20-39):\$6959 (\$9731.79),
MC(40-59):\$6237 (\$8722.11),
MC(60-79):\$5887 (\$8232.66),
MC(80-100):\$3808 (\$5325.29),
Hypertension:
TC(1-19):\$4878 (\$6821.62),
TC(20-39):\$6062 (\$8477.39),
TC(40-59):\$5297 (\$7407.57),
TC(60-79):\$5262 (\$7358.63),
TC(80-100):\$4871 (\$6811.84),
PC(1-19):\$31 (\$43.35),
PC(20-39):\$89(\$124.46),
PC(40-59):\$184 (\$257.31),
PC(60-79):\$285 (\$398.56),
PC(80-100):\$489 (\$683.84),
MC(1-19):\$4847 (\$6778.27),
MC(20-39):\$5973 (\$8352.92),
MC(40-59):\$5113 (\$7150.26),
MC(60-79):\$4977 (\$6960.07),
MC(80-100):\$4383 (\$6129.39),
Hypercholesterolemia:
TC(1-19):\$6888 (\$9632.50),
TC(20-39):\$4999 (\$6990.84),
TC(40-59):\$3825 (\$5349.06),
TC(60-79):\$5541 (\$7748.79),
TC(80-100):\$3924(\$5487.51),
PC(1-19):\$78 (\$109.08),
PC(20-39):\$213 (\$297.87),
PC(40-59):\$373 (\$521.62),
PC(60-79):\$603 (\$843.26),

For peer review only

PC(80-100):\$801 (\$1120.16),
 MC(1-19):\$6810 (\$9523.42),
 MC(20-39):\$4786 (\$6692.97),
 MC(40-59):\$3452 (\$4827.44),
 MC(60-79):\$4938 (\$6905.53),
 MC(80-100):\$3124 (\$4368.75),
 CHF:
 TC(1-19):\$9841 (\$13762.12),
 TC(20-39):\$7733 (\$10814.19),
 TC(40-59):\$11378 (\$15911.53),
 TC(60-79):\$13924 (\$19471.98),
 TC(80-100):\$12698 (\$17787.48),
 PC(1-19):\$15 (\$20.98),
 PC(20-39):\$90 (\$125.86),
 PC(40-59):\$134 (\$187.39),
 PC(60-79):\$158 (\$220.95),
 PC(80-100):\$437 (\$611.12),
 MC(1-19):\$9826 (\$13741.14),
 MC(20-39):\$7643 (\$10688.33),
 MC(40-59):\$11244 (\$15724.14),
 MC(60-79):\$13766 (\$19251.02),
 MC(80-100):\$12261 (\$17146.36)

28	<i>Stroupe et al</i> [10]	To determine the rates of undersupply, appropriate supply, and oversupply of antihypertensive drugs as measured by refill adherence, among patient with complicated and uncomplicated hypertension and to	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 3.3 years <u>Sample Size:</u> 15206 (not specified)	<u>Measure:</u> MPR <u>Classification:</u> MPR<80 = undersupply, MPR >120 = oversupply <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs Pharmacy Costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence**:</u> THC:\$6032.5 (\$7830.11), IC:\$2067 (\$2682.94), OC:\$3965 (\$5146.52), PC:\$130 (\$168.74)	<u>Quality:</u> medium <u>Classification:</u> cost description
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examine the association of refill adherence with hospitalization and healthcare costs among these patients.

Wu et al[11]
2011
US

To study statin adherence and assess associated medical utilisation and healthcare costs in patients with type 2 diabetes, based on national Medicaid database.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 1705 (A:624, NA:1081)

Measure: MPR
Classification: MPR≥80 = adherent, MPR <80 = nonadherent
Method of Assessment: pharmacy claims data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2005
Cost of Nonadherence: all cause: THC:\$17807 (\$21370.30), PC:\$4915 (\$5898.52) MC:\$12892 (\$15471.77)
Disease state specific: THC:\$2789 (\$3347.10), PC:\$489(\$586.85) MC:\$2300 (\$2760.25)

Quality: medium
Classification: cost description

Zhao et al[12]
2014
US

To evaluate the associations between statin adherence level, healthcare costs, hospital admissions and emergency room visits after statin therapy is taken for 1 year.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 10312 (96-100: 2453, 90-95: 1496, 85-89: 584, 80-84: 768, 70-79: 960, 60-69: 777, 40-59: 1687, <40:1587)

Measure: MPR
Classification: <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100%
Method of Assessment: pharmacy claims data, census data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2010
Cost of Nonadherence: all cause: PC(96-100):\$2976.80 (\$3247.04), PC(90-95):\$2826.99 (\$3083.63), PC(85-89):\$2795.39 (\$3049.16), PC(80-84):\$2690.89 (\$2935.17), PC(70-79):\$2192.83 (\$2391.90), PC(60-69):\$2323.27 (\$2534.18), PC(40-59):\$2153.93 (\$2349.47), PC(<40):\$1749.18 (\$1907.97)
Disease state specific: THC(96-100):\$6536.05 (\$7129.40), THC(90-95):\$6493.80 (\$7083.31),

Quality: medium
Classification: cost description

For peer review only

THC(85-89):\$6459.40 (\$7045.79),
 THC(80-84):\$6227.47 (\$6792.80),
 THC(70-79):\$5713.47 (\$6232.14),
 THC(60-69):\$5875.26 (\$6408.62),
 THC(40-59):\$5817.58 (\$6345.70),
 THC(<40):\$5249.12 (\$5725.64),
 PC(96-100):\$449.86 (\$490.70), PC(90-95):\$439.74 (\$479.66),
 PC(85-89):\$458.83 (\$500.48),
 PC(80-84):\$423.15 (\$461.56),
 PC(70-79):\$356.74 (\$389.13),
 PC(60-69):\$371.30 (\$405.01),
 PC(40-59):\$279.21 (\$304.56),
 PC(<40):\$133.92 (\$146.08),
 MC(96-100):\$3559.25 (\$3882.36),
 MC(90-95):\$3666.81 (\$3999.69),
 MC(85-89):\$3664 (\$3996.62), MC(80-84):\$3586.58 (\$3912.17), MC(70-79):\$3520.64 (\$3840.25), MC(60-69):\$3551.99 (\$3874.44), MC(40-59):\$3663.65 (\$3996.24),
 MC(<40):\$3499.95 (\$3817.68)

Mental Health

<p>29 <i>Bagalman et al</i>[13] 30 2010 31 US</p>	<p>To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 1258 (A:444, NA:814)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> MPR≥80 = adherent, MPR <80 = nonadherent <u>Method of</u> <u>Assessment:</u> pharmacy claims data</p>	<p>Total Costs Short term disability cost Workers compensation cost Paid time off cost</p>	<p><u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence:</u> TC:\$6894 (\$8273.53), STDC:\$2134 (\$2561.03), WCC:\$762 (\$914.48), PTOC:\$3998 (\$4798.03)</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost description</p>
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<i>Becker et al</i> [14] 2007 US	Examine treatment outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505)	<u>Measure:</u> prescription refill rate <u>Classification:</u> 75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, <25% = negligible adherence	Total Costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2006 <u>Cost of Nonadherence*:</u> TC(75-100):\$13564 (\$15792.91), TC(50-74):\$13772 (\$16035.09), TC(25-49):\$15792 (\$18387.03), TC(<25):\$16156 (\$18810.84)	<u>Quality:</u> low <u>Classification:</u> cost description
<i>Eddy et al</i> [15] 2005 US	To evaluate the effect of partial compliance of patients with prescribed oral atypical and conventional antipsychotic agents and the corresponding impact on resource utilisation.	<u>Design:</u> Retrospective database analysis <u>Follow Up:</u> 1 year <u>Sample Size:</u> 7864 (<80%:2655, 80-125%:5065, >125%:144)	<u>Measure:</u> continuous multiple interval medications available <u>Classification:</u> <80% = partially compliant, 80-125% = compliant, >125% = overly compliant	Inpatient costs Outpatient costs Pharmacy costs Medical costs Physician office visit costs Other costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence*:</u> IC:\$3780 (\$4906.39), OC:\$504 (\$654.19), PC:\$1872 (\$2429.83), MC:\$6228 (\$8083.86), POC:\$1944 (\$2523.29) OtC:\$12 (\$15.58)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Gilmer et al</i> [16] 2004	To evaluate the relationship between	<u>Design:</u> Retrospective database analysis	<u>Measure:</u> cumulative	Total costs Outpatient	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific	<u>Quality:</u> medium <u>Classification:</u> cost

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3	US	adherence to	<u>Follow Up:</u> 1 year	possession ratio	costs	<u>Currency Year:</u> USD, 1999	description
4		treatment with	<u>Sample Size:</u> 1619	<u>Classification:</u>	Pharmacy	<u>Cost of Nonadherence:</u>	
5		antipsychotic	(<49%:388, 50-	<49% =	costs	TC:\$8168 (\$11261.74),	
6		medication and health	79%:259, 80-100%:664,	nonadherent, 50-	Hospitalization	OC:\$3464 (\$4776.04),	
7		expenditures.	>110%:308)	79% = partially	costs	PC:\$1542 (\$2126.05),	
8		Secondary objective		adherent, 80-		HC:\$3413 (\$4705.72)	
9		was to identify risk		100% = adherent,			
10		factors predictive of		>110% = excess			
11		non-adherence.		medication fillers			
12				<u>Method of</u>			
13				<u>Assessment:</u>			
14				pharmacy claims			
15				data			
16				<u>Measure:</u>	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
17				assessed by	Inpatient costs	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
18	Hong et al[17]	To investigate clinical	<u>Design:</u> Prospective	treating	Outpatient	state specific	description
19	2011	and economic	<u>Follow Up:</u> 21 months	psychiatrist	costs	<u>Currency Year:</u> GBP, 2008	
20	UK	consequences of	<u>Sample Size:</u>	<u>Classification:</u>	Pharmacy	<u>Cost of Nonadherence*:</u> all cause:	
21		medication non-	1341(A:1024, NA:317)	adherent vs.	costs	PC:£55.43 (\$94.47)	
22		adherence in the		nonadherent	Hospitalization	Disease state specific:	
23		treatment of bipolar		<u>Method of</u>	costs	TC:£5846.29 (\$9964.10)	
24		disorder following a		<u>Assessment:</u>		IC:£2740.57 (\$4670.88),	
25		manic or mixed		observational		OC:£1082.86 (\$1845.57),	
26		episode.		assessment		PC:£1630.29 (\$2778.58),	
27						HC:£337.14 (\$574.60)	
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31	Jiang et al[18]	To estimate the impact	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> low
32	2015	of adherence to and	cohort study	<u>Classification:</u>	Pharmacy	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
33		persistence with	<u>Follow Up:</u> 2 years	(PDC≥80% =	costs	<u>Currency Year:</u> USD, 2011	description
34	US	atypical antipsychotics	<u>Sample Size:</u> 32374	adherent,	Medical	<u>Cost of Nonadherence:</u>	
35		on healthcare costs	(A:11642, NA:20732)	PDC<80% =	services costs	Disease state specific:	
36		and risk of		nonadherent)		TC:\$14141 (\$14517.37)	
37		hospitalization by		<u>Method of</u>		PC:\$3971 (\$4076.69),	
38		controlling potential		<u>Assessment:</u>		MSC:\$10170 (\$10440.68)	
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sources of endogeneity

medical and pharmacy claims data

Joe et al[19] 2016 South Korea

To investigate the association between psychiatric medication non-compliance and psychiatric and non-psychiatric service utilisation and costs.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 7848 (A:2774, NA:2774, P:1956, NP:1956)

Measure: percentage of days of psychiatric prescription (PDP)
Classification: PDP≥80% = adherent, PDP<80% = nonadherent; persistent = continued medication without interruption ≥ 56 day, non-persistent = at least one medication interruption > 56 days

Total costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2011
Cost of Nonadherence: all cause: TC:\$4961 (\$5271.40)
Disease state specific: TC:\$3061 (\$3252.50)

Quality: medium
Classification: cost outcome description

Knapp et al[20] 2004 UK

To assess the relative impact of non-adherence and other factors associated with resource use and costs incurred by people

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 658 (A:549, NA:109)

Measure: self-report
Classification: adherent vs. nonadherent
Method of Assessment: health insurance data

Total costs
Inpatient costs
External services costs

Type of Costs: predicted
Classification: disease state specific
Currency Year: GBP, 2001
Cost of Nonadherence: TC:£57580 (\$116434.12)
IC:£6714 (\$13576.57),

Quality: medium
Classification: cost analysis

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3		with schizophrenia.		<u>Assessment:</u>		ESC:£1603 (\$3241.47)
4				survey		
5	<i>Offord et al[21]</i>	To quantify early	<u>Design:</u> Retrospective	<u>Measure:</u> time to	Total costs	<u>Type of Costs:</u> adjusted
6	2013	nonadherence to	cohort study	discontinuation	Outpatient	<u>Classification:</u> all cause and disease
7	US	antipsychotic	<u>Follow Up:</u> 1 year	<u>Classification:</u>	costs	state specific
8		medications in patients	<u>Sample Size:</u> 1462	adherent vs.	Pharmacy	<u>Currency Year:</u> USD, 2008
9		with schizophrenia and	(A:589, NA:873)	nonadherent	costs	<u>Cost of Nonadherence:</u> all cause:
10		its impact on short-		<u>Method of</u>	Hospitalization	TC:\$15400 (\$17132.34)
11		term antipsychotic		<u>Assessment:</u>	costs	OC:\$5773 (\$6422.40),
12		adherence, healthcare		pharmacy claims		PC:\$3777 (\$4201.87),
13		utilisation and costs.		data		HC:\$5850 (\$6508.06)
14						Disease state specific:
15						TC:\$5358 (\$5960.72)
16						OC:\$858 (\$954.52),
17						PC:\$1549 (\$1723.25),
18						HC:\$2952 (\$3284.07)
19						<u>Type of Costs:</u> adjusted
20						<u>Classification:</u> all cause and disease
21	<i>Offord et al[22]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Inpatient	<u>Quality:</u> low
22	2013	of medication	cohort study	<u>Classification:</u>	costs	<u>Classification:</u> cost
23	US	adherence on	<u>Follow Up:</u> 1 year	MPR ≥ 70= high	Pharmacy	description
24		healthcare utilisation	<u>Sample Size:</u> 354	adherence, MPR <	costs	
25		among Medicare	(A:126, NA:228)	70 = low		<u>Currency Year:</u> USD, 2008
26		insured schizophrenia		adherence		<u>Cost of Nonadherence:</u> all cause:
27		patients.		<u>Method of</u>		IC:\$9053 (\$10071.37),
28				<u>Assessment:</u>		PC:\$4267 (\$4746.99),
29				pharmacy claims		Disease state specific:
30				data		IC:\$2468 (\$2745.62),
31						PC:\$1085 (\$1207.05)
32	<i>Robertson et al[23]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
33	2014	of the combination of	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
34	US	treatment utilization	<u>Follow Up:</u> 90 days	MPR ≥80% =	Outpatient	<u>Currency Year:</u> USD,2005
35		and medication	<u>Sample Size:</u> 1376	adherent	costs	<u>Cost of Nonadherence*:</u>
36		possession on arrest	(90/90:637, 60/90:240,	<u>Method of</u>	Emergency	TC(90/90):\$28068 (\$33495.65),
37		and incarceration	30/90:174, 0/90:316)	<u>Assessment:</u>	department	TC(60/90):\$21720 (\$25920.11),
38		outcomes and on		Medicaid claims	costs	TC(30/90):\$21084 (\$25161.12),
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3	costs.	data	Pharmacy	TC(0/90):\$12516 (\$14936.28),
4			costs	IC(90/90):\$12168 (\$14520.99),
5			Target case	IC(60/90):\$10068 (\$12014.90),
6			management	IC(30/90):\$11376 (\$13575.84),
7			costs	IC(0/90):\$5592 (\$6673.35),
8			Psychiatric	OC(90/90):\$6468 (\$7718.75),
9			assessment	OC(60/90):\$4152 (\$4954.89),
10			costs	OC(30/90):\$2916 (\$3479.88),
11			Arrest costs	OC(0/90):\$2136 (\$2549.05),
12			Incarceration	EDC(90/90):\$96 (\$114.56),
13			costs	EDC(60/90):\$108 (\$128.88),
14				EDC(30/90):\$144 (\$171.85),
15				EDC(0/90):\$84 (\$100.24),
16				PC(90/90):\$5316 (\$6343.98),
17				PC(60/90):\$3468 (\$4138.63),
18				PC(30/90):\$2232 (\$2663.61),
19				PC(0/90):\$984 (\$1174.28),
20				TCMC(90/90):\$2100 (\$2506.09),
21				TCMC(60/90):\$1404 (\$1675.50),
22				TCMC(30/90):\$1596 (\$1904.63),
23				TCMC(0/90):\$516 (\$615.78),
24				PAC(90/90):\$240 (\$286.41),
25				PAC(60/90):\$228 (\$272.09),
26				PAC(30/90):\$204 (\$243.45),
27				PAC(0/90):\$156 (\$186.17),
28				ArC(90/90):\$780 (\$930.83),
29				ArC(60/90):\$1032 (\$1231.56),
30				ArC(30/90):\$1140 (\$1360.45),
31				ArC(0/90):\$1200 (\$1432.05),
32				InC(90/90):\$888 (\$1059.72),
33				InC(60/90):\$1272 (\$1517.97),
34				InC(30/90):\$1476 (\$1761.42),
35				InC(0/90):\$1860 (\$2219.68)
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3	<i>Robinson et al</i> [24]	To determine if the	<u>Design:</u> Retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> unadjusted
4	2006	type of antidepressant	claims analysis	Antidepressant	Inpatient	<u>Classification:</u> all cause and disease
5	US	drug is related to	<u>Follow Up:</u> 6 months	medication	costs	state specific
6		adherence and assess	<u>Sample Size:</u> 60386	management	Outpatient	<u>Currency Year:</u> USD, 2004
7		the 6 month health	(A:11526, NA:8860)	measures	costs	<u>Cost of Nonadherence*:</u> all cause:
8		care costs among		<u>Classification:</u>	ED visit costs	TC:\$12658 (\$15678.21)
9		newly diagnosed		meeting less than	Pharmacy	IC:\$3006 (\$3723.24),
10		patients.		<3 medication	costs	OC:\$6118 (\$7577.76),
11				management	Physician	EDC:\$334 (\$413.69)
12				measures =	office visit	PC:\$3200 (\$3963.52),
13				nonadherent	costs	POC:\$178 (\$220.47)
14				<u>Method of</u>		Disease state specific:
15				<u>Assessment:</u>		TC:\$2028 (\$2511.88)
16				pharmacy claims		IC:\$102 (\$126.34),
17				data, Medicaid		OC:\$734 (\$909.13),
18				data,		EDC:\$18 (\$22.29)
19				observational		PC:\$1174 (\$1454.12),
20				assessment		POC:\$120 (\$148.63)
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23	<i>Svarstad et al</i> [25]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> quarter	Hospitalization	<u>Type of Costs:</u> unadjusted
24	2001	relationship of	database analysis	pharmacy claims	costs	<u>Classification:</u> all cause and disease
25	US	medication non-	<u>Follow Up:</u> 1 year	<u>Classification:</u> one		state specific
26		adherence to hospital	<u>Sample Size:</u> 619	or more quarters		<u>Currency Year:</u> USD, 1990
27		use and costs among	(A:413, NA:206)	without a claim =		<u>Cost of Nonadherence:</u> all cause:
28		severely mentally ill		nonadherent		HC:\$3992 (\$6593.06)
29		clients.		<u>Method of</u>		Disease state specific:
30				<u>Assessment:</u>		Schizophrenia/schizoaffective disorder:
31				pharmacy claims		HC:\$3421 (\$5650.01)
32				data, previous		Bipolar disorder:
33				study data		HC:\$9701 (\$16021.85),
34						Other severe mental illness:
35						HCD:\$3024 (\$4994.34)
36						
37						
38	<i>White et al</i> [26]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
39	2003	economic impact of	database analysis	<u>Classification:</u>	Pharmacy	<u>Classification:</u> disease state specific
40						<u>Quality:</u> medium
41						<u>Classification:</u> cost
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US	antidepressant treatment adherence among patients treated for depression	<u>Follow Up:</u> 6 months <u>Sample Size:</u> 14190 (A:5638, NA:8552)	<u>Measure:</u> MPR≥70% = adherent, MPR<70% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	costs Medical costs	<u>Currency Year:</u> USD, 1999 <u>Cost of Nonadherence:</u> TC:\$11815 (\$16290.09) PC:\$1123 (\$1548.35), MC:\$10692 (\$14741.74)	description
Diabetes <i>An et al[27]</i> 2014 Korea	This study evaluated the association between medication adherence and clinical/economic outcomes in patients with type II diabetes mellitus in the republic of Korea over 3 year period.	<u>Design:</u> Prospective cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 608 (A:472, NA:136)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥90% = adherent, MPR<90% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	Total costs Outpatient costs Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2007 <u>Cost of Nonadherence*:</u> TC:\$1657.11 (\$1884.14) OC: \$1413.99 (\$1608.20), HC: \$243.11 (\$276.12)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Egede et al[28]</i> 2012 US	To examine the longitudinal effects of medication nonadherence on key costs and estimate potential savings from increased adherence using novel methodology that accounts for shared correlation among cost categories.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 5 years <u>Sample Size:</u> 740195 (A:427390, NA:312805)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥80% = adherent, MPR<80% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	Inpatient costs Outpatient costs Pharmacy costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2006 <u>Cost of Nonadherence*:</u> IC:\$14515.24 (\$17886.40) OC: \$3599.27 (\$4434.16), PC: \$1073.12 (\$1322.42)	<u>Quality:</u> high <u>Classification:</u> cost outcome description
Gentil et al[29] 2015	To examine healthcare costs associated with	<u>Design:</u> Retrospective, observational cohort	<u>Measure:</u> MPR <u>Classification:</u>	Total costs Inpatient costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> all cause and disease	<u>Quality:</u> medium <u>Classification:</u> cost

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3	Canada	adherence to oral	analysis	MPR \geq 80% =	Outpatient	state specific
4		antihyperglycemic	<u>Follow Up:</u> 1 year	adherent,	costs	<u>Currency Year:</u> CAD, 2010
5		agents and the effects	<u>Sample Size:</u> 301	MPR<80% =	Pharmacy	<u>Cost of Nonadherence:</u>
6		of depression and	(A:224, NA:77)	nonadherent	costs	Adjusted all cause:
7		anxiety disorders on		<u>Method of</u>	Physician	TC:\$11124 (\$9818.67),
8		these in older adults		<u>Assessment:</u>	office visit	IC:\$7419 (\$6548.43)
9		with type 2 diabetes		pharmacy claims	costs	OC: \$2687 (\$2371.70),
10				data		PC: \$504 (\$444.86),
11						POC:\$513 (\$452.80)
12						Adjusted disease state specific:
13						TC:\$4477 (\$3951.65),
14						IC:\$2836 (\$2503.21)
15						OC: \$1518 (\$1339.87),
16						PC ^{###} : \$-444 (\$-391.90),
17						POC:\$568 (\$517.24)
18						Unadjusted all cause:
19						TC:\$14979 (\$13221.30),
20						IC:\$6351 (\$5605.75)
21						OC: \$4058 (\$3581.82),
22						PC: \$3503 (\$3091.94),
23						POC:\$1066 (\$940.91)
24						Unadjusted disease state specific:
25						TC:\$9008 (\$7950.97),
26						IC:\$2854 (\$2519.10)
27						OC: \$2654 (\$2342.57),
28						PC: \$2498 (\$2204.87),
29						POC:\$1002 (\$884.42)
30						<u>Type of Costs:</u> adjusted and unadjusted
31						<u>Classification:</u> all cause and disease
32						state specific
33	<i>Hagen et al</i> [30]	To evaluate the	<u>Design:</u> Retrospective,	<u>Measure:</u> PDC	Healthcare	<u>Quality:</u> medium
34	2014	relationships between	observational cohort	<u>Classification:</u>	costs	<u>Classification:</u> cost
35	US	compliance with oral	analysis	PDC \geq 80% =	Pharmacy	state specific
36		hypoglycemic agents	<u>Follow Up:</u> 1 year	compliant,	costs	<u>Currency Year:</u> USD, 2003
37		and healthcare/ short	<u>Sample Size:</u> 4978	PDC<80% =	Medical costs	<u>Cost of Nonadherence:</u> Adjusted all
38		term disability costs	(A:2820, NA:2158)	noncompliant	Short term	cause:
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			<u>Method of Assessment:</u> pharmacy claims data	disability costs	PC: \$1668 (\$2065.99), Adjusted disease state specific: HC:\$7642 (\$9465.39), PC:\$614 (\$760.50), MC:\$5974 (\$7399.40), STDC:\$1840 (\$2279.03) Unadjusted all cause: PC:\$1727 (\$2139.06) Unadjusted disease state specific: HC:\$6919 (\$8569.88), PC:\$785 (\$972.30), MC:\$5192 (\$6430.82), STDC:\$1717 (\$2126.68)	
<i>Hansen et al</i> [31] 2010 US	To compare all cause total health care costs and diabetes mellitus specific health care costs between patients who were adherent or non-adherent to monotherapy with metformin, pioglitazone or a sulfonylurea and to examine whether cost differences varied among patients using these oral antidiabetic drugs.	<u>Design:</u> Retrospective, cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 108592 (A:63830, NA:44762)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥80% = adherent, MPR<80% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare costs Inpatient costs Outpatient costs Pharmacy costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence#:</u> Adjusted all cause: THC:\$13258 (\$15911.01) Adjusted disease state specific: THC:\$2284 (\$2741.04) Unadjusted all cause: THC:\$15448.50 (\$18539.90), IC:\$4242.33 (\$5091.25), OC:\$ 7377.83, PC:\$3828 (\$4594.01) Unadjusted disease state specific: THC:\$3232.33 (\$3879.15), IC:\$873.50 (\$1048.29), OC:\$1545.67(\$1854.96), PC:\$812.67 (\$975.29)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Hong et al</i> [32] 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and	<u>Design:</u> Retrospective, cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 40082 (A:11800, NA:28282)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥80% = adherent, MPR<80% =	Total costs Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> KRW, 2007 <u>Cost of Nonadherence:</u> TC:₩765453 (\$1142.31),	<u>Quality:</u> medium <u>Classification:</u> cost description

subsequent health outcomes.

nonadherent

HC: \$397549 (\$593.28)

Method of

Assessment:

pharmacy claims data

Jha et al[33]
2012
US

How often do previously non-adherent patients become adherent and vice versa?

Design: Retrospective, observational claims analysis

Follow Up: unclear

Sample Size: 135639

(A:99976, NA:36553)

Measure: MPR

Classification:

MPR \geq 80% =

adherent,

MPR<80% =

nonadherent

Method of

Assessment:

pharmacy claims data

Total costs

ED costs

Hospitalization costs

Type of Costs: adjusted

Classification: disease state specific

Currency Year: USD, 2011

Cost of Nonadherence^{***}:

TC:\$4680000000 (\$5006563305.49),

EDC:\$735000000 (\$786287185.80),

HC:\$3950000000 (\$4225625012.11)

Quality: high

Classification: cost

outcome

description

White et al[34]
2004
US

To assess the relationship between diabetic medication adherence, total

Design: Retrospective, database analysis

Follow Up: 1 year

Sample Size: 67029

Measure: MPR

Classification:

MPR \geq 95%,

MPR>75%<95%,

Total costs

Pharmacy costs

costs

Non-pharmacy

Type of Costs: adjusted and unadjusted

Classification: disease state specific

Currency Year: USD, 2000

Cost of Nonadherence: adjusted:

Quality: low

Classification: cost

analysis

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healthcare costs and utilisation with patients with type 2 diabetes mellitus and concomitant diabetes and cardiovascular disease.

(>95:20170, 75-95: 14074, <75:16713)

MPR<75%
Method of Assessment:
pharmacy claims data

costs

TC(≥95):\$4835 (\$6518.17),
TC(75-95):\$5314 (\$7163.92),
TC(<75):\$5706 (\$7692.38),
PC(≥95):\$1429 (\$1926.47),
PC(75-95):\$1157 (\$1559.78),
PC(<75):\$762 (\$1027.27),
NPC(≥95):\$3406 (\$4591.70),
NPC(75-95):\$4157 (\$5604.14),
NPC(<75):\$4944 (\$6665.11)
Unadjusted:
TC(≥95):\$4809 (\$6483.12),
TC(75-95):\$5333 (\$7189.53),
TC(<75):\$5605 (\$7556.22),
PC(≥95):\$1402 (\$1890.07),
PC(75-95):\$1153 (\$1554.38),
PC(<75):\$766 (\$1032.66),
NPC(≥95):\$3407 (\$4593.05),
NPC(75-95):\$4180 (\$5635.15),
NPC(<75):\$4839 (\$6523.56)

Wu et al[35]
2009
US

To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

Design: Retrospective, cohort study
Follow Up: 1 year
Sample Size: 2354 (A:830, NA:1524)

Measure: MPR
Classification:
MPR≥80%= high compliance,
MPR<80% = low compliance
Subgroup
Analysis:
commercial and Medicare supplemental
Method of Assessment:
pharmacy claims

Total healthcare costs
Inpatient costs
Outpatient costs
Pharmacy costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2006
Cost of Nonadherence: adjusted all cause:
THC(com):\$32407 (\$37732.29),
THC(med):\$24622 (\$28668.02),
IC(com):\$ 12851(\$14692.74),
IC(med):\$ 6754 (\$7863.85),
OC(com):\$11888 (\$13841.50),
OC(med):\$10598 (\$12339.52),
PC(com):\$7667 (\$8926.88),
PC(med):\$7270 (\$8464.65)

Quality: medium
Classification: cost description

data

Adjusted disease state specific:

Diabetes:

THC(com):\$10024 (\$11671.20),

THC(med):\$5015 (\$5839.09),

IC(com):\$2232 (\$2598.77),

IC(med):\$2606 (\$3034.23),

OC(com):\$1989 (\$2315.84),

OC(med):\$1231 (\$1433.28),

PC(com):\$1451 (\$1689.44),

PC(med):\$1179 (\$1372.74)

DPNP:

THC(com):\$3565 (\$4150.82),

THC(med):\$2384 (\$2775.75),

IC(com):\$1739 (\$2024.76),

IC(med):\$1048 (\$1220.21),

OC(com):\$362 (\$421.49),

OC(med):\$181 (\$210.74),

PC(com):\$1464 (\$1704.57)

PC(med):\$1155 (\$1344.80)

Osteoporosis

Briesacher et al[36]
2007
US

To assess rates of osteoporotic fractures and health care utilisation as a function of bisphosphonate compliance in usual clinical practice.

Design: Retrospective, cohort study
Follow Up: 3 years
Sample Size: 17988 (not specified)

Measure: MPR
Classification: 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent
Method of

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2004
Cost of Nonadherence****: adjusted:
TC(80-100):-\$859 (-\$1063.96),
TC(60-79):-\$474 (-\$587.10),
TC(40-59):-\$366 (-\$453.33),
TC(20-39):\$151 (\$187.03),
IC(80-100):-\$3233 (-\$4004.40),
IC(60-79):-\$856(-\$1060.24),
IC(40-59):-\$6221 (-\$7705.34),
IC(20-39):-\$585 (-\$724.58),
OC(80-100):-\$445 (-\$551.18),

Quality: medium
Classification: cost description

Assessment:pharmacy claims
data

OC(60-79):-\$538 (-\$666.37),

OC(40-59):-\$236 (-\$292.31),

OC(20-39):\$60 (\$74.32),

PC(80-100):\$997 (\$1234.89),

PC(60-79):\$923 (\$1143.23),

PC(40-59):\$402 (\$497.92),

PC(20-39):\$160(\$198.18)

Unadjusted:

TC(80-100):-\$1273 (-\$1576.74),

TC(60-79):-\$294 (-\$364.15),

TC(40-59):-\$573 (-\$709.72),

TC(20-39):\$101 (\$125.10),

IC(80-100):-\$883 (-\$1093.68),

IC(60-79):-\$384 (-\$475.62),

IC(40-59):-\$597 (-\$739.44),

IC(20-39):-\$93 (-\$115.19),

OC(80-100):-\$774 (-\$958.68),

OC(60-79):-\$193 (-\$239.05),

OC(40-59):-\$145 (-\$179.60),

OC(20-39):\$148 (\$183.31),

PC(80-100):\$384 (\$475.62),

PC(60-79):\$284 (\$351.76),

PC(40-59):\$170 (\$210.56),

PC(20-39):\$48 (\$59.45)

Eisenberg et al[37]

2015

US

To determine
healthcare outcomes
associated with
compliance and
noncompliance to
bisphosphonate
therapy in women
diagnosed with
osteoporosisDesign: Retrospective
claims studyFollow Up: 2 yearsSample Size: 27905

(A:11368, NA:16537)

Measure: MPRClassification:

(≥70% =

compliant, <70%

= noncompliant

Method ofAssessment:pharmacy claims
data

Total costs

Inpatient costs

Outpatient

costs

ED costs

Pharmacy

costs

Physician

office visit

Type of Costs: unadjustedClassification: all cause and disease

state specific

Currency Year: USD, 2012Cost of Nonadherence: all cause:

TC:\$7237 (\$7550.72),

IC:\$1986 (\$2072.09),

OC:\$2057 (\$2146.17),

EDC:\$258 (\$269.18),

Quality: mediumClassification: cost

description

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3					costs	PC:\$2197 (\$2292.24),	
4						POC:\$738 (\$769.99)	
5						Disease state specific:	
6						TC:\$674 (\$703.22),	
7						IC:\$334 (\$348.48),	
8						OC:\$77 (\$80.34),	
9						EDC:\$5 (\$5.22),	
10						PC:\$213 (\$222.23),	
11						POC:\$44 (\$45.91)	
12							
13	<i>Halpern et al</i> [38]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Medical costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
14	2011	associations of	analysis	<u>Classification:</u>		<u>Classification:</u> all cause	<u>Classification:</u> cost
15	US	adherence to	<u>Follow Up:</u> 540 days	(≥80% = high		<u>Currency Year:</u> USD, 2006	outcome
16		osteoporosis therapies	<u>Sample Size:</u> 21655	adherence,		<u>Cost of Nonadherence:</u> commercial:	description
17		with occurrence of	(≥80%:8759,	≥50<80% =		MC(≥80):\$4295 (\$5000.78),	
18		closed fracture, all	≥50<80%:5237,	moderate		MC(50-80):\$4697 (\$5468.84),	
19		cause medical costs	<50%:7659)	adherence, <50%		MC(<50):\$5596 (\$6515.56)	
20		and all cause		= low adherence		Medicare:	
21		hospitalizations.		<u>Method of</u>		MC(≥80):\$4590 (\$5344.25),	
22				<u>Assessment:</u>		MC(50-80):\$5536 (\$6445.71),	
23				pharmacy claims		MC(<50):\$5801 (\$6754.25)	
24				data			
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26							
27	<i>Hazel-Fernandez et al</i> [39]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
28	2013	healthcare utilisation	cohort study	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific and	<u>Classification:</u> cost
29	US	patterns of medicare	<u>Follow Up:</u> 12 months	(≥80% = high	costs	fracture related	outcome
30		part D beneficiaries	<u>Sample Size:</u> 761	adherence,	Inpatient costs	<u>Currency Year:</u> USD, 2010	description
31		newly initiating	(≥80%:163,	≥50<80% =	Outpatient	<u>Cost of Nonadherence*:</u>	
32		teriparatide and to	≥50<80%:57,	moderate	costs	Disease state specific:	
33		assess the association	<50%:541)	adherence, <50%	ED costs	THC(≥80):\$21033 (\$22942.39),	
34		of medication		= low adherence	Pharmacy	THC(50-80):\$25574 (\$27895.62),	
35		adherence and		<u>Method of</u>	costs	THC(<50):\$15528 (\$16937.64),	
36		persistence with bone		<u>Assessment:</u>		IC(≥80):\$2198 (\$2397.54),	
37		fracture.		pharmacy claims		IC(50-80):\$8448 (\$9214.91),	
38				data		IC(<50):\$4897 (\$5341.55),	
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For peer review only

OC(≥80):\$5151 (\$5618.61),
OC(50-80):\$6439 (\$7023.54),
OC(<50):\$5806 (\$6333.07),
EDC(≥80):\$211 (\$230.15),
EDC(50-80):\$330 (\$359.96),
EDC(<50):\$465 (\$507.21),
PC(≥80):\$13472 (\$14695),
PC(50-80):\$10358 (\$11298.31),
PC(<50):\$4361 (\$4756.89)
Fracture related:
THC(≥80):\$12670 (\$13820.19),
THC(50-80):\$9292 (\$10135.53),
THC(<50):\$4419 (\$4820.16),
IC(≥80):\$366 (\$399.23),
IC(50-80):\$830 (\$905.35),
IC(<50):\$1325 (\$1445.28),
OC(≥80):\$1048 (\$1143.14),
OC(50-80):\$955 (\$1041.70),
OC(<50):\$767 (\$836.63),
EDC(≥80):\$6 (\$6.54),
EDC(50-80):\$9 (\$9.82),
EDC(<50):\$44 (\$47.99),
PC(≥80):\$10810 (\$11791.34),
PC(50-80):\$7420 (\$8093.59),
PC(<50):\$2068 (\$2255.73)

<p><i>Huybrechts et al</i>^[40] 2006 US</p>	<p>To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 5 years <u>Sample Size:</u> 38120 (A:9530, NA:28590)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> (≥80% = compliant, <50% = noncompliant) <u>Method of Assessment:</u> pharmacy claims</p>	<p>Total costs Medical costs Institutional costs</p>	<p><u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2000 <u>Cost of Nonadherence:</u> TC:\$7200 (\$9706.44), MC:\$1476 (\$1989.84), InstC:\$5736 (\$7732.80)</p>	<p><u>Quality:</u> low <u>Classification:</u> cost description</p>
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4	<i>Kjellberget al[41]</i>	To estimate the rate of	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
5	2016	oral bisphosphonate	cohort study	<u>Classification:</u>	Medical costs	<u>Classification:</u> all cause and disease
6	Denmark	compliance among	<u>Follow Up:</u> 1 year	(≥70% =		state specific
7		Danish women and to	<u>Sample Size:</u> 38234	compliant, <70%		<u>Currency Year:</u> Euro, 2011
8		examine the	(A:26806, NA:11428)	= noncompliant)		<u>Cost of Nonadherence:</u> all cause:
9		association of		<u>Method of</u>		TC:€4933 (\$6209.58),
10		noncompliance with		<u>Assessment:</u>		MC:€3471 (\$4369.20),
11		health care resource		pharmacy claims		Disease state specific:
12		use and cost.		data		TC:€754 (\$949.12),
13						MC:€426 (\$536.24),
14						
15	<i>Modi et al[42]</i>	To evaluate	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
16	2015	compliance with	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease
17	US	osteoporosis	<u>Follow Up:</u> 1 year	(≥80% =	Outpatient	state specific
18		treatments and	<u>Sample Size:</u> 27913	compliant, <80%	costs	<u>Currency Year:</u> USD, 2011
19		determine fracture and	(A:23430, NA:34483)	= noncompliant)	ED costs	<u>Cost of Nonadherence:</u> all cause:
20		healthcare burden		<u>Method of</u>	Pharmacy	TC:\$11749 (\$12484.12),
21		associated with		<u>Assessment:</u>	costs	IC:\$8768 (\$9316.60),
22		noncompliance		healthcare claims	Medical costs	OC:\$3945 (\$4191.83),
23				data	Other costs	EDC:\$104 (\$110.51),
24						PC:\$2981 (\$3167.52),
25						MC:\$8768 (\$9316.60),
26						OtC:\$997 (\$1059.38)
27						Disease state specific:
28						TC:\$630 (\$669.42),
29						IC:\$443 (\$470.72),
30						OC:\$158 (\$167.89),
31						EDC:\$3 (\$3.19),
32						PC:\$325 (\$345.33),
33						OtC:\$26 (\$27.63)
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37	<i>Olsen et al[43]</i>	To assess the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Fracture costs	<u>Type of Costs:</u> unadjusted
38	2013	association between	observational study	<u>Classification:</u>		<u>Classification:</u> fracture site specific
39	Denmark	refill compliance and	<u>Follow Up:</u> 2 years	(≥80% = optimal)		<u>Currency Year:</u> DKK, 2010
40						<u>Quality:</u> medium
41						<u>Classification:</u> cost
42						analysis
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all cause health care costs.

Sample Size: 47176 (not specified)

compliance, >50<80% = suboptimal compliance, <50% = low compliance
Method of Assessment: pharmacy claims data

Cost of Nonadherence:
Hip fracture:
FC(50-80):kr817575.50 (\$74531.41),
FC(<50):kr4454954 (\$549987.04)
Spine fracture:
FC(50-80):kr174700 (\$21568.12),
FC(<50):kr226472 (\$27959.14)
Humerus fracture:
FC(50-80):kr117776.50 (\$14540.12),
FC(<50):kr795217.50 (\$98173.70)
Forearm fracture:
FC(50-80):-kr463024 (-\$57162.70),
FC(<50):kr45072.50 (\$8665.81)
Other fracture:
FC(50-80):-kr19261.50 (-\$2377.93),
FC(<50):kr684067.50 (\$84451.66)

Sunycz et al[44] 2008 US

To examine the relationship between persistence and compliance with bisphosphonate therapy and total and osteoporosis related costs and healthcare resource utilisation in a cohort of female bisphosphonate naïve users.

Design: Retrospective observational study
Follow Up: 3 years
Sample Size: 32944 (A:12186, NA:20758)

Measure: MPR
Classification: (≥80% = compliant, <80% = noncompliant)
Method of Assessment: pharmacy claims data

Total healthcare costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Radiology costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2005
Cost of Nonadherence:
All cause:
THC:\$23660 (\$28394.52),
IC:\$18839 (\$22608.81),
OC:\$10061 (\$12074.27),
EDC:\$832 (\$988.49),
PC:\$6941 (\$8329.94),
RC:\$1079 (\$1294.91)
Disease state specific:
THC:\$1602 (\$1922.57),
IC:\$14074 (\$16890.30),
OC:\$501 (\$601.25),
EDC:\$452 (\$542.45),

Quality: low
Classification: cost description

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4					PC:\$918 (\$1101.70),	
5					RC:\$184 (\$220.82)	
6	<i>Zhao et al</i> [45]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total	<u>Type of Costs:</u> adjusted and unadjusted
7	2014	association between	cohort study	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
8	US	teriparatide adherence	<u>Follow Up:</u> 36 months	(≥80% = high, 50-	costs	<u>Currency Year:</u> USD, 2010
9		and healthcare	<u>Sample Size:</u> 824	80% = medium,	Inpatient costs	<u>Cost of Nonadherence*:</u>
10		utilisation and costs	(≥80:362, 50-80%:219,	<50% = low)	Outpatient	Adjusted:
11		among hip fracture	<50%:243)	<u>Method of</u>	costs	THC(≥80):\$34428 (\$37553.4),
12		patients.		<u>Assessment:</u>	Pharmacy	THC(50-80):\$37956 (\$41401.68),
13				pharmacy claims	costs	THC(<50):\$31188 (\$34019.28),
14				data		IC(≥80):\$7548 (\$8233.20),
15						IC(50-80):\$11520 (\$1256.80),
16						IC(<50):\$11556 (\$12605.04),
17						OC(≥80):\$9312 (\$10157.40),
18						OC(50-80):\$12816 (\$13979.40),
19						OC(<50):\$13044 (\$14228.16),
20						PC(≥80):\$18864 (\$20576.52),
21						PC(50-80):\$13116 (\$14306.64),
22						PC(<50):\$7452 (\$8128.44)
23						Unadjusted:
24						THC(≥80):\$37464 (\$40865.04),
25						THC(50-80):\$35076 (\$38260.20),
26						THC(<50):\$29484 (\$32160.60),
27						IC(≥80):\$7092 (\$7735.80),
28						IC(50-80):\$11100 (\$12107.64),
29						IC(<50):\$10632 (\$11597.16),
30						OC(≥80):\$9900 (\$10798.68),
31						OC(50-80):\$11352 (\$12382.56),
32						OC(<50):\$11988 (\$13076.28),
33						PC(≥80):\$20484 (\$22343.52),
34						PC(50-80):\$12624 (\$13770),
35						PC(<50):\$6864 (\$7487.16)
36						
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39	<i>Zhao et al</i> [46]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total	<u>Type of Costs:</u> adjusted and unadjusted
40						<u>Quality:</u> medium
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2013 US	association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty (KV) patients.	observational cohort study <u>Follow Up:</u> 36 months <u>Sample Size:</u> 1568 (≥80: 783, 50-80%: 382, <50%: 403)	<u>Classification:</u> (≥80% = high, 50-80% = medium, <50% = low) <u>Method of Assessment:</u> pharmacy claims data	healthcare costs Inpatient costs Outpatient costs Pharmacy costs	<u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2010 <u>Cost of Nonadherence*:</u> Adjusted: THC(≥80):\$40212 (\$43862.52), THC(50-80):\$40512 (\$44189.76), THC(<50):\$40128 (\$43770.84), IC(≥80):\$8136 (\$8874.60), IC(50-80):\$12060 (\$13154.76), IC(<50):\$15444 (\$43404.36), OC(≥80):\$12924 (\$14097.24), OC(50-80):\$14928 (\$16283.16), OC(<50):\$17568 (\$19162.80), PC(≥80):\$19392 (\$21152.40), PC(50-80):\$13908 (\$15170.52), PC(<50):\$8700 (\$9843.24) Unadjusted: THC(≥80):\$42768 (\$46650.48), THC(50-80):\$36780 (\$40118.88), THC(<50):\$39792 (\$43404.36), IC(≥80):\$7620 (\$8311.80), IC(50-80):\$12228 (\$13338.12), IC(<50):\$15768 (\$17199.48), OC(≥80):\$14580 (\$15903.60), OC(50-80):\$12108 (\$13207.20), OC(<50):\$15324 (\$16715.16), PC(≥80):\$20568 (\$22435.20), PC(50-80):\$12444 (\$13573.68), PC(<50):\$8700 (\$9489.84)	<u>Classification:</u> cost description
Respiratory Disease <i>Delea et al</i> [47] 2008	To assess the association between	<u>Design:</u> Retrospective longitudinal cohort	<u>Measure:</u> MPR <u>Classification:</u>	Total costs Outpatient	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific	<u>Quality:</u> medium <u>Classification:</u> cost

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3	US	adherence with	study	(≥75, 50-75%, 25-	costs	Currency Year: USD, 2003
4		fluticasone	<u>Follow Up:</u> 24 months	50%, <25%)	ED costs	<u>Cost of Nonadherence*:</u>
5		propionate/salmeterol	<u>Sample Size:</u> 12907	<u>Method of</u>	Other costs	TC(≥75):\$1564 (\$1990.27),
6		combination product in	(≥75: 2612, 50-75%:	<u>Assessment:</u>		TC(50-75):\$1128 (\$1435.44),
7		a single inhaler and	3608, 25-50%: 5035,	pharmacy claims		TC(25-50):\$900 (\$1145.30),
8		asthma care utilisation	<25%: 1652)	data		TC(<25):\$632 (\$804.25),
9		and costs in asthma				OC(≥75):\$1272 (\$1618.69),
10		patients in typical US				OC(50-75):\$852 (\$1084.21),
11		clinical practice				OC(25-50):\$600 (\$763.53),
12						OC(<25):\$388 (\$493.75),
13						EDC(≥75):\$32 (\$40.72),
14						EDC(50-75):\$36 (\$45.81),
15						EDC(25-50):\$60 (\$76.35),
16						EDC(<25):\$48 (\$61.08),
17						OtC(≥75):\$292 (\$371.59),
18						OtC(50-75):\$276 (\$351.22),
19						OtC(25-50):\$300 (\$381.77),
20						OtC(<25):\$240 (\$305.41)
21						
22						
23	<i>Diehl et al</i> [48]	To evaluate	<u>Design:</u> Retrospective	<u>Measure:</u> 37 day	Total costs	<u>Type of Costs:</u> unadjusted
24	2010	respiratory-related	claims analysis	gap in claims	Pharmacy	<u>Classification:</u> disease state specific
25	US	medical outcomes and	<u>Follow Up:</u> 7 months	<u>Classification:</u> (>37	costs	<u>Currency Year:</u> USD, 2007
26		cost for infants who	<u>Sample Size:</u> 245 (A:73,	day gap in claims =	Services costs	<u>Cost of Nonadherence:</u>
27		were prescribed and	NA:172)	noncompliant)		TC:\$19093.46 (\$21656.12),
28		received palivizumab in		<u>Method of</u>		PC:\$7647.40 (\$8673.81),
29		accordance with the		<u>Assessment:</u>		SC**:\$11604.03 (\$13161.45)
30		dosing schedule		pharmacy claims		
31		recommended by the		data		
32		American Academy of				
33		Paediatrics in 2006				
34		versus those who did				
35		not.				
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38	<i>Joshi et al</i> [49]	Examine the	<u>Design:</u> quantitative	<u>Measure:</u> Morisky	Total	<u>Type of Costs:</u> unadjusted
39	2006	association of	analysis	scale	productivity	<u>Classification:</u> disease state specific
40						<u>Quality:</u> medium
41						<u>Classification:</u> cost
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US	medication adherence with workplace productivity and health related quality of life in asthma patients.	<u>Follow Up:</u> <u>Sample Size:</u> 385 (high:150, medium:73, low: 162)	<u>Classification:</u> (0= high adherence, 1-2 = medium adherence, >2 = low adherence) <u>Method of Assessment:</u> questionnaire	cost Absenteeism costs Presenteeism costs	<u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence^{##}:</u> TPC(0):\$1210.90 (\$1571.73), TPC(1-2):\$1428.50 (\$1854.17), TPC(>2):\$1073.10 (\$1392.87), AbC(0):\$633.70 (\$822.53), AbC(1-2):\$608.90 (\$790.34), AbC(>2):\$474.80 (\$616.28), PrC(0):\$577.20 (\$749.20), PrC(1-2):\$819.60 (\$1063.83), PrC(>2):\$598.30 (\$776.59)	outcome description
<i>Miravittles et al</i> [50] 2013 Spain	To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).	<u>Design:</u> multicentre, retrospective, observational study <u>Follow Up:</u> 18 months <u>Sample Size:</u> 1365 (A:246, NA:1119)	<u>Measure:</u> GOLD 2007 Guidelines <u>Classification:</u> (adherent, nonadherent) <u>Method of Assessment:</u> GOLD guidelines	ED costs Pharmacy costs Physician office visit costs Hospitalization costs Primary care costs Interdisciplinary visit costs Medical test costs Radiology costs Laboratory costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> EUR, 2009 <u>Cost of Nonadherence:</u> EDC:€40.83 (\$57.91), PC:€771.50 (\$1094.27), POC:€106.29 (\$150.76), HC:€101.61 (\$144.12), PCC:€123.84 (\$175.65), IntC:€321.44 (\$455.92), MTC:€36.66 (\$51.99), RC:€24.24 (\$34.38), LC:€17.35 (\$24.61)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Quittner et al</i> [51] 2014 US	To evaluate associations of adherence to	<u>Design:</u> retrospective, cohort study <u>Follow Up:</u> 2 years	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = high	Total healthcare costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific	<u>Quality:</u> medium <u>Classification:</u> cost description

pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.

Sample Size: 3287
(≥80%: 663, 50-80%: 949, <50%: 1675)

adherence, 50-80% = moderate adherence, <50% = low adherence)
Method of Assessment:
pharmacy claims data

Currency Year: USD, 2011
Cost of Nonadherence*:
All cause:
THC(≥80):\$35749.50 (\$38244.05),
THC(50-80):\$45031.50 (\$48173.73),
THC(<50):\$50284.50 (\$53793.28)
Disease state specific:
THC(≥80):\$23764 (\$25422.22),
THC(50-80):\$33132.50 (\$35444.44),
THC(<50):\$33894 (\$36259.07)

Gastrointestinal Disease

Carter et al[52]
2011
US

To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.

Design: retrospective, observational cohort claims analysis
Follow Up: 12 months
Sample Size: 638
(A:466, NA:172)

Measure: number of infusions in 12 month period
Classification: (7-9 infusions = adherent, <7 infusions = nonadherent)
Method of Assessment:
health claims data

Hospitalization costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2007
Cost of Nonadherence:
HC:\$37783 (\$42854.12)

Quality: medium
Classification: cost outcome description

Gosselin et al[53]
2009
US

To examine the effects of gastroesophageal reflux disease (GERD) patients compliance with PPI therapy on health care resource utilisation and costs.

Design: retrospective cohort study
Follow Up:
Sample Size: 41837
(A:28321, NA:13516)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment:
pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs
Medical costs

Type of Costs: adjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence:
TC:\$9497 (\$12085.43),
IC:\$2116 (\$2692.72),
OC:\$5458 (\$6945.59),
PC:\$1922 (\$2445.85),
MC:\$7575 (\$9639.58)

Quality: medium
Classification: cost description

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<i>Kane et al</i> [54] 2009 US	To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by patients.	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 571 (A:375, NA:196)	<u>Measure:</u> number of infusions in 12 month period <u>Classification:</u> (≥ 8 infusions = adherent, < 7 infusions = nonadherent) <u>Method of Assessment:</u> health claims data	Outpatient costs ED costs Pharmacy costs Medical costs Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> All cause: OC:\$6679 (\$8272.62), EDC:\$314 (\$388.92), MC:\$16129 (\$19977.40), HC:\$6893 (\$8537.68) Disease state specific: OC:\$3931 (\$4868.94), EDC:\$91 (\$112.71), PC:\$18751 (\$23225.01), MC:\$10243 (\$12686.99), HC:\$4494 (\$5566.27)	<u>Quality:</u> medium <u>Classification:</u> cost outcome description
<i>Mitra et al</i> [55] 2012 US	To assess the association between adherence to oral 5-aminosalicylates (5-ASAs) and all cause costs and health care utilisation among patients with active ulcerative colitis.	<u>Design:</u> retrospective, observational cohort study <u>Follow Up:</u> 12 months <u>Sample Size:</u> 1693 (A:476, NA:1216)	<u>Measure:</u> MPR <u>Classification:</u> ($\geq 80\%$ = adherent, $< 80\%$ = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Ancillary costs Non-pharmacy costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2010 <u>Cost of Nonadherence:</u> All cause: PC:\$1541.60 (\$1681.55) Disease state specific: IC:\$28726.65 (\$31334.47), OC:\$1145.67 (\$1249.67), EDC:\$635.95 (\$693.68), AC:\$4923.29 (\$5370.23), NPC:\$14226.32 (\$15517.79)	<u>Quality:</u> high <u>Classification:</u> cost description
<i>Wan et al</i> [56] 2014 US	To examine the effect of adherence versus non-adherence on healthcare costs in	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 360 days <u>Sample Size:</u> 1646	<u>Measure:</u> MPR <u>Classification:</u> ($\geq 80\%$ = adherent, $< 80\%$ =	Total costs Total healthcare costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2009	<u>Quality:</u> high <u>Classification:</u> cost description

patients with inflammatory bowel disease.

(A:674, NA:972)

nonadherent)
Method of Assessment:
pharmacy claims data

Inpatient costs
Outpatient costs
ED costs
Pharmacy costs

Cost of Nonadherence:
All cause:
TC:\$47411 (\$52341.27),
THC:\$32522 (\$35903.96),
IC:\$17634 (\$19467.76),
OC:\$10909 (\$12043.43),
EDC:\$458 (\$505.63),
PC:\$18410 (\$20324.46)
Disease state specific:
TC:\$33652 (\$37151.47),
THC:\$18764 (\$20715.27),
IC:\$12564 (\$13870.53),
OC:\$5890 (\$6502.50),
EDC:\$48 (\$52.99),
PC:\$15150 (\$16725.45)

Epilepsy

Davis et al[57]
2008
US

To assess the extent of refill non-adherence with antiepileptic drugs (AEDs) and the potential association between AED non-adherence and healthcare costs in an adult managed care population.

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 10892 (A:6644, NA:4248)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
ED costs
Pharmacy costs
Other pharmacy costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence^{###}:
TC:\$1466 (\$1865.56),
IC:\$1799 (\$2289.32),
EDC:\$260 (\$330.86),
PC:-\$71 (-\$90.35),
OtPC:-\$358 (-\$455.57)

Quality: medium
Classification: cost description

Ettinger et al[58]
2009
US

To assess the extent to which elderly patients diagnosed with epilepsy are non-adherent to antiepileptic drugs (AEDs) and the

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 1278 (A:758, NA:520)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment:

Total costs
Inpatient costs
ED costs
Pharmacy costs
Physician Office visit

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence:
TC:\$17817 (\$22673.06),
IC:\$2714 (\$3453.71),
EDC:\$526 (\$669.36),

Quality: medium
Classification: cost outcome description

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3		potential association	pharmacy claims	costs	PC:\$347 (\$441.58),	
4		between AED non-	data	Ancillary costs	POC:\$3063 (\$3897.83),	
5		adherence and seizure		Other	AC:\$8344 (\$10618.18),	
6		recurrence, resource		pharmacy	OtPC:\$2822 (\$3591.14)	
7		utilisation and annual		costs		
8		direct medical costs.				
9						
10	<i>Faught et al[59]</i>	To study the impact of	<u>Design:</u> retrospective	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
11	2009	non-adherence to	observational open	Inpatient costs	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
12	US	antiepileptic drugs	cohort design	Outpatient	<u>Currency Year:</u> USD, 2002	<u>description</u>
13		(AEDs) on healthcare	<u>Follow Up:</u> 4.65 years	costs	<u>Cost of Nonadherence*:</u>	
14		utilisation and direct	<u>Sample Size:</u> 33658	ED costs	TC:\$14417.64 (\$18713.91),	
15		medical costs in a	(A:24907, NA:8751)	Pharmacy	IC:\$6682.28 (\$6873.51),	
16		Medicaid population.	<u>Method of</u>	costs	OC:\$2172.40 (\$2819.75),	
17			<u>Assessment:</u>	Other	EDC:\$405.96 (\$526.93),	
18			pharmacy claims	pharmacy	PC:\$822.40 (\$1067.46),	
19			data	costs	OtPC:\$4334.60 (\$5626.26)	
20						
21	HIV/AIDS					
22	<i>Barnett et al[60]</i>	To characterise the	<u>Design:</u> retrospective	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
23	2011	cost of HIV care	observational cohort		<u>Classification:</u> disease state specific;	<u>Classification:</u> cost
24	US	including combination	study		viral load count	<u>description</u>
25		antiretroviral	<u>Follow Up:</u> 1 year		<u>Currency Year:</u> USD, 2006	
26		treatment.	<u>Sample Size:</u> 1896		<u>Cost of Nonadherence**:</u>	
27			(not specified)		High viral load:	
28					TC:\$25824 (\$30067.54)	
29					Low viral load:	
30					TC:\$20509.67 (\$23879.92)	
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39	<i>Cooke et al[61]</i>	To measure adherence	<u>Design:</u> retrospective	Total	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
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2014 US	to antiretroviral therapy regimens in commercially insured patients with HIV infection and analyse the clinical and demographic factors associated with ≥90% adherence.	claims analysis <u>Follow Up:</u> 1 year <u>Sample Size:</u> 3528 (A:1737, NA:640)	<u>Classification:</u> (≥90% = adherent, <90% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	healthcare costs Inpatient costs Outpatient costs Pharmacy costs	<u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence:</u> THC:\$18868 (\$20184.58), IC:\$2700 (\$2888.40), OC:\$915 (\$978.85), PC:\$15253 (\$16317.33)	<u>Classification:</u> cost description
<i>Pruitt et al</i> [62] 2015 US	To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.	<u>Design:</u> retrospective cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 502 (A:56, NA:176)	<u>Measure:</u> MPR <u>Classification:</u> (≥90% = adherent, <90% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Other pharmacy costs Behavioural health inpatient costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2009 <u>Cost of Nonadherence*:</u> HIV: TC:\$15360 (\$16957.32), IC:\$3864 (\$4265.76), OC:\$3948 (\$4358.52), PC:\$4956 (\$5471.40), OtPC:\$1764 (\$1947.48), BHIC:\$840 (\$927.36) AIDS: TC:\$27648 (\$30523.08), IC:\$13008 (\$14360.76), OC:\$5880 (\$6491.52), PC:\$5640 (\$6226.56), OtPC:\$2580 (\$2848.32), BHIC:\$528 (\$582.96)	<u>Quality:</u> medium <u>Classification:</u> cost description
Parkinson's Disease <i>Davis et al</i> [63] 2010 US	To assess the extent to which patients diagnosed with Parkinson's disease are	<u>Design:</u> retrospective administrative claims study <u>Follow Up:</u> 12 months	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% =	Total costs Pharmacy costs Medical costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2001 <u>Cost of Nonadherence:</u>	<u>Quality:</u> medium <u>Classification:</u> cost outcome description

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non-adherent with antiparkinson therapy and the potential association between non-adherence and all cause medical costs.
To assess the associations between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilisation and costs.

Sample Size: 3119 (A:1211, NA:1908)
Design: retrospective historical cohort study
Follow Up: 12 months
Sample Size: 1215 (A:617, NA:598)

nonadherent)
Method of Assessment: pharmacy claims data
Measure: PDC
Classification: (≥80% = satisfactory, <80% = unsatisfactory)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Pharmacy costs
Other costs

TC:\$18511 (\$24262.36),
PC:\$2684 (\$3537.36),
MC:\$15827 (\$20859.12)
Type of Costs: adjusted and unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2005
Cost of Nonadherence:
Adjusted all cause:
TC:\$19686 (\$23625.30),
IC:\$5954 (\$7145.43),
PC:\$6391 (\$7669.88),
OtC:\$8795 (\$10554.94)
Adjusted disease state specific:
TC:\$8574 (\$10289.71),
IC:\$3705 (\$4446.39),
PC:\$3850 (\$4620.41),
OtC:\$1884 (\$2261)
Unadjusted all cause:
TC:\$19362 (\$23236.46),
IC:\$5463 (\$6556.18),
PC:\$6158 (\$7390.26),
OtC:\$7740 (\$9288.82)
Unadjusted disease state specific:
TC:\$9156 (\$10988.18),
IC:\$3238 (\$3885.94),
PC:\$3789 (\$4547.20),
OtC:\$2129 (\$2555.03)

Quality: high
Classification: cost description

Delea et al[64]
2011
US

To examine the associations of

Design: retrospective cross-sectional study

Measure: MPR
Classification:

Total costs
Inpatient costs

Type of Costs: unadjusted
Classification: disease state specific

Quality: medium
Classification: cost

Wei et al[65]
2014

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3	US	adherence to	<u>Follow Up:</u> 19 months	(>90<100% = high,	Outpatient	<u>Currency Year:</u> USD, 2007
4		antiparkinson drugs	<u>Sample Size:</u> 7583 (90-	>80<89% =	costs	<u>Cost of Nonadherence:</u>
5		with healthcare	100%:3948, 80-	moderate, ≤79% =	Pharmacy	TC(90-100):\$36407 (\$41293.43),
6		utilisation and	89%:1456, ≤79%:2179)	low)	costs	TC(80-89):\$43417 (\$49244.29),
7		economic outcomes.		<u>Method of</u>		TC(≤79):\$45867 (\$52023.13),
8				<u>Assessment:</u>		IC(90-100):\$15294 (\$17346.71),
9				pharmacy claims		IC(80-89):\$21603 (\$24502.49),
10				data		IC(≤79):\$24727 (\$28045.78),
11						OC(90-100):\$10155 (\$11517.97),
12						OC(80-89):\$11838 (\$13426.86),
13						OC(≤79):\$12889 (\$14618.92),
14						PC(90-100):\$10957 (\$12427.61),
15						PC(80-89):\$9976 (\$11314.95),
16						PC(≤79):\$8251 (\$9358.42)
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19	Musculoskeletal					
20	<i>Ivanova et al</i> [66]	To compare the rates	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
21	2012	of severe relapse and	cohort study	<u>Classification:</u>	Total	<u>Classification:</u> all cause, disease state
22	US	total direct and	<u>Follow Up:</u> 2 years	(≥80% = adherent,	healthcare	specific and indirect
23		indirect costs over a 2	<u>Sample Size:</u> 648	<80% =	costs	<u>Currency Year:</u> USD, 2007
24		year period between	(A:448, NA:200)	nonadherent)	Inpatient costs	<u>Cost of Nonadherence*:</u>
25		US based employees		<u>Method of</u>	Outpatient	All cause:
26		with MS who were		<u>Assessment:</u>	costs	TC:\$8079 (\$9276.76),
27		adherent and non-		pharmacy claims	ED costs	THC:\$6022 (\$6830.25),
28		adherent to disease		data	Pharmacy	IC:\$1030.50 (\$1168.81),
29		modifying drugs.			costs	OC:\$3231 (\$3664.65),
30					Medical costs	EDC:\$143.50 (\$162.76),
31					Short term	PC:\$1617 (\$1834.03),
32					disability costs	MC:\$4405.50 (\$4996.79)
33					Absenteeism	Disease state specific:
34					cost	TC:\$3005 (\$3408.32),
35						IC:\$505 (\$572.78),
36						OC:\$1710 (\$1939.51),
37						EDC:\$37 (\$41.97),
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					PC:\$753 (\$854.07), MC:\$2252 (\$2554.26) Indirect: STDC:\$1231 (\$1396.22), AbC:\$826 (\$936.86)	
<i>Tan et al</i> [67] 2011 US	To assess the impact of treatment adherence on MS related hospitalizations (inpatient), ER visits, MS relapses and medical costs.	<u>Design:</u> retrospective cohort study <u>Follow Up:</u> 12 months <u>Sample Size:</u> 2446 (A:1459, NA:987)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Medical costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2007 <u>Cost of Nonadherence:</u> Adjusted: MC:\$4348 (\$5062.49) Unadjusted: MC:\$5179 (\$6030.04)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Zhao et al</i> [68] 2011 US	To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 5435 (A:1744, NA:3691)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2008 <u>Cost of Nonadherence:</u> commercial: TC:\$20323 (\$22609.12), IC:\$4808 (\$5348.85), OC:\$9822 (\$10926.87), PC:\$5693 (\$6333.40) <u>Medicare:</u> TC:\$25282 (\$28125.96), IC:\$8604 (\$9571.86), OC:\$10068 (\$11200.54), PC:\$6611 (\$7354.67)	<u>Quality:</u> medium <u>Classification:</u> cost analysis
Cancer <i>Darkow et al</i> [69] 2007 US	Estimate the association between treatment interruptions and non-adherence with	<u>Design:</u> retrospective observational cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 267	<u>Measure:</u> MPR <u>Classification:</u> (≥95% = very high, >90<95% = high, >50<90% =	Total healthcare costs Inpatient costs Outpatient	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> THC(≥95):\$42250 (\$52330.90),	<u>Quality:</u> high <u>Classification:</u> cost description

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3	imatinib and	(≥95%:120, 90-95%:25,	intermediate,	costs	THC(90-95):\$39236 (\$48597.76),		
4	healthcare costs for US	50-90%:69, <50%:53)	<50% = low)	ED costs	THC(50-90):\$54770 (\$67838.19),		
5	managed care patients.		<u>Method of</u>	Pharmacy	THC(<50):\$131357 (\$162698.93),		
6			<u>Assessment:</u>	costs	IC(≥95):\$1156 (\$1431.82),		
7			pharmacy claims	Medical costs	IC(90-95):\$1362 (\$1686.97),		
8			data	Other	IC(50-90):\$19096 (\$23652.33),		
9				pharmacy	IC(<50):\$81572 (\$101035.18),		
10				costs	OC(≥95):\$9299 (\$11517.75),		
11				Other costs	OC(90-95):\$11148 (\$13807.93),		
12					OC(50-90):\$14631 (\$18121.97),		
13					OC(<50):\$33956 (\$42057.94),		
14					EDC(≥95):\$36 (\$44.59),		
15					EDC(90-95):\$568 (\$703.53),		
16					EDC(50-90):\$104 (\$128.81),		
17					EDC(<50):\$183 (\$226.66),		
18					PC(≥95):\$29056 (\$35988.80),		
19					PC(90-95):\$23693 (\$29346.18),		
20					PC(50-90):\$18330 (\$22703.56),		
21					PC(<50):\$8733 (\$10816.70),		
22					MC(≥95):\$10731 (\$13291.43),		
23					MC(90-95):\$13452 (\$16661.66),		
24					MC(50-90):\$34202 (\$42362.64),		
25					MC(<50):\$116892		
26					(\$144782.57),OtPC(≥95):\$2462		
27					(\$3049.44),		
28					OtPC(90-95):\$2091 (\$2589.92),		
29					OtPC(50-90):\$2238 (\$2771.99),		
30					OtPC(<50):\$5732 (\$7099.66),		
31					OtC(≥95):\$241 (\$298.50),		
32					OtC(90-95):\$374 (\$463.24),		
33					OtC(50-90):\$371 (\$459.52),		
34					OtC(<50):\$1181 (\$1462.79)		
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39	<i>Wu et al[70]</i>	To examine the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
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2010 US	association between adherence with imatinib and direct healthcare costs and resource utilisation	observational cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 592 (A:350, NA:242)	<u>Classification:</u> ($\geq 85\%$ = high adherence, $< 85\%$ = low adherence) <u>Method of Assessment:</u> pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Other pharmacy costs	<u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2008 <u>Cost of Nonadherence:</u> TC:\$107341 (\$119415.73), IC:\$44498 (\$49503.55), OC:\$34097 (\$37932.55), EDC:\$248 (\$275.90), PC:\$22846 (\$25415.93), OtPC:\$5652 (\$6287.79)	<u>Classification:</u> cost description
Addiction <i>Leider et al</i> [71] 2011 US	To assess the economic burden of chronic opioid users and to determine whether opioid regimen non-adherence contributes to increased healthcare costs.	<u>Design:</u> retrospective claims based analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 2100 (A:442, NA:1658)	<u>Measure:</u> urine testing <u>Classification:</u> (positive test = nonadherent, negative test = adherent) <u>Method of Assessment:</u> health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2008 <u>Cost of Nonadherence:</u> THC:\$26433 (\$29406.43), IC:\$6361 (\$7076.55), OC:\$9734 (\$10828.97), EDC:\$421 (\$468.36), PC:\$7960 (\$8855.42), MC:\$1957 (\$2177.14)	<u>Quality:</u> medium <u>Classification:</u> cost analysis
<i>Tkacz et al</i> [72] 2014 US	To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent members.	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 455 (A:146, NA:309)	<u>Measure:</u> MPR <u>Classification:</u> ($\geq 80\%$ = adherent, $< 80\%$ = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2010 <u>Cost of Nonadherence:</u> Adjusted: THC:\$49051 (\$53503.88), IC:\$26470 (\$28872.96), OC:\$14570 (\$15892.67), EDC:\$4439 (\$4841.98), PC:\$3581 (\$3906.09) Unadjusted: THC:\$47868 (\$52213.49), IC:\$26043 (\$28407.20),	<u>Quality:</u> medium <u>Classification:</u> cost description

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7	Metabolic					
8	conditions other					
9	than diabetes					
10	mellitus					
11	<i>Lee et al</i> [73]	To assess the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
12	2011	relationship between	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease
13	US	medication adherence	<u>Follow Up:</u> 12 months	(≥80% = high	Outpatient	state specific
14		and healthcare costs	<u>Sample Size:</u> 4923	adherent, <80% =	costs	<u>Currency Year:</u> USD, 2010
15		among US patients on	(A:1372, NA:1304)	low adherent)	ED costs	<u>Cost of Nonadherence:</u>
16		dialysis given		<u>Method of</u>	Pharmacy	All cause:
17		cinacalcet to manage		<u>Assessment:</u>	costs	PC:\$5556 (\$6060.38)
18		secondary		pharmacy claims	Other	Disease state specific:
19		hypoparathyroidism.		data	pharmacy	TC:\$126996 (\$138524.78),
20					costs	IC:\$14844 (\$16191.55),
21						OC:\$101854 (\$111100.37),
22						EDC:\$734 (\$800.63),
23						PC:\$3244 (\$3538.49),
24						OtPC:\$9564 (\$10432.23)
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27	Blood					
28	<i>Candrilli et al</i> [74]	To investigate the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
29	2011	relationships among	longitudinal study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease
30	US	hydroxyurea	<u>Follow Up:</u> 12 months	(≥80% = adherent,	ED costs	state specific
31		adherence, healthcare	<u>Sample Size:</u> 312	<80% =	Pharmacy	<u>Currency Year:</u> USD, 2008
32		utilisation and	(A:110, NA:202)	nonadherent)	costs	<u>Cost of Nonadherence:</u>
33		healthcare costs.		<u>Method of</u>	Physician	All cause:
34				<u>Assessment:</u>	office visit	TC:\$ 20436 (\$22734.83),
35				pharmacy claims	costs	IC:\$9780 (\$10880.15),
36				data	Ancillary costs	EDC:\$837 (\$931.15),
37						PC:\$2579 (\$2869.11),
38						POC:\$3483 (\$3874.80),
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					AC:\$3911 (\$4350.95) Disease state specific: TC:\$12097 (\$13457.78), IC:\$7315 (\$8137.86), EDC:\$552 (\$614.09), PC:\$158 (\$175.77), POC:\$1865 (\$2074.79), AC:\$2466 (\$2743.40)	
All						
<i>Alvarez Payero et al</i> ^[75]	To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.	<u>Design:</u> retrospective observational study <u>Follow Up:</u> 1527 days <u>Sample Size:</u> 87 (A:21, NA:66)	<u>Measure:</u> pharmacy records <u>Classification:</u> (>75% = adherent, ≤75% = nonadherent) <u>Method of Assessment:</u> pharmacy and hospital claims data	Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause <u>Currency Year:</u> EUR, 2012 <u>Cost of Nonadherence</u> ^{####} : All cause: HC:€6275.80 (\$8893.94)	<u>Quality:</u> low <u>Classification:</u> cost outcome description

A: adherent, NA: nonadherent, MA: moderate adherence, LA: low adherence, NC: noncompliance, NP: nonpersistent, P: persistent, T: turbulent, NE: no exposure, CHF: chronic heart failure, THC: total healthcare costs, TC: total costs, IC: inpatient costs, OC: outpatient costs, EDC: emergency department visit costs, PC: pharmacy costs, MC: medical costs, HC: hospitalization costs, POC: physician office visit costs, NPC: non-pharmacy costs, AC: ancillary costs, OtPC: other pharmacy costs, PAC: psychiatric assessment costs, TCMC: targeted case management costs, ArC: arrest costs, InC: incarceration costs, RC: radiology costs, SC: services costs, InstC: institutional costs, ESC: external services costs, MSC: medical services costs, PCC: primary care costs, MTC: medical test costs, FC: fracture costs, LC: laboratory costs, IntC: interdisciplinary costs, BHIC: behavioural health inpatient costs, STDC: short term disability costs, WCC: workers compensation costs, PTOC: paid time off costs, TPC: total productivity costs, AbC: absenteeism costs, PrC: presenteeism costs, OtC: other costs, com: commercial patients, med: Medicare supplemental patients, USD: United States dollar, GBP: Great British Pound, EUR: Euro, DKK: Danish krone, CAD: Canadian dollar, KRW: South Korean won

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3 *: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group;
4 #: extrapolated annual cost and subgroups averaged; ##: cost represents losses in workplace productivity; ###: negative value as costs modelled against
5 adherent group; ####: cost per episode of nonadherence
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PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Economic impact of medication nonadherence by disease groups: a systematic review

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Title: Economic impact of medication nonadherence by disease groups: a systematic review

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Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A comprehensive literature search was conducted in PubMed and Scopus in September 2017. Studies quantifying the cost of medication nonadherence in relation to economic impact were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Seventy nine individual studies assessing the cost of medication nonadherence across fourteen disease groups were included. Wide scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease specific economic cost of nonadherence per person ranged from \$949-\$44,190 (in 2015 US dollars). Costs attributed to “all causes” nonadherence ranged from \$5,271 to \$52,341. Medication possession ratio was the metric most utilized to calculate patient adherence, with varying cut-off points defining nonadherence. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (83% of studies), pharmacy costs (70%), inpatient costs (46%), outpatient costs (50%), emergency department visit costs (27%), medical costs (29%) and hospitalization costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. Current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system. Differences in methods make the comparison amongst studies challenging and an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338

Strengths and Limitations of this study:

- This is a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of medication nonadherence via quantifying the cost of medication nonadherence across different disease groups.
- A large comprehensive review – 2,768 citations identified, 79 studies included.
- Inability to perform a meaningful meta-analysis- insufficient statistical data and considerable heterogeneity according to outcome/indicators.
- Robust application of adapted Drummond checklist to evaluate the quality of economic evaluations.

1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources[2]. Medications represent a cost-effective treatment modality[3], but with estimates of 50% nonadherence to long term therapy for chronic illnesses[4], intentional and unintentional medication nonadherence signifies a prevalent and persistent healthcare problem. Medication adherence is defined as 'the extent to which the patients' behavior matches agreed recommendations from the prescriber', emphasizing the importance on the patients' decisions and highlighting the modifiable aspect of nonadherence[5].

Given the proportion of the population who do not adhere to their medication efforts to improve medication adherence represent an opportunity to enhance health outcomes and health system efficiency. Annual costings of medication nonadherence range from US\$100-\$290 billion[6] in the United States, €1.25 billion[7] in Europe and approximately A\$7 billion[8 9] in Australia. Additionally ten percent of hospitalizations in older adults are attributed to medication nonadherence [10 11] with the typical nonadherent patient requiring three extra medical visits per year leading to \$2000 increased treatment costs per annum[12]. In diabetes the estimated costs savings associated with improving medication nonadherence range from \$661 million to \$1.16 billion [13]. Nonadherence is thus a critical clinical and economic problem[4].

Addressing the economic impact of medication nonadherence provides an opportunity for policy makers to help loosen the ever tightening constraints placed on health budgets. Healthcare reformers and payers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[14]. However there is still a budgetary problem that needs to be considered, especially given the widespread policy debate over how to best bend the healthcare cost curve downward[15] and the proportion of healthcare budgets spent on prescription medication[16]. Quantifying the cost of medication nonadherence will help demonstrate the causal effect between medication nonadherence, increased disease prevalence and healthcare resource use. Justification of the associated financial benefit may incentivize health policy discussion about the value of medication adherence and promote the adoption of medication adherence intervention programs [15].

The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the

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literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.

For peer review only

2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[17].

2.1 Search strategy and selection criteria

A literature search was conducted in September 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB])) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases (eTable 1). Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence as a monetary value, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[18] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-

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3 group analysis and statistical significance), conclusions and miscellaneous (funding source,
4 references to other relevant studies, limitations and reviewers comments).
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7 Costs were defined as any indicator associated with medication nonadherence that was quantified
8 with a monetary value in the original study. This included direct costs (those costs borne by the
9 healthcare system, community and patients' families in addressing the illness), indirect costs (mainly
10 productivity losses to society caused by the health problem or disease) and avoidable costs (those
11 costs incurred for patients suffering complications, resulting from suboptimal medicines use, and
12 patients with the same disease who experienced no complications). The indicators were grouped for
13 analysis based on the original studies classification of the cost. All costs were converted to US
14 dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and
15 Practice Information and Coordinating -Centre Cost Converter tool [19], allowing meaningful
16 comparisons between nonadherence cost data. This online tool uses a two stage computation
17 process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product
18 deflator index and Purchasing Power Parities for Gross Domestic Product[19]. The PPP values given
19 by the International Monetary Fund were chosen. If details of the original price year could not be
20 ascertained from a study the mid-point year of the study period was used for calculations. The mean
21 cost was calculated and reported where studies separated out costs for different confounding
22 factors within the one outcome measure in a disease state. Annual costs were extrapolated from the
23 original study data if results were not presented in this manner.
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35 The definition of medication nonadherence was derived from the included studies; with
36 nonadherence referring to differing degrees of adherence based on the studies metric of estimation.
37 Multiple nonadherence costs from individual studies may have been included where further sub-
38 classification of nonadherence levels was defined. The analysis assessed nonadherence costs within
39 disease groups, with disease group and cost classification derived from the study. Total healthcare
40 costs included direct costs to the healthcare system while total costs incorporated direct and indirect
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50 **2.3 Quality criteria and economic evaluation classification**

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52 Economic evaluation requires a comparison of two or more alternative courses of action, while
53 considering both the inputs and outputs associated with each [20]. All studies were classified in
54 accordance with Drummond's distinguishing characteristics of healthcare evaluations as either
55 partial evaluations (outcome description, cost description, cost-outcome description, efficacy or
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3 effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility
4 analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).
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7 The Drummond checklist [21] for economic evaluation was used to assess the quality of studies. The
8 original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full
9 economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the
10 required item and zero if it did not with a maximum potential score of 28. The study was classified as
11 high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were
12 satisfied and low quality if 50% of the criteria or less were satisfied.
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20 **2.4 Meta-Analysis**

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22 Outcome/indicator costs were independently extracted utilizing predesigned data extraction forms
23 (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs,
24 emergency department costs, and hospitalisation costs) for the purpose of integrating the findings
25 on the cost of medication nonadherence to pool data and increase the power of analysis.
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3 Results

3.1 Study Selection

Search strategies retrieved 2768 potential articles after duplicates were removed. Two hundred and eighty nine articles were selected for full text review. Seventy nine studies were included in the review (Figure 1). Numerous other papers do discuss nonadherence costs however addressed tangential issues or did not present primary relevant data. Many studies failed to report the monetary value of medication nonadherence associated with a range of cost estimate indicators.

3.2 Characteristics of individual studies

Sixty-six studies (83%) were conducted in the United States[10 22-86], four in Europe[87-90], four in Asia[91-94], three in Canada[95-97], one in the United Kingdom[98] and one across multiple countries throughout Europe and the United Kingdom[99]. Publication years ranged from 1997 to 2017, no date restriction filters were utilized with the earliest eligible study published in 1997. Individual studies reported a large variety of costs, calculated by varying means. Forty-four studies (56%) reported unadjusted costs[22 26 27 30 32-36 38-43 46 48-50 52-56 58 63-68 72 75 81-83 86 88-90 92-94 99], 21 (26%) adjusted costs[10 23-25 29 31 44 51 57 59-61 71 73 76-78 84 85 87 91], 11 a combination of adjusted and unadjusted[28 37 45 47 62 69 70 74 79 80 97], two unadjusted and predicted[95 96] and one predicted costs[98]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy and/or healthcare claims data (97%)[10 22-29 31-52 55 57 59-88 92-97]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data and disease state specific recommended guidelines. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 51 studies (63%) reporting nonadherence based on this measure[24 25 28 29 32-36 40-44 46 47 49-51 55 57 58 60-64 67-78 81 82 86-88 92-97]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g., 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (11%)[31 37 45 48 52 79 80 83-85], with all other studies utilizing an array of measures including self-report[98], urine testing[56], observational assessment[99], time to discontinuation[59], cumulative possession ratio[23], disease specific medication management guidelines[66 89], Morisky 4-Item scale[53], medication gaps[38],

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3 prescription refill rates[22 27] and medication supplies[10]. The main characteristics of the included
4 studies are summarized in eTable 2.
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8 9 **3.3 Quality assessment and classification of economic evaluations**

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11 The quality assessment of economic evaluations yielded 10 studies of high[33 37 40 50 51 57 71 75
12 87 93], 59 of medium[10 22-26 28-32 34-36 38 39 41-48 53-56 58 59 61-64 66 67 69 70 72 73 76-82
13 84-86 88 89 91 94-99] and ten of low quality[27 49 60 65 68 74 83 90 92]. Scores ranged from 26.1%
14 to 87.5% (mean 62.63%). Only one study identified the form of economic evaluation used and
15 justified it in relation to the questions that were being addressed [71]. The item 'the choice of
16 discount rate is stated and justified' was applicable only to studies covering a time period of more
17 than one year; all studies that cover more than one year failed to identify or explain why costs had
18 not been discounted. Details of the analysis and interpretation of results were lacking in the majority
19 of studies resulting in medium or low quality scores.
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27 Through utilization of Drummond's distinguishing characteristics of healthcare evaluations
28 criteria[20] it is apparent that no full economic evaluation was conducted in any of the included
29 studies. All studies performed partial economic evaluations of varying extents. The classification of
30 economic evaluations resulted in 59 cost description studies (74% of those included), 15 cost
31 outcome descriptions and five cost analysis studies (eTable 2).
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38 **3.4 Medication nonadherence and costs**

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40 The cost analysis of studies (figure 2 and figure 3) reported annual medication nonadherence costs
41 incurred by the patient per year. The adjusted total cost of nonadherence across all disease groups
42 ranged from \$949 to \$52,341, while the unadjusted total cost ranged from \$669 to \$162,699. Figure
43 2 and figure 3 highlight the minimum, maximum and interquartile range of annual costs incurred by
44 patients across disease groups where three or more studies were included for review. All cause costs
45 encompass nonadherence costs incurred in mixed disease state studies, taking into account other
46 confounding factors such as comorbidities.
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53 Many different indicators were used to estimate medication nonadherence costs with no clear
54 definition of what was incorporated in each cost component. The composition of included costs to
55 estimate total cost or total healthcare cost varied significantly between studies thus indicators were
56 grouped for analysis based on the original studies classification of the cost. The main ones were total
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3 cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs
4 (46%), medical costs (29%), emergency department costs (27%), and hospitalization costs (18%)
5 (eTable 2). Avoidable costs (e.g., unnecessary hospitalizations, physician office visits and healthcare
6 resource utilization) were not well defined with majority of studies failing to quantify these costs.
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10 Lower levels of adherence across all measures (e.g., MPR, PDC) were generally associated with
11 higher total costs. From those that reported total or total healthcare costs, 39 studies (49%)
12 reported nonadherence costs to be greater than adherence costs[24 25 27 29 31 32 34 37-39 42 43
13 47 49 50 55 56 58 61-65 70-78 84 86 87 96-99] and 11 studies (15%) reported nonadherence costs to
14 be less than adherence costs[23 26 36 44 59 63 66 81 92 94 95]. Four reported fluctuating findings
15 based on varying nonadherence cost subcategories[33 48 67 93] and two studies reported
16 conflicting findings between adjusted and unadjusted costs [79 80]. Higher all cause total
17 nonadherence costs and lower disease group specific nonadherence costs were reported in four
18 studies[41 68 85 91], whereas Hansen et al[47] reported all cause total nonadherence costs to be
19 lower (\$18540 vs. \$52302) but disease group specific nonadherence total costs to be higher (\$3,879
20 vs. \$2,954).
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24 The association between nonadherence and cost was determined through use of a variety of scaling
25 systems. The most utilized methods were MPR and PDC. These measures could then further be sub-
26 categorized based on the percentage of adherence/nonadherence. The 80-100% category was
27 classified as the most adherent group across both scales, with the most common definition of
28 nonadherence being <80% MPR or PDC.
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40 **3.5 Cost of medication nonadherence via disease group**

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42 Cancer exhibited more than double the cost variation of all other disease groups (\$114,101).
43 Osteoporosis (\$43,240 vs. \$42,734), diabetes mellitus (\$7,077 vs. \$6,808) and mental health
44 (\$16,110 vs. \$23,408) cost variations were similar between adjusted and unadjusted costs while
45 cardiovascular disease adjusted costs were more than double unadjusted costs (\$16,124 vs. \$6,943).
46 Inpatient costs represented the greatest proportion of costs contributing to total costs and/or total
47 healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy
48 and parkinson's disease. HIV/AIDS, cancer and gastrointestinal disease groups highest proportion of
49 costs were attributed to pharmacy costs while outpatient costs were greatest in musculoskeletal
50 conditions. Direct costs had greater economic bearing than indirect costs across all disease groups.
51 Cost comparisons across disease groups are summarized in eTable 3.
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3.5.1 Cardiovascular Disease

Twelve studies measured the economic impact of medication nonadherence in cardiovascular disease [10 24 31 61 62 65 67 76 81 93 95 96]. Six studies reported adjusted costs [10 24 31 61 62 76] with annual costs being extrapolated for two of these [31 61]. Total healthcare costs and/or total costs were assessed in all of the studies with the major indicators measured including pharmacy costs [10 31 61 62 76], medical costs [10 24 31 61 76] and outpatient costs [31 62]. The annual economic cost of nonadherence ranged from \$3,347 to \$19,472. Sokol et al [10] evaluated the economic impact of medication nonadherence across three cardiovascular conditions; hypertension, hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined, pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups. Total costs and medical costs were lower for the adherent groups of hypertension and hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.

Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total costs of nonadherence ranging from \$1,433 to \$8,377 [65 67 81 93 95 96]. Rizzo et al [65] reported cost findings through subgroup analysis of five conditions. For all conditions the total healthcare costs were higher for nonadherent groups compared with adherent. While Zhao et al [81], categorized participants into adherence subgroups; finding that total healthcare costs were lower for the nonadherent population. The remaining studies used five key indicators to determine the economic impact: inpatient costs [67 93], outpatient costs [67 93], pharmacy costs [67 95 96], medical costs [95 96] and hospitalization costs [95 96].

3.5.2 Mental Health

The analyses used to report the economic impact of medication nonadherence in mental health varied widely. Eleven of 14 studies provided a total nonadherence cost estimate in mental health [23 25 27 52 59 66 73 82 91 98 99], with annual cost data being extrapolated for four of these [27 66 82 99]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged from \$3,252 to \$19,363 [23 25 59 60 73 91]. Bagalman et al [25] focused primarily on the indirect costs associated with nonadherence – short-term disability, workers compensation and paid time off costs while Robertson et al [82] highlighted the association between medication nonadherence and incarceration, with findings indicating incarceration and arrest costs are higher for worsening degrees of nonadherence. All other studies addressed direct costs. The main indicators used to measure the direct economic impact of medication nonadherence were pharmacy

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3 costs[23 39 52 59 60 66 73 99], inpatient costs[39 60 66 98 99], outpatient costs[23 39 59 66 99] and
4 hospitalization costs[22 23 59 99].
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7 The total unadjusted cost for medication nonadherence ranged from \$2,512 to \$25,920 as reported
8 in four studies [52 66 82 99]. Becker et al[27] used a subgroup analysis to classify patients based on
9 their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%,
10 <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual
11 costs that were \$3,018 more than those of the maximal adherence group (75-100%).
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16 Knapp et al[98] outlined the predicted cost of nonadherence with reference to relative impact and
17 other factors associated with resource use and costs in patients with schizophrenia. Total costs
18 (\$116,434) were substantially higher than the other two indicators, which were inpatient costs
19 (\$13,577) and external services costs (\$3,241).
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23 **3.5.3 Diabetes mellitus:**

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26 Eleven studies reported a cost measurement of the impact of medication nonadherence with
27 reference to the health system and the individual[40 45 47 51 74 76 83 84 92 94 97]. One study
28 estimated that the total US cost attributable to nonadherence in diabetes was slightly over \$5
29 billion[51]. Five studies reported the adjusted total healthcare costs and/or total costs with annual
30 costs per patient ranging from \$2,741 to \$9,819 [47 51 74 76 84 97]. One study reported total costs
31 in relation to subgroup analysis based on MPR level[74], and another reported total healthcare costs
32 through subgroup analysis of commercially insured and Medicare supplemental patients[76]. Curtis
33 et al[84] utilized a diabetic population to report all cause costs, with nonadherence costs being
34 higher than adherence costs across all outcome indicators bar pharmacy costs.
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41 A further four studies reported unadjusted cost findings[40 83 92 94] with an additional four studies
42 reporting unadjusted costs in combination with adjusted values[45 47 74 97]. Unadjusted total
43 healthcare costs and/or total costs ranged from \$1,142 to \$7,951. Extrapolated annual costs were
44 determined for two studies based on cost data presented [40 94].
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48 The most prominent indicators used to determine costs were pharmacy costs[40 45 47 74 76 83 84
49 97], outpatient costs[40 47 76 84 94 97], inpatient costs[47 76 97] and hospitalization costs[51 92
50 94]. All studies assessed the direct costs associated with medication nonadherence. One study
51 evaluated the relationship between nonadherence and short term disability costs in addition to
52 assessing direct costs[45].
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3.5.4 Osteoporosis:

The cost of medication nonadherence in relation to osteoporosis was predominately examined through analysis of the direct costs associated with nonadherence using total healthcare costs and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department costs. Two studies further assessed the economic impact of nonadherence through evaluation of fracture related costs [48 88]. Four out of 11 studies reported the adjusted cost of medication nonadherence in addition to reporting unadjusted costs [28 79 80 87]. Three studies further classified nonadherence through subgroup analysis, with Briesacher et al[28] using MPR 20% interval increases and the two studies conducted by Zhao et al[79 80] using PDC, with $\geq 80\%$ classified as high adherence, 50-79% medium adherence and $< 50\%$ low adherence. In the studies conducted by Zhao et al[79 80], total healthcare costs were highest for the medium adherence group (\$41,402 and \$44,190) followed by the highest adherence group (\$37,553 and \$43,863), and lowest for the low adherence group (\$34,019 and \$43,771). These annual costs were extrapolated from study data. In contrast, Briesacher et al[28] modelled the subgroup analyses against the lowest adherence group ($< 20\%$ MPR), finding that costs decreased as adherence increased.

Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from \$669 to \$43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In the three studies that reported the lowest level of nonadherence to be PDC $< 50\%$, the cost of this category ranged from \$16,938 to \$43,404 [48 79 80].

One study examined only the medical costs of nonadherence through MPR subgroup analysis in commercial and Medicare supplemental populations. The findings were that, for all levels of nonadherence, costs of nonadherence were higher for Medicare supplemental patients [46].

3.5.5 Respiratory Disease:

The majority of studies reported unadjusted cost of medication nonadherence, with significant variation in the method of adherence classification[36 38 53 64 89]. Two studies used MPR[36 64], one the Morisky 4-Item scale[53], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[89] and one a 37 day gap in claims data[38]. Joshi et al[53] reported on the indirect costs of medication nonadherence through consideration of losses in total productivity costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs. Delea et al[36] reported a direct relationship between decreases in medication nonadherence level and total costs, whereas Quittner et al[64] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the

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3 lowest subgroup of adherence across all measures ranged from \$804 to \$36,259. Contrastingly Davis
4 et al[85] utilized adjusted costs across four sub classifications of PDC adherence ranges to
5 demonstrate that nonadherence costs were lower than adherence costs in all costing outcomes
6 reported except hospitalization costs .
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9 10 **3.5.6 Gastrointestinal Disease:**

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12 Three of five studies reported the adjusted annual cost of medication nonadherence per patient
13 utilizing the MPR method [44 57 71]. Of these, two reported the total cost (\$12,085 and \$37,151)[44
14 71] with the main contributors to the overall total cost being inpatient costs (22% and 37%),
15 outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).
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19 The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the
20 total cost nor total healthcare costs[30 54]. Carter et al[30] reported hospitalization costs to be
21 \$42,854 while Kane et al[54] reported a significantly lower cost at \$5,566 in addition to other direct
22 cost contributors.
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29 Three studies reported the economic impact of medication nonadherence in epilepsy. All reported
30 unadjusted costs using an MPR cut off of <80%[35 42 43]. The main economic indicators used to
31 assess total costs were inpatient costs (\$2,289 to \$6,874), emergency department visit costs (\$331
32 to \$669) and pharmacy costs (\$442 to \$1,067). Davis et al[35] modelled the costs of the
33 nonadherent group against the adherent group. The annual costs reported by Faught et al[43] were
34 extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from \$1,866
35 to \$22,673.
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42 43 **3.5.8 HIV/AIDS:**

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45 The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all
46 three studies was similar [26 32 63]. Two of the three studies examined the costs only for HIV[26
47 32], while Pruitt et al[63] assessed the cost in AIDS as well as HIV. The total unadjusted costs for
48 nonadherent HIV patients ranged from \$16,957 to \$30,068 with one study further categorizing
49 patients with HIV as having either a high viral load or low viral load[26]. The total cost of
50 nonadherence in AIDS was \$30,523[63]. All studies used comparable indicators (total cost, inpatient
51 cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.
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3.5.9 Parkinson's Disease:

The direct costs associated with Parkinson's disease were assessed in all three studies. The unadjusted total cost ranged from \$10,988 to \$52,023 [34 37 72]. Wei et al[72] further sub-grouped patients into MPR adherence percentage categories, and found that costs increased in all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with nonadherence. One study additionally reported the adjusted cost, estimating that \$10,290 could be attributed to medication nonadherence annually[37].

3.5.10 Musculoskeletal Conditions:

Differing subgroup analyses was used to measure the impact of medication nonadherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of nonadherence[50], one assessed only the medical costs[69] and one examined the direct costs in commercial and Medicare supplemental patient populations[78]. Zhao et al[78] reported the adjusted annual cost in the commercial population to be \$22,609, and in the Medicare supplemental group, \$28,126. Ivanova et al[50] reported only unadjusted costs and the annual total cost of \$3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

3.5.11 Cancer:

Two studies evaluated the effects of medication nonadherence in cancer[33 75]. One study reported total annual costs of \$119,416[75], while the other gave a subgroup analysis based on classified adherence levels[33]. In general the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs (\$162,699 and \$67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

3.5.12 Addiction:

The adjusted annual total healthcare cost of medication nonadherence was reported as \$53,504[56] while the unadjusted cost ranged from \$16,996 to \$52,213 [56 70 86]. Leider et al[56] reported the main contributors to this cost to be outpatient costs (\$10,829) and pharmacy costs (\$8,855), whereas Tkacz et al[70] and Ruetsch et al[86] reported them to be inpatient costs (\$28,407 and \$5,808) and outpatient costs (\$15,460 and \$5,743).

3.5.13 Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication nonadherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of \$138,525[55]. The economic indicators used to derive this cost were inpatient costs (\$16,192), outpatient costs (\$111,100), emergency department visit costs (\$801) and pharmacy costs (\$3,538).

3.5.14 Blood conditions:

Candrilli et al[29] reported cost findings on the relationship between nonadherence and healthcare costs, giving an adjusted total cost estimate of \$13,458 for nonadherence classified as MPR <80%.

3.5.15 All causes:

In addition to disease-specific studies of the economic impact of medication nonadherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of these studies, annual costs were extrapolated from the original data[47 50 61 64 66 85 99]. Eleven studies reported on economic indicators without giving total cost or total healthcare cost[22 45 46 54 55 57 60 81 83 90 99], and one study reported on costs per episode of nonadherence[90] .

The adjusted cost of medication nonadherence was reported in 14 studies with an estimated range of \$5,271 to \$52,341 [10 29 31 57 59-61 71 76 77 84 85 87 91]. Sokol et al[10] reported the all-cause cost of nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[61] reported only using MPR level breakdown.

Fifteen studies reported the unadjusted economic impact of medication nonadherence with an estimated range of \$1,037 to \$53,793 [22 41 46 50 54 55 58 64-66 68 81 83 90 99]. A further four studies reported adjusted and unadjusted costs[37 45 47 97]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).

3.6 Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication nonadherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of

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3 required statistical parameters in particular standard deviation[100]. Combining studies that differ
4 substantially in design and other factors would have yielded meaningless summary results.
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4 Discussion

This systemic review broadens the scope of knowledge associated with the economic impact of medication nonadherence across different disease groups while building upon previous reviews where greater focus was on targeting overall risk factors or conceptual issues associated with medication nonadherence. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence with studies failing to quantify avoidable costs separately to direct and indirect costs possibly due to coding restraints in healthcare claims databases. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesize costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g., mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g., cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty. Given the complexity of medication nonadherence in terms of varying study designs, methods of estimation and adherence definitions there is a limitation as to the ability to truly estimate costs attributed to nonadherence until further streamlined processes are defined.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, with few studies defining exactly what that cost category incorporated, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to

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3 medication nonadherence thus enabling greater planning in terms of health policy to help
4 counteract increasing avoidable costs.
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7 The economic, clinical and humanistic consequences of medication nonadherence will continue to
8 grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to
9 adequately address the determinants of adherence through utilization of effective health
10 interventions. Haynes et al [101] highlights that “increasing the effectiveness of adherence
11 interventions may have a far greater impact on the health of the population than any improvement
12 in specific medical treatments”. Improving medication adherence provides an opportunity for major
13 cost savings to healthcare systems. Predictions of population health outcomes through utilization of
14 treatment efficacy data need to be used in conjunction with adherence rates to inform planning and
15 project evaluation[4]. The correlation between increased nonadherence and higher disease
16 prevalence should be used to inform policy makers to help circumvent avoidable costs to the
17 healthcare system.
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25 The metric of adherence estimation varied substantially within and across disease groups; likely
26 affecting the comparisons between studies. However, Hess et al [102], who compared six key
27 adherence measures on the same study participants, found that the measures produced similar
28 adherence values for all participants, although PDC and continuous measure of medication gaps
29 produced slightly lower values. While this highlights the comparability of the measures of
30 medication nonadherence, it further justifies the need to agree on consistent methods for
31 estimating nonadherence through use of pharmacy claims data.
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38 MPR was the most commonly used measure to estimate medication nonadherence. MPR was used
39 in 63% of studies, followed by PDC, which was used in 11%. These percentages were consistent with
40 those found recently by Sattler et al [103]. Even though the measures of medication nonadherence
41 may be comparable, the definition of MPR and the cut-off points to define nonadherence differed
42 significantly. Dragomir et al[95] defined MPR as the total days’ supply of medication dispensed in the
43 period, divided by the follow up period, with the assumption of 100% adherence during
44 hospitalization; Wu et al[76] removed the number of hospitalized days from the calculation; and
45 Pittman et al[61] calculated the total number of days between the dates of the last filling of a
46 prescription in the first six months in a given year and the first filling of a prescription in the 365 days
47 before the last filling. Nonadherence could also be further classified into subcategories within MPR
48 and PDC based on percentages. Thirty studies defined nonadherence as $MPR < 80\%$, and 12 studies
49 categorized nonadherence into varying percentage subgroups. While Karve et al[104] validated the
50 empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent
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3 hospitalizations in patients across a broad array of chronic diseases, 76 of the 79 studies included in
4 this review examined more than just hospitalization costs as an indicator metric. Further research is
5 required to identify and standardize nonadherence thresholds using other outcomes such as
6 laboratory, productivity and pharmacy measures.
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10 Within the 79 studies covered, 35 different indicators were used to measure the cost of
11 nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a
12 meta-analysis was impossible. It is imperative that a standardized approach be established to
13 measure and report the economic impact of medication nonadherence. The core outcome set must
14 take into consideration the perspective of the intended audience and the proportion of
15 nonadherence cost that is attributable to each outcome to determine an appropriate model[105].
16 The critical indicators based on the findings of this review include total costs, pharmacy costs,
17 inpatient costs, outpatient costs, emergency department visit costs, medical costs and
18 hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes
19 include short term disability costs, workers compensation costs, paid time off costs, absenteeism
20 costs and productivity costs. We suggest that further analysis of the contribution of each outcome to
21 the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future
22 research.
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32 Many studies have examined the relationship between nonadherence and economic outcomes using
33 a cross-sectional analysis[51]. The implications of this are that potentially crucial confounders such
34 as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for
35 example, did greater adherence result in reduced costs and improved health outcomes, or was the
36 patient healthier initially and more capable of being adherent? A longitudinal design is needed to
37 overcome this limitation.
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42 Economic evaluations inform decisions on how to best make use of scarce societal health resources
43 through offering an organized consideration of the range of possible alternative courses of action
44 and the evidence of the likely effects of each[20]. While none of the studies taken separately could
45 inform a choice between alternative courses of action, they did provide key evidence for decision
46 makers about costs associated with medication nonadherence. Pharmacy claims data were utilized
47 by the majority of studies to model cost estimates. Three-quarters of the studies were classified as
48 cost descriptions, providing a cost or outcome overview of the health consequences associated with
49 nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall
50 conclusions that are able to be drawn and emphasized the need for future study design to
51 incorporate elements allowing full economic evaluations to be conducted. Hughes et al[106]
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3 highlighted the need for more information on the consequences of nonadherence, so that economic
4 evaluations could reflect the potential long-term effect of this growing problem.
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7 Of the seventy nine included studies, sixty six of the studies were conducted in the United States.
8 Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and
9 disease groups. Comparison of costs between healthcare systems is difficult as no two are the same
10 and as healthcare is generally more expensive in the United States cost estimates may not reflect
11 average values. Thus caution needs to be taken when interpreting results however findings help to
12 represent the significance of the economic burden medication nonadherence plays. Analysis of
13 studies not conducted in the United States support the finding that generally medication
14 nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.
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20 Due to the advances in technology available to record and assess medication nonadherence, the
21 inclusion of studies undertaken in the late 1990s and early 2000s may have affected the
22 comparability of results, despite the fact that these studies met the inclusion criteria[22 23 65 73 74
23 98]. The quality of data presents a limitation. Information on disease groups with fewer included
24 studies may be less reliable than information on those with more. However, our findings affirm the
25 pattern of association between nonadherence and increasing healthcare costs.
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5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilization of existing data could help to better define costs and provide valuable input into the development of an economic framework to standardize the economic impact of medication nonadherence.

6 Footnotes

Contributors: RC, VGC, SB, FFL and MF conceived the paper. RC and VGC performed all the data extraction and quality assessment. RC drafted the initial form and all revisions of this manuscript. All other authors (RC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

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Figure Legends

Figure 1: PRISMA Flow Diagram

The PRISMA diagram details the search and selection process applied during the overview. The search yielded a total of 2768 citations. Studies were selected based on the inclusion criteria; studies reporting the cost of medication nonadherence using original cost data. Intervention studies were required to report baseline data. Seventy nine original studies met the inclusion criteria.

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year

Encompass the minimum, maximum and interquartile range of adjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Gastrointestinal only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Figure 1: Annual Unadjusted Medication Nonadherence Costs per patient per year

Encompass the minimum, maximum and interquartile range of unadjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Epilepsy and addiction only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

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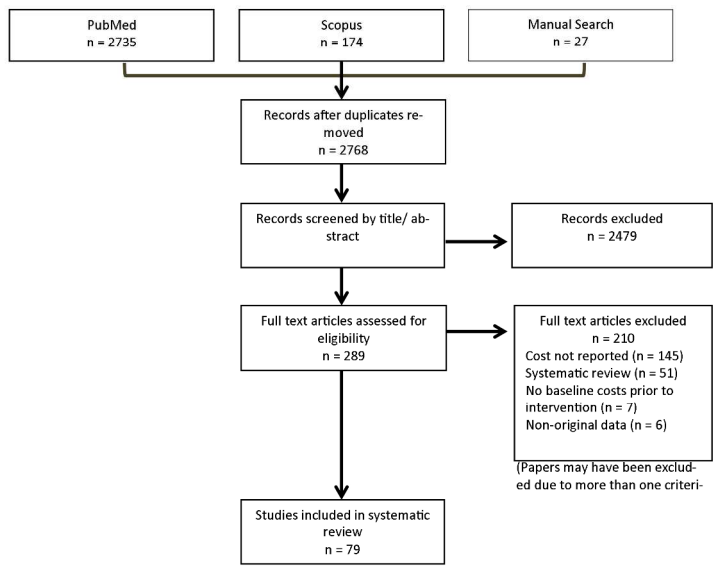


Figure 1: Flow diagram of references identified, retrieved and included in the systematic review

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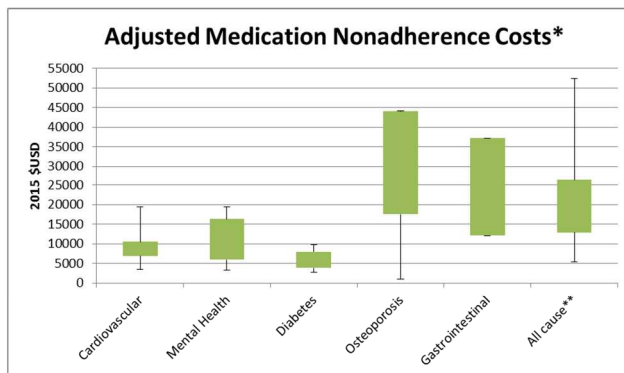


Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year
 *Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.
 ** All cause costs: mixed disease state studies

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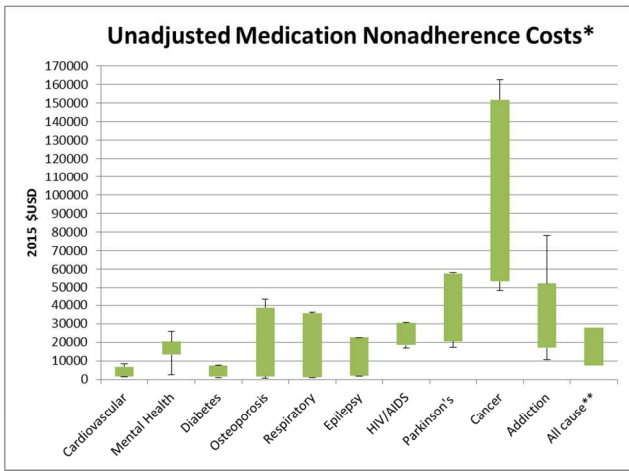


Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year
 *Disease groups with three or more studies were included. Epilepsy and Addiction only included three studies limiting the range of costs.
 ** All cause costs: mixed disease state studies

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eTable 1 Search Strategy

Database	Search Strategy
PubMed	((costs[TIAB] OR "Costs and Cost Analysis"[MH] OR burden[TIAB]) AND (nonadherence[TIAB] OR ("Patient Compliance"[MH] AND ("Drug Therapy"[MH] OR medication[TIAB])) OR "Medication adherence"[MH]))
Scopus	(TITLE-ABS-KEY (medication AND compliance OR patient AND compliance)) AND (TITLE-ABS-KEY (statistical AND model)) AND (TITLE-ABS-KEY (health AND care AND cost))

eTable 2: Studies identified with costs reported by adherence level and disease group

Author, Year, Country	Objective	Study Characteristics	Adherence (as reported in paper)	Outcomes/ Indicators	Results (USD, 2015)	Quality
Cardiovascular Disease						
<i>Aubert et al</i> [1] 2010 US	To investigate whether compliance during the first 2 years of statin therapy is associated with reduced hospitalization rates and direct medical costs during year 3.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 10227 (A:3512, NA:6715)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = non-compliant <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence:</u> THC:\$5289.61 (\$6865.90), MC:\$4908.09 (\$6370.60)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Casciano et al</i> [2] 2013 US	To assess the economic burden of underuse and nonadherence of warfarin therapy among patients with non-valvular atrial fibrillation in a commercially insured population.	<u>Design:</u> Retrospective, observational, quasi-experimental study <u>Follow Up:</u> 18months <u>Sample Size:</u> 13289 (A:2852, NA:4184, NE:6253)	<u>Measure:</u> PDC <u>Classification:</u> PDC <80 = low adherence, 0 = no warfarin exposure <u>Method of Assessment:</u> pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence*:</u> TC:\$16612.44(\$19936.70), IC:\$9382.56 (\$11260.10), OC:\$8605.92 (\$10328), PC:\$2388.24 (\$2866.20), MC:\$15235.80(\$18285)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Dilokthornsakul et al</i> [3] 2012 Thailand	To determine the effects of medication supplies on healthcare costs and hospitalizations in patients with chronic heart failure receiving angiotensin converting enzyme inhibitors or	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 393 (A:168, NA:219, OA:6)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = undersupply, MPR >120 = oversupply <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> THC:\$1157 (\$1433.06), IC:\$1019 (\$1262.13), OC:\$138 (\$170.93)	<u>Quality:</u> high <u>Classification:</u> cost description

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4		angiotensin receptor				
5		blockers.				
6	<i>Dragomir et al</i> [4]	To evaluate the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted and predicted
7	2010	of low adherence to	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific and
8	Canada	antihypertensive	<u>Follow Up:</u> 3 years	MPR \geq 80 =	Costs	hospitalized patients
9		agents on	<u>Sample Size:</u> 56896	adherent, MPR <	Pharmacy	<u>Currency Year:</u> CAD, 2006
10		cardiovascular	(A:38217, NA:18679)	80 = nonadherent	Costs	<u>Cost of Nonadherence:</u> Unadjusted
11		outcomes and		<u>Method of</u>	Medical Costs	Disease state specific: THC:\$7165
12		hospitalization costs.		<u>Assessment:</u>	Hospitalization	(\$6900.87), PC: \$1800 (\$1733.64),
13				pharmacy claims	Costs	MC: \$1370 (\$1319.50), HC: \$3995
14				data		(\$3847.73)
15						Unadjusted Hospitalized patients:
16						THC: \$17397 (\$16755.67), PC:\$2685
17						(\$2586.02), MC:\$2608 (\$2511.86),
18						HC: \$12104 (\$11657.79)
19						Predicted disease state specific:
20						HC:\$3877 (\$3734.08)
21						Predicted hospitalized patient:
22						HC:\$11715 (\$11283.13)
23						
24						
25	<i>Dragomir et al</i> [5]	To evaluate the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted and predicted
26	2010	of low adherence to	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific and
27	Canada	statins on clinical	<u>Follow Up:</u> 3 years	MPR \geq 80 =	Costs	hospitalized patients
28		issues and direct	<u>Sample Size:</u> 55134	adherent, MPR <	Pharmacy	<u>Currency Year:</u> CAD, 2005
29		healthcare costs.	(A:28549, NA:26585)	80 = nonadherent	Costs	<u>Cost of Nonadherence:</u> Unadjusted
30				<u>Method of</u>	Medical Costs	Disease state specific:
31				<u>Assessment:</u>	Hospitalization	THC:\$6243 (\$6175.76), PC:\$2506
32				pharmacy claims	Costs	(\$2479.01), MC:\$1241 (\$1227.63),
33				data		HC:\$2496 (\$2469.12)
34						Unadjusted Hospitalized patients:
35						THC:\$14725 (\$14566.40), PC:\$3374
36						(\$3337.66), MC:\$2475 (\$2448.34),
37						HC:\$8876 (\$8780.40)
38						Predicted disease state specific:
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4					HC:\$2669 (\$2640.25)		
5					Predicted hospitalized patient: HC\$9214		
6					(\$9114.76)		
7	<i>Pittman et al</i> [6]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted	<u>Quality:</u> medium
8	2011	relation among statin	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
9	US	adherence, subsequent	<u>Follow Up:</u> 18 months	MPR \geq 80 =	Costs	state specific	description
10		hospitalizations and	<u>Sample Size:</u> 381422	>60<79% =	Pharmacy	<u>Currency Year:</u> USD, 2009	
11		healthcare costs.	(A:258013, MA:65795,	moderate	Costs	<u>Cost of Nonadherence*:</u> all cause:	
12			LA:57614)	adherence, MPR	Medical Costs	THC(>80):\$6798.67 (\$7505.66),	
13				<59 =low		THC(60-79):\$7072.67 (\$7808.16),	
14				adherence		THC(<59):\$7401.33 (\$8170.99),	
15				<u>Method of</u>		PC(>80):\$1767.33 (\$1951.11),	
16				<u>Assessment:</u>		PC(60-79):\$1789.33 (\$1975.40),	
17				pharmacy claims		PC(<59):\$1937.33 (\$2138.79),	
18				data		MC(>80):\$4472.67 (\$4937.78),	
19						MC(60-79):\$4840.67 (\$5344.05),	
20						MC(<59):\$5138.67 (\$5673.04)	
21						Disease state specific:	
22						PC(>80):\$558.67 (\$616.77),	
23						PC(60-79):\$442.67 (\$488.70),	
24						PC(<59):\$325.33 (\$359.16),	
25						MC(>80):\$1596.67 (\$1762.71),	
26						MC(60-79):\$1722 (\$1901.07),	
27						MC(<59):\$1792.67 (\$1979.09)	
28							
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31	<i>Pittman et al</i> [7]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted and unadjusted	<u>Quality:</u> medium
32	2010	relationship between	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
33	US	adherence to	<u>Follow Up:</u> 2 years	MPR \geq 80 =	Costs	<u>Currency Year:</u> USD, 2008	description
34		antihypertensive	<u>Sample Size:</u>	adherent, MPR	Outpatient	<u>Cost of Nonadherence:</u> Adjusted:	
35		medications and	625620(A:467006,	>60<79% =	Costs	THC(>80):\$7261 (\$8077.79),	
36		subsequent	MA:96226, LA:62388)	moderate	ED Costs	THC(60-79):\$7530 (\$8377.05),	
37		hospitalizations,		adherence, MPR	Pharmacy	THC(<59):\$7370 (\$8199.05),	
38		emergency		<59 =low	Costs	OC(>80):\$3390 (\$3771.34),	
39		department visits and		adherence	Hospitalization	OC(60-79):\$3705 (\$4121.77),	
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costs of care.

Method of Assessment:
pharmacy claims data

Costs

OC(<59):\$3776 (\$4200.76),
EDC(>80):\$101 (\$112.36),
EDC(60-79):\$134 (\$149.07),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2383 (\$2651.06),
PC(60-79):\$1932 (\$2149.33),
PC(<59):\$1509 (\$1678.75),
HC(>80):\$1386 (\$1541.91),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$1913 (\$2128.19)
Unadjusted:
THC(>80):\$7182 (\$7989.90),
THC(60-79):\$7560 (\$8410.42),
THC(<59):\$7995 (\$8894.35),
OC(>80):\$3396 (\$3778.01),
OC(60-79):\$3635 (\$4043.90),
OC(<59):\$3887 (\$4324.25),
EDC(>80):\$102 (\$113.47),
EDC(60-79):\$131 (\$145.74),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2317 (\$2577.64),
PC(60-79):\$2034 (\$2262.80),
PC(<59):\$1880 (\$2091.48),
HC(>80):\$1366 (\$1519.66),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$2057 (\$2288.39)

For peer review

Rizzo *et al*[8]
1997
US

To investigate variations in compliance with four classes of antihypertensive agents- diuretics, ACEIs, CCBs and β-

Design: Retrospective cohort study
Follow Up: 12 months
Sample Size: 7211(P:2668, NC:3101, NP:649, T:793)

Measure: ordinary least square regression analysis
Classification: >80% = persistent, ≥30<80% = non-compliance, <30%

Total Healthcare Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 1994
Cost of Nonadherence: All cause:
THC(>80):\$341 (\$509.66),
THC(30-80):\$694 (\$1037.26),

Quality: low
Classification: cost description

blockers and the health care costs associated with various degrees of compliance.

= non-persistence
Method of Assessment:
 pharmacy claims data

THC(<30):\$735 (\$1098.53)
 Disease state specific:
 Renal:
 THC(>80):\$2135 (\$3190.98),
 THC(30-80):\$2488 (\$3718.58),
 THC(<30):\$2529 (\$3779.86),
 Acute MI:
 THC(>80):\$1358 (\$2029.67),
 THC(30-80):\$1711 (\$2557.27),
 THC(<30):\$1752 (\$2618.55), Diabetes:
 THC(>80):\$770 (\$1150.85),
 THC(30-80):\$1123 (\$1678.44),
 THC(<30):\$1164 (\$1739.72),
 CHF:
 THC(>80):\$698 (\$1043.23),
 THC(30-80):\$1051 (\$1570.83),
 THC(<30):\$1092 (\$1632.11),
 Angina:
 THC(>80):\$702 (\$1049.21),
 THC(30-80):\$1055 (\$1576.81),
 THC(<30):\$1096 (\$1638.09)
Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 1998
Cost of Nonadherence: All cause:
 Diabetes:
 TC(1-19):\$16498 (\$23071.58),
 TC(20-39):\$13077 (\$18287.49),
 TC(40-59):\$12978 (\$18149.05),
 TC(60-79):\$11484 (\$16059.77),
 TC(80-100):\$8886 (\$12426.60),
 PC(1-19):\$1312 (\$1834.76),

Sokol et al[9]
 2005
 US

To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Design: Retrospective cohort observational study
Follow Up: 12 months
Sample Size: 137277
 Diabetes:(≥80: 1801, 60-79: 599, 40-59: 419, 20-39: 259, <19: 182)
 Hypertension:(≥80: 5804, 60-79: 921, 40-59: 562, 20-39: 344, <19: 350)

Measure:
 medication supply
Classification: 1-19%, 20-39%, 40-59%, 60-79%, 80-100%
Method of Assessment:
 pharmacy claims data

Total Costs
 Pharmacy Costs
 Medical Costs

Quality: medium
Classification: cost description

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Hypercholesterolemia:
(≥80: 1754, 60-79: 520,
40-59: 324, 20-39: 216,
<19: 167)
CHF: (≥80: 518, 60-79:
107, 40-59: 82, 20-39:
70, <19: 86)

PC(20-39):\$1877 (\$2624.89),
PC(40-59):\$1970 (\$2754.94),
PC(60-79):\$2121 (\$2966.11),
PC(80-100):\$2510 (\$3510.10),
MC(1-19):\$15186 (\$21236.82),
MC(20-39):\$11200 (\$15662.61),
MC(40-59):\$11008 (\$15394.10),
MC(60-79):\$9363 (\$13093.66),
MC(80-100):\$6377 (\$8917.90),
Hypertension:
TC(1-19):\$9747 (\$13630.66),
TC(20-39):\$11238 (\$15715.75),
TC(40-59):\$9491 (\$13272.66),
TC(60-79):\$8929 (\$12486.73),
TC(80-100):\$8386 (\$11272.38),
PC(1-19):\$916 (\$1280.98),
PC(20-39):\$952 (\$1331.32),
PC(40-59):\$1123 (\$1570.46),
PC(60-79):\$1271 (\$1777.43),
PC(80-100):\$1817 (\$2540.98),
MC(1-19):\$8831 (\$12349.69),
MC(20-39):\$10286 (\$14384.43),
MC(40-59):\$8368 (\$11702.20),
MC(60-79):\$7658 (\$10709.31),
MC(80-100):\$6570 (\$9187.80),
Hypercholesterolemia:
TC(1-19):\$10916 (\$15265.45),
TC(20-39):\$7982 (\$11162.40),
TC(40-59):\$6756 (\$9447.91),
TC(60-79):\$8412 (\$11763.74),
TC(80-100):\$6752 (\$9442.31),
PC(1-19):\$1067 (\$1492.14),
PC(20-39):\$1152 (\$1611.01),

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PC(40-59):\$1247 (\$1743.86),
PC(60-79):\$1736 (\$2427.70),
PC(80-100):\$1972 (\$2757.74),
MC(1-19):\$9849(\$13773.30),
MC(20-39):\$6830 (\$9551.39),
MC(40-59):\$5509 (\$7704.04),
MC(60-79):\$6676 (\$9336.03),
MC(80-100):\$4780 (\$6684.58),
CHF:
TC(1-19):\$23964 (\$33512.38),
TC(20-39):\$19188 (\$26833.40),
TC(40-59):\$26311 (\$36794.54),
TC(60-79):\$29785 (\$41652.74),
TC(80-100):\$22164 (\$30995.18),
PC(1-19):\$1961 (\$2742.35),
PC(20-39):\$2055 (\$2873.81),
PC(40-59):\$2208 (\$3087.77),
PC(60-79):\$3412 (\$4771.50),
PC(80-100):\$3107 (\$4344.97),
MC(1-19):\$22003 (\$30770.03),
MC(20-39):\$17133 (\$23959.59),
MC(40-59):\$24103 (\$33706.77),
MC(60-79):\$26373 (\$36881.24),
MC(80-100):\$19056 (\$26648.81)
Disease state specific: Diabetes:
TC(1-19):\$8867 (\$12400.03),
TC(20-39):\$7124 (\$9916.90),
TC(40-59):\$6522 (\$9120.67),
TC(60-79):\$6291 (\$8797.63),
TC(80-100):\$4570 (\$6390.90),
PC(1-19):\$55 (\$76.91),
PC(20-39):\$165 (\$230.74),
PC(40-59):\$285 (\$398.56),

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PC(60-79):\$404 (\$564.97),
PC(80-100):\$763 (\$1067.02),
MC(1-19):\$8812 (\$12323.11),
MC(20-39):\$6959 (\$9731.79),
MC(40-59):\$6237 (\$8722.11),
MC(60-79):\$5887 (\$8232.66),
MC(80-100):\$3808 (\$5325.29),
Hypertension:
TC(1-19):\$4878 (\$6821.62),
TC(20-39):\$6062 (\$8477.39),
TC(40-59):\$5297 (\$7407.57),
TC(60-79):\$5262 (\$7358.63),
TC(80-100):\$4871 (\$6811.84),
PC(1-19):\$31 (\$43.35),
PC(20-39):\$89(\$124.46),
PC(40-59):\$184 (\$257.31),
PC(60-79):\$285 (\$398.56),
PC(80-100):\$489 (\$683.84),
MC(1-19):\$4847 (\$6778.27),
MC(20-39):\$5973 (\$8352.92),
MC(40-59):\$5113 (\$7150.26),
MC(60-79):\$4977 (\$6960.07),
MC(80-100):\$4383 (\$6129.39),
Hypercholesterolemia:
TC(1-19):\$6888 (\$9632.50),
TC(20-39):\$4999 (\$6990.84),
TC(40-59):\$3825 (\$5349.06),
TC(60-79):\$5541 (\$7748.79),
TC(80-100):\$3924(\$5487.51),
PC(1-19):\$78 (\$109.08),
PC(20-39):\$213 (\$297.87),
PC(40-59):\$373 (\$521.62),
PC(60-79):\$603 (\$843.26),

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For peer review

PC(80-100):\$801 (\$1120.16),
 MC(1-19):\$6810 (\$9523.42),
 MC(20-39):\$4786 (\$6692.97),
 MC(40-59):\$3452 (\$4827.44),
 MC(60-79):\$4938 (\$6905.53),
 MC(80-100):\$3124 (\$4368.75),
 CHF:

TC(1-19):\$9841 (\$13762.12),
 TC(20-39):\$7733 (\$10814.19),
 TC(40-59):\$11378 (\$15911.53),
 TC(60-79):\$13924 (\$19471.98),
 TC(80-100):\$12698 (\$17787.48),
 PC(1-19):\$15 (\$20.98),
 PC(20-39):\$90 (\$125.86),
 PC(40-59):\$134 (\$187.39),
 PC(60-79):\$158 (\$220.95),
 PC(80-100):\$437 (\$611.12),
 MC(1-19):\$9826 (\$13741.14),
 MC(20-39):\$7643 (\$10688.33),
 MC(40-59):\$11244 (\$15724.14),
 MC(60-79):\$13766 (\$19251.02),
 MC(80-100):\$12261 (\$17146.36)

Stroupe *et al*[10]
 2006
 US

To determine the rates
 of undersupply,
 appropriate supply,
 and oversupply of
 antihypertensive drugs
 as measured by refill
 adherence, among
 patient with
 complicated and
 uncomplicated
 hypertension and to

Design: Retrospective
 cohort study
Follow Up: 3.3 years
Sample Size: 15206
 (not specified)

Measure: MPR
Classification:
 MPR<80 =
 undersupply, MPR
 >120 = oversupply
Method of
Assessment:
 pharmacy claims
 data

Total
 Healthcare
 Costs
 Inpatient
 Costs
 Outpatient
 Costs
 Pharmacy
 Costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002
Cost of Nonadherence **: THC:\$6032.5
 (\$7830.11), IC:\$2067 (\$2682.94),
 OC:\$3965 (\$5146.52), PC:\$130
 (\$168.74)

Quality: medium
Classification: cost
 description

examine the association of refill adherence with hospitalization and healthcare costs among these patients.

10 *Wu et al*[11]
11 2011
12 US

To study statin adherence and assess associated medical utilisation and healthcare costs in patients with type 2 diabetes, based on national Medicaid database.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 1705 (A:624, NA:1081)

Measure: MPR
Classification: MPR≥80 = adherent, MPR <80 = nonadherent
Method of Assessment: pharmacy claims data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2005
Cost of Nonadherence: all cause: THC:\$17807 (\$21370.30), PC:\$4915 (\$5898.52) MC:\$12892 (\$15471.77)
Disease state specific: THC:\$2789 (\$3347.10), PC:\$489(\$586.85) MC:\$2300 (\$2760.25)

Quality: medium
Classification: cost description

22 *Zhao et al*[12]
23 2014
24 US

To evaluate the associations between statin adherence level, healthcare costs, hospital admissions and emergency room visits after statin therapy is taken for 1 year.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 10312 (96-100: 2453, 90-95: 1496, 85-89: 584, 80-84: 768, 70-79: 960, 60-69: 777, 40-59: 1687, <40:1587)

Measure: MPR
Classification: <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100%
Method of Assessment: pharmacy claims data, census data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2010
Cost of Nonadherence: all cause: PC(96-100):\$2976.80 (\$3247.04), PC(90-95):\$2826.99 (\$3083.63), PC(85-89):\$2795.39 (\$3049.16), PC(80-84):\$2690.89 (\$2935.17), PC(70-79):\$2192.83 (\$2391.90), PC(60-69):\$2323.27 (\$2534.18), PC(40-59):\$2153.93 (\$2349.47), PC(<40):\$1749.18 (\$1907.97)
Disease state specific: THC(96-100):\$6536.05 (\$7129.40), THC(90-95):\$6493.80 (\$7083.31), THC(85-89):\$6459.40 (\$7045.79),

Quality: medium
Classification: cost description

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For peer review

THC(80-84):\$6227.47 (\$6792.80),
THC(70-79):\$5713.47 (\$6232.14),
THC(60-69):\$5875.26 (\$6408.62),
THC(40-59):\$5817.58 (\$6345.70),
THC(<40):\$5249.12 (\$5725.64),
PC(96-100):\$449.86 (\$490.70), PC(90-95):\$439.74 (\$479.66),
PC(85-89):\$458.83 (\$500.48),
PC(80-84):\$423.15 (\$461.56),
PC(70-79):\$356.74 (\$389.13),
PC(60-69):\$371.30 (\$405.01),
PC(40-59):\$279.21 (\$304.56),
PC(<40):\$133.92 (\$146.08),
MC(96-100):\$3559.25 (\$3882.36),
MC(90-95):\$3666.81 (\$3999.69),
MC(85-89):\$3664 (\$3996.62), MC(80-84):\$3586.58 (\$3912.17), MC(70-79):\$3520.64 (\$3840.25), MC(60-69):\$3551.99 (\$3874.44), MC(40-59):\$3663.65 (\$3996.24),
MC(<40):\$3499.95 (\$3817.68)

Mental Health

<p><i>Bagalman et al</i>[13] 2010 US</p> <p>To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 1258 (A:444, NA:814)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> MPR≥80 = adherent, MPR <80 = nonadherent <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Total Costs Short term disability cost Workers compensation cost Paid time off cost</p>	<p><u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence:</u> TC:\$6894 (\$8273.53), STDC:\$2134 (\$2561.03), WCC:\$762 (\$914.48), PTOC:\$3998 (\$4798.03)</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost description</p>
<p><i>Becker et al</i>[14]</p>	<p><u>Design:</u> Retrospective</p>	<p><u>Measure:</u></p>	<p>Total Costs</p>	<p><u>Type of Costs:</u> unadjusted</p>	<p><u>Quality:</u> low</p>

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3	2007	outcomes and costs	cohort study	prescription refill		<u>Classification:</u> disease state specific
4	US	associated with	<u>Follow Up:</u> 2 years	rate		<u>Classification:</u> cost
5		adherence rates by	<u>Sample Size:</u> 10330	<u>Classification:</u> 75-		<u>Currency Year:</u> USD, 2006
6		antipsychotic	(>75%:6609, 50-	100% = maximal		<u>Cost of Nonadherence</u> * :
7		medication class for	74%:1276, 25-	adherence, 50-		TC(75-100):\$13564 (\$15792.91),
8		Medicaid beneficiaries.	49%:1940, <25%:505)	74.9% = moderate		TC(50-74):\$13772 (\$16035.09),
9				adherence, 25-		TC(25-49):\$15792 (\$18387.03),
10				49.9% = minimal		TC(<25):\$16156 (\$18810.84)
11				adherence, <25%		
12				= negligible		
13				adherence		
14				<u>Method of</u>		
15				<u>Assessment:</u>		
16				pharmacy claims		
17				data		
18				<u>Measure:</u>	Inpatient costs	<u>Type of Costs:</u> unadjusted
19	<i>Eddy et al[15]</i>	To evaluate the effect	<u>Design:</u> Retrospective	continuous	Outpatient	<u>Classification:</u> disease state specific
20	2005	of partial compliance	database analysis	multiple interval	costs	<u>Currency Year:</u> USD, 2002
21	US	of patients with	<u>Follow Up:</u> 1 year	medications	Pharmacy	<u>Cost of Nonadherence</u> * :
22		prescribed oral atypical	<u>Sample Size:</u> 7864	available	costs	IC:\$3780 (\$4906.39),
23		and conventional	(<80%:2655, 80-	<u>Classification:</u>	Medical costs	OC:\$504 (\$654.19),
24		antipsychotic agents	125%:5065,	<80% = partially	Physician	PC:\$1872 (\$2429.83),
25		and the corresponding	>125%:144)	compliant, 80-	office visit	MC:\$6228 (\$8083.86),
26		impact on resource		125% = compliant,	costs	POC:\$1944 (\$2523.29)
27		utilisation.		>125% = overly	Other costs	OtC:\$12 (\$15.58)
28				compliant		
29				<u>Method of</u>		
30				<u>Assessment:</u>		
31				pharmacy claims		
32				data		
33				<u>Measure:</u>	Total costs	<u>Type of Costs:</u> adjusted
34	<i>Gilmer et al[16]</i>	To evaluate the	<u>Design:</u> Retrospective	cumulative	Outpatient	<u>Classification:</u> disease state specific
35	2004	relationship between	database analysis	possession ratio	costs	<u>Currency Year:</u> USD, 1999
36	US	adherence to	<u>Follow Up:</u> 1 year			<u>Classification:</u> cost
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treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.

Sample Size: 1619 (<49%:388, 50-79%:259, 80-100%:664, >110%:308)

Classification: <49% = nonadherent, 50-79% = partially adherent, 80-100% = adherent, >110% = excess medication fillers

Pharmacy costs
Hospitalization costs

Cost of Nonadherence:
TC:\$8168 (\$11261.74),
OC:\$3464 (\$4776.04),
PC:\$1542 (\$2126.05),
HC:\$3413 (\$4705.72)

Method of Assessment:
pharmacy claims data

Hong et al[17]
2011
UK

To investigate clinical and economic consequences of medication non-adherence in the treatment of bipolar disorder following a manic or mixed episode.

Design: Prospective observational study
Follow Up: 21 months
Sample Size: 1341(A:1024, NA:317)

Measure: assessed by treating psychiatrist
Classification: adherent vs. nonadherent
Method of Assessment: observational assessment

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs
Hospitalization costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: GBP, 2008
Cost of Nonadherence *: all cause:
PC:£55.43 (\$94.47)
Disease state specific:
TC:£5846.29 (\$9964.10)
IC:£2740.57 (\$4670.88),
OC:£1082.86 (\$1845.57),
PC:£1630.29 (\$2778.58),
HC:£337.14 (\$574.60)

Quality: medium
Classification: cost description

Jiang et al[18]
2015
US

To estimate the impact of adherence to and persistence with atypical antipsychotics on healthcare costs and risk of hospitalization by controlling potential sources of endogeneity

Design: Retrospective cohort study
Follow Up: 2 years
Sample Size: 32374 (A:11642, NA:20732)

Measure: PDC
Classification: (PDC≥80% = adherent, PDC<80% = nonadherent)
Method of Assessment: medical and

Total costs
Pharmacy costs
Medical services costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2011
Cost of Nonadherence:
Disease state specific:
TC:\$14141 (\$14517.37)
PC:\$3971 (\$4076.69),
MSC:\$10170 (\$10440.68)

Quality: low
Classification: cost description

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3			pharmacy claims			
4			data			
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6	<i>Joe et al[19]</i>	To investigate the	<u>Design:</u> Retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> adjusted
7	2016	association between	cohort study	percentage of		<u>Classification:</u> all cause and disease
8	South Korea	psychiatric medication	<u>Follow Up:</u> 1 year	days of psychiatric		state specific
9		non-compliance and	<u>Sample Size:</u> 7848	prescription (PDP)		<u>Currency Year:</u> USD, 2011
10		psychiatric and non-	(A:2774, NA:2774,	<u>Classification:</u>		<u>Cost of Nonadherence:</u> all cause:
11		psychiatric service	P:1956, NP:1956)	PDP≥80% =		TC:\$4961 (\$5271.40)
12		utilisation and costs.		adherent,		Disease state specific:
13				PDP<80% =		TC:\$3061 (\$3252.50)
14				nonadherent;		
15				persistent =		
16				continued		
17				medication		
18				without		
19				interruption ≥ 56		
20				day, non-		
21				persistent = at		
22				least one		
23				medication		
24				interruption > 56		
25				days		
26				<u>Method of</u>		
27				<u>Assessment:</u>		
28				health insurance		
29				data		
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33	<i>Knapp et al[20]</i>	To assess the relative	<u>Design:</u> Retrospective	<u>Measure:</u> self-	Total costs	<u>Type of Costs:</u> predicted
34	2004	impact of non-	cohort study	report	Inpatient costs	<u>Classification:</u> disease state specific
35	UK	adherence and other	<u>Follow Up:</u> 1 year	<u>Classification:</u>	External	<u>Currency Year:</u> GBP, 2001
36		factors associated with	<u>Sample Size:</u> 658	adherent vs.	services costs	<u>Cost of Nonadherence:</u>
37		resource use and costs	(A:549, NA:109)	nonadherent		TC:£57580 (\$116434.12)
38		incurred by people		<u>Method of</u>		IC:£6714 (\$13576.57),
39		with schizophrenia.		<u>Assessment:</u>		ESC:£1603 (\$3241.47)
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4	<i>Offord et al[21]</i>	To quantify early	<u>Design:</u> Retrospective	<u>Measure:</u> time to	Total costs	<u>Type of Costs:</u> adjusted	<u>Quality:</u> medium
5	2013	nonadherence to	cohort study	discontinuation	Outpatient	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
6	US	antipsychotic	<u>Follow Up:</u> 1 year	<u>Classification:</u>	costs	state specific	description
7		medications in patients	<u>Sample Size:</u> 1462	adherent vs.	Pharmacy	<u>Currency Year:</u> USD, 2008	
8		with schizophrenia and	(A:589, NA:873)	nonadherent	costs	<u>Cost of Nonadherence:</u> all cause:	
9		its impact on short-		<u>Method of</u>	Hospitalization	TC:\$15400 (\$17132.34)	
10		term antipsychotic		<u>Assessment:</u>	costs	OC:\$5773 (\$6422.40),	
11		adherence, healthcare		pharmacy claims		PC:\$3777 (\$4201.87),	
12		utilisation and costs.		data		HC:\$5850 (\$6508.06)	
13						Disease state specific:	
14						TC:\$5358 (\$5960.72)	
15						OC:\$858 (\$954.52),	
16						PC:\$1549 (\$1723.25),	
17						HC:\$2952 (\$3284.07)	
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20	<i>Offord et al[22]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Inpatient	<u>Type of Costs:</u> adjusted	<u>Quality:</u> low
21	2013	of medication	cohort study	<u>Classification:</u>	costs	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
22	US	adherence on	<u>Follow Up:</u> 1 year	MPR \geq 70= high	Pharmacy	state specific	description
23		healthcare utilisation	<u>Sample Size:</u> 354	adherence, MPR <	costs	<u>Currency Year:</u> USD, 2008	
24		among Medicare	(A:126, NA:228)	70 = low		<u>Cost of Nonadherence:</u> all cause:	
25		insured schizophrenia		adherence		IC:\$9053 (\$10071.37),	
26		patients.		<u>Method of</u>		PC:\$4267 (\$4746.99),	
27				<u>Assessment:</u>		Disease state specific:	
28				pharmacy claims		IC:\$2468 (\$2745.62),	
29				data		PC:\$1085 (\$1207.05)	
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32	<i>Robertson et al[23]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
33	2014	of the combination of	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
34	US	treatment utilization	<u>Follow Up:</u> 90 days	MPR \geq 80% =	Outpatient	<u>Currency Year:</u> USD, 2005	description
35		and medication	<u>Sample Size:</u> 1376	adherent	costs	<u>Cost of Nonadherence*:</u>	
36		possession on arrest	(90/90:637, 60/90:240,	<u>Method of</u>	Emergency	TC(90/90):\$28068 (\$33495.65),	
37		and incarceration	30/90:174, 0/90:316)	<u>Assessment:</u>	department	TC(60/90):\$21720 (\$25920.11),	
38		outcomes and on		Medicaid claims	costs	TC(30/90):\$21084 (\$25161.12),	
39		costs.		data	Pharmacy	TC(0/90):\$12516 (\$14936.28),	
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costs IC(90/90):\$12168 (\$14520.99),
 Target case IC(60/90):\$10068 (\$12014.90),
 management IC(30/90):\$11376 (\$13575.84),
 costs IC(0/90):\$5592 (\$6673.35),
 Psychiatric OC(90/90):\$6468 (\$7718.75),
 assessment OC(60/90):\$4152 (\$4954.89),
 costs OC(30/90):\$2916 (\$3479.88),
 Arrest costs OC(0/90):\$2136 (\$2549.05),
 Incarceration EDC(90/90):\$96 (\$114.56),
 costs EDC(60/90):\$108 (\$128.88),
 EDC(30/90):\$144 (\$171.85),
 EDC(0/90):\$84 (\$100.24),
 PC(90/90):\$5316 (\$6343.98),
 PC(60/90):\$3468 (\$4138.63),
 PC(30/90):\$2232 (\$2663.61),
 PC(0/90):\$984 (\$1174.28),
 TCMC(90/90):\$2100 (\$2506.09),
 TCMC(60/90):\$1404 (\$1675.50),
 TCMC(30/90):\$1596 (\$1904.63),
 TCMC(0/90):\$516 (\$615.78),
 PAC(90/90):\$240 (\$286.41),
 PAC(60/90):\$228 (\$272.09),
 PAC(30/90):\$204 (\$243.45),
 PAC(0/90):\$156 (\$186.17),
 ArC(90/90):\$780 (\$930.83),
 ArC(60/90):\$1032 (\$1231.56),
 ArC(30/90):\$1140 (\$1360.45),
 ArC(0/90):\$1200 (\$1432.05),
 InC(90/90):\$888 (\$1059.72),
 InC(60/90):\$1272 (\$1517.97),
 InC(30/90):\$1476 (\$1761.42),
 InC(0/90):\$1860 (\$2219.68)

Robinson et al[24] To determine if the Design: Retrospective Measure: Total costs Type of Costs: unadjusted Quality: medium

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3	2006	type of antidepressant	claims analysis	Antidepressant	Inpatient	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
4	US	drug is related to	<u>Follow Up:</u> 6 months	medication	costs	state specific	description
5		adherence and assess	<u>Sample Size:</u> 60386	management	Outpatient	<u>Currency Year:</u> USD, 2004	
6		the 6 month health	(A:11526, NA:8860)	measures	costs	<u>Cost of Nonadherence*:</u> all cause:	
7		care costs among		<u>Classification:</u>	ED visit costs	TC:\$12658 (\$15678.21)	
8		newly diagnosed		meeting less than	Pharmacy	IC:\$3006 (\$3723.24),	
9		patients.		<3 medication	costs	OC:\$6118 (\$7577.76),	
10				management	Physician	EDC:\$334 (\$413.69)	
11				measures =	office visit	PC:\$3200 (\$3963.52),	
12				nonadherent	costs	POC:\$178 (\$220.47)	
13				<u>Method of</u>		Disease state specific:	
14				<u>Assessment:</u>		TC:\$2028 (\$2511.88)	
15				pharmacy claims		IC:\$102 (\$126.34),	
16				data, Medicaid		OC:\$734 (\$909.13),	
17				data,		EDC:\$18 (\$22.29)	
18				observational		PC:\$1174 (\$1454.12),	
19				assessment		POC:\$120 (\$148.63)	
20				<u>Measure:</u> quarter	Hospitalization	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
21	Svarstad et al[25]	To examine the	<u>Design:</u> Retrospective	pharmacy claims	costs	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
22	2001	relationship of	database analysis	<u>Classification:</u> one		state specific	description
23	US	medication non-	<u>Follow Up:</u> 1 year	or more quarters		<u>Currency Year:</u> USD, 1990	
24		adherence to hospital	<u>Sample Size:</u> 619	without a claim =		<u>Cost of Nonadherence:</u> all cause:	
25		use and costs among	(A:413, NA:206)	nonadherent		HC:\$3992 (\$6593.06)	
26		severely mentally ill		<u>Method of</u>		Disease state specific:	
27		clients.		<u>Assessment:</u>		Schizophrenia/schizo affective disorder:	
28				pharmacy claims		HC:\$3421 (\$5650.01)	
29				data, previous		Bipolar disorder:	
30				study data		HC:\$9701 (\$16021.85),	
31						Other severe mental illness:	
32						HCD:\$3024 (\$4994.34)	
33						<u>Type of Costs:</u> adjusted	<u>Quality:</u> medium
34	White et al[26]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
35	2003	economic impact of	database analysis	<u>Classification:</u>	Pharmacy	<u>Currency Year:</u> USD, 1999	description
36	US	antidepressant	<u>Follow Up:</u> 6 months	MPR≥70% =	costs		
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4		treatment adherence	<u>Sample Size:</u> 14190	adherent,	Medical costs	<u>Cost of Nonadherence:</u>
5		among patients	(A:5638, NA:8552)	MPR<70% =		TC:\$11815 (\$16290.09)
6		treated for depression		nonadherent		PC:\$1123 (\$1548.35),
7				<u>Method of</u>		MC:\$10692 (\$14741.74)
8				<u>Assessment:</u>		
9				pharmacy claims		
10				data		
11	Diabetes					
12	<i>An et al[27]</i>	This study evaluated	<u>Design:</u> Prospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
13	2014	the association	cohort study	<u>Classification:</u>	Outpatient	<u>Classification:</u> disease state specific
14	Korea	between medication	<u>Follow Up:</u> 3 years	MPR≥90% =	costs	<u>Currency Year:</u> USD, 2007
15		adherence and	<u>Sample Size:</u> 608	adherent,	Hospitalization	<u>Cost of Nonadherence*:</u>
16		clinical/economic	(A:472, NA:136)	MPR<90% =	costs	TC:\$1657.11 (\$1884.14)
17		outcomes in patients		nonadherent		OC: \$1413.99 (\$1608.20),
18		with type II diabetes		<u>Method of</u>		HC: \$243.11 (\$276.12)
19		mellitus in the republic		<u>Assessment:</u>		
20		of Korea over 3 year		pharmacy claims		
21		period.		data		
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24	<i>Buysman et al[28]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Pharmacy	<u>Type of Costs:</u> unadjusted
25	2017	of real world	database analysis	<u>Classification:</u>	costs	<u>Classification:</u> all cause and disease
26	US	adherence on	<u>Follow Up:</u> 12 months	PDC≥80% = highly		state specific
27		glycaemic control in	<u>Sample Size:</u> 2261	adherent,		<u>Currency Year:</u> USD, 2014
28		type 2 diabetes	(A:1215, NA:1046)	PDC<80% = less		<u>Cost of Nonadherence:</u> all cause:
29		patients treated with		than highly		PC: \$7225 (\$7297.39)
30		canagliflozin.		adherent		Disease state specific:
31				<u>Method of</u>		PC: \$4660 (\$4706.69)
32				<u>Assessment:</u>		
33				healthcare claims		
34				data		
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37	<i>Curtis et al[29]</i>	Examine the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total costs	<u>Type of Costs:</u> adjusted
38	2017	association between	analysis	<u>Classification:</u>	Outpatient	<u>Classification:</u> all cause
39	US	adherence to glucose	<u>Follow Up:</u> 3 years	PDC≥80% =	costs	<u>Currency Year:</u> USD, 2014
40		lowering agents and	<u>Sample Size:</u> 228074	adherent,	Pharmacy	<u>Cost of Nonadherence:</u>
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patient outcomes in an adult type 2 diabetes population

(A:117864, NA:110210)

PDC<80% = nonadherent
Method of Assessment: healthcare claims data

costs
Acute care costs

TC:\$38633 (\$39020.09)
OC: \$16964 (\$17134),
PC: \$9390 (\$9484.08),
ACC:\$12153 (\$12274.77)

Egede et al[30] 2012 US

To examine the longitudinal effects of medication nonadherence on key costs and estimate potential savings from increased adherence using novel methodology that accounts for shared correlation among cost categories.

Design: Retrospective cohort study
Follow Up: 5 years
Sample Size: 740195 (A:427390, NA:312805)

Measure: MPR
Classification: MPR≥80% = adherent, MPR<80% = nonadherent
Method of Assessment: pharmacy claims data

Inpatient costs
Outpatient costs
Pharmacy costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2006
Cost of Nonadherence*: IC:\$14515.24 (\$17886.40)
OC: \$3599.27 (\$4434.16),
PC: \$1073.12 (\$1322.42)

Quality: high
Classification: cost outcome description

Gentil et al[31] 2015 Canada

To examine healthcare costs associated with adherence to oral antihyperglycemic agents and the effects of depression and anxiety disorders on these in older adults with type 2 diabetes

Design: Retrospective, observational cohort analysis
Follow Up: 1 year
Sample Size: 301 (A:224, NA:77)

Measure: MPR
Classification: MPR≥80% = adherent, MPR<80% = nonadherent
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs
Physician office visit costs

Type of Costs: adjusted and unadjusted
Classification: all cause and disease state specific
Currency Year: CAD, 2010
Cost of Nonadherence:
Adjusted all cause:
TC:\$11124 (\$9818.67),
IC:\$7419 (\$6548.43)
OC: \$2687 (\$2371.70),
PC: \$504 (\$444.86),
POC:\$513 (\$452.80)
Adjusted disease state specific:
TC:\$4477 (\$3951.65),
IC:\$2836 (\$2503.21)
OC: \$1518 (\$1339.87),

Quality: medium
Classification: cost description

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					PC###: \$-444 (\$-391.90), POC:\$568 (\$517.24) Unadjusted all cause: TC:\$14979 (\$13221.30), IC:\$6351 (\$5605.75) OC: \$4058 (\$3581.82), PC: \$3503 (\$3091.94), POC:\$1066 (\$940.91) Unadjusted disease state specific: TC:\$9008 (\$7950.97), IC:\$2854 (\$2519.10) OC: \$2654 (\$2342.57), PC: \$2498 (\$2204.87), POC:\$1002 (\$884.42)	
Hagen et al[32] 2014 US	To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/ short term disability costs	<u>Design:</u> Retrospective, observational cohort analysis <u>Follow Up:</u> 1 year <u>Sample Size:</u> 4978 (A:2820, NA:2158)	<u>Measure:</u> PDC <u>Classification:</u> PDC≥80% = compliant, PDC<80% = noncompliant <u>Method of Assessment:</u> pharmacy claims data	Healthcare costs Pharmacy costs Medical costs Short term disability costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2003 <u>Cost of Nonadherence:</u> Adjusted all cause: PC: \$1668 (\$2065.99), Adjusted disease state specific: HC:\$7642 (\$9465.39), PC:\$614 (\$760.50), MC:\$5974 (\$7399.40), STDC:\$1840 (\$2279.03) Unadjusted all cause: PC:\$1727 (\$2139.06) Unadjusted disease state specific: HC:\$6919 (\$8569.88), PC:\$785 (\$972.30), MC:\$5192 (\$6430.82), STDC:\$1717 (\$2126.68)	<u>Quality:</u> medium <u>Classification:</u> cost description
Hansen et al[33] 2010	To compare all cause total health care costs	<u>Design:</u> Retrospective, cohort study	<u>Measure:</u> MPR <u>Classification:</u>	Total Healthcare	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> all cause and disease	<u>Quality:</u> medium <u>Classification:</u> cost

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US	and diabetes mellitus specific health care costs between patients who were adherent or non-adherent to monotherapy with metformin, pioglitazone or a sulfonylurea and to examine whether cost differences varied among patients using these oral antidiabetic drugs.	<u>Follow Up:</u> 2 years <u>Sample Size:</u> 108592 (A:63830, NA:44762)	<u>MPR</u> ≥80% = adherent, <u>MPR</u> <80% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	costs Inpatient costs Outpatient costs Pharmacy costs	state specific <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence#:</u> Adjusted all cause: THC:\$13258 (\$15911.01) Adjusted disease state specific: THC:\$2284 (\$2741.04) Unadjusted all cause: THC:\$15448.50 (\$18539.90), IC:\$4242.33 (\$5091.25), OC:\$ 7377.83, PC:\$3828 (\$4594.01) Unadjusted disease state specific: THC:\$3232.33 (\$3879.15), IC:\$873.50 (\$1048.29), OC:\$1545.67(\$1854.96), PC:\$812.67 (\$975.29)	description
<i>Hong et al</i> [34] 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.	<u>Design:</u> Retrospective, cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 40082 (A:11800, NA:28282)	<u>Measure:</u> MPR <u>Classification:</u> <u>MPR</u> ≥80% = adherent, <u>MPR</u> <80% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	Total costs Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> KRW, 2007 <u>Cost of Nonadherence:</u> TC:₩765453 (\$1142.31), HC:₩397549 (\$593.28)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Jha et al</i> [35] 2012 US	How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or	<u>Design:</u> Retrospective, observational claims analysis <u>Follow Up:</u> unclear <u>Sample Size:</u> 135639 (A:99976, NA:36553)	<u>Measure:</u> MPR <u>Classification:</u> <u>MPR</u> ≥80% = adherent, <u>MPR</u> <80% = nonadherent <u>Method of Assessment:</u>	Total costs ED costs Hospitalization costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence***:</u> TC:\$4680000000 (\$5006563305.49), EDC:\$735000000 (\$786287185.80), HC:\$3950000000 (\$4225625012.11)	<u>Quality:</u> high <u>Classification:</u> cost outcome description

decreased pharmacy claims
hospitalizations or data
emergency
department visits?

Are there certain
subgroups of
populations that seem
to benefit more than
others when they
adhere to their
medication?
What are the financial
implications of changes
in adherence for the
nation at large and for
Medicare?

White et al[36]
2004
US

To assess the
relationship between
diabetic medication
adherence, total
healthcare costs and
utilisation with
patients with type 2
diabetes mellitus and
concomitant diabetes
and cardiovascular
disease.

Design: Retrospective,
database analysis
Follow Up: 1 year
Sample Size: 67029
(>95:20170, 75-95:
14074, <75:16713)

Measure: MPR
Classification:
MPR≥95%,
MPR>75%<95%,
MPR<75%
Method of
Assessment:
pharmacy claims
data

Total costs
Pharmacy
costs
Non-pharmacy
costs

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2000
Cost of Nonadherence: adjusted:
TC(≥95):\$4835 (\$6518.17),
TC(75-95):\$5314 (\$7163.92),
TC(<75):\$5706 (\$7692.38),
PC(≥95):\$1429 (\$1926.47),
PC(75-95):\$1157 (\$1559.78),
PC(<75):\$762 (\$1027.27),
NPC(≥95):\$3406 (\$4591.70),
NPC(75-95):\$4157 (\$5604.14),
NPC(<75):\$4944 (\$6665.11)
Unadjusted:
TC(≥95):\$4809 (\$6483.12),
TC(75-95):\$5333 (\$7189.53),
TC(<75):\$5605 (\$7556.22),

Quality: low
Classification: cost
analysis

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10 *Wu et al*[37]
11 2009
12 US

To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

Design: Retrospective, cohort study
Follow Up: 1 year
Sample Size: 2354 (A:830, NA:1524)

Measure: MPR
Classification: MPR \geq 80%= high compliance, MPR<80% = low compliance
Subgroup Analysis: commercial and Medicare supplemental
Method of Assessment: pharmacy claims data

Total healthcare costs
Inpatient costs
Outpatient costs
Pharmacy costs

PC(\geq 95):\$1402 (\$1890.07),
PC(75-95):\$1153 (\$1554.38),
PC(<75):\$766 (\$1032.66),
NPC(\geq 95):\$3407 (\$4593.05),
NPC(75-95):\$4180 (\$5635.15),
NPC(<75):\$4839 (\$6523.56)
Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2006
Cost of Nonadherence: adjusted all cause:
THC(com):\$32407 (\$37732.29),
THC(med):\$24622 (\$28668.02),
IC(com):\$ 12851(\$14692.74),
IC(med):\$ 6754 (\$7863.85),
OC(com):\$11888 (\$13841.50),
OC(med):\$10598 (\$12339.52),
PC(com):\$7667 (\$8926.88),
PC(med):\$7270 (\$8464.65)
Adjusted disease state specific:
Diabetes:
THC(com):\$10024 (\$11671.20),
THC(med):\$5015 (\$5839.09),
IC(com):\$2232 (\$2598.77),
IC(med):\$2606 (\$3034.23),
OC(com):\$1989 (\$2315.84),
OC(med):\$1231 (\$1433.28),
PC(com):\$1451 (\$1689.44),
PC(med):\$1179 (\$1372.74)
DPNP:
THC(com):\$3565 (\$4150.82),
THC(med):\$2384 (\$2775.75),

Quality: medium
Classification: cost description

Osteoporosis

Briesacher et al[38]
2007
US

To assess rates of osteoporotic fractures and health care utilisation as a function of bisphosphonate compliance in usual clinical practice.

Design: Retrospective, cohort study
Follow Up: 3 years
Sample Size: 17988 (not specified)

Measure: MPR
Classification: 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs

IC(com):\$1739 (\$2024.76),
IC(med):\$1048 (\$1220.21),
OC(com):\$362 (\$421.49),
OC(med):\$181 (\$210.74),
PC(com):\$1464 (\$1704.57)
PC(med):\$1155 (\$1344.80)

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2004
Cost of Nonadherence****: adjusted:
TC(80-100):-\$859 (-\$1063.96),
TC(60-79):-\$474 (-\$587.10),
TC(40-59):-\$366 (-\$453.33),
TC(20-39):\$151 (\$187.03),
IC(80-100):-\$3233 (-\$4004.40),
IC(60-79):-\$856(-\$1060.24),
IC(40-59):-\$6221 (-\$7705.34),
IC(20-39):-\$585 (-\$724.58),
OC(80-100):-\$445 (-\$551.18),
OC(60-79):-\$538 (-\$666.37),
OC(40-59):-\$236 (-\$292.31),
OC(20-39):\$60 (\$74.32),
PC(80-100):\$997 (\$1234.89),
PC(60-79):\$923 (\$1143.23),
PC(40-59):\$402 (\$497.92),
PC(20-39):\$160(\$198.18)
Unadjusted:
TC(80-100):-\$1273 (-\$1576.74),
TC(60-79):-\$294 (-\$364.15),
TC(40-59):-\$573 (-\$709.72),
TC(20-39):\$101 (\$125.10),
IC(80-100):-\$883 (-\$1093.68),

Quality: medium
Classification: cost description

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					IC(60-79):-\$384 (-\$475.62), IC(40-59):-\$597 (-\$739.44), IC(20-39):-\$93 (-\$115.19), OC(80-100):-\$774 (-\$958.68), OC(60-79):-\$193 (-\$239.05), OC(40-59):-\$145 (-\$179.60), OC(20-39):\$148 (\$183.31), PC(80-100):\$384 (\$475.62), PC(60-79):\$284 (\$351.76), PC(40-59):\$170 (\$210.56), PC(20-39):\$48 (\$59.45)	
<i>Eisenberg et al</i> [39] 2015 US	To determine healthcare outcomes associated with compliance and noncompliance to bisphosphonate therapy in women diagnosed with osteoporosis	<u>Design:</u> Retrospective claims study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 27905 (A:11368, NA:16537)	<u>Measure:</u> MPR <u>Classification:</u> (≥70% = compliant, <70% = noncompliant <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Physician office visit costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2012 <u>Cost of Nonadherence:</u> all cause: TC:\$7237 (\$7550.72), IC:\$1986 (\$2072.09), OC:\$2057 (\$2146.17), EDC:\$258 (\$269.18), PC:\$2197 (\$2292.24), POC:\$738 (\$769.99) Disease state specific: TC:\$674 (\$703.22), IC:\$334 (\$348.48), OC:\$77 (\$80.34), EDC:\$5 (\$5.22), PC:\$213 (\$222.23), POC:\$44 (\$45.91)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Halpern et al</i> [40] 2011 US	To examine the associations of adherence to osteoporosis therapies	<u>Design:</u> Retrospective analysis <u>Follow Up:</u> 540 days <u>Sample Size:</u> 21655	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = high adherence,	Medical costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause <u>Currency Year:</u> USD, 2006 <u>Cost of Nonadherence:</u> commercial:	<u>Quality:</u> medium <u>Classification:</u> cost outcome description

with occurrence of closed fracture, all cause medical costs and all cause hospitalizations.

(≥80%:8759, ≥50<80%:5237, <50%:7659)

≥50<80% = moderate adherence, <50% = low adherence
Method of Assessment:
 pharmacy claims data

MC(≥80):\$4295 (\$5000.78), MC(50-80):\$4697 (\$5468.84), MC(<50):\$5596 (\$6515.56)
 Medicare:
 MC(≥80):\$4590 (\$5344.25), MC(50-80):\$5536 (\$6445.71), MC(<50):\$5801 (\$6754.25)

Hazel-Fernandez et al[41]
 2013
 US

To evaluate the healthcare utilisation patterns of medicare part D beneficiaries newly initiating teriparatide and to assess the association of medication adherence and persistence with bone fracture.

Design: Retrospective cohort study
Follow Up: 12 months
Sample Size: 761
 (≥80%:163, ≥50<80%:57, <50%:541)

Measure: PDC
Classification:
 (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence
Method of Assessment:
 pharmacy claims data

Total healthcare costs
 Inpatient costs
 Outpatient costs
 ED costs
 Pharmacy costs

Type of Costs: unadjusted
Classification: disease state specific and fracture related
Currency Year: USD, 2010
Cost of Nonadherence*:
 Disease state specific:
 THC(≥80):\$21033 (\$22942.39), THC(50-80):\$25574 (\$27895.62), THC(<50):\$15528 (\$16937.64), IC(≥80):\$2198 (\$2397.54), IC(50-80):\$8448 (\$9214.91), IC(<50):\$4897 (\$5341.55), OC(≥80):\$5151 (\$5618.61), OC(50-80):\$6439 (\$7023.54), OC(<50):\$5806 (\$6333.07), EDC(≥80):\$211 (\$230.15), EDC(50-80):\$330 (\$359.96), EDC(<50):\$465 (\$507.21), PC(≥80):\$13472 (\$14695), PC(50-80):\$10358 (\$11298.31), PC(<50):\$4361 (\$4756.89)
 Fracture related:
 THC(≥80):\$12670 (\$13820.19), THC(50-80):\$9292 (\$10135.53), THC(<50):\$4419 (\$4820.16),

Quality: medium
Classification: cost outcome description

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4						IC(\geq 80):\$366 (\$399.23),	
5						IC(50-80):\$830 (\$905.35),	
6						IC(<50):\$1325 (\$1445.28),	
7						OC(\geq 80):\$1048 (\$1143.14),	
8						OC(50-80):\$955 (\$1041.70),	
9						OC(<50):\$767 (\$836.63),	
10						EDC(\geq 80):\$6 (\$6.54),	
11						EDC(50-80):\$9 (\$9.82),	
12						EDC(<50):\$44 (\$47.99),	
13						PC(\geq 80):\$10810 (\$11791.34),	
14						PC(50-80):\$7420 (\$8093.59),	
15						PC(<50):\$2068 (\$2255.73)	
16							
17	<i>Huybrechts et al</i> [42]	To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 5 years <u>Sample Size:</u> 38120 (A:9530, NA:28590)	<u>Measure:</u> MPR <u>Classification:</u> (\geq 80% = compliant, <50% = noncompliant) <u>Method of Assessment:</u> pharmacy claims data	Total costs Medical costs Institutional costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2000 <u>Cost of Nonadherence:</u> TC:\$7200 (\$9706.44), MC:\$1476 (\$1989.84), InstC:\$5736 (\$7732.80)	<u>Quality:</u> low <u>Classification:</u> cost description
18	2006						
19	US						
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27	<i>Kjellberge al</i> [43]	To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of noncompliance with health care resource use and cost.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 38234 (A:26806, NA:11428)	<u>Measure:</u> MPR <u>Classification:</u> (\geq 70% = compliant, <70% = noncompliant) <u>Method of Assessment:</u> pharmacy claims data	Total costs Medical costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> Euro, 2011 <u>Cost of Nonadherence:</u> all cause: TC:€4933 (\$6209.58), MC:€3471 (\$4369.20), Disease state specific: TC:€754 (\$949.12), MC:€426 (\$536.24),	<u>Quality:</u> high <u>Classification:</u> cost outcome description
28	2016						
29	Denmark						
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39	<i>Modi et al</i> [44]	To evaluate compliance with	<u>Design:</u> Retrospective cohort study	<u>Measure:</u> MPR <u>Classification:</u>	Total costs Inpatient costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease	<u>Quality:</u> medium <u>Classification:</u> cost
40	2015						
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3	US	osteoporosis	<u>Follow Up:</u> 1 year	(≥80% =	Outpatient	state specific
4		treatments and	<u>Sample Size:</u> 27913	compliant, <80%	costs	<u>Currency Year:</u> USD, 2011
5		determine fracture and	(A:23430, NA:34483)	= noncompliant)	ED costs	<u>Cost of Nonadherence:</u> all cause:
6		healthcare burden		<u>Method of</u>	Pharmacy	TC:\$11749 (\$12484.12),
7		associated with		<u>Assessment:</u>	costs	IC:\$8768 (\$9316.60),
8		noncompliance		healthcare claims	Medical costs	OC:\$3945 (\$4191.83),
9				data	Other costs	EDC:\$104 (\$110.51),
10						PC:\$2981 (\$3167.52),
11						MC:\$8768 (\$9316.60),
12						OtC:\$997 (\$1059.38)
13						Disease state specific:
14						TC:\$630 (\$669.42),
15						IC:\$443 (\$470.72),
16						OC:\$158 (\$167.89),
17						EDC:\$3 (\$3.19),
18						PC:\$325 (\$345.33),
19						OtC:\$26 (\$27.63)
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23	<i>Olsen et al</i> [45]	To assess the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Fracture costs	<u>Type of Costs:</u> unadjusted
24	2013	association between	observational study	<u>Classification:</u>		<u>Classification:</u> fracture site specific
25	Denmark	refill compliance and	<u>Follow Up:</u> 2 years	(≥80% = optimal		<u>Currency Year:</u> DKK, 2010
26		all cause health care	<u>Sample Size:</u> 47176	compliance,		<u>Cost of Nonadherence:</u>
27		costs.	(not specified)	>50<80% =		Hip fracture:
28				suboptimal		FC(50-80):kr817575.50 (\$74531.41),
29				compliance, <50%		FC(<50):kr4454954 (\$549987.04)
30				= low compliance		Spine fracture:
31				<u>Method of</u>		FC(50-80):kr174700 (\$21568.12),
32				<u>Assessment:</u>		FC(<50):kr226472 (\$27959.14)
33				pharmacy claims		Humerus fracture:
34				data		FC(50-80):kr117776.50 (\$14540.12),
35						FC(<50):kr795217.50 (\$98173.70)
36						Forearm fracture:
37						FC(50-80):-kr463024 (-\$57162.70),
38						FC(<50):kr45072.50 (\$8665.81)
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<p><i>Sunycz et al</i>[46] 2008 US</p>	<p>To examine the relationship between persistence and compliance with bisphosphonate therapy and total and osteoporosis related costs and healthcare resource utilisation in a cohort of female bisphosphonate naïve users.</p>	<p><u>Design:</u> Retrospective observational study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 32944 (A:12186, NA:20758)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> (≥80% = compliant, <80% = noncompliant) <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Radiology costs</p>	<p>Other fracture: FC(50-80):-kr19261.50 (-\$2377.93), FC(<50):kr684067.50 (\$84451.66) <u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence:</u> All cause: THC:\$23660 (\$28394.52), IC:\$18839 (\$22608.81), OC:\$10061 (\$12074.27), EDC:\$832 (\$988.49), PC:\$6941 (\$8329.94), RC:\$1079 (\$1294.91) Disease state specific: THC:\$1602 (\$1922.57), IC:\$14074 (\$16890.30), OC:\$501 (\$601.25), EDC:\$452 (\$542.45), PC:\$918 (\$1101.70), RC:\$184 (\$220.82)</p>	<p><u>Quality:</u> low <u>Classification:</u> cost description</p>
<p><i>Zhao et al</i>[47] 2014 US</p>	<p>To examine the association between teriparatide adherence and healthcare utilisation and costs among hip fracture patients.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 36 months <u>Sample Size:</u> 824 (≥80:362, 50-80%:219, <50%:243)</p>	<p><u>Measure:</u> PDC <u>Classification:</u> (≥80% = high, 50-80% = medium, <50% = low) <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Total healthcare costs Inpatient costs Outpatient costs Pharmacy costs</p>	<p><u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2010 <u>Cost of Nonadherence*:</u> Adjusted: THC(≥80):\$34428 (\$37553.4), THC(50-80):\$37956 (\$41401.68), THC(<50):\$31188 (\$34019.28), IC(≥80):\$7548 (\$8233.20), IC(50-80):\$11520 (\$1256.80), IC(<50):\$11556 (\$12605.04),</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost description</p>

For peer review

OC(≥80):\$9312 (\$10157.40),
 OC(50-80):\$12816 (\$13979.40),
 OC(<50):\$13044 (\$14228.16),
 PC(≥80):\$18864 (\$20576.52),
 PC(50-80):\$13116 (\$14306.64),
 PC(<50):\$7452 (\$8128.44)

Unadjusted:
 THC(≥80):\$37464 (\$40865.04),
 THC(50-80):\$35076 (\$38260.20),
 THC(<50):\$29484 (\$32160.60),
 IC(≥80):\$7092 (\$7735.80),
 IC(50-80):\$11100 (\$12107.64),
 IC(<50):\$10632 (\$11597.16),
 OC(≥80):\$9900 (\$10798.68),
 OC(50-80):\$11352 (\$12382.56),
 OC(<50):\$11988 (\$13076.28),
 PC(≥80):\$20484 (\$22343.52),
 PC(50-80):\$12624 (\$13770),
 PC(<50):\$6864 (\$7487.16)

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2010
Cost of Nonadherence*:
 Adjusted:
 THC(≥80):\$40212 (\$43862.52),
 THC(50-80):\$40512 (\$44189.76),
 THC(<50):\$40128 (\$43770.84),
 IC(≥80):\$8136 (\$8874.60),
 IC(50-80):\$12060 (\$13154.76),
 IC(<50):\$15444 (\$43404.36),
 OC(≥80):\$12924 (\$14097.24),
 OC(50-80):\$14928 (\$16283.16),
 OC(<50):\$17568 (\$19162.80)

25 *Zhao et al*[48]
 26 2013
 27 US
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 29 To examine the
 30 association between
 31 teriparatide (TPTD)
 32 adherence and
 33 healthcare utilisation
 34 and costs in real world
 35 US
 36 kyphoplasty/vertebroplasty (KV) patients.

Design: Retrospective
 observational cohort
 study
Follow Up: 36 months
Sample Size: 1568
 (≥80: 783, 50-80%:
 382, <50%: 403)

Measure: PDC
Classification:
 (≥80% = high, 50-
 80% = medium,
 <50% = low)
Method of
Assessment:
 pharmacy claims
 data

Total
 healthcare
 costs
 Inpatient costs
 Outpatient
 costs
 Pharmacy
 costs

Quality: medium
Classification: cost
 description

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47**Respiratory
Disease***Davis et al*[49]
2017
US

To assess the association between adherence levels to different inhaled corticosteroid/long acting β_2 -adrenergic agonist and COPD exacerbation rates and costs in commercially insured population

Design: Observational cohort study
Follow Up: 12 months
Sample Size: 13657 ($\geq 80\%$: 1898, $\geq 50 < 80\%$: 1971, $\geq 30 < 50\%$: 2443, $< 30\%$:7345)

Measure: PDC
Classification: (≥ 80 = adherent, $\geq 50 < 80\%$ = mildly nonadherent, $\geq 30 < 50\%$ = moderately nonadherent, $< 30\%$ highly nonadherent)
Method of Assessment: commercially insured healthcare claims data

Total costs
Outpatient costs
Pharmacy costs
Hospitalization costs

PC(≥ 80):\$19392 (\$21152.40),
PC(50-80):\$13908 (\$15170.52),
PC(< 50):\$8700 (\$9843.24)
Unadjusted:
THC(≥ 80):\$42768 (\$46650.48),
THC(50-80):\$36780 (\$40118.88),
THC(< 50):\$39792 (\$43404.36),
IC(≥ 80):\$7620 (\$8311.80),
IC(50-80):\$12228 (\$13338.12),
IC(< 50):\$15768 (\$17199.48),
OC(≥ 80):\$14580 (\$15903.60),
OC(50-80):\$12108 (\$13207.20),
OC(< 50):\$15324 (\$16715.16),
PC(≥ 80):\$20568 (\$22435.20),
PC(50-80):\$12444 (\$13573.68),
PC(< 50):\$8700 (\$9489.84)

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2014
Cost of Nonadherence*:
All cause:
TC(≥ 80):\$22546 (\$22772.24),
TC(50-80):\$25545 (\$25800.95),
TC(30-50):\$24303 (\$24546.51),
TC(< 30):\$25148 (\$25399.98),
OC(≥ 80):\$7816 (\$7894.31),
OC(50-80):\$8225 (\$8307.41),
OC(30-50):\$8365 (\$8448.81),
OC(< 30):\$8857 (\$8945.74),
PC(≥ 80):\$7954 (\$8033.70),

Quality: medium
Classification: cost description

For peer review

PC(50-80):\$6862 (\$6930.76),
 PC(30-50):\$5485 (\$5539.96),
 PC(<30):\$4395 (\$4439.04),
 HC(≥80):\$6106 (\$6167.51),
 HC(50-80):\$9391 (\$9485.09),
 HC(30-50):\$9171 (\$9262.89),
 HC(<30):\$10849 (\$10957.70)
 Disease state specific:
 TC(≥80):\$8075.33 (\$8156.24),
 TC(50-80):\$7053 (\$7123.67),
 TC(30-50):\$6623 (\$6689.36),
 TC(<30):\$5644 (\$5700.55),
 OC(≥80):\$2194.33 (\$2216.32),
 OC(50-80):\$1947 (\$1966.51),
 OC(30-50):\$1997 (\$2017.01),
 OC(<30):\$2152 (\$2173.56),
 PC(≥80):\$4464 (\$4508.73),
 PC(50-80):\$3345 (\$3378.52),
 PC(30-50):\$2307 (\$2330.12),
 PC(<30):\$1569 (\$1584.72),
 HC(≥80):\$1074.67 (\$1085.44),
 HC(50-80):\$1155 (\$1166.57),
 HC(30-50):\$1619 (\$1635.22),
 HC(<30):\$1405 (\$1419.08)

31 *Delea et al*[50]
 32 2008
 33 US

To assess the
 association between
 adherence with
 fluticasone
 propionate/salmeterol
 combination product in
 a single inhaler and
 asthma care utilisation
 and costs in asthma

Design: Retrospective
 longitudinal cohort
 study
Follow Up: 24 months
Sample Size: 12907
 (≥75: 2612, 50-75%:
 3608, 25-50%: 5035,
 <25%: 1652)

Measure: MPR
Classification:
 (≥75, 50-75%, 25-
 50%, <25%)
Method of
Assessment:
 pharmacy claims
 data

Total costs
 Outpatient
 costs
 ED costs
 Other costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence *:
 TC(≥75):\$1564 (\$1990.27),
 TC(50-75):\$1128 (\$1435.44),
 TC(25-50):\$900 (\$1145.30),
 TC(<25):\$632 (\$804.25),
 OC(≥75):\$1272 (\$1618.69),

Quality: medium
Classification: cost
 description

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patients in typical US
clinical practice

OC(50-75):\$852 (\$1084.21),
OC(25-50):\$600 (\$763.53),
OC(<25):\$388 (\$493.75),
EDC(≥75):\$32 (\$40.72),
EDC(50-75):\$36 (\$45.81),
EDC(25-50):\$60 (\$76.35),
EDC(<25):\$48 (\$61.08),
OtC(≥75):\$292 (\$371.59),
OtC(50-75):\$276 (\$351.22),
OtC(25-50):\$300 (\$381.77),
OtC(<25):\$240 (\$305.41)

Diehl et al[51]
2010
US

To evaluate
respiratory-related
medical outcomes and
cost for infants who
were prescribed and
received palivizumab in
accordance with the
dosing schedule
recommended by the
American Academy of
Paediatrics in 2006
versus those who did
not.

Design: Retrospective
claims analysis
Follow Up: 7 months
Sample Size: 245 (A:73,
NA:172)

Measure: 37 day
gap in claims
Classification: (>37
day gap in claims =
noncompliant)
Method of
Assessment:
pharmacy claims
data

Total costs
Pharmacy
costs
Services costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2007
Cost of Nonadherence:
TC:\$19093.46 (\$21656.12),
PC:\$7647.40 (\$8673.81),
SC^{**}:\$11604.03 (\$13161.45)

Quality: medium
Classification: cost
description

Joshi et al[52]
2006
US

Examine the
association of
medication adherence
with workplace
productivity and health
related quality of life in
asthma patients.

Design: quantitative
analysis
Follow Up:
Sample Size: 385
(high:150, medium:73,
low: 162)

Measure: Morisky
scale
Classification: (0=
high adherence, 1-
2 = medium
adherence, >2 =
low adherence)
Method of
Assessment:

Total
productivity
cost
Absenteeism
costs
Presenteeism
costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002
Cost of Nonadherence^{##}:
TPC(0):\$1210.90 (\$1571.73),
TPC(1-2):\$1428.50 (\$1854.17),
TPC(>2):\$1073.10 (\$1392.87),
AbC(0):\$633.70 (\$822.53),
AbC(1-2):\$608.90 (\$790.34),

Quality: medium
Classification: cost
outcome
description

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3							
4				questionnaire			
5					AbC(>2):\$474.80 (\$616.28),		
6					PrC(0):\$577.20 (\$749.20),		
7					PrC(1-2):\$819.60 (\$1063.83),		
8	<i>Miravittles et al</i> [53]	To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).	<u>Design:</u> multicentre, retrospective, observational study <u>Follow Up:</u> 18 months <u>Sample Size:</u> 1365 (A:246, NA:1119)	<u>Measure:</u> GOLD 2007 Guidelines <u>Classification:</u> (adherent, nonadherent) <u>Method of Assessment:</u> GOLD guidelines	ED costs Pharmacy costs Physician office visit costs Hospitalization costs Primary care costs Interdisciplinary visit costs Medical test costs Radiology costs Laboratory costs Total healthcare costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> EUR, 2009 <u>Cost of Nonadherence:</u> EDC:€40.83 (\$57.91), PC:€771.50 (\$1094.27), POC:€106.29 (\$150.76), HC:€101.61 (\$144.12) PCC:€123.84 (\$175.65), IntC:€321.44 (\$455.92), MTC:€36.66 (\$51.99), RC:€24.24 (\$34.38), LC:€17.35 (\$24.61)	<u>Quality:</u> medium <u>Classification:</u> cost description
9	2013						
10	Spain						
11							
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13							
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19							
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21							
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28	<i>Quittner et al</i> [54]	To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.	<u>Design:</u> retrospective, cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 3287 (>80%: 663, 50-80%: 949, <50%: 1675)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence) <u>Method of Assessment:</u> pharmacy claims data		<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence*:</u> All cause: THC(≥80):\$35749.50 (\$38244.05), THC(50-80):\$45031.50 (\$48173.73), THC(<50):\$50284.50 (\$53793.28) Disease state specific: THC(≥80):\$23764 (\$25422.22),	<u>Quality:</u> medium <u>Classification:</u> cost description
29	2014						
30	US						
31							
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6 **Gastrointestinal**
7 **Disease**

8 *Carter et al*[55]
9 2011
10 US

To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.

Design: retrospective, observational cohort claims analysis
Follow Up: 12 months
Sample Size: 638 (A:466, NA:172)

Measure: number of infusions in 12 month period
Classification: (7-9 infusions = adherent, <7 infusions = nonadherent)
Method of Assessment: health claims data

Hospitalization costs

THC(50-80):\$33132.50 (\$35444.44),
THC(<50):\$33894 (\$36259.07)

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2007
Cost of Nonadherence: HC:\$37783 (\$42854.12)

Quality: medium
Classification: cost outcome description

20 *Gosselin et al*[56]
21 2009
22 US

To examine the effects of gastroesophageal reflux disease (GERD) patients compliance with PPI therapy on health care resource utilisation and costs.

Design: retrospective cohort study
Follow Up:
Sample Size: 41837 (A:28321, NA:13516)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs
Medical costs

Type of Costs: adjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence: TC:\$9497 (\$12085.43), IC:\$2116 (\$2692.72), OC:\$5458 (\$6945.59), PC:\$1922 (\$2445.85), MC:\$7575 (\$9639.58)

Quality: medium
Classification: cost description

30 *Kane et al*[57]
31 2009
32 US

To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by patients.

Design: retrospective cohort analysis
Follow Up: 12 months
Sample Size: 571 (A:375, NA:196)

Measure: number of infusions in 12 month period
Classification: (≥8 infusions = adherent, <7 infusions = nonadherent)
Method of

Outpatient costs
ED costs
Pharmacy costs
Medical costs
Hospitalization costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2004
Cost of Nonadherence: All cause: OC:\$6679 (\$8272.62), EDC:\$314 (\$388.92), MC:\$16129 (\$19977.40),

Quality: medium
Classification: cost outcome description

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4			<u>Assessment:</u>		HC:\$6893 (\$8537.68)	
5			health claims data		Disease state specific:	
6					OC:\$3931 (\$4868.94),	
7					EDC:\$91 (\$112.71),	
8					PC:\$18751 (\$23225.01),	
9					MC:\$10243 (\$12686.99),	
10					HC:\$4494 (\$5566.27)	
11	<i>Mitra et al</i> [58]	To assess the	<u>Design:</u> retrospective,	<u>Measure:</u> MPR	Inpatient costs	<u>Type of Costs:</u> adjusted
12	2012	association between	observational cohort	<u>Classification:</u>	Outpatient	<u>Classification:</u> all cause and disease
13	US	adherence to oral 5-	study	(≥80% = adherent,	costs	state specific
14		aminosalicylates (5-	<u>Follow Up:</u> 12 months	<80% =	ED costs	<u>Currency Year:</u> USD, 2010
15		ASAs) and all cause	<u>Sample Size:</u> 1693	nonadherent)	Pharmacy	<u>Cost of Nonadherence:</u>
16		costs and health care	(A:476, NA:1216)	<u>Method of</u>	costs	All cause:
17		utilisation among		<u>Assessment:</u>	Ancillary costs	PC:\$1541.60 (\$1681.55)
18		patients with active		pharmacy claims	Non-pharmacy	Disease state specific:
19		ulcerative colitis.		data	costs	IC:\$28726.65 (\$31334.47),
20						OC:\$1145.67 (\$1249.67),
21						EDC:\$635.95 (\$693.68),
22						AC:\$4923.29 (\$5370.23),
23						NPC:\$14226.32 (\$15517.79)
24						
25						
26	<i>Wan et al</i> [59]	To examine the effect	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
27	2014	of adherence versus	cohort analysis	<u>Classification:</u>	Total	<u>Classification:</u> all cause and disease
28	US	non-adherence on	<u>Follow Up:</u> 360 days	(≥80% = adherent,	healthcare	state specific
29		healthcare costs in	<u>Sample Size:</u> 1646	<80% =	costs	<u>Currency Year:</u> USD, 2009
30		patients with	(A:674, NA:972)	nonadherent)	Inpatient costs	<u>Cost of Nonadherence:</u>
31		inflammatory bowel		<u>Method of</u>	Outpatient	All cause:
32		disease.		<u>Assessment:</u>	costs	TC:\$47411 (\$52341.27),
33				pharmacy claims	ED costs	THC:\$32522 (\$35903.96),
34				data	Pharmacy	IC:\$17634 (\$19467.76),
35					costs	OC:\$10909 (\$12043.43),
36						EDC:\$458 (\$505.63),
37						PC:\$18410 (\$20324.46)
38						Disease state specific:
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Epilepsy
Davis et al[60]
2008
US

To assess the extent of refill non-adherence with antiepileptic drugs (AEDs) and the potential association between AED non-adherence and healthcare costs in an adult managed care population.

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 10892 (A:6644, NA:4248)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
ED costs
Pharmacy costs
Other pharmacy costs

TC:\$33652 (\$37151.47),
THC:\$18764 (\$20715.27),
IC:\$12564 (\$13870.53),
OC:\$5890 (\$6502.50),
EDC:\$48 (\$52.99),
PC:\$15150 (\$16725.45)

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence###:
TC:\$1466 (\$1865.56),
IC:\$1799 (\$2289.32),
EDC:\$260 (\$330.86),
PC:-\$71 (-\$90.35),
OtPC:-\$358 (-\$455.57)

Quality: medium
Classification: cost description

Ettinger et al[61]
2009
US

To assess the extent to which elderly patients diagnosed with epilepsy are non-adherent to antiepileptic drugs (AEDs) and the potential association between AED non-adherence and seizure recurrence, resource utilisation and annual direct medical costs.

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 1278 (A:758, NA:520)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
ED costs
Pharmacy costs
Physician Office visit costs
Ancillary costs
Other pharmacy costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence:
TC:\$17817 (\$22673.06),
IC:\$2714 (\$3453.71),
EDC:\$526 (\$669.36),
PC:\$347 (\$441.58),
POC:\$3063 (\$3897.83),
AC:\$8344 (\$10618.18),
OtPC:\$2822 (\$3591.14)

Quality: medium
Classification: cost outcome description

Faught et al[62]
2009
US

To study the impact of non-adherence to antiepileptic drugs

Design: retrospective observational open cohort design

Measure: MPR
Classification: (≥80% = adherent,

Total costs
Inpatient costs
Outpatient

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002

Quality: medium
Classification: cost description

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3		(AEDs) on healthcare	<u>Follow Up:</u> 4.65 years	<80% =	costs	<u>Cost of Nonadherence</u> * :
4		utilisation and direct	<u>Sample Size:</u> 33658	nonadherent)	ED costs	TC:\$14417.64 (\$18713.91),
5		medical costs in a	(A:24907, NA:8751)	<u>Method of</u>	Pharmacy	IC:\$6682.28 (\$6873.51),
6		Medicaid population.		<u>Assessment:</u>	costs	OC:\$2172.40 (\$2819.75),
7				pharmacy claims	Other	EDC:\$405.96 (\$526.93),
8				data	pharmacy	PC:\$822.40 (\$1067.46),
9					costs	OtPC:\$4334.60 (\$5626.26)
10						
11	HIV/AIDS					
12	<i>Barnett et al</i> [63]	To characterise the	<u>Design:</u> retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> unadjusted
13	2011	cost of HIV care	observational cohort	antiretroviral		<u>Classification:</u> disease state specific;
14	US	including combination	study	taking behaviour		viral load count
15		antiretroviral	<u>Follow Up:</u> 1 year	<u>Classification:</u>		<u>Currency Year:</u> USD, 2006
16		treatment.	<u>Sample Size:</u> 1896	(85% adherence		<u>Cost of Nonadherence</u> ** :
17			(not specified)	with 3		High viral load:
18				antiretroviral		TC:\$25824 (\$30067.54)
19				therapy regimen =		Low viral load:
20				adherent, all other		TC:\$20509.67 (\$23879.92)
21				use =		
22				nonadherent)		
23				<u>Method of</u>		
24				<u>Assessment:</u>		
25				pharmacy claims		
26				data		
27						
28						
29						
30	<i>Cooke et al</i> [64]	To measure adherence	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted
31	2014	to antiretroviral	claims analysis	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
32	US	therapy regimens in	<u>Follow Up:</u> 1 year	(≥90% = adherent,	costs	<u>Currency Year:</u> USD, 2011
33		commercially insured	<u>Sample Size:</u> 3528	<90% =	Inpatient costs	<u>Cost of Nonadherence:</u>
34		patients with HIV	(A:1737, NA:640)	nonadherent)	Outpatient	THC:\$18868 (\$20184.58),
35		infection and analyse		<u>Method of</u>	costs	IC:\$2700 (\$2888.40),
36		the clinical and		<u>Assessment:</u>	Pharmacy	OC:\$915 (\$978.85),
37		demographic factors		pharmacy claims	costs	PC:\$15253 (\$16317.33)
38		associated with ≥90%		data		
39		adherence.				
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3	<i>Pruitt et al</i> [65]	To examine Medicaid	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
4	2015	insured HIV positive	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
5	US	and AIDS diagnosed	<u>Follow Up:</u> 2 years	(≥90% = adherent,	Outpatient	<u>Currency Year:</u> USD, 2009
6		patient groups	<u>Sample Size:</u> 502 (A:56,	<90% =	costs	<u>Cost of Nonadherence*:</u>
7		separately to	NA:176)	nonadherent)	Pharmacy	HIV:
8		determine association		<u>Method of</u>	costs	TC:\$15360 (\$16957.32),
9		of ART adherence to		<u>Assessment:</u>	Other	IC:\$3864 (\$4265.76),
10		mean monthly total		pharmacy claims	pharmacy	OC:\$3948 (\$4358.52),
11		healthcare		data	costs	PC:\$4956 (\$5471.40),
12		expenditures in the 24			Behavioural	OtPC:\$1764 (\$1947.48),
13		month measurement			health	BHIC:\$840 (\$927.36)
14		period.			inpatient costs	AIDS:
15						TC:\$27648 (\$30523.08),
16						IC:\$13008 (\$14360.76),
17						OC:\$5880 (\$6491.52),
18						PC:\$5640 (\$6226.56),
19						OtPC:\$2580 (\$2848.32),
20						BHIC:\$528 (\$582.96)
21						
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23						
24	Parkinson's					
25	Disease					
26	<i>Davis et al</i> [66]	To assess the extent to	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
27	2010	which patients	administrative claims	<u>Classification:</u>	Pharmacy	<u>Classification:</u> disease state specific
28	US	diagnosed with	study	(≥80% = adherent,	costs	<u>Currency Year:</u> USD, 2001
29		Parkinson's disease are	<u>Follow Up:</u> 12 months	<80% =	Medical costs	<u>Cost of Nonadherence:</u>
30		non-adherent with	<u>Sample Size:</u> 3119	nonadherent)		TC:\$18511 (\$24262.36),
31		antiparkinson therapy	(A:1211, NA:1908)	<u>Method of</u>		PC:\$2684 (\$3537.36),
32		and the potential		<u>Assessment:</u>		MC:\$15827 (\$20859.12)
33		association between		pharmacy claims		
34		non-adherence and all		data		
35		cause medical costs.				
36						
37						
38	<i>Delea et al</i> [67]	To assess the	<u>Design:</u> retrospective	<u>Measure:</u> PDC	Total costs	<u>Type of Costs:</u> adjusted and unadjusted
39	2011	associations between	historical cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease
40	US	adherence to	<u>Follow Up:</u> 12 months	(≥80% =	Pharmacy	state specific
41						<u>Quality:</u> high
42						<u>Classification:</u> cost
43						description
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levodopa/carbidopa/e
ntacapone therapy and
healthcare utilisation
and costs.

Sample Size: 1215
(A:617, NA:598)

satisfactory, <80%
= unsatisfactory)
Method of
Assessment:
pharmacy claims
data

costs
Other costs

Currency Year: USD, 2005

Cost of Nonadherence:

Adjusted all cause:

TC:\$19686 (\$23625.30),

IC:\$5954 (\$7145.43),

PC:\$6391 (\$7669.88),

OtC:\$8795 (\$10554.94)

Adjusted disease state specific:

TC:\$8574 (\$10289.71),

IC:\$3705 (\$4446.39),

PC:\$3850 (\$4620.41),

OtC:\$1884 (\$2261)

Unadjusted all cause:

TC:\$19362 (\$23236.46),

IC:\$5463 (\$6556.18),

PC:\$6158 (\$7390.26),

OtC:\$7740 (\$9288.82)

Unadjusted disease state specific:

TC:\$9156 (\$10988.18),

IC:\$3238 (\$3885.94),

PC:\$3789 (\$4547.20),

OtC:\$2129 (\$2555.03)

Wei et al[68]
2014
US

To examine the
associations of
adherence to
antiparkinson drugs
with healthcare
utilisation and
economic outcomes.

Design: retrospective
cross-sectional study
Follow Up: 19 months
Sample Size: 7583 (90-
100%:3948, 80-
89%:1456, ≤79%:2179)

Measure: MPR
Classification:
(>90<100% = high,
>80<89% =
moderate, ≤79% =
low)
Method of
Assessment:
pharmacy claims
data

Total costs
Inpatient costs
Outpatient
costs
Pharmacy
costs

Type of Costs: unadjusted

Classification: disease state specific

Currency Year: USD, 2007

Cost of Nonadherence:

TC(90-100):\$36407 (\$41293.43),

TC(80-89):\$43417 (\$49244.29),

TC(≤79):\$45867 (\$52023.13),

IC(90-100):\$15294 (\$17346.71),

IC(80-89):\$21603 (\$24502.49),

IC(≤79):\$24727 (\$28045.78),

OC(90-100):\$10155 (\$11517.97),

Quality: medium

Classification: cost
description

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4					OC(80-89):\$11838 (\$13426.86),	
5					OC(≤79):\$12889 (\$14618.92),	
6					PC(90-100):\$10957 (\$12427.61),	
7					PC(80-89):\$9976 (\$11314.95),	
8					PC(≤79):\$8251 (\$9358.42)	
9	Musculoskeletal					
10	<i>Ivanova et al</i> [69]	To compare the rates	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
11	2012	of severe relapse and	cohort study	<u>Classification:</u>	Total	<u>Classification:</u> all cause, disease state
12	US	total direct and	<u>Follow Up:</u> 2 years	(≥80% = adherent,	healthcare	specific and indirect
13		indirect costs over a 2	<u>Sample Size:</u> 648	<80% =	costs	<u>Currency Year:</u> USD, 2007
14		year period between	(A:448, NA:200)	nonadherent)	Inpatient costs	<u>Cost of Nonadherence</u> *:
15		US based employees		<u>Method of</u>	Outpatient	All cause:
16		with MS who were		<u>Assessment:</u>	costs	TC:\$8079 (\$9276.76),
17		adherent and non-		pharmacy claims	ED costs	THC:\$6022 (\$6830.25),
18		adherent to disease		data	Pharmacy	IC:\$1030.50 (\$1168.81),
19		modifying drugs.			costs	OC:\$3231 (\$3664.65),
20					Medical costs	EDC:\$143.50 (\$162.76),
21					Short term	PC:\$1617 (\$1834.03),
22					disability costs	MC:\$4405.50 (\$4996.79)
23					Absenteeism	Disease state specific:
24					cost	TC:\$3005 (\$3408.32),
25						IC:\$505 (\$572.78),
26						OC:\$1710 (\$1939.51),
27						EDC:\$37 (\$41.97),
28						PC:\$753 (\$854.07),
29						MC:\$2252 (\$2554.26)
30						Indirect:
31						STDC:\$1231 (\$1396.22),
32						AbC:\$826 (\$936.86)
33						
34						
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36						
37	<i>Tan et al</i> [70]	To assess the impact of	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Medical costs	<u>Type of Costs:</u> adjusted and unadjusted
38	2011	treatment adherence	cohort study	<u>Classification:</u>		<u>Classification:</u> disease state specific
39	US	on MS related	<u>Follow Up:</u> 12 months	(≥80% = adherent,		<u>Currency Year:</u> USD, 2007
40		hospitalizations	<u>Sample Size:</u> 2446	<80% =		<u>Cost of Nonadherence:</u>
41						description
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3		(inpatient), ER visits,	(A:1459, NA:987)	nonadherent)	Adjusted:	
4		MS relapses and		<u>Method of</u>	MC:\$4348 (\$5062.49)	
5		medical costs.		<u>Assessment:</u>	Unadjusted:	
6				pharmacy claims	MC:\$5179 (\$6030.04)	
7				data		
8						
9	Zhao et al[71]	To examine predictors	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
10	2011	associated with	cohort analysis	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
11	US	duloxetine adherence	<u>Follow Up:</u> 12 months	(≥80% = adherent,	Outpatient	<u>Currency Year:</u> USD, 2008
12		and its association with	<u>Sample Size:</u> 5435	<80% =	costs	<u>Cost of Nonadherence:</u> commercial:
13		healthcare costs	(A:1744, NA:3691)	nonadherent)	Pharmacy	TC:\$20323 (\$22609.12),
14		among fibromyalgia		<u>Method of</u>	costs	IC:\$4808 (\$5348.85),
15		patients.		<u>Assessment:</u>		OC:\$9822 (\$10926.87),
16				pharmacy claims		PC:\$5693 (\$6333.40)
17				data		<u>Medicare:</u>
18						TC:\$25282 (\$28125.96),
19						IC:\$8604 (\$9571.86),
20						OC:\$10068 (\$11200.54),
21						PC:\$6611 (\$7354.67)
22						
23						
24	Cancer					
25	Darkow et al[72]	Estimate the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted
26	2007	association between	observational cohort	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
27	US	treatment	analysis	(≥95% = very high,	costs	<u>Currency Year:</u> USD, 2004
28		interruptions and non-	<u>Follow Up:</u> 12 months	>90<95% = high,	Inpatient costs	<u>Cost of Nonadherence:</u>
29		adherence with	<u>Sample Size:</u> 267	>50<90% =	Outpatient	THC(≥95):\$42250 (\$52330.90),
30		imatinib and	(≥95%:120, 90-95%:25,	intermediate,	costs	THC(90-95):\$39236 (\$48597.76),
31		healthcare costs for US	50-90%:69, <50%:53)	<50% = low)	ED costs	THC(50-90):\$54770 (\$67838.19),
32		managed care patients.		<u>Method of</u>	Pharmacy	THC(<50):\$131357 (\$162698.93),
33				<u>Assessment:</u>	costs	IC(≥95):\$1156 (\$1431.82),
34				pharmacy claims	Medical costs	IC(90-95):\$1362 (\$1686.97),
35				data	Other	IC(50-90):\$19096 (\$23652.33),
36					pharmacy	IC(<50):\$81572 (\$101035.18),
37					costs	OC(≥95):\$9299 (\$11517.75),
38					Other costs	OC(90-95):\$11148 (\$13807.93),
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OC(50-90):\$14631 (\$18121.97),
 OC(<50):\$33956 (\$42057.94),
 EDC(≥95):\$36 (\$44.59),
 EDC(90-95):\$568 (\$703.53),
 EDC(50-90):\$104 (\$128.81),
 EDC(<50):\$183 (\$226.66),
 PC(≥95):\$29056 (\$35988.80),
 PC(90-95):\$23693 (\$29346.18),
 PC(50-90):\$18330 (\$22703.56),
 PC(<50):\$8733 (\$10816.70),
 MC(≥95):\$10731 (\$13291.43),
 MC(90-95):\$13452 (\$16661.66),
 MC(50-90):\$34202 (\$42362.64),
 MC(<50):\$116892
 (\$144782.57),OtPC(≥95):\$2462
 (\$3049.44),
 OtPC(90-95):\$2091 (\$2589.92),
 OtPC(50-90):\$2238 (\$2771.99),
 OtPC(<50):\$5732 (\$7099.66),
 OtC(≥95):\$241 (\$298.50),
 OtC(90-95):\$374 (\$463.24),
 OtC(50-90):\$371 (\$459.52),
 OtC(<50):\$1181 (\$1462.79)

30 *Wu et al*[73]
 31 2010
 32 US

To examine the
 association between
 adherence with
 imatinib and direct
 healthcare costs and
 resource utilisation

Design: retrospective
 observational cohort
 analysis
Follow Up: 12 months
Sample Size: 592
 (A:350, NA:242)

Measure: MPR
Classification:
 (≥85% = high
 adherence, <85%
 = low adherence)
Method of
 Assessment:
 pharmacy claims
 data

Total costs
 Inpatient costs
 Outpatient
 costs
 ED costs
 Pharmacy
 costs
 Other
 pharmacy
 costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence:
 TC:\$107341 (\$119415.73),
 IC:\$44498 (\$49503.55),
 OC:\$34097 (\$37932.55),
 EDC:\$248 (\$275.90),
 PC:\$22846 (\$25415.93),
 OtPC:\$5652 (\$6287.79)

Quality: medium
Classification: cost
 description

Addiction

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	<i>Leider et al</i> [74] 2011 US	To assess the economic burden of chronic opioid users and to determine whether opioid regimen non-adherence contributes to increased healthcare costs.	<u>Design:</u> retrospective claims based analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 2100 (A:442, NA:1658)	<u>Measure:</u> urine testing <u>Classification:</u> (positive test = nonadherent, negative test = adherent) <u>Method of Assessment:</u> health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2008 <u>Cost of Nonadherence:</u> THC:\$26433 (\$29406.43), IC:\$6361 (\$7076.55), OC:\$9734 (\$10828.97), EDC:\$421 (\$468.36), PC:\$7960 (\$8855.42), MC:\$1957 (\$2177.14)	<u>Quality:</u> medium <u>Classification:</u> cost analysis
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	<i>Ruetsch et al</i> [75] 2017 US	To examine patient characteristics and outcomes associated with nonadherence to buprenorphine and to identify specific patterns of nonadherent behaviour.	<u>Design:</u> cross sectional, retrospective analysis health claims data <u>Follow Up:</u> 12 months <u>Sample Size:</u> 477 (A:172, NA:305)	<u>Measure:</u> MPR <u>Classification:</u> ($\geq 80\%$ = adherent, $< 80\%$ = nonadherent) <u>Method of Assessment:</u> health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Physician office visit costs Medical costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2013 <u>Cost of Nonadherence:</u> THC:\$16555 (\$16995.62), IC:\$5657 (\$5807.57), OC:\$5594 (\$5742.89), EDC:\$1147 (\$1177.53), PC:\$2365 (\$2427.95), POC:\$1765 (\$1811.98), MC:\$14190 (\$14567.68)	<u>Quality:</u> medium <u>Classification:</u> cost description
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	<i>Tkacz et al</i> [76] 2014 US	To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 455 (A:146, NA:309)	<u>Measure:</u> MPR <u>Classification:</u> ($\geq 80\%$ = adherent, $< 80\%$ = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2010 <u>Cost of Nonadherence:</u> Adjusted: THC:\$49051 (\$53503.88), IC:\$26470 (\$28872.96), OC:\$14570 (\$15892.67), EDC:\$4439 (\$4841.98),	<u>Quality:</u> medium <u>Classification:</u> cost description

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3 members.

4 PC:\$3581 (\$3906.09)
5 Unadjusted:
6 THC:\$47868 (\$52213.49),
7 IC:\$26043 (\$28407.20),
8 OC:\$14173 (\$15459.63),
9 EDC:\$4058 (\$4426.39),
10 PC:\$3557 (\$3879.91)

11 **Metabolic**
12 **conditions other**
13 **than diabetes**
14 **mellitus**

15 *Lee et al*[77]
16 2011
17 US

18 To assess the
19 relationship between
20 medication adherence
21 and healthcare costs
22 among US patients on
23 dialysis given
24 cinacalcet to manage
25 secondary
26 hypoparathyroidism.

27 Design: retrospective
28 cohort study
29 Follow Up: 12 months
30 Sample Size: 4923
31 (A:1372, NA:1304)

32 Measure: MPR
33 Classification:
34 ($\geq 80\%$ = high
35 adherent, $< 80\%$ =
36 low adherent)
37 Method of
38 Assessment:
39 pharmacy claims
40 data

41 Total costs
42 Inpatient costs
43 Outpatient
44 costs
45 ED costs
46 Pharmacy
47 costs
48 Other
49 pharmacy
50 costs

51 Type of Costs: unadjusted
52 Classification: all cause and disease
53 state specific
54 Currency Year: USD, 2010
55 Cost of Nonadherence:
56 All cause:
57 PC:\$5556 (\$6060.38)
58 Disease state specific:
59 TC:\$126996 (\$138524.78),
60 IC:\$14844 (\$16191.55),
61 OC:\$101854 (\$111100.37),
62 EDC:\$734 (\$800.63),
63 PC:\$3244 (\$3538.49),
64 OtPC:\$9564 (\$10432.23)

65 Quality: medium
66 Classification: cost
67 description

68 **Blood**

69 *Candrilli et al*[78]
70 2011
71 US

72 To investigate the
73 relationships among
74 hydroxyurea
75 adherence, healthcare
76 utilisation and
77 healthcare costs.

78 Design: retrospective
79 longitudinal study
80 Follow Up: 12 months
81 Sample Size: 312
82 (A:110, NA:202)

83 Measure: MPR
84 Classification:
85 ($\geq 80\%$ = adherent,
86 $< 80\%$ =
87 nonadherent)
88 Method of
89 Assessment:

90 Total costs
91 Inpatient costs
92 ED costs
93 Pharmacy
94 costs
95 Physician
96 office visit

97 Type of Costs: adjusted
98 Classification: all cause and disease
99 state specific
100 Currency Year: USD, 2008
101 Cost of Nonadherence:
102 All cause:
103 TC:\$ 20436 (\$22734.83),

104 Quality: medium
105 Classification: cost
106 description

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pharmacy claims data	costs Ancillary costs	IC:\$9780 (\$10880.15), EDC:\$837 (\$931.15), PC:\$2579 (\$2869.11), POC:\$3483 (\$3874.80), AC:\$3911 (\$4350.95) Disease state specific: TC:\$12097 (\$13457.78), IC:\$7315 (\$8137.86), EDC:\$552 (\$614.09), PC:\$158 (\$175.77), POC:\$1865 (\$2074.79), AC:\$2466 (\$2743.40)
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<p>All <i>Alvarez Payero et al</i> [79] 2014 Spain</p>	<p>To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.</p>	<p><u>Design:</u> retrospective observational study <u>Follow Up:</u> 1527 days <u>Sample Size:</u> 87 (A:21, NA:66)</p>	<p><u>Measure:</u> pharmacy records <u>Classification:</u> (>75% = adherent, ≤75% = nonadherent) <u>Method of Assessment:</u> pharmacy and hospital claims data</p>	<p>Hospitalization costs</p>	<p><u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause <u>Currency Year:</u> EUR, 2012 <u>Cost of Nonadherence</u>^{####}: All cause: HC:€6275.80 (\$8893.94)</p>	<p><u>Quality:</u> low <u>Classification:</u> cost outcome description</p>
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A: adherent, NA: nonadherent, MA: moderate adherence, LA: low adherence, NC: noncompliance, NP: nonpersistent, P: persistent, T: turbulent, NE: no exposure, CHF: chronic heart failure, THC: total healthcare costs, TC: total costs, IC: inpatient costs, OC: outpatient costs, EDC: emergency department visit costs, PC: pharmacy costs, MC: medical costs, HC: hospitalization costs, POC: physician office visit costs, NPC: non-pharmacy costs, AC: ancillary costs, OtPC: other pharmacy costs, PAC: psychiatric assessment costs, TCMC: targeted case management costs, ArC: arrest costs, InC: incarceration costs, RC: radiology costs, SC: services costs, InstC: institutional costs, ESC: external services costs, MSC: medical services costs, PCC: primary care costs, MTC: medical test costs, FC: fracture costs, LC: laboratory costs, IntC: interdisciplinary costs, BHIC: behavioural health inpatient costs, STDC: short term disability costs, WCC: workers compensation costs, PTOC: paid time off costs, TPC: total productivity costs, AbC: absenteeism costs, PrC: presenteeism costs, ACC: acute care

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3 costs, OtC: other costs, com: commercial patients, med: Medicare supplemental patients, USD: United States dollar, GBP: Great British Pound, EUR: Euro,
4 DKK: Danish krone, CAD: Canadian dollar, KRW: South Korean won
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7 *: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group;
8 #: extrapolated annual cost and subgroups averaged; ##: cost represents losses in workplace productivity; ###: negative value as costs modelled against
9 adherent group; ####: cost per episode of nonadherence
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eTable 3: Total cost or total healthcare cost comparison across disease groups

Disease State	Min adj cost per annum per person	Max adj cost per annum per person	Median adj cost per annum per person	Mean adj cost per annum per person	No. adj studies	Min unadj cost per annum per person	Max unadj cost per annum per person	Median unadj cost per annum per person	Mean unadj cost per annum per person	No. unadj studies	Total studies ¹
Cardiovascular Disease	3347	19472	8080	9204	6	1433	8377.05	5951	4701	7	12
Mental Health	3253	19363	11262	11052	6	2512	25920	17211	16486	7	14
Diabetes Mellitus	2741	9819	6907	6310	7	1142	7950	5534	4934	8	11
Osteoporosis	949	44190	41402	32866	4	669	43404	9921	18190	10	11
Respiratory Disease	5701	7124	6689	6505	1	804	36259	11546	16124	5	6
Gastrointestinal Disease	12085	37151	20715	23317	3					2	5
Epilepsy					0	1866	22673	18714	14418	3	3
HIV/AIDS					0	16957	30523	23880	24322	3	3
Parkinson's Disease				10290*	1	10988	52023	36753	34129	3	3
Musculoskeletal conditions				25368*	2				3408.32*	2	3
Cancer					0	48598	162699	93627	99638	2	2
Addiction				53504*	1	16996	52213	29406	32872	3	3
Metabolic conditions other than diabetes mellitus					0				138525*	1	1
Blood conditions				13458*	1					0	1
All causes	5271	52341	17132	21257	14	1037	53793	16308	19352	10	30**

Costs reported in \$US2015 dollars

¹Some studies included both adjusted and unadjusted costs

*Single total cost/total healthcare cost reported

** In addition to disease-specific studies of the economic impact of medication nonadherence, studies reported the all-causes costs, encompassing cost drivers such as comorbidities. Alvarez Payero et al reported all cause costs only.

Do not report total cost/total healthcare cost

Single total cost/total healthcare cost reported



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Economic impact of medication nonadherence by disease groups: a systematic review

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Title Page

Title: Economic impact of medication nonadherence by disease groups: a systematic review

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Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A comprehensive literature search was conducted in PubMed and Scopus in September 2017. Studies quantifying the cost of medication nonadherence in relation to economic impact were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Seventy nine individual studies assessing the cost of medication nonadherence across fourteen disease groups were included. Wide scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease specific economic cost of nonadherence per person ranged from \$949-\$44,190 (in 2015 US dollars). Costs attributed to "all causes" nonadherence ranged from \$5,271 to \$52,341. Medication possession ratio was the metric most utilized to calculate patient adherence, with varying cut-off points defining nonadherence. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (83% of studies), pharmacy costs (70%), inpatient costs (46%), outpatient costs (50%), emergency department visit costs (27%), medical costs (29%) and hospitalization costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. Current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system. Differences in methods make the comparison amongst studies challenging and an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338

Strengths and Limitations of this study:

- This is a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of medication nonadherence via quantifying the cost of medication nonadherence across different disease groups.
- A large comprehensive review – 2,768 citations identified, 79 studies included.
- Inability to perform a meaningful meta-analysis- insufficient statistical data and considerable heterogeneity according to outcome/indicators.
- Robust application of adapted Drummond checklist to evaluate the quality of economic evaluations.

1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources[2]. Medications represent a cost-effective treatment modality[3], but with estimates of 50% nonadherence to long term therapy for chronic illnesses[4], intentional and unintentional medication nonadherence signifies a prevalent and persistent healthcare problem. Medication adherence is defined as 'the extent to which the patients' behavior matches agreed recommendations from the prescriber', emphasizing the importance on the patients' decisions and highlighting the modifiable aspect of nonadherence[5].

Given the proportion of the population who do not adhere to their medication efforts to improve medication adherence represent an opportunity to enhance health outcomes and health system efficiency. Annual costings of medication nonadherence range from US\$100-\$290 billion[6] in the United States, €1.25 billion[7] in Europe and approximately A\$7 billion[8 9] in Australia. Additionally ten percent of hospitalizations in older adults are attributed to medication nonadherence [10 11] with the typical nonadherent patient requiring three extra medical visits per year leading to \$2000 increased treatment costs per annum[12]. In diabetes the estimated costs savings associated with improving medication nonadherence range from \$661 million to \$1.16 billion [13]. Nonadherence is thus a critical clinical and economic problem[4].

Healthcare reformers and payers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[14]. However there is still a budgetary problem that needs to be considered, especially given the widespread policy debate over how to best bend the healthcare cost curve downward[15] and the proportion of healthcare budgets spent on prescription medication[16]. Quantifying the cost of medication nonadherence will help demonstrate the causal effect between medication nonadherence, increased disease prevalence and healthcare resource use. Justification of the associated financial benefit may incentivize health policy discussion about the value of medication adherence and promote the adoption of medication adherence intervention programs [15].

The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.

2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[17].

2.1 Search strategy and selection criteria

A literature search was conducted in September 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB])) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases (eTable 1). Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence as a monetary value, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[18] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-

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3 group analysis and statistical significance), conclusions and miscellaneous (funding source,
4 references to other relevant studies, limitations and reviewers comments).
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7 Costs were defined as any indicator associated with medication nonadherence that was quantified
8 with a monetary value in the original study. This included direct costs (those costs borne by the
9 healthcare system, community and patients' families in addressing the illness), indirect costs (mainly
10 productivity losses to society caused by the health problem or disease) and avoidable costs (those
11 costs incurred for patients suffering complications, resulting from suboptimal medicines use, and
12 patients with the same disease who experienced no complications). The indicators were grouped for
13 analysis based on the original studies classification of the cost. All costs were converted to US
14 dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and
15 Practice Information and Coordinating -Centre Cost Converter tool [19], allowing meaningful
16 comparisons between nonadherence cost data. This online tool uses a two stage computation
17 process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product
18 deflator index and Purchasing Power Parities for Gross Domestic Product[19]. The PPP values given
19 by the International Monetary Fund were chosen. If details of the original price year could not be
20 ascertained from a study the mid-point year of the study period was used for calculations. The mean
21 cost was calculated and reported where studies separated out costs for different confounding
22 factors within the one outcome measure in a disease state. Annual costs were extrapolated from the
23 original study data if results were not presented in this manner.
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35 The definition of medication nonadherence was derived from the included studies; with
36 nonadherence referring to differing degrees of adherence based on the studies metric of estimation.
37 Multiple nonadherence costs from individual studies may have been included where further sub-
38 classification of nonadherence levels was defined. The analysis assessed nonadherence costs within
39 disease groups, with disease group and cost classification derived from the study. Total healthcare
40 costs included direct costs to the healthcare system while total costs incorporated direct and indirect
41 costs.
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50 **2.3 Quality criteria and economic evaluation classification**

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52 Economic evaluation requires a comparison of two or more alternative courses of action, while
53 considering both the inputs and outputs associated with each [20]. All studies were classified in
54 accordance with Drummond's distinguishing characteristics of healthcare evaluations as either
55 partial evaluations (outcome description, cost description, cost-outcome description, efficacy or
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3 effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility
4 analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).
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7 The Drummond checklist [21] for economic evaluation was used to assess the quality of studies. The
8 original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full
9 economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the
10 required item and zero if it did not with a maximum potential score of 28. The study was classified as
11 high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were
12 satisfied and low quality if 50% of the criteria or less were satisfied.
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20 **2.4 Meta-Analysis**

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22 Outcome/indicator costs were independently extracted utilizing predesigned data extraction forms
23 (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs,
24 emergency department costs, and hospitalisation costs) for the purpose of integrating the findings
25 on the cost of medication nonadherence to pool data and increase the power of analysis.
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3 Results

3.1 Study Selection

Search strategies retrieved 2768 potential articles after duplicates were removed. Two hundred and eighty nine articles were selected for full text review. Seventy nine studies were included in the review (Figure 1). Numerous other papers do discuss nonadherence costs however addressed tangential issues or did not present primary relevant data. Many studies failed to report the monetary value of medication nonadherence associated with a range of cost estimate indicators.

3.2 Characteristics of individual studies

Sixty-six studies (83%) were conducted in the United States[10 22-86], four in Europe[87-90], four in Asia[91-94], three in Canada[95-97], one in the United Kingdom[98] and one across multiple countries throughout Europe and the United Kingdom[99]. Publication years ranged from 1997 to 2017; in accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used[18] with earlier studies following the same pattern of association between medication nonadherence and increasing healthcare costs. Individual studies reported a large variety of costs, calculated by varying means. Forty-four studies (56%) reported unadjusted costs[22 26 27 30 32-36 38-43 46 48-50 52-56 58 63-68 72 75 81-83 86 88-90 92-94 99], 21 (26%) adjusted costs[10 23-25 29 31 44 51 57 59-61 71 73 76-78 84 85 87 91], 11 a combination of adjusted and unadjusted[28 37 45 47 62 69 70 74 79 80 97], two unadjusted and predicted[95 96] and one predicted costs[98]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy and/or healthcare claims data (97%)[10 22-29 31-52 55 57 59-88 92-97]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data and disease state specific recommended guidelines. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 51 studies (63%) reporting nonadherence based on this measure[24 25 28 29 32-36 40-44 46 47 49-51 55 57 58 60-64 67-78 81 82 86-88 92-97]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g., 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (11%)[31 37 45 48 52 79 80 83-85], with all other studies utilizing an array of measures including self-report[98], urine testing[56], observational assessment[99], time to discontinuation[59], cumulative possession

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3 ratio[23], disease specific medication management guidelines[66 89], Morisky 4-Item scale[53],
4 medication gaps[38], prescription refill rates[22 27] and medication supplies[10]. The main
5 characteristics of the included studies are summarized in eTable 2.
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10 **3.3 Quality assessment and classification of economic evaluations**

11 The quality assessment of economic evaluations yielded 10 studies of high[33 37 40 50 51 57 71 75
12 87 93], 59 of medium[10 22-26 28-32 34-36 38 39 41-48 53-56 58 59 61-64 66 67 69 70 72 73 76-82
13 84-86 88 89 91 94-99] and ten of low quality[27 49 60 65 68 74 83 90 92]. Scores ranged from 26.1%
14 to 87.5% (mean 62.63%). Only one study identified the form of economic evaluation used and
15 justified it in relation to the questions that were being addressed [71]. The item 'the choice of
16 discount rate is stated and justified' was applicable only to studies covering a time period of more
17 than one year; all studies that cover more than one year failed to identify or explain why costs had
18 not been discounted. Details of the analysis and interpretation of results were lacking in the majority
19 of studies resulting in medium or low quality scores.
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28 Through utilization of Drummond's distinguishing characteristics of healthcare evaluations
29 criteria[20] it is apparent that no full economic evaluation was conducted in any of the included
30 studies. All studies performed partial economic evaluations of varying extents. The classification of
31 economic evaluations resulted in 59 cost description studies (74% of those included), 15 cost
32 outcome descriptions and five cost analysis studies (eTable 2).
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40 **3.4 Medication nonadherence and costs**

41 The cost analysis of studies (figure 2 and figure 3) reported annual medication nonadherence costs
42 incurred by the patient per year. The adjusted total cost of nonadherence across all disease groups
43 ranged from \$949 to \$52,341, while the unadjusted total cost ranged from \$669 to \$162,699. Figure
44 2 and figure 3 highlight the minimum, maximum and interquartile range of annual costs incurred by
45 patients across disease groups where three or more studies were included for review. All cause costs
46 encompass nonadherence costs incurred in mixed disease state studies, taking into account other
47 confounding factors such as comorbidities.
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54 Many different indicators were used to estimate medication nonadherence costs with no clear
55 definition of what was incorporated in each cost component. The composition of included costs to
56 estimate total cost or total healthcare cost varied significantly between studies thus indicators were
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3 grouped for analysis based on the original studies classification of the cost. The main ones were total
4 cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs
5 (46%), medical costs (29%), emergency department costs (27%), and hospitalization costs (18%)
6 (eTable 2). Avoidable costs (e.g., unnecessary hospitalizations, physician office visits and healthcare
7 resource utilization) were not well defined with majority of studies failing to quantify these costs.
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11 Lower levels of adherence across all measures (e.g., MPR, PDC) were generally associated with
12 higher total costs. From those that reported total or total healthcare costs, 39 studies (49%)
13 reported nonadherence costs to be greater than adherence costs[24 25 27 29 31 32 34 37-39 42 43
14 47 49 50 55 56 58 61-65 70-78 84 86 87 96-99] and 11 studies (15%) reported nonadherence costs to
15 be less than adherence costs[23 26 36 44 59 63 66 81 92 94 95]. Four reported fluctuating findings
16 based on varying nonadherence cost subcategories[33 48 67 93] and two studies reported
17 conflicting findings between adjusted and unadjusted costs [79 80]. Higher all cause total
18 nonadherence costs and lower disease group specific nonadherence costs were reported in four
19 studies[41 68 85 91], whereas Hansen et al[47] reported all cause total nonadherence costs to be
20 lower (\$18540 vs. \$52302) but disease group specific nonadherence total costs to be higher (\$3,879
21 vs. \$2,954).
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25 The association between nonadherence and cost was determined through use of a variety of scaling
26 systems. The most utilized methods were MPR and PDC. These measures could then further be sub-
27 categorized based on the percentage of adherence/nonadherence. The 80-100% category was
28 classified as the most adherent group across both scales, with the most common definition of
29 nonadherence being <80% MPR or PDC.
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32 33 34 35 36 37 38 39 40 41 42 **3.5 Cost of medication nonadherence via disease group**

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44 Cancer exhibited more than double the cost variation of all other disease groups (\$114,101).
45 Osteoporosis (\$43,240 vs. \$42,734), diabetes mellitus (\$7,077 vs. \$6,808) and mental health
46 (\$16,110 vs. \$23,408) cost variations were similar between adjusted and unadjusted costs while
47 cardiovascular disease adjusted costs were more than double unadjusted costs (\$16,124 vs. \$6,943).
48 Inpatient costs represented the greatest proportion of costs contributing to total costs and/or total
49 healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy
50 and parkinson's disease. HIV/AIDS, cancer and gastrointestinal disease groups highest proportion of
51 costs were attributed to pharmacy costs while outpatient costs were greatest in musculoskeletal
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3 conditions. Direct costs had greater economic bearing than indirect costs across all disease groups.
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5 Cost comparisons across disease groups are summarized in eTable 3.
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7 **3.5.1 Cardiovascular Disease**

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9 Twelve studies measured the economic impact of medication nonadherence in cardiovascular
10 disease [10 24 31 61 62 65 67 76 81 93 95 96]. Six studies reported adjusted costs [10 24 31 61 62
11 76] with annual costs being extrapolated for two of these[31 61]. Total healthcare costs and/or total
12 costs were assessed in all of the studies with the major indicators measured including pharmacy
13 costs[10 31 61 62 76], medical costs[10 24 31 61 76] and outpatient costs[31 62]. The annual
14 economic cost of nonadherence ranged from \$3,347 to \$19,472. Sokol et al[10] evaluated the
15 economic impact of medication nonadherence across three cardiovascular conditions; hypertension,
16 hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined,
17 pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups.
18 Total costs and medical costs were lower for the adherent groups of hypertension and
19 hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical
20 costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.
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24 Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total
25 costs of nonadherence ranging from \$1,433 to \$8,377 [65 67 81 93 95 96]. Rizzo et al[65] reported
26 cost findings through subgroup analysis of five conditions. For all conditions the total healthcare
27 costs were higher for nonadherent groups compared with adherent. While Zhao et al[81],
28 categorized participants into adherence subgroups; finding that total healthcare costs were lower
29 for the nonadherent population. The remaining studies used five key indicators to determine the
30 economic impact: inpatient costs[67 93], outpatient costs[67 93], pharmacy costs[67 95 96], medical
31 costs[95 96] and hospitalization costs[95 96].
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43 **3.5.2 Mental Health**

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45 The analyses used to report the economic impact of medication nonadherence in mental health
46 varied widely. Eleven of 14 studies provided a total nonadherence cost estimate in mental health[23
47 25 27 52 59 66 73 82 91 98 99], with annual cost data being extrapolated for four of these[27 66 82
48 99]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient
49 ranged from \$3,252 to \$19,363 [23 25 59 60 73 91]. Bagalman et al[25] focused primarily on the
50 indirect costs associated with nonadherence – short-term disability, workers compensation and paid
51 time off costs while Robertson et al[82] highlighted the association between medication
52 nonadherence and incarceration, with findings indicating incarceration and arrest costs are higher
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3 for worsening degrees of nonadherence. All other studies addressed direct costs. The main
4 indicators used to measure the direct economic impact of medication nonadherence were pharmacy
5 costs[23 39 52 59 60 66 73 99], inpatient costs[39 60 66 98 99], outpatient costs[23 39 59 66 99] and
6 hospitalization costs[22 23 59 99].
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10 The total unadjusted cost for medication nonadherence ranged from \$2,512 to \$25,920 as reported
11 in four studies [52 66 82 99]. Becker et al[27] used a subgroup analysis to classify patients based on
12 their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%,
13 <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual
14 costs that were \$3,018 more than those of the maximal adherence group (75-100%).
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18 Knapp et al[98] outlined the predicted cost of nonadherence with reference to relative impact and
19 other factors associated with resource use and costs in patients with schizophrenia. Total costs
20 (\$116,434) were substantially higher than the other two indicators, which were inpatient costs
21 (\$13,577) and external services costs (\$3,241).
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24 **3.5.3 Diabetes mellitus:**

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29 Eleven studies reported a cost measurement of the impact of medication nonadherence with
30 reference to the health system and the individual[40 45 47 51 74 76 83 84 92 94 97]. One study
31 estimated that the total US cost attributable to nonadherence in diabetes was slightly over \$5
32 billion[51]. Five studies reported the adjusted total healthcare costs and/or total costs with annual
33 costs per patient ranging from \$2,741 to \$9,819 [47 51 74 76 84 97]. One study reported total costs
34 in relation to subgroup analysis based on MPR level[74], and another reported total healthcare costs
35 through subgroup analysis of commercially insured and Medicare supplemental patients[76]. Curtis
36 et al[84] utilized a diabetic population to report all cause costs, with nonadherence costs being
37 higher than adherence costs across all outcome indicators bar pharmacy costs.
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44 A further four studies reported unadjusted cost findings[40 83 92 94] with an additional four studies
45 reporting unadjusted costs in combination with adjusted values[45 47 74 97]. Unadjusted total
46 healthcare costs and/or total costs ranged from \$1,142 to \$7,951. Extrapolated annual costs were
47 determined for two studies based on cost data presented [40 94].
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52 The most prominent indicators used to determine costs were pharmacy costs[40 45 47 74 76 83 84
53 97], outpatient costs[40 47 76 84 94 97], inpatient costs[47 76 97] and hospitalization costs[51 92
54 94]. All studies assessed the direct costs associated with medication nonadherence. One study
55 evaluated the relationship between nonadherence and short term disability costs in addition to
56 assessing direct costs[45].
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3.5.4 Osteoporosis:

The cost of medication nonadherence in relation to osteoporosis was predominately examined through analysis of the direct costs associated with nonadherence using total healthcare costs and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department costs. Two studies further assessed the economic impact of nonadherence through evaluation of fracture related costs [48 88]. Four out of 11 studies reported the adjusted cost of medication nonadherence in addition to reporting unadjusted costs [28 79 80 87]. Three studies further classified nonadherence through subgroup analysis, with Briesacher et al[28] using MPR 20% interval increases and the two studies conducted by Zhao et al[79 80] using PDC, with $\geq 80\%$ classified as high adherence, 50-79% medium adherence and $< 50\%$ low adherence. In the studies conducted by Zhao et al[79 80], total healthcare costs were highest for the medium adherence group (\$41,402 and \$44,190) followed by the highest adherence group (\$37,553 and \$43,863), and lowest for the low adherence group (\$34,019 and \$43,771). These annual costs were extrapolated from study data. In contrast, Briesacher et al[28] modelled the subgroup analyses against the lowest adherence group ($< 20\%$ MPR), finding that costs decreased as adherence increased.

Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from \$669 to \$43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In the three studies that reported the lowest level of nonadherence to be PDC $< 50\%$, the cost of this category ranged from \$16,938 to \$43,404 [48 79 80].

One study examined only the medical costs of nonadherence through MPR subgroup analysis in commercial and Medicare supplemental populations. The findings were that, for all levels of nonadherence, costs of nonadherence were higher for Medicare supplemental patients [46].

3.5.5 Respiratory Disease:

The majority of studies reported unadjusted cost of medication nonadherence, with significant variation in the method of adherence classification[36 38 53 64 89]. Two studies used MPR[36 64], one the Morisky 4-Item scale[53], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[89] and one a 37 day gap in claims data[38]. Joshi et al[53] reported on the indirect costs of medication nonadherence through consideration of losses in total productivity costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs. Delea et al[36] reported a direct relationship between decreases in medication nonadherence level and total costs, whereas Quittner et al[64] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the

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3 lowest subgroup of adherence across all measures ranged from \$804 to \$36,259. In contrast Davis et
4 al[85] utilized adjusted costs across four sub-classifications of PDC adherence ranges to demonstrate
5 that nonadherence costs were lower than adherence costs in all costing outcomes reported except
6 hospitalization costs .
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9 10 **3.5.6 Gastrointestinal Disease:**

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12 Three of five studies reported the adjusted annual cost of medication nonadherence per patient
13 utilizing the MPR method [44 57 71]. Of these, two reported the total cost (\$12,085 and \$37,151)[44
14 71] with the main contributors to the overall total cost being inpatient costs (22% and 37%),
15 outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).
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19 The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the
20 total cost nor total healthcare costs[30 54]. Carter et al[30] reported hospitalization costs to be
21 \$42,854 while Kane et al[54] reported a significantly lower cost at \$5,566 in addition to other direct
22 cost contributors.
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25 26 27 **3.5.7 Epilepsy:**

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29 Three studies reported the economic impact of medication nonadherence in epilepsy. All reported
30 unadjusted costs using an MPR cut off of <80%[35 42 43]. The main economic indicators used to
31 assess total costs were inpatient costs (\$2,289 to \$6,874), emergency department visit costs (\$331
32 to \$669) and pharmacy costs (\$442 to \$1,067). Davis et al[35] modelled the costs of the
33 nonadherent group against the adherent group. The annual costs reported by Faught et al[43] were
34 extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from \$1,866
35 to \$22,673.
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38 39 40 41 **3.5.8 HIV/AIDS:**

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43 The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all
44 three studies was similar [26 32 63]. Two of the three studies examined the costs only for HIV[26
45 32], while Pruitt et al[63] assessed the cost in AIDS as well as HIV. The total unadjusted costs for
46 nonadherent HIV patients ranged from \$16,957 to \$30,068 with one study further categorizing
47 patients with HIV as having either a high viral load or low viral load[26]. The total cost of
48 nonadherence in AIDS was \$30,523[63]. All studies used comparable indicators (total cost, inpatient
49 cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.
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3.5.9 Parkinson's Disease:

The direct costs associated with Parkinson's disease were assessed in all three studies. The unadjusted total cost ranged from \$10,988 to \$52,023 [34 37 72]. Wei et al[72] further sub-grouped patients into MPR adherence percentage categories, and found that costs increased in all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with nonadherence. One study additionally reported the adjusted cost, estimating that \$10,290 could be attributed to medication nonadherence annually[37].

3.5.10 Musculoskeletal Conditions:

Differing subgroup analyses was used to measure the impact of medication nonadherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of nonadherence[50], one assessed only the medical costs[69] and one examined the direct costs in commercial and Medicare supplemental patient populations[78]. Zhao et al[78] reported the adjusted annual cost in the commercial population to be \$22,609, and in the Medicare supplemental group, \$28,126. Ivanova et al[50] reported only unadjusted costs and the annual total cost of \$3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

3.5.11 Cancer:

Two studies evaluated the effects of medication nonadherence in cancer[33 75]. One study reported total annual costs of \$119,416[75], while the other gave a subgroup analysis based on classified adherence levels[33]. In general the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs (\$162,699 and \$67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

3.5.12 Addiction:

The adjusted annual total healthcare cost of medication nonadherence was reported as \$53,504[56] while the unadjusted cost ranged from \$16,996 to \$52,213 [56 70 86]. Leider et al[56] reported the main contributors to this cost to be outpatient costs (\$10,829) and pharmacy costs (\$8,855), whereas Tkacz et al[70] and Ruetsch et al[86] reported them to be inpatient costs (\$28,407 and \$5,808) and outpatient costs (\$15,460 and \$5,743).

3.5.13 Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication nonadherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of \$138,525[55]. The economic indicators used to derive this cost were inpatient costs (\$16,192), outpatient costs (\$111,100), emergency department visit costs (\$801) and pharmacy costs (\$3,538).

3.5.14 Blood conditions:

Candrilli et al[29] reported cost findings on the relationship between nonadherence and healthcare costs, giving an adjusted total cost estimate of \$13,458 for nonadherence classified as MPR <80%.

3.5.15 All causes:

In addition to disease-specific studies of the economic impact of medication nonadherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of these studies, annual costs were extrapolated from the original data[47 50 61 64 66 85 99]. Eleven studies reported on economic indicators without giving total cost or total healthcare cost[22 45 46 54 55 57 60 81 83 90 99], and one study reported on costs per episode of nonadherence[90] .

The adjusted cost of medication nonadherence was reported in 14 studies with an estimated range of \$5,271 to \$52,341 [10 29 31 57 59-61 71 76 77 84 85 87 91]. Sokol et al[10] reported the all-cause cost of nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[61] reported only using MPR level breakdown.

Fifteen studies reported the unadjusted economic impact of medication nonadherence with an estimated range of \$1,037 to \$53,793 [22 41 46 50 54 55 58 64-66 68 81 83 90 99]. A further four studies reported adjusted and unadjusted costs[37 45 47 97]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).

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3.6 Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication nonadherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of required statistical parameters in particular standard deviation[100]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.

For peer review only

4 Discussion

This systemic review broadens the scope of knowledge associated with the economic impact of medication nonadherence across different disease groups while building upon previous reviews where greater focus was on targeting overall risk factors or conceptual issues associated with medication nonadherence. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence with studies failing to quantify avoidable costs separately to direct and indirect costs possibly due to coding restraints in healthcare claims databases. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesize costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g., mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g., cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty. Given the complexity of medication nonadherence in terms of varying study designs, methods of estimation and adherence definitions there is a limitation as to the ability to truly estimate costs attributed to nonadherence until further streamlined processes are defined.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, with few studies defining exactly what that cost category incorporated, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to

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3 medication nonadherence thus enabling greater planning in terms of health policy to help
4 counteract increasing avoidable costs.
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7 The economic, clinical and humanistic consequences of medication nonadherence will continue to
8 grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to
9 adequately address the determinants of adherence through utilization of effective health
10 interventions. Haynes et al [101] highlights that “increasing the effectiveness of adherence
11 interventions may have a far greater impact on the health of the population than any improvement
12 in specific medical treatments”. Improving medication adherence provides an opportunity for major
13 cost savings to healthcare systems. Predictions of population health outcomes through utilization of
14 treatment efficacy data need to be used in conjunction with adherence rates to inform planning and
15 project evaluation[4]. The correlation between increased nonadherence and higher disease
16 prevalence should be used to inform policy makers to help circumvent avoidable costs to the
17 healthcare system.
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21 The metric of adherence estimation varied substantially within and across disease groups; likely
22 affecting the comparisons between studies. However, Hess et al [102], who compared six key
23 adherence measures on the same study participants, found that the measures produced similar
24 adherence values for all participants, although PDC and continuous measure of medication gaps
25 produced slightly lower values. While this highlights the comparability of the measures of
26 medication nonadherence, it further justifies the need to agree on consistent methods for
27 estimating nonadherence through use of pharmacy claims data.
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31 MPR was the most commonly used measure to estimate medication nonadherence. MPR was used
32 in 63% of studies, followed by PDC, which was used in 11%. These percentages were consistent with
33 those found recently by Sattler et al [103]. Even though the measures of medication nonadherence
34 may be comparable, the definition of MPR and the cut-off points to define nonadherence differed
35 significantly. Dragomir et al[95] defined MPR as the total days’ supply of medication dispensed in the
36 period, divided by the follow up period, with the assumption of 100% adherence during
37 hospitalization; Wu et al[76] removed the number of hospitalized days from the calculation; and
38 Pittman et al[61] calculated the total number of days between the dates of the last filling of a
39 prescription in the first six months in a given year and the first filling of a prescription in the 365 days
40 before the last filling. Nonadherence could also be further classified into subcategories within MPR
41 and PDC based on percentages. Thirty studies defined nonadherence as $MPR < 80\%$, and 12 studies
42 categorized nonadherence into varying percentage subgroups. While Karve et al[104] validated the
43 empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent
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3 hospitalizations in patients across a broad array of chronic diseases, 76 of the 79 studies included in
4 this review examined more than just hospitalization costs as an indicator metric. Further research is
5 required to identify and standardize nonadherence thresholds using other outcomes such as
6 laboratory, productivity and pharmacy measures.
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10 Within the 79 studies covered, 35 different indicators were used to measure the cost of
11 nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a
12 meta-analysis was impossible. It is imperative that a standardized approach be established to
13 measure and report the economic impact of medication nonadherence. The core outcome set must
14 take into consideration the perspective of the intended audience and the proportion of
15 nonadherence cost that is attributable to each outcome to determine an appropriate model[105].
16 The critical indicators based on the findings of this review include total costs, pharmacy costs,
17 inpatient costs, outpatient costs, emergency department visit costs, medical costs and
18 hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes
19 include short term disability costs, workers compensation costs, paid time off costs, absenteeism
20 costs and productivity costs. We suggest that further analysis of the contribution of each outcome to
21 the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future
22 research.
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32 Many studies have examined the relationship between nonadherence and economic outcomes using
33 a cross-sectional analysis[51]. The implications of this are that potentially crucial confounders such
34 as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for
35 example, did greater adherence result in reduced costs and improved health outcomes, or was the
36 patient healthier initially and more capable of being adherent? A longitudinal design is needed to
37 overcome this limitation.
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42 Economic evaluations inform decisions on how to best make use of scarce societal health resources
43 through offering an organized consideration of the range of possible alternative courses of action
44 and the evidence of the likely effects of each[20]. While none of the studies taken separately could
45 inform a choice between alternative courses of action, they did provide key evidence for decision
46 makers about costs associated with medication nonadherence. Pharmacy claims data were utilized
47 by the majority of studies to model cost estimates. Three-quarters of the studies were classified as
48 cost descriptions, providing a cost or outcome overview of the health consequences associated with
49 nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall
50 conclusions that are able to be drawn and emphasized the need for future study design to
51 incorporate elements allowing full economic evaluations to be conducted. Hughes et al[106]
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3 highlighted the need for more information on the consequences of nonadherence, so that economic
4 evaluations could reflect the potential long-term effect of this growing problem.
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7 Of the seventy nine included studies, sixty six of the studies were conducted in the United States.
8 Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and
9 disease groups. Comparison of costs between healthcare systems is difficult as no two are the same
10 and as healthcare is generally more expensive in the United States cost estimates may not reflect
11 average values. Thus caution needs to be taken when interpreting results however findings help to
12 represent the significance of the economic burden medication nonadherence plays. Analysis of
13 studies not conducted in the United States support the finding that generally medication
14 nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.
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20 Due to the advances in technology available to record and assess medication nonadherence, the
21 inclusion of studies undertaken in the late 1990s and early 2000s may have affected the
22 comparability of results, despite the fact that these studies met the inclusion criteria[22 23 65 73 74
23 98]. The quality of data presents a limitation. Information on disease groups with fewer included
24 studies may be less reliable than information on those with more. However, our findings affirm the
25 pattern of association between nonadherence and increasing healthcare costs.
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5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilization of existing data could help to better define costs and provide valuable input into the development of an economic framework to standardize the economic impact of medication nonadherence.

6 Footnotes

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Figure Legends**Figure 1: PRISMA Flow Diagram**

The PRISMA diagram details the search and selection process applied during the overview. The search yielded a total of 2768 citations. Studies were selected based on the inclusion criteria; studies reporting the cost of medication nonadherence using original cost data. Intervention studies were required to report baseline data. Seventy nine original studies met the inclusion criteria.

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year

Encompass the minimum, maximum and interquartile range of adjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Gastrointestinal only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Figure 1: Annual Unadjusted Medication Nonadherence Costs per patient per year

Encompass the minimum, maximum and interquartile range of unadjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Epilepsy and addiction only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

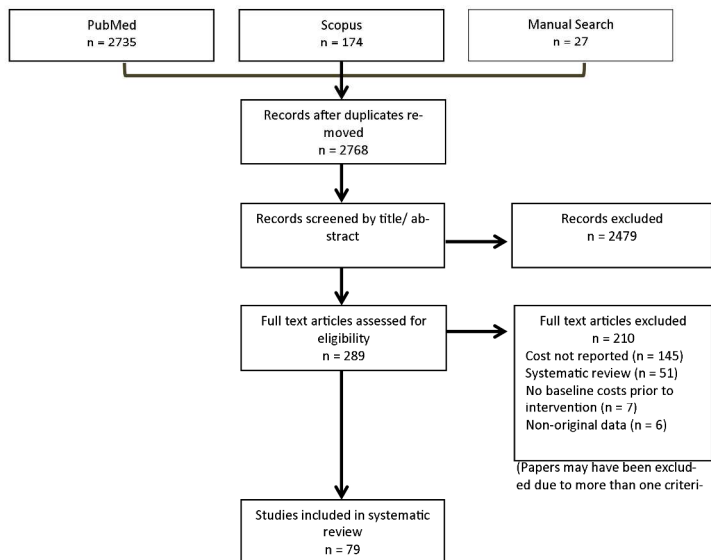


Figure 1: Flow diagram of references identified, retrieved and included in the systematic review

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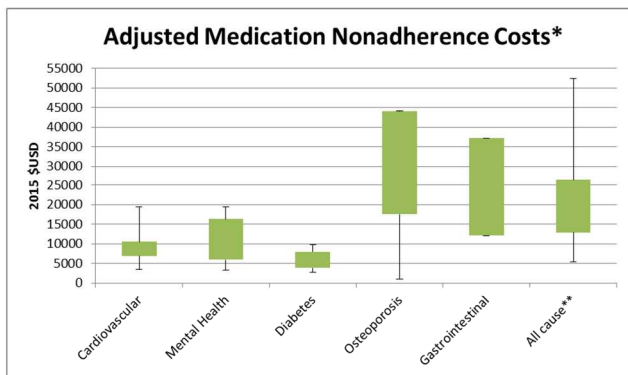


Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year
*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.
** All cause costs: mixed disease state studies

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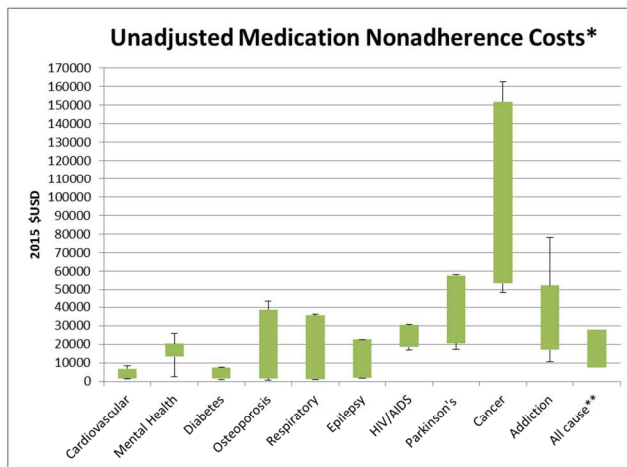


Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year
 *Disease groups with three or more studies were included. Epilepsy and Addiction only included three studies limiting the range of costs.
 ** All cause costs: mixed disease state studies

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eTable 1 Search Strategy¹

Database	Search Strategy
PubMed	((costs[TIAB] OR "Costs and Cost Analysis"[MH] OR burden[TIAB]) AND (nonadherence[TIAB] OR ("Patient Compliance"[MH] AND ("Drug Therapy"[MH] OR medication[TIAB]))) OR "Medication adherence"[MH]))
Scopus	(TITLE-ABS-KEY (medication AND compliance OR patient AND compliance)) AND (TITLE-ABS-KEY (statistical AND model)) AND (TITLE-ABS-KEY (health AND care AND cost))

¹ In accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used.

eTable 2: Studies identified with costs reported by adherence level and disease group

Author, Year, Country	Objective	Study Characteristics	Adherence (as reported in paper)	Outcomes/ Indicators	Results (USD, 2015)	Quality
Cardiovascular Disease						
<i>Aubert et al</i> [1] 2010 US	To investigate whether compliance during the first 2 years of statin therapy is associated with reduced hospitalization rates and direct medical costs during year 3.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 10227 (A:3512, NA:6715)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = non-compliant <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2002 <u>Cost of Nonadherence:</u> THC:\$5289.61 (\$6865.90), MC:\$4908.09 (\$6370.60)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Casciano et al</i> [2] 2013 US	To assess the economic burden of underuse and nonadherence of warfarin therapy among patients with non-valvular atrial fibrillation in a commercially insured population.	<u>Design:</u> Retrospective, observational, quasi-experimental study <u>Follow Up:</u> 18months <u>Sample Size:</u> 13289 (A:2852, NA:4184, NE:6253)	<u>Measure:</u> PDC <u>Classification:</u> PDC <80 = low adherence, 0 = no warfarin exposure <u>Method of Assessment:</u> pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence*:</u> TC:\$16612.44(\$19936.70), IC:\$9382.56 (\$11260.10), OC:\$8605.92 (\$10328), PC:\$2388.24 (\$2866.20), MC:\$15235.80(\$18285)	<u>Quality:</u> medium <u>Classification:</u> cost description
<i>Dilokthornsakul et al</i> [3] 2012 Thailand	To determine the effects of medication supplies on healthcare costs and hospitalizations in patients with chronic heart failure receiving angiotensin converting enzyme inhibitors or	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 393 (A:168, NA:219, OA:6)	<u>Measure:</u> MPR <u>Classification:</u> MPR < 80 = undersupply, MPR >120 = oversupply <u>Method of Assessment:</u> pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> THC:\$1157 (\$1433.06), IC:\$1019 (\$1262.13), OC:\$138 (\$170.93)	<u>Quality:</u> high <u>Classification:</u> cost description

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4		angiotensin receptor				
5		blockers.				
6	<i>Dragomir et al</i> [4]	To evaluate the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted and predicted
7	2010	of low adherence to	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific and
8	Canada	antihypertensive	<u>Follow Up:</u> 3 years	MPR \geq 80 =	Costs	hospitalized patients
9		agents on	<u>Sample Size:</u> 56896	adherent, MPR <	Pharmacy	<u>Currency Year:</u> CAD, 2006
10		cardiovascular	(A:38217, NA:18679)	80 = nonadherent	Costs	<u>Cost of Nonadherence:</u> Unadjusted
11		outcomes and		<u>Method of</u>	Medical Costs	Disease state specific: THC:\$7165
12		hospitalization costs.		<u>Assessment:</u>	Hospitalization	(\$6900.87), PC: \$1800 (\$1733.64),
13				pharmacy claims	Costs	MC: \$1370 (\$1319.50), HC: \$3995
14				data		(\$3847.73)
15						Unadjusted Hospitalized patients:
16						THC: \$17397 (\$16755.67), PC:\$2685
17						(\$2586.02), MC:\$2608 (\$2511.86),
18						HC: \$12104 (\$11657.79)
19						Predicted disease state specific:
20						HC:\$3877 (\$3734.08)
21						Predicted hospitalized patient:
22						HC:\$11715 (\$11283.13)
23						
24						
25	<i>Dragomir et al</i> [5]	To evaluate the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted and predicted
26	2010	of low adherence to	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific and
27	Canada	statins on clinical	<u>Follow Up:</u> 3 years	MPR \geq 80 =	Costs	hospitalized patients
28		issues and direct	<u>Sample Size:</u> 55134	adherent, MPR <	Pharmacy	<u>Currency Year:</u> CAD, 2005
29		healthcare costs.	(A:28549, NA:26585)	80 = nonadherent	Costs	<u>Cost of Nonadherence:</u> Unadjusted
30				<u>Method of</u>	Medical Costs	Disease state specific:
31				<u>Assessment:</u>	Hospitalization	THC:\$6243 (\$6175.76), PC:\$2506
32				pharmacy claims	Costs	(\$2479.01), MC:\$1241 (\$1227.63),
33				data		HC:\$2496 (\$2469.12)
34						Unadjusted Hospitalized patients:
35						THC:\$14725 (\$14566.40), PC:\$3374
36						(\$3337.66), MC:\$2475 (\$2448.34),
37						HC:\$8876 (\$8780.40)
38						Predicted disease state specific:
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4						HC:\$2669 (\$2640.25)	
5						Predicted hospitalized patient: HC\$9214	
6						(\$9114.76)	
7	<i>Pittman et al</i> [6]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted	<u>Quality:</u> medium
8	2011	relation among statin	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
9	US	adherence, subsequent	<u>Follow Up:</u> 18 months	MPR \geq 80 =	Costs	state specific	description
10		hospitalizations and	<u>Sample Size:</u> 381422	>60<79% =	Pharmacy	<u>Currency Year:</u> USD, 2009	
11		healthcare costs.	(A:258013, MA:65795,	moderate	Costs	<u>Cost of Nonadherence*:</u> all cause:	
12			LA:57614)	adherence, MPR	Medical Costs	THC(>80):\$6798.67 (\$7505.66),	
13				<59 =low		THC(60-79):\$7072.67 (\$7808.16),	
14				adherence		THC(<59):\$7401.33 (\$8170.99),	
15				<u>Method of</u>		PC(>80):\$1767.33 (\$1951.11),	
16				<u>Assessment:</u>		PC(60-79):\$1789.33 (\$1975.40),	
17				pharmacy claims		PC(<59):\$1937.33 (\$2138.79),	
18				data		MC(>80):\$4472.67 (\$4937.78),	
19						MC(60-79):\$4840.67 (\$5344.05),	
20						MC(<59):\$5138.67 (\$5673.04)	
21						Disease state specific:	
22						PC(>80):\$558.67 (\$616.77),	
23						PC(60-79):\$442.67 (\$488.70),	
24						PC(<59):\$325.33 (\$359.16),	
25						MC(>80):\$1596.67 (\$1762.71),	
26						MC(60-79):\$1722 (\$1901.07),	
27						MC(<59):\$1792.67 (\$1979.09)	
28							
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31	<i>Pittman et al</i> [7]	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted and unadjusted	<u>Quality:</u> medium
32	2010	relationship between	cohort study	<u>Classification:</u>	Healthcare	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
33	US	adherence to	<u>Follow Up:</u> 2 years	MPR \geq 80 =	Costs	<u>Currency Year:</u> USD, 2008	description
34		antihypertensive	<u>Sample Size:</u>	adherent, MPR	Outpatient	<u>Cost of Nonadherence:</u> Adjusted:	
35		medications and	625620(A:467006,	>60<79% =	Costs	THC(>80):\$7261 (\$8077.79),	
36		subsequent	MA:96226, LA:62388)	moderate	ED Costs	THC(60-79):\$7530 (\$8377.05),	
37		hospitalizations,		adherence, MPR	Pharmacy	THC(<59):\$7370 (\$8199.05),	
38		emergency		<59 =low	Costs	OC(>80):\$3390 (\$3771.34),	
39		department visits and		adherence	Hospitalization	OC(60-79):\$3705 (\$4121.77),	
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costs of care.

Method of Assessment:
pharmacy claims data

Costs

OC(<59):\$3776 (\$4200.76),
EDC(>80):\$101 (\$112.36),
EDC(60-79):\$134 (\$149.07),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2383 (\$2651.06),
PC(60-79):\$1932 (\$2149.33),
PC(<59):\$1509 (\$1678.75),
HC(>80):\$1386 (\$1541.91),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$1913 (\$2128.19)
Unadjusted:
THC(>80):\$7182 (\$7989.90),
THC(60-79):\$7560 (\$8410.42),
THC(<59):\$7995 (\$8894.35),
OC(>80):\$3396 (\$3778.01),
OC(60-79):\$3635 (\$4043.90),
OC(<59):\$3887 (\$4324.25),
EDC(>80):\$102 (\$113.47),
EDC(60-79):\$131 (\$145.74),
EDC(<59):\$172 (\$191.35),
PC(>80):\$2317 (\$2577.64),
PC(60-79):\$2034 (\$2262.80),
PC(<59):\$1880 (\$2091.48),
HC(>80):\$1366 (\$1519.66),
HC(60-79):\$1759 (\$1956.87),
HC(<59):\$2057 (\$2288.39)

Rizzo *et al*[8]
1997
US

To investigate variations in compliance with four classes of antihypertensive agents- diuretics, ACEIs, CCBs and β -

Design: Retrospective cohort study
Follow Up: 12 months
Sample Size: 7211(P:2668, NC:3101, NP:649, T:793)

Measure: ordinary least square regression analysis
Classification: >80% = persistent, \geq 30<80% = non-compliance, <30%

Total Healthcare Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 1994
Cost of Nonadherence: All cause:
THC(>80):\$341 (\$509.66),
THC(30-80):\$694 (\$1037.26),

Quality: low
Classification: cost description

blockers and the health care costs associated with various degrees of compliance.

= non-persistence
Method of Assessment:
 pharmacy claims data

THC(<30):\$735 (\$1098.53)
 Disease state specific:
 Renal:
 THC(>80):\$2135 (\$3190.98),
 THC(30-80):\$2488 (\$3718.58),
 THC(<30):\$2529 (\$3779.86),
 Acute MI:
 THC(>80):\$1358 (\$2029.67),
 THC(30-80):\$1711 (\$2557.27),
 THC(<30):\$1752 (\$2618.55), Diabetes:
 THC(>80):\$770 (\$1150.85),
 THC(30-80):\$1123 (\$1678.44),
 THC(<30):\$1164 (\$1739.72),
 CHF:
 THC(>80):\$698 (\$1043.23),
 THC(30-80):\$1051 (\$1570.83),
 THC(<30):\$1092 (\$1632.11),
 Angina:
 THC(>80):\$702 (\$1049.21),
 THC(30-80):\$1055 (\$1576.81),
 THC(<30):\$1096 (\$1638.09)

Sokol et al[9]
 2005
 US

To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Design: Retrospective cohort observational study
Follow Up: 12 months
Sample Size: 137277
 Diabetes:(≥80: 1801, 60-79: 599, 40-59: 419, 20-39: 259, <19: 182)
 Hypertension:(≥80: 5804, 60-79: 921, 40-59: 562, 20-39: 344, <19: 350)

Measure:
 medication supply
Classification: 1-19%, 20-39%, 40-59%, 60-79%, 80-100%
Method of Assessment:
 pharmacy claims data

Total Costs
 Pharmacy Costs
 Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 1998
Cost of Nonadherence: All cause:
 Diabetes:
 TC(1-19):\$16498 (\$23071.58),
 TC(20-39):\$13077 (\$18287.49),
 TC(40-59):\$12978 (\$18149.05),
 TC(60-79):\$11484 (\$16059.77),
 TC(80-100):\$8886 (\$12426.60),
 PC(1-19):\$1312 (\$1834.76),

Quality: medium
Classification: cost description

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Hypercholesterolemia:
(≥ 80 : 1754, 60-79: 520,
40-59: 324, 20-39: 216,
<19: 167)
CHF: (≥ 80 : 518, 60-79:
107, 40-59: 82, 20-39:
70, <19: 86)

PC(20-39):\$1877 (\$2624.89),
PC(40-59):\$1970 (\$2754.94),
PC(60-79):\$2121 (\$2966.11),
PC(80-100):\$2510 (\$3510.10),
MC(1-19):\$15186 (\$21236.82),
MC(20-39):\$11200 (\$15662.61),
MC(40-59):\$11008 (\$15394.10),
MC(60-79):\$9363 (\$13093.66),
MC(80-100):\$6377 (\$8917.90),
Hypertension:
TC(1-19):\$9747 (\$13630.66),
TC(20-39):\$11238 (\$15715.75),
TC(40-59):\$9491 (\$13272.66),
TC(60-79):\$8929 (\$12486.73),
TC(80-100):\$8386 (\$11272.38),
PC(1-19):\$916 (\$1280.98),
PC(20-39):\$952 (\$1331.32),
PC(40-59):\$1123 (\$1570.46),
PC(60-79):\$1271 (\$1777.43),
PC(80-100):\$1817 (\$2540.98),
MC(1-19):\$8831 (\$12349.69),
MC(20-39):\$10286 (\$14384.43),
MC(40-59):\$8368 (\$11702.20),
MC(60-79):\$7658 (\$10709.31),
MC(80-100):\$6570 (\$9187.80),
Hypercholesterolemia:
TC(1-19):\$10916 (\$15265.45),
TC(20-39):\$7982 (\$11162.40),
TC(40-59):\$6756 (\$9447.91),
TC(60-79):\$8412 (\$11763.74),
TC(80-100):\$6752 (\$9442.31),
PC(1-19):\$1067 (\$1492.14),
PC(20-39):\$1152 (\$1611.01),

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PC(40-59):\$1247 (\$1743.86),
PC(60-79):\$1736 (\$2427.70),
PC(80-100):\$1972 (\$2757.74),
MC(1-19):\$9849(\$13773.30),
MC(20-39):\$6830 (\$9551.39),
MC(40-59):\$5509 (\$7704.04),
MC(60-79):\$6676 (\$9336.03),
MC(80-100):\$4780 (\$6684.58),
CHF:
TC(1-19):\$23964 (\$33512.38),
TC(20-39):\$19188 (\$26833.40),
TC(40-59):\$26311 (\$36794.54),
TC(60-79):\$29785 (\$41652.74),
TC(80-100):\$22164 (\$30995.18),
PC(1-19):\$1961 (\$2742.35),
PC(20-39):\$2055 (\$2873.81),
PC(40-59):\$2208 (\$3087.77),
PC(60-79):\$3412 (\$4771.50),
PC(80-100):\$3107 (\$4344.97),
MC(1-19):\$22003 (\$30770.03),
MC(20-39):\$17133 (\$23959.59),
MC(40-59):\$24103 (\$33706.77),
MC(60-79):\$26373 (\$36881.24),
MC(80-100):\$19056 (\$26648.81)
Disease state specific: Diabetes:
TC(1-19):\$8867 (\$12400.03),
TC(20-39):\$7124 (\$9916.90),
TC(40-59):\$6522 (\$9120.67),
TC(60-79):\$6291 (\$8797.63),
TC(80-100):\$4570 (\$6390.90),
PC(1-19):\$55 (\$76.91),
PC(20-39):\$165 (\$230.74),
PC(40-59):\$285 (\$398.56),

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PC(60-79):\$404 (\$564.97),
PC(80-100):\$763 (\$1067.02),
MC(1-19):\$8812 (\$12323.11),
MC(20-39):\$6959 (\$9731.79),
MC(40-59):\$6237 (\$8722.11),
MC(60-79):\$5887 (\$8232.66),
MC(80-100):\$3808 (\$5325.29),
Hypertension:
TC(1-19):\$4878 (\$6821.62),
TC(20-39):\$6062 (\$8477.39),
TC(40-59):\$5297 (\$7407.57),
TC(60-79):\$5262 (\$7358.63),
TC(80-100):\$4871 (\$6811.84),
PC(1-19):\$31 (\$43.35),
PC(20-39):\$89(\$124.46),
PC(40-59):\$184 (\$257.31),
PC(60-79):\$285 (\$398.56),
PC(80-100):\$489 (\$683.84),
MC(1-19):\$4847 (\$6778.27),
MC(20-39):\$5973 (\$8352.92),
MC(40-59):\$5113 (\$7150.26),
MC(60-79):\$4977 (\$6960.07),
MC(80-100):\$4383 (\$6129.39),
Hypercholesterolemia:
TC(1-19):\$6888 (\$9632.50),
TC(20-39):\$4999 (\$6990.84),
TC(40-59):\$3825 (\$5349.06),
TC(60-79):\$5541 (\$7748.79),
TC(80-100):\$3924(\$5487.51),
PC(1-19):\$78 (\$109.08),
PC(20-39):\$213 (\$297.87),
PC(40-59):\$373 (\$521.62),
PC(60-79):\$603 (\$843.26),

For peer review

PC(80-100):\$801 (\$1120.16),
 MC(1-19):\$6810 (\$9523.42),
 MC(20-39):\$4786 (\$6692.97),
 MC(40-59):\$3452 (\$4827.44),
 MC(60-79):\$4938 (\$6905.53),
 MC(80-100):\$3124 (\$4368.75),
 CHF:
 TC(1-19):\$9841 (\$13762.12),
 TC(20-39):\$7733 (\$10814.19),
 TC(40-59):\$11378 (\$15911.53),
 TC(60-79):\$13924 (\$19471.98),
 TC(80-100):\$12698 (\$17787.48),
 PC(1-19):\$15 (\$20.98),
 PC(20-39):\$90 (\$125.86),
 PC(40-59):\$134 (\$187.39),
 PC(60-79):\$158 (\$220.95),
 PC(80-100):\$437 (\$611.12),
 MC(1-19):\$9826 (\$13741.14),
 MC(20-39):\$7643 (\$10688.33),
 MC(40-59):\$11244 (\$15724.14),
 MC(60-79):\$13766 (\$19251.02),
 MC(80-100):\$12261 (\$17146.36)

29 *Stroupe et al*[10]
 30 2006
 31 US

To determine the rates
 of undersupply,
 appropriate supply,
 and oversupply of
 antihypertensive drugs
 as measured by refill
 adherence, among
 patient with
 complicated and
 uncomplicated
 hypertension and to

Design: Retrospective
 cohort study
Follow Up: 3.3 years
Sample Size: 15206
 (not specified)

Measure: MPR
Classification:
 MPR<80 =
 undersupply, MPR
 >120 = oversupply
Method of
Assessment:
 pharmacy claims
 data

Total
 Healthcare
 Costs
 Inpatient
 Costs
 Outpatient
 Costs
 Pharmacy
 Costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002
Cost of Nonadherence **: THC:\$6032.5
 (\$7830.11), IC:\$2067 (\$2682.94),
 OC:\$3965 (\$5146.52), PC:\$130
 (\$168.74)

Quality: medium
Classification: cost
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examine the association of refill adherence with hospitalization and healthcare costs among these patients.

Wu et al[11]
2011
US

To study statin adherence and assess associated medical utilisation and healthcare costs in patients with type 2 diabetes, based on national Medicaid database.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 1705 (A:624, NA:1081)

Measure: MPR
Classification: MPR≥80 = adherent, MPR <80 = nonadherent
Method of Assessment: pharmacy claims data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2005
Cost of Nonadherence: all cause: THC:\$17807 (\$21370.30), PC:\$4915 (\$5898.52) MC:\$12892 (\$15471.77)
Disease state specific: THC:\$2789 (\$3347.10), PC:\$489(\$586.85) MC:\$2300 (\$2760.25)

Quality: medium
Classification: cost description

Zhao et al[12]
2014
US

To evaluate the associations between statin adherence level, healthcare costs, hospital admissions and emergency room visits after statin therapy is taken for 1 year.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 10312 (96-100: 2453, 90-95: 1496, 85-89: 584, 80-84: 768, 70-79: 960, 60-69: 777, 40-59: 1687, <40:1587)

Measure: MPR
Classification: <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100%
Method of Assessment: pharmacy claims data, census data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2010
Cost of Nonadherence: all cause: PC(96-100):\$2976.80 (\$3247.04), PC(90-95):\$2826.99 (\$3083.63), PC(85-89):\$2795.39 (\$3049.16), PC(80-84):\$2690.89 (\$2935.17), PC(70-79):\$2192.83 (\$2391.90), PC(60-69):\$2323.27 (\$2534.18), PC(40-59):\$2153.93 (\$2349.47), PC(<40):\$1749.18 (\$1907.97)
Disease state specific: THC(96-100):\$6536.05 (\$7129.40), THC(90-95):\$6493.80 (\$7083.31), THC(85-89):\$6459.40 (\$7045.79),

Quality: medium
Classification: cost description

THC(80-84):\$6227.47 (\$6792.80),
 THC(70-79):\$5713.47 (\$6232.14),
 THC(60-69):\$5875.26 (\$6408.62),
 THC(40-59):\$5817.58 (\$6345.70),
 THC(<40):\$5249.12 (\$5725.64),
 PC(96-100):\$449.86 (\$490.70), PC(90-95):\$439.74 (\$479.66),
 PC(85-89):\$458.83 (\$500.48),
 PC(80-84):\$423.15 (\$461.56),
 PC(70-79):\$356.74 (\$389.13),
 PC(60-69):\$371.30 (\$405.01),
 PC(40-59):\$279.21 (\$304.56),
 PC(<40):\$133.92 (\$146.08),
 MC(96-100):\$3559.25 (\$3882.36),
 MC(90-95):\$3666.81 (\$3999.69),
 MC(85-89):\$3664 (\$3996.62), MC(80-84):\$3586.58 (\$3912.17), MC(70-79):\$3520.64 (\$3840.25), MC(60-69):\$3551.99 (\$3874.44), MC(40-59):\$3663.65 (\$3996.24),
 MC(<40):\$3499.95 (\$3817.68)

For peer review

Mental Health

<p><i>Bagalman et al</i>[13] 2010 US</p>	<p>To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 1258 (A:444, NA:814)</p>	<p><u>Measure:</u> MPR <u>Classification:</u> MPR≥80 = adherent, MPR <80 = nonadherent <u>Method of Assessment:</u> pharmacy claims data</p>	<p>Total Costs Short term disability cost Workers compensation cost Paid time off cost</p>	<p><u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence:</u> TC:\$6894 (\$8273.53), STDC:\$2134 (\$2561.03), WCC:\$762 (\$914.48), PTOC:\$3998 (\$4798.03)</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost description</p>
<p><i>Becker et al</i>[14]</p>	<p>Examine treatment</p>	<p><u>Design:</u> Retrospective</p>	<p><u>Measure:</u></p>	<p>Total Costs</p>	<p><u>Type of Costs:</u> unadjusted</p>	<p><u>Quality:</u> low</p>

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3	2007	outcomes and costs	cohort study	prescription refill		<u>Classification:</u> disease state specific
4	US	associated with	<u>Follow Up:</u> 2 years	rate		<u>Classification:</u> cost
5		adherence rates by	<u>Sample Size:</u> 10330	<u>Classification:</u> 75-		<u>Currency Year:</u> USD, 2006
6		antipsychotic	(>75%:6609, 50-	100% = maximal		<u>Cost of Nonadherence</u> * :
7		medication class for	74%:1276, 25-	adherence, 50-		TC(75-100):\$13564 (\$15792.91),
8		Medicaid beneficiaries.	49%:1940, <25%:505)	74.9% = moderate		TC(50-74):\$13772 (\$16035.09),
9				adherence, 25-		TC(25-49):\$15792 (\$18387.03),
10				49.9% = minimal		TC(<25):\$16156 (\$18810.84)
11				adherence, <25%		
12				= negligible		
13				adherence		
14				<u>Method of</u>		
15				<u>Assessment:</u>		
16				pharmacy claims		
17				data		
18	<i>Eddy et al[15]</i>	To evaluate the effect	<u>Design:</u> Retrospective	<u>Measure:</u>	Inpatient costs	<u>Type of Costs:</u> unadjusted
19	2005	of partial compliance	database analysis	continuous	Outpatient	<u>Classification:</u> disease state specific
20	US	of patients with	<u>Follow Up:</u> 1 year	multiple interval	costs	<u>Currency Year:</u> USD, 2002
21		prescribed oral atypical	<u>Sample Size:</u> 7864	medications	Pharmacy	<u>Cost of Nonadherence</u> * :
22		and conventional	(<80%:2655, 80-	available	costs	IC:\$3780 (\$4906.39),
23		antipsychotic agents	125%:5065,	<u>Classification:</u>	Medical costs	OC:\$504 (\$654.19),
24		and the corresponding	>125%:144)	<80% = partially	Physician	PC:\$1872 (\$2429.83),
25		impact on resource		compliant, 80-	office visit	MC:\$6228 (\$8083.86),
26		utilisation.		125% = compliant,	costs	POC:\$1944 (\$2523.29)
27				>125% = overly	Other costs	OtC:\$12 (\$15.58)
28				compliant		
29				<u>Method of</u>		
30				<u>Assessment:</u>		
31				pharmacy claims		
32				data		
33	<i>Gilmer et al[16]</i>	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> adjusted
34	2004	relationship between	database analysis	cumulative	Outpatient	<u>Classification:</u> disease state specific
35	US	adherence to	<u>Follow Up:</u> 1 year	possession ratio	costs	<u>Currency Year:</u> USD, 1999
36						<u>Classification:</u> cost
37						description
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treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.

Sample Size: 1619 (<49%:388, 50-79%:259, 80-100%:664, >110%:308)

Classification: <49% = nonadherent, 50-79% = partially adherent, 80-100% = adherent, >110% = excess medication fillers

Pharmacy costs
Hospitalization costs

Cost of Nonadherence:
TC:\$8168 (\$11261.74),
OC:\$3464 (\$4776.04),
PC:\$1542 (\$2126.05),
HC:\$3413 (\$4705.72)

Method of

Assessment:

pharmacy claims data

Hong et al[17]
2011
UK

To investigate clinical and economic consequences of medication non-adherence in the treatment of bipolar disorder following a manic or mixed episode.

Design: Prospective observational study
Follow Up: 21 months
Sample Size: 1341(A:1024, NA:317)

Measure: assessed by treating psychiatrist
Classification: adherent vs. nonadherent
Method of
Assessment: observational assessment

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs
Hospitalization costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: GBP, 2008
Cost of Nonadherence *: all cause:
PC:£55.43 (\$94.47)
Disease state specific:
TC:£5846.29 (\$9964.10)
IC:£2740.57 (\$4670.88),
OC:£1082.86 (\$1845.57),
PC:£1630.29 (\$2778.58),
HC:£337.14 (\$574.60)

Quality: medium
Classification: cost description

Jiang et al[18]
2015
US

To estimate the impact of adherence to and persistence with atypical antipsychotics on healthcare costs and risk of hospitalization by controlling potential sources of endogeneity

Design: Retrospective cohort study
Follow Up: 2 years
Sample Size: 32374 (A:11642, NA:20732)

Measure: PDC
Classification: (PDC≥80% = adherent, PDC<80% = nonadherent)
Method of
Assessment: medical and

Total costs
Pharmacy costs
Medical services costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2011
Cost of Nonadherence:
Disease state specific:
TC:\$14141 (\$14517.37)
PC:\$3971 (\$4076.69),
MSC:\$10170 (\$10440.68)

Quality: low
Classification: cost description

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<p><i>Joe et al[19]</i> 2016 South Korea</p>	<p>To investigate the association between psychiatric medication non-compliance and psychiatric and non-psychiatric service utilisation and costs.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 7848 (A:2774, NA:2774, P:1956, NP:1956)</p>	<p>pharmacy claims data <u>Measure:</u> percentage of days of psychiatric prescription (PDP) <u>Classification:</u> PDP≥80% = adherent, PDP<80% = nonadherent; persistent = continued medication without interruption ≥ 56 day, non-persistent = at least one medication interruption > 56 days <u>Method of Assessment:</u> health insurance data</p>	<p>Total costs Inpatient costs External services costs</p>	<p><u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence:</u> all cause: TC:\$4961 (\$5271.40) Disease state specific: TC:\$3061 (\$3252.50)</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost outcome description</p>
<p><i>Knapp et al[20]</i> 2004 UK</p>	<p>To assess the relative impact of non-adherence and other factors associated with resource use and costs incurred by people with schizophrenia.</p>	<p><u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 658 (A:549, NA:109)</p>	<p><u>Measure:</u> self-report <u>Classification:</u> adherent vs. nonadherent <u>Method of Assessment:</u></p>	<p>Total costs Inpatient costs External services costs</p>	<p><u>Type of Costs:</u> predicted <u>Classification:</u> disease state specific <u>Currency Year:</u> GBP, 2001 <u>Cost of Nonadherence:</u> TC:£57580 (\$116434.12) IC:£6714 (\$13576.57), ESC:£1603 (\$3241.47)</p>	<p><u>Quality:</u> medium <u>Classification:</u> cost analysis</p>

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5	<i>Offord et al[21]</i>	To quantify early	<u>Design:</u> Retrospective	<u>Measure:</u> time to	Total costs	<u>Type of Costs:</u> adjusted
6	2013	nonadherence to	cohort study	discontinuation	Outpatient	<u>Classification:</u> all cause and disease
7	US	antipsychotic	<u>Follow Up:</u> 1 year	<u>Classification:</u>	costs	state specific
8		medications in patients	<u>Sample Size:</u> 1462	adherent vs.	Pharmacy	<u>Currency Year:</u> USD, 2008
9		with schizophrenia and	(A:589, NA:873)	nonadherent	costs	<u>Cost of Nonadherence:</u> all cause:
10		its impact on short-		<u>Method of</u>	Hospitalization	TC:\$15400 (\$17132.34)
11		term antipsychotic		<u>Assessment:</u>	costs	OC:\$5773 (\$6422.40),
12		adherence, healthcare		pharmacy claims		PC:\$3777 (\$4201.87),
13		utilisation and costs.		data		HC:\$5850 (\$6508.06)
14						Disease state specific:
15						TC:\$5358 (\$5960.72)
16						OC:\$858 (\$954.52),
17						PC:\$1549 (\$1723.25),
18						HC:\$2952 (\$3284.07)
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21	<i>Offord et al[22]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Inpatient	<u>Type of Costs:</u> adjusted
22	2013	of medication	cohort study	<u>Classification:</u>	costs	<u>Classification:</u> all cause and disease
23	US	adherence on	<u>Follow Up:</u> 1 year	MPR \geq 70= high	Pharmacy	state specific
24		healthcare utilisation	<u>Sample Size:</u> 354	adherence, MPR <	costs	<u>Currency Year:</u> USD, 2008
25		among Medicare	(A:126, NA:228)	70 = low		<u>Cost of Nonadherence:</u> all cause:
26		insured schizophrenia		adherence		IC:\$9053 (\$10071.37),
27		patients.		<u>Method of</u>		PC:\$4267 (\$4746.99),
28				<u>Assessment:</u>		Disease state specific:
29				pharmacy claims		IC:\$2468 (\$2745.62),
30				data		PC:\$1085 (\$1207.05)
31						
32	<i>Robertson et al[23]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
33	2014	of the combination of	cohort study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
34	US	treatment utilization	<u>Follow Up:</u> 90 days	MPR \geq 80% =	Outpatient	<u>Currency Year:</u> USD,2005
35		and medication	<u>Sample Size:</u> 1376	adherent	costs	<u>Cost of Nonadherence*:</u>
36		possession on arrest	(90/90:637, 60/90:240,	<u>Method of</u>	Emergency	TC(90/90):\$28068 (\$33495.65),
37		and incarceration	30/90:174, 0/90:316)	<u>Assessment:</u>	department	TC(60/90):\$21720 (\$25920.11),
38		outcomes and on		Medicaid claims	costs	TC(30/90):\$21084 (\$25161.12),
39		costs.		data	Pharmacy	TC(0/90):\$12516 (\$14936.28),
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costs	IC(90/90):\$12168 (\$14520.99),
Target case	IC(60/90):\$10068 (\$12014.90),
management	IC(30/90):\$11376 (\$13575.84),
costs	IC(0/90):\$5592 (\$6673.35),
Psychiatric	OC(90/90):\$6468 (\$7718.75),
assessment	OC(60/90):\$4152 (\$4954.89),
costs	OC(30/90):\$2916 (\$3479.88),
Arrest costs	OC(0/90):\$2136 (\$2549.05),
Incarceration	EDC(90/90):\$96 (\$114.56),
costs	EDC(60/90):\$108 (\$128.88),
	EDC(30/90):\$144 (\$171.85),
	EDC(0/90):\$84 (\$100.24),
	PC(90/90):\$5316 (\$6343.98),
	PC(60/90):\$3468 (\$4138.63),
	PC(30/90):\$2232 (\$2663.61),
	PC(0/90):\$984 (\$1174.28),
	TCMC(90/90):\$2100 (\$2506.09),
	TCMC(60/90):\$1404 (\$1675.50),
	TCMC(30/90):\$1596 (\$1904.63),
	TCMC(0/90):\$516 (\$615.78),
	PAC(90/90):\$240 (\$286.41),
	PAC(60/90):\$228 (\$272.09),
	PAC(30/90):\$204 (\$243.45),
	PAC(0/90):\$156 (\$186.17),
	ArC(90/90):\$780 (\$930.83),
	ArC(60/90):\$1032 (\$1231.56),
	ArC(30/90):\$1140 (\$1360.45),
	ArC(0/90):\$1200 (\$1432.05),
	InC(90/90):\$888 (\$1059.72),
	InC(60/90):\$1272 (\$1517.97),
	InC(30/90):\$1476 (\$1761.42),
	InC(0/90):\$1860 (\$2219.68)

<i>Robinson et al[24]</i>	To determine if the	<u>Design:</u> Retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	2006 US	type of antidepressant drug is related to adherence and assess the 6 month health care costs among newly diagnosed patients.	claims analysis <u>Follow Up:</u> 6 months <u>Sample Size:</u> 60386 (A:11526, NA:8860)	Antidepressant medication management measures <u>Classification:</u> meeting less than <3 medication management measures = nonadherent <u>Method of Assessment:</u> pharmacy claims data, Medicaid data, observational assessment	Inpatient costs Outpatient costs ED visit costs Pharmacy costs Physician office visit costs	<u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence*:</u> all cause: TC:\$12658 (\$15678.21) IC:\$3006 (\$3723.24), OC:\$6118 (\$7577.76), EDC:\$334 (\$413.69) PC:\$3200 (\$3963.52), POC:\$178 (\$220.47) Disease state specific: TC:\$2028 (\$2511.88) IC:\$102 (\$126.34), OC:\$734 (\$909.13), EDC:\$18 (\$22.29) PC:\$1174 (\$1454.12), POC:\$120 (\$148.63)	<u>Classification:</u> cost description
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	Svarstad et al[25] 2001 US	To examine the relationship of medication non-adherence to hospital use and costs among severely mentally ill clients.	<u>Design:</u> Retrospective database analysis <u>Follow Up:</u> 1 year <u>Sample Size:</u> 619 (A:413, NA:206)	<u>Measure:</u> quarter pharmacy claims <u>Classification:</u> one or more quarters without a claim = nonadherent <u>Method of Assessment:</u> pharmacy claims data, previous study data	Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 1990 <u>Cost of Nonadherence:</u> all cause: HC:\$3992 (\$6593.06) Disease state specific: Schizophrenia/schizo affective disorder: HC:\$3421 (\$5650.01) Bipolar disorder: HC:\$9701 (\$16021.85), Other severe mental illness: HCD:\$3024 (\$4994.34)	<u>Quality:</u> medium <u>Classification:</u> cost description
38 39 40 41 42 43 44 45 46 47	White et al[26] 2003 US	To evaluate the economic impact of antidepressant	<u>Design:</u> Retrospective database analysis <u>Follow Up:</u> 6 months	<u>Measure:</u> MPR <u>Classification:</u> MPR≥70% =	Total costs Pharmacy costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 1999	<u>Quality:</u> medium <u>Classification:</u> cost description

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3		treatment adherence	<u>Sample Size:</u> 14190	adherent,	Medical costs	<u>Cost of Nonadherence:</u>
4		among patients	(A:5638, NA:8552)	MPR<70% =		TC:\$11815 (\$16290.09)
5		treated for depression		nonadherent		PC:\$1123 (\$1548.35),
6				<u>Method of</u>		MC:\$10692 (\$14741.74)
7				<u>Assessment:</u>		
8				pharmacy claims		
9				data		
10						
11	Diabetes					
12	<i>An et al[27]</i>	This study evaluated	<u>Design:</u> Prospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
13	2014	the association	cohort study	<u>Classification:</u>	Outpatient	<u>Classification:</u> disease state specific
14	Korea	between medication	<u>Follow Up:</u> 3 years	MPR≥90% =	costs	<u>Currency Year:</u> USD, 2007
15		adherence and	<u>Sample Size:</u> 608	adherent,	Hospitalization	<u>Cost of Nonadherence*:</u>
16		clinical/economic	(A:472, NA:136)	MPR<90% =	costs	TC:\$1657.11 (\$1884.14)
17		outcomes in patients		nonadherent		OC: \$1413.99 (\$1608.20),
18		with type II diabetes		<u>Method of</u>		HC: \$243.11 (\$276.12)
19		mellitus in the republic		<u>Assessment:</u>		
20		of Korea over 3 year		pharmacy claims		
21		period.		data		
22						
23						
24	<i>Buysman et al[28]</i>	To examine the impact	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Pharmacy	<u>Type of Costs:</u> unadjusted
25	2017	of real world	database analysis	<u>Classification:</u>	costs	<u>Classification:</u> all cause and disease
26	US	adherence on	<u>Follow Up:</u> 12 months	PDC≥80% = highly		state specific
27		glycaemic control in	<u>Sample Size:</u> 2261	adherent,		<u>Currency Year:</u> USD, 2014
28		type 2 diabetes	(A:1215, NA:1046)	PDC<80% = less		<u>Cost of Nonadherence:</u> all cause:
29		patients treated with		than highly		PC: \$7225 (\$7297.39)
30		canagliflozin.		adherent		Disease state specific:
31				<u>Method of</u>		PC: \$4660 (\$4706.69)
32				<u>Assessment:</u>		
33				healthcare claims		
34				data		
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37	<i>Curtis et al[29]</i>	Examine the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total costs	<u>Type of Costs:</u> adjusted
38	2017	association between	analysis	<u>Classification:</u>	Outpatient	<u>Classification:</u> all cause
39	US	adherence to glucose	<u>Follow Up:</u> 3 years	PDC≥80% =	costs	<u>Currency Year:</u> USD, 2014
40		lowering agents and	<u>Sample Size:</u> 228074	adherent,	Pharmacy	<u>Cost of Nonadherence:</u>
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3		patient outcomes in an	(A:117864, NA:110210)	PDC<80% =	costs	TC:\$38633 (\$39020.09)	
4		adult type 2 diabetes		nonadherent	Acute care	OC: \$16964 (\$17134),	
5		population		<u>Method of</u>	costs	PC: \$9390 (\$9484.08),	
6				<u>Assessment:</u>		ACC:\$12153 (\$12274.77)	
7				healthcare claims			
8				data			
9							
10	<i>Egede et al</i> [30]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Inpatient costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> high
11	2012	longitudinal effects of	cohort study	<u>Classification:</u>	Outpatient	<u>Classification:</u> disease state specific	<u>Classification:</u> cost
12	US	medication	<u>Follow Up:</u> 5 years	MPR≥80% =	costs	<u>Currency Year:</u> USD, 2006	outcome
13		nonadherence on key	<u>Sample Size:</u> 740195	adherent,	Pharmacy	<u>Cost of Nonadherence*:</u>	description
14		costs and estimate	(A:427390, NA:312805)	MPR<80% =	costs	IC:\$14515.24 (\$17886.40)	
15		potential savings from		nonadherent		OC: \$3599.27 (\$4434.16),	
16		increased adherence		<u>Method of</u>		PC: \$1073.12 (\$1322.42)	
17		using novel		<u>Assessment:</u>			
18		methodology that		pharmacy claims			
19		accounts for shared		data			
20		correlation among cost					
21		categories.					
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23							
24	Gentil et al[31]	To examine healthcare	<u>Design:</u> Retrospective,	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted and unadjusted	<u>Quality:</u> medium
25	2015	costs associated with	observational cohort	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease	<u>Classification:</u> cost
26	Canada	adherence to oral	analysis	MPR≥80% =	Outpatient	state specific	description
27		antihyperglycemic	<u>Follow Up:</u> 1 year	adherent,	costs	<u>Currency Year:</u> CAD, 2010	
28		agents and the effects	<u>Sample Size:</u> 301	MPR<80% =	Pharmacy	<u>Cost of Nonadherence:</u>	
29		of depression and	(A:224, NA:77)	nonadherent	costs	Adjusted all cause:	
30		anxiety disorders on		<u>Method of</u>	Physician	TC:\$11124 (\$9818.67),	
31		these in older adults		<u>Assessment:</u>	office visit	IC:\$7419 (\$6548.43)	
32		with type 2 diabetes		pharmacy claims	costs	OC: \$2687 (\$2371.70),	
33				data		PC: \$504 (\$444.86),	
34						POC:\$513 (\$452.80)	
35						Adjusted disease state specific:	
36						TC:\$4477 (\$3951.65),	
37						IC:\$2836 (\$2503.21)	
38						OC: \$1518 (\$1339.87),	
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					PC###: \$-444 (\$-391.90), POC:\$568 (\$517.24) Unadjusted all cause: TC:\$14979 (\$13221.30), IC:\$6351 (\$5605.75) OC: \$4058 (\$3581.82), PC: \$3503 (\$3091.94), POC:\$1066 (\$940.91) Unadjusted disease state specific: TC:\$9008 (\$7950.97), IC:\$2854 (\$2519.10) OC: \$2654 (\$2342.57), PC: \$2498 (\$2204.87), POC:\$1002 (\$884.42)	
Hagen et al[32] 2014 US	To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/ short term disability costs	<u>Design:</u> Retrospective, observational cohort analysis <u>Follow Up:</u> 1 year <u>Sample Size:</u> 4978 (A:2820, NA:2158)	<u>Measure:</u> PDC <u>Classification:</u> PDC≥80% = compliant, PDC<80% = noncompliant <u>Method of Assessment:</u> pharmacy claims data	Healthcare costs Pharmacy costs Medical costs Short term disability costs	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2003 <u>Cost of Nonadherence:</u> Adjusted all cause: PC: \$1668 (\$2065.99), Adjusted disease state specific: HC:\$7642 (\$9465.39), PC:\$614 (\$760.50), MC:\$5974 (\$7399.40), STDC:\$1840 (\$2279.03) Unadjusted all cause: PC:\$1727 (\$2139.06) Unadjusted disease state specific: HC:\$6919 (\$8569.88), PC:\$785 (\$972.30), MC:\$5192 (\$6430.82), STDC:\$1717 (\$2126.68)	<u>Quality:</u> medium <u>Classification:</u> cost description
Hansen et al[33] 2010	To compare all cause total health care costs	<u>Design:</u> Retrospective, cohort study	<u>Measure:</u> MPR <u>Classification:</u>	Total Healthcare	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> all cause and disease	<u>Quality:</u> medium <u>Classification:</u> cost

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	US	and diabetes mellitus specific health care costs between patients who were adherent or non-adherent to monotherapy with metformin, pioglitazone or a sulfonylurea and to examine whether cost differences varied among patients using these oral antidiabetic drugs.	<u>Follow Up:</u> 2 years <u>Sample Size:</u> 108592 (A:63830, NA:44762)	MPR≥80% = adherent, MPR<80% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	costs Inpatient costs Outpatient costs Pharmacy costs	state specific <u>Currency Year:</u> USD, 2005 <u>Cost of Nonadherence#:</u> Adjusted all cause: THC:\$13258 (\$15911.01) Adjusted disease state specific: THC:\$2284 (\$2741.04) Unadjusted all cause: THC:\$15448.50 (\$18539.90), IC:\$4242.33 (\$5091.25), OC:\$ 7377.83, PC:\$3828 (\$4594.01) Unadjusted disease state specific: THC:\$3232.33 (\$3879.15), IC:\$873.50 (\$1048.29), OC:\$1545.67(\$1854.96), PC:\$812.67 (\$975.29)	description
20 21 22 23 24 25 26 27 28 29 30 31	<i>Hong et al</i> [34] 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.	<u>Design:</u> Retrospective, cohort study <u>Follow Up:</u> 3 years <u>Sample Size:</u> 40082 (A:11800, NA:28282)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥80% = adherent, MPR<80% = nonadherent <u>Method of Assessment:</u> pharmacy claims data	Total costs Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> KRW, 2007 <u>Cost of Nonadherence:</u> TC:₩765453 (\$1142.31), HC:₩397549 (\$593.28)	<u>Quality:</u> medium <u>Classification:</u> cost description
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	<i>Jha et al</i> [35] 2012 US	How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or	<u>Design:</u> Retrospective, observational claims analysis <u>Follow Up:</u> unclear <u>Sample Size:</u> 135639 (A:99976, NA:36553)	<u>Measure:</u> MPR <u>Classification:</u> MPR≥80% = adherent, MPR<80% = nonadherent <u>Method of Assessment:</u>	Total costs ED costs Hospitalization costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence***:</u> TC:\$4680000000 (\$5006563305.49), EDC:\$735000000 (\$786287185.80), HC:\$3950000000 (\$4225625012.11)	<u>Quality:</u> high <u>Classification:</u> cost outcome description

decreased pharmacy claims
hospitalizations or data
emergency
department visits?

Are there certain
subgroups of
populations that seem
to benefit more than
others when they
adhere to their
medication?
What are the financial
implications of changes
in adherence for the
nation at large and for
Medicare?

White et al[36]
2004
US

To assess the
relationship between
diabetic medication
adherence, total
healthcare costs and
utilisation with
patients with type 2
diabetes mellitus and
concomitant diabetes
and cardiovascular
disease.

Design: Retrospective,
database analysis
Follow Up: 1 year
Sample Size: 67029
(>95:20170, 75-95:
14074, <75:16713)

Measure: MPR
Classification:
MPR≥95%,
MPR>75%<95%,
MPR<75%
Method of
Assessment:
pharmacy claims
data

Total costs
Pharmacy
costs
Non-pharmacy
costs

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2000
Cost of Nonadherence: adjusted:
TC(≥95):\$4835 (\$6518.17),
TC(75-95):\$5314 (\$7163.92),
TC(<75):\$5706 (\$7692.38),
PC(≥95):\$1429 (\$1926.47),
PC(75-95):\$1157 (\$1559.78),
PC(<75):\$762 (\$1027.27),
NPC(≥95):\$3406 (\$4591.70),
NPC(75-95):\$4157 (\$5604.14),
NPC(<75):\$4944 (\$6665.11)
Unadjusted:
TC(≥95):\$4809 (\$6483.12),
TC(75-95):\$5333 (\$7189.53),
TC(<75):\$5605 (\$7556.22),

Quality: low
Classification: cost
analysis

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10 *Wu et al*[37]
11 2009
12 US

To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

Design: Retrospective, cohort study
Follow Up: 1 year
Sample Size: 2354 (A:830, NA:1524)

Measure: MPR
Classification: MPR \geq 80%= high compliance, MPR<80% = low compliance
Subgroup Analysis: commercial and Medicare supplemental
Method of Assessment: pharmacy claims data

Total healthcare costs
Inpatient costs
Outpatient costs
Pharmacy costs

PC(\geq 95):\$1402 (\$1890.07),
PC(75-95):\$1153 (\$1554.38),
PC(<75):\$766 (\$1032.66),
NPC(\geq 95):\$3407 (\$4593.05),
NPC(75-95):\$4180 (\$5635.15),
NPC(<75):\$4839 (\$6523.56)
Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2006
Cost of Nonadherence: adjusted all cause:
THC(com):\$32407 (\$37732.29),
THC(med):\$24622 (\$28668.02),
IC(com):\$ 12851(\$14692.74),
IC(med):\$ 6754 (\$7863.85),
OC(com):\$11888 (\$13841.50),
OC(med):\$10598 (\$12339.52),
PC(com):\$7667 (\$8926.88),
PC(med):\$7270 (\$8464.65)
Adjusted disease state specific:
Diabetes:
THC(com):\$10024 (\$11671.20),
THC(med):\$5015 (\$5839.09),
IC(com):\$2232 (\$2598.77),
IC(med):\$2606 (\$3034.23),
OC(com):\$1989 (\$2315.84),
OC(med):\$1231 (\$1433.28),
PC(com):\$1451 (\$1689.44),
PC(med):\$1179 (\$1372.74)
DPNP:
THC(com):\$3565 (\$4150.82),
THC(med):\$2384 (\$2775.75),

Quality: medium
Classification: cost description

Osteoporosis

Briesacher et al[38]
2007
US

To assess rates of osteoporotic fractures and health care utilisation as a function of bisphosphonate compliance in usual clinical practice.

Design: Retrospective, cohort study
Follow Up: 3 years
Sample Size: 17988 (not specified)

Measure: MPR
Classification: 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
Pharmacy costs

IC(com):\$1739 (\$2024.76),
IC(med):\$1048 (\$1220.21),
OC(com):\$362 (\$421.49),
OC(med):\$181 (\$210.74),
PC(com):\$1464 (\$1704.57)
PC(med):\$1155 (\$1344.80)

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2004
Cost of Nonadherence****: adjusted:
TC(80-100):-\$859 (-\$1063.96),
TC(60-79):-\$474 (-\$587.10),
TC(40-59):-\$366 (-\$453.33),
TC(20-39):\$151 (\$187.03),
IC(80-100):-\$3233 (-\$4004.40),
IC(60-79):-\$856(-\$1060.24),
IC(40-59):-\$6221 (-\$7705.34),
IC(20-39):-\$585 (-\$724.58),
OC(80-100):-\$445 (-\$551.18),
OC(60-79):-\$538 (-\$666.37),
OC(40-59):-\$236 (-\$292.31),
OC(20-39):\$60 (\$74.32),
PC(80-100):\$997 (\$1234.89),
PC(60-79):\$923 (\$1143.23),
PC(40-59):\$402 (\$497.92),
PC(20-39):\$160(\$198.18)
Unadjusted:
TC(80-100):-\$1273 (-\$1576.74),
TC(60-79):-\$294 (-\$364.15),
TC(40-59):-\$573 (-\$709.72),
TC(20-39):\$101 (\$125.10),
IC(80-100):-\$883 (-\$1093.68),

Quality: medium
Classification: cost description

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4					IC(60-79):-\$384 (-\$475.62),	
5					IC(40-59):-\$597 (-\$739.44),	
6					IC(20-39):-\$93 (-\$115.19),	
7					OC(80-100):-\$774 (-\$958.68),	
8					OC(60-79):-\$193 (-\$239.05),	
9					OC(40-59):-\$145 (-\$179.60),	
10					OC(20-39):\$148 (\$183.31),	
11					PC(80-100):\$384 (\$475.62),	
12					PC(60-79):\$284 (\$351.76),	
13					PC(40-59):\$170 (\$210.56),	
14					PC(20-39):\$48 (\$59.45)	
15						
16	<i>Eisenberg et al</i> [39]	To determine	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
17	2015	healthcare outcomes	claims study	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> all cause and disease
18	US	associated with	<u>Follow Up:</u> 2 years	(≥70% =	Outpatient	state specific
19		compliance and	<u>Sample Size:</u> 27905	compliant, <70%	costs	<u>Currency Year:</u> USD, 2012
20		noncompliance to	(A:11368, NA:16537)	= noncompliant	ED costs	<u>Cost of Nonadherence:</u> all cause:
21		bisphosphonate		<u>Method of</u>	Pharmacy	TC:\$7237 (\$7550.72),
22		therapy in women		<u>Assessment:</u>	costs	IC:\$1986 (\$2072.09),
23		diagnosed with		pharmacy claims	Physician	OC:\$2057 (\$2146.17),
24		osteoporosis		data	office visit	EDC:\$258 (\$269.18),
25					costs	PC:\$2197 (\$2292.24),
26						POC:\$738 (\$769.99)
27						Disease state specific:
28						TC:\$674 (\$703.22),
29						IC:\$334 (\$348.48),
30						OC:\$77 (\$80.34),
31						EDC:\$5 (\$5.22),
32						PC:\$213 (\$222.23),
33						POC:\$44 (\$45.91)
34						
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37	<i>Halpern et al</i> [40]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Medical costs	<u>Type of Costs:</u> unadjusted
38	2011	associations of	analysis	<u>Classification:</u>		<u>Classification:</u> all cause
39	US	adherence to	<u>Follow Up:</u> 540 days	(≥80% = high		<u>Currency Year:</u> USD, 2006
40		osteoporosis therapies	<u>Sample Size:</u> 21655	adherence,		<u>Cost of Nonadherence:</u> commercial:
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4		with occurrence of	(≥80%:8759,	≥50<80% =		MC(≥80):\$4295 (\$5000.78),	
5		closed fracture, all	≥50<80%:5237,	moderate		MC(50-80):\$4697 (\$5468.84),	
6		cause medical costs	<50%:7659)	adherence, <50%		MC(<50):\$5596 (\$6515.56)	
7		and all cause		= low adherence		Medicare:	
8		hospitalizations.		<u>Method of</u>		MC(≥80):\$4590 (\$5344.25),	
9				<u>Assessment:</u>		MC(50-80):\$5536 (\$6445.71),	
10				pharmacy claims		MC(<50):\$5801 (\$6754.25)	
11				data			
12							
13	Hazel-Fernandez et	To evaluate the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium
14	al[41]	healthcare utilisation	cohort study	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific and	<u>Classification:</u> cost
15	2013	patterns of medicare	<u>Follow Up:</u> 12 months	(≥80% = high	costs	fracture related	outcome
16	US	part D beneficiaries	<u>Sample Size:</u> 761	adherence,	Inpatient costs	<u>Currency Year:</u> USD, 2010	description
17		newly initiating	(≥80%:163,	≥50<80% =	Outpatient	<u>Cost of Nonadherence</u> * :	
18		teriparatide and to	≥50<80%:57,	moderate	costs	Disease state specific:	
19		assess the association	<50%:541)	adherence, <50%	ED costs	THC(≥80):\$21033 (\$22942.39),	
20		of medication		= low adherence	Pharmacy	THC(50-80):\$25574 (\$27895.62),	
21		adherence and		<u>Method of</u>	costs	THC(<50):\$15528 (\$16937.64),	
22		persistence with bone		<u>Assessment:</u>		IC(≥80):\$2198 (\$2397.54),	
23		fracture.		pharmacy claims		IC(50-80):\$8448 (\$9214.91),	
24				data		IC(<50):\$4897 (\$5341.55),	
25						OC(≥80):\$5151 (\$5618.61),	
26						OC(50-80):\$6439 (\$7023.54),	
27						OC(<50):\$5806 (\$6333.07),	
28						EDC(≥80):\$211 (\$230.15),	
29						EDC(50-80):\$330 (\$359.96),	
30						EDC(<50):\$465 (\$507.21),	
31						PC(≥80):\$13472 (\$14695),	
32						PC(50-80):\$10358 (\$11298.31),	
33						PC(<50):\$4361 (\$4756.89)	
34						Fracture related:	
35						THC(≥80):\$12670 (\$13820.19),	
36						THC(50-80):\$9292 (\$10135.53),	
37						THC(<50):\$4419 (\$4820.16),	
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4						IC(\geq 80):\$366 (\$399.23),	
5						IC(50-80):\$830 (\$905.35),	
6						IC(<50):\$1325 (\$1445.28),	
7						OC(\geq 80):\$1048 (\$1143.14),	
8						OC(50-80):\$955 (\$1041.70),	
9						OC(<50):\$767 (\$836.63),	
10						EDC(\geq 80):\$6 (\$6.54),	
11						EDC(50-80):\$9 (\$9.82),	
12						EDC(<50):\$44 (\$47.99),	
13						PC(\geq 80):\$10810 (\$11791.34),	
14						PC(50-80):\$7420 (\$8093.59),	
15						PC(<50):\$2068 (\$2255.73)	
16							
17	<i>Huybrechts et al</i> [42]	To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 5 years <u>Sample Size:</u> 38120 (A:9530, NA:28590)	<u>Measure:</u> MPR <u>Classification:</u> (\geq 80% = compliant, <50% = noncompliant) <u>Method of Assessment:</u> pharmacy claims data	Total costs Medical costs Institutional costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2000 <u>Cost of Nonadherence:</u> TC:\$7200 (\$9706.44), MC:\$1476 (\$1989.84), InstC:\$5736 (\$7732.80)	<u>Quality:</u> low <u>Classification:</u> cost description
18	2006						
19	US						
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27	<i>Kjellberge al</i> [43]	To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of noncompliance with health care resource use and cost.	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 1 year <u>Sample Size:</u> 38234 (A:26806, NA:11428)	<u>Measure:</u> MPR <u>Classification:</u> (\geq 70% = compliant, <70% = noncompliant) <u>Method of Assessment:</u> pharmacy claims data	Total costs Medical costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> Euro, 2011 <u>Cost of Nonadherence:</u> all cause: TC:€4933 (\$6209.58), MC:€3471 (\$4369.20), Disease state specific: TC:€754 (\$949.12), MC:€426 (\$536.24),	<u>Quality:</u> high <u>Classification:</u> cost outcome description
28	2016						
29	Denmark						
30							
31							
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39	<i>Modi et al</i> [44]	To evaluate compliance with	<u>Design:</u> Retrospective cohort study	<u>Measure:</u> MPR <u>Classification:</u>	Total costs Inpatient costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease	<u>Quality:</u> medium <u>Classification:</u> cost
40	2015						
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3	US	osteoporosis	<u>Follow Up:</u> 1 year	(≥80% =	Outpatient	state specific
4		treatments and	<u>Sample Size:</u> 27913	compliant, <80%	costs	<u>Currency Year:</u> USD, 2011
5		determine fracture and	(A:23430, NA:34483)	= noncompliant)	ED costs	<u>Cost of Nonadherence:</u> all cause:
6		healthcare burden		<u>Method of</u>	Pharmacy	TC:\$11749 (\$12484.12),
7		associated with		<u>Assessment:</u>	costs	IC:\$8768 (\$9316.60),
8		noncompliance		healthcare claims	Medical costs	OC:\$3945 (\$4191.83),
9				data	Other costs	EDC:\$104 (\$110.51),
10						PC:\$2981 (\$3167.52),
11						MC:\$8768 (\$9316.60),
12						OtC:\$997 (\$1059.38)
13						Disease state specific:
14						TC:\$630 (\$669.42),
15						IC:\$443 (\$470.72),
16						OC:\$158 (\$167.89),
17						EDC:\$3 (\$3.19),
18						PC:\$325 (\$345.33),
19						OtC:\$26 (\$27.63)
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22						
23	<i>Olsen et al</i> [45]	To assess the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Fracture costs	<u>Type of Costs:</u> unadjusted
24	2013	association between	observational study	<u>Classification:</u>		<u>Classification:</u> fracture site specific
25	Denmark	refill compliance and	<u>Follow Up:</u> 2 years	(≥80% = optimal		<u>Currency Year:</u> DKK, 2010
26		all cause health care	<u>Sample Size:</u> 47176	compliance,		<u>Cost of Nonadherence:</u>
27		costs.	(not specified)	>50<80% =		Hip fracture:
28				suboptimal		FC(50-80):kr817575.50 (\$74531.41),
29				compliance, <50%		FC(<50):kr4454954 (\$549987.04)
30				= low compliance		Spine fracture:
31				<u>Method of</u>		FC(50-80):kr174700 (\$21568.12),
32				<u>Assessment:</u>		FC(<50):kr226472 (\$27959.14)
33				pharmacy claims		Humerus fracture:
34				data		FC(50-80):kr117776.50 (\$14540.12),
35						FC(<50):kr795217.50 (\$98173.70)
36						Forearm fracture:
37						FC(50-80):-kr463024 (-\$57162.70),
38						FC(<50):kr45072.50 (\$8665.81)
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4					Other fracture:	
5					FC(50-80):-kr19261.50 (-\$2377.93),	
6					FC(<50):kr684067.50 (\$84451.66)	
7	<i>Sunycz et al</i> [46]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted
8	2008	relationship between	observational study	<u>Classification:</u>	healthcare	<u>Classification:</u> all cause and disease
9	US	persistence and	<u>Follow Up:</u> 3 years	(≥80% =	costs	state specific
10		compliance with	<u>Sample Size:</u> 32944	compliant, <80%	Inpatient costs	<u>Currency Year:</u> USD, 2005
11		bisphosphonate	(A:12186, NA:20758)	= noncompliant)	Outpatient	<u>Cost of Nonadherence:</u>
12		therapy and total and		<u>Method of</u>	costs	All cause:
13		osteoporosis related		<u>Assessment:</u>	ED costs	THC:\$23660 (\$28394.52),
14		costs and healthcare		pharmacy claims	Pharmacy	IC:\$18839 (\$22608.81),
15		resource utilisation in a		data	costs	OC:\$10061 (\$12074.27),
16		cohort of female			Radiology	EDC:\$832 (\$988.49),
17		bisphosphonate naïve			costs	PC:\$6941 (\$8329.94),
18		users.				RC:\$1079 (\$1294.91)
19						Disease state specific:
20						THC:\$1602 (\$1922.57),
21						IC:\$14074 (\$16890.30),
22						OC:\$501 (\$601.25),
23						EDC:\$452 (\$542.45),
24						PC:\$918 (\$1101.70),
25						RC:\$184 (\$220.82)
26						<u>Type of Costs:</u> adjusted and unadjusted
27						<u>Classification:</u> disease state specific
28						<u>Currency Year:</u> USD, 2010
29	<i>Zhao et al</i> [47]	To examine the	<u>Design:</u> Retrospective	<u>Measure:</u> PDC	Total	<u>Quality:</u> medium
30	2014	association between	cohort study	<u>Classification:</u>	healthcare	<u>Classification:</u> cost
31	US	teriparatide adherence	<u>Follow Up:</u> 36 months	(≥80% = high, 50-	costs	description
32		and healthcare	<u>Sample Size:</u> 824	80% = medium,	Inpatient costs	<u>Cost of Nonadherence</u> *:
33		utilisation and costs	(≥80:362, 50-80%:219,	<50% = low)	Outpatient	Adjusted:
34		among hip fracture	<50%:243)	<u>Method of</u>	costs	THC(≥80):\$34428 (\$37553.4),
35		patients.		<u>Assessment:</u>	Pharmacy	THC(50-80):\$37956 (\$41401.68),
36				pharmacy claims	costs	THC(<50):\$31188 (\$34019.28),
37				data		IC(≥80):\$7548 (\$8233.20),
38						IC(50-80):\$11520 (\$1256.80),
39						IC(<50):\$11556 (\$12605.04),
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For peer review

Zhao *et al*[48]
2013
US

To examine the association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty (KV) patients.

Design: Retrospective observational cohort study
Follow Up: 36 months
Sample Size: 1568
(≥80: 783, 50-80%: 382, <50%: 403)

Measure: PDC
Classification: (≥80% = high, 50-80% = medium, <50% = low)
Method of Assessment: pharmacy claims data

Total healthcare costs
Inpatient costs
Outpatient costs
Pharmacy costs

OC(≥80):\$9312 (\$10157.40),
OC(50-80):\$12816 (\$13979.40),
OC(<50):\$13044 (\$14228.16),
PC(≥80):\$18864 (\$20576.52),
PC(50-80):\$13116 (\$14306.64),
PC(<50):\$7452 (\$8128.44)

Unadjusted:

THC(≥80):\$37464 (\$40865.04),
THC(50-80):\$35076 (\$38260.20),
THC(<50):\$29484 (\$32160.60),
IC(≥80):\$7092 (\$7735.80),
IC(50-80):\$11100 (\$12107.64),
IC(<50):\$10632 (\$11597.16),
OC(≥80):\$9900 (\$10798.68),
OC(50-80):\$11352 (\$12382.56),
OC(<50):\$11988 (\$13076.28),
PC(≥80):\$20484 (\$22343.52),
PC(50-80):\$12624 (\$13770),
PC(<50):\$6864 (\$7487.16)

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2010
Cost of Nonadherence*:

Adjusted:
THC(≥80):\$40212 (\$43862.52),
THC(50-80):\$40512 (\$44189.76),
THC(<50):\$40128 (\$43770.84),
IC(≥80):\$8136 (\$8874.60),
IC(50-80):\$12060 (\$13154.76),
IC(<50):\$15444 (\$43404.36),
OC(≥80):\$12924 (\$14097.24),
OC(50-80):\$14928 (\$16283.16),
OC(<50):\$17568 (\$19162.80),

Quality: medium
Classification: cost description

PC(≥80):\$19392 (\$21152.40),
 PC(50-80):\$13908 (\$15170.52),
 PC(<50):\$8700 (\$9843.24)
 Unadjusted:
 THC(≥80):\$42768 (\$46650.48),
 THC(50-80):\$36780 (\$40118.88),
 THC(<50):\$39792 (\$43404.36),
 IC(≥80):\$7620 (\$8311.80),
 IC(50-80):\$12228 (\$13338.12),
 IC(<50):\$15768 (\$17199.48),
 OC(≥80):\$14580 (\$15903.60),
 OC(50-80):\$12108 (\$13207.20),
 OC(<50):\$15324 (\$16715.16),
 PC(≥80):\$20568 (\$22435.20),
 PC(50-80):\$12444 (\$13573.68),
 PC(<50):\$8700 (\$9489.84)

Respiratory Disease

Davis et al[49]
 2017
 US

To assess the association between adherence levels to different inhaled corticosteroid/long acting β₂-adrenergic agonist and COPD exacerbation rates and costs in commercially insured population

Design: Observational cohort study
Follow Up: 12 months
Sample Size: 13657 (≥80%: 1898, ≥50<80%: 1971, ≥30 <50%: 2443, <30% :7345)

Measure: PDC
Classification: (≥80 = adherent, ≥50<80% = mildly nonadherent, ≥30 <50% = moderately nonadherent, <30% highly nonadherent)
Method of Assessment: commercially insured healthcare claims data

Total costs
 Outpatient costs
 Pharmacy costs
 Hospitalization costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2014
Cost of Nonadherence*:
 All cause:
 TC(≥80):\$22546 (\$22772.24),
 TC(50-80):\$25545 (\$25800.95),
 TC(30-50):\$24303 (\$24546.51),
 TC(<30):\$25148 (\$25399.98),
 OC(≥80):\$7816 (\$7894.31),
 OC(50-80):\$8225 (\$8307.41),
 OC(30-50):\$8365 (\$8448.81),
 OC(<30):\$8857 (\$8945.74),
 PC(≥80):\$7954 (\$8033.70),

Quality: medium
Classification: cost description

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For peer review

PC(50-80):\$6862 (\$6930.76),
 PC(30-50):\$5485 (\$5539.96),
 PC(<30):\$4395 (\$4439.04),
 HC(≥80):\$6106 (\$6167.51),
 HC(50-80):\$9391 (\$9485.09),
 HC(30-50):\$9171 (\$9262.89),
 HC(<30):\$10849 (\$10957.70)
 Disease state specific:
 TC(≥80):\$8075.33 (\$8156.24),
 TC(50-80):\$7053 (\$7123.67),
 TC(30-50):\$6623 (\$6689.36),
 TC(<30):\$5644 (\$5700.55),
 OC(≥80):\$2194.33 (\$2216.32),
 OC(50-80):\$1947 (\$1966.51),
 OC(30-50):\$1997 (\$2017.01),
 OC(<30):\$2152 (\$2173.56),
 PC(≥80):\$4464 (\$4508.73),
 PC(50-80):\$3345 (\$3378.52),
 PC(30-50):\$2307 (\$2330.12),
 PC(<30):\$1569 (\$1584.72),
 HC(≥80):\$1074.67 (\$1085.44),
 HC(50-80):\$1155 (\$1166.57),
 HC(30-50):\$1619 (\$1635.22),
 HC(<30):\$1405 (\$1419.08)

Delea et al[50]
 2008
 US

To assess the
 association between
 adherence with
 fluticasone
 propionate/salmeterol
 combination product in
 a single inhaler and
 asthma care utilisation
 and costs in asthma

Design: Retrospective
 longitudinal cohort
 study
Follow Up: 24 months
Sample Size: 12907
 (≥75: 2612, 50-75%:
 3608, 25-50%: 5035,
 <25%: 1652)

Measure: MPR
Classification:
 (≥75, 50-75%, 25-
 50%, <25%)
Method of
Assessment:
 pharmacy claims
 data

Total costs
 Outpatient
 costs
 ED costs
 Other costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence *:
 TC(≥75):\$1564 (\$1990.27),
 TC(50-75):\$1128 (\$1435.44),
 TC(25-50):\$900 (\$1145.30),
 TC(<25):\$632 (\$804.25),
 OC(≥75):\$1272 (\$1618.69),

Quality: medium
Classification: cost
 description

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3 patients in typical US
4 clinical practice
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OC(50-75):\$852 (\$1084.21),
OC(25-50):\$600 (\$763.53),
OC(<25):\$388 (\$493.75),
EDC(≥75):\$32 (\$40.72),
EDC(50-75):\$36 (\$45.81),
EDC(25-50):\$60 (\$76.35),
EDC(<25):\$48 (\$61.08),
OtC(≥75):\$292 (\$371.59),
OtC(50-75):\$276 (\$351.22),
OtC(25-50):\$300 (\$381.77),
OtC(<25):\$240 (\$305.41)

16 *Diehl et al*[51]
17 2010
18 US

To evaluate
19 respiratory-related
20 medical outcomes and
21 cost for infants who
22 were prescribed and
23 received palivizumab in
24 accordance with the
25 dosing schedule
26 recommended by the
27 American Academy of
28 Paediatrics in 2006
29 versus those who did
30 not.

Design: Retrospective
claims analysis
Follow Up: 7 months
Sample Size: 245 (A:73,
NA:172)

Measure: 37 day
gap in claims
Classification: (>37
day gap in claims =
noncompliant)
Method of
Assessment:
pharmacy claims
data

Total costs
Pharmacy
costs
Services costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2007
Cost of Nonadherence:
TC:\$19093.46 (\$21656.12),
PC:\$7647.40 (\$8673.81),
SC^{**}:\$11604.03 (\$13161.45)

Quality: medium
Classification: cost
description

31 *Joshi et al*[52]
32 2006
33 US

34 Examine the
35 association of
36 medication adherence
37 with workplace
38 productivity and health
39 related quality of life in
40 asthma patients.
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Design: quantitative
analysis
Follow Up:
Sample Size: 385
(high:150, medium:73,
low: 162)

Measure: Morisky
scale
Classification: (0=
high adherence, 1-
2 = medium
adherence, >2 =
low adherence)
Method of
Assessment:

Total
productivity
cost
Absenteeism
costs
Presenteeism
costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002
Cost of Nonadherence^{##}:
TPC(0):\$1210.90 (\$1571.73),
TPC(1-2):\$1428.50 (\$1854.17),
TPC(>2):\$1073.10 (\$1392.87),
AbC(0):\$633.70 (\$822.53),
AbC(1-2):\$608.90 (\$790.34),

Quality: medium
Classification: cost
outcome
description

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4			questionnaire		AbC(>2):\$474.80 (\$616.28),		
5					PrC(0):\$577.20 (\$749.20),		
6					PrC(1-2):\$819.60 (\$1063.83),		
7					PrC(>2):\$598.30 (\$776.59)		
8	<i>Miravittles et al</i> [53]	To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).	<u>Design:</u> multicentre, retrospective, observational study <u>Follow Up:</u> 18 months <u>Sample Size:</u> 1365 (A:246, NA:1119)	<u>Measure:</u> GOLD 2007 Guidelines <u>Classification:</u> (adherent, nonadherent) <u>Method of Assessment:</u> GOLD guidelines	ED costs Pharmacy costs Physician office visit costs Hospitalization costs Primary care costs Interdisciplinary visit costs Medical test costs Radiology costs Laboratory costs Total healthcare costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> EUR, 2009 <u>Cost of Nonadherence:</u> EDC:€40.83 (\$57.91), PC:€771.50 (\$1094.27), POC:€106.29 (\$150.76), HC:€101.61 (\$144.12) PCC:€123.84 (\$175.65), IntC:€321.44 (\$455.92), MTC:€36.66 (\$51.99), RC:€24.24 (\$34.38), LC:€17.35 (\$24.61)	<u>Quality:</u> medium <u>Classification:</u> cost description
9	2013						
10	Spain						
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28	<i>Quittner et al</i> [54]	To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.	<u>Design:</u> retrospective, cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 3287 (>80%: 663, 50-80%: 949, <50%: 1675)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence) <u>Method of Assessment:</u> pharmacy claims data	Total healthcare costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2011 <u>Cost of Nonadherence*:</u> All cause: THC(≥80):\$35749.50 (\$38244.05), THC(50-80):\$45031.50 (\$48173.73), THC(<50):\$50284.50 (\$53793.28) Disease state specific: THC(≥80):\$23764 (\$25422.22),	<u>Quality:</u> medium <u>Classification:</u> cost description
29	2014						
30	US						
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6 **Gastrointestinal**
7 **Disease**

8 <i>Carter et al</i> [55] 9 2011 10 US	To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.	<u>Design:</u> retrospective, observational cohort claims analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 638 (A:466, NA:172)	<u>Measure:</u> number of infusions in 12 month period <u>Classification:</u> (7-9 infusions = adherent, <7 infusions = nonadherent) <u>Method of Assessment:</u> health claims data	Hospitalization costs	THC(50-80):\$33132.50 (\$35444.44), THC(<50):\$33894 (\$36259.07) <u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2007 <u>Cost of Nonadherence:</u> HC:\$37783 (\$42854.12)	<u>Quality:</u> medium <u>Classification:</u> cost outcome description
21 <i>Gosselin et al</i> [56] 22 2009 23 US	To examine the effects of gastroesophageal reflux disease (GERD) patients compliance with PPI therapy on health care resource utilisation and costs.	<u>Design:</u> retrospective cohort study <u>Follow Up:</u> <u>Sample Size:</u> 41837 (A:28321, NA:13516)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Medical costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2003 <u>Cost of Nonadherence:</u> TC:\$9497 (\$12085.43), IC:\$2116 (\$2692.72), OC:\$5458 (\$6945.59), PC:\$1922 (\$2445.85), MC:\$7575 (\$9639.58)	<u>Quality:</u> medium <u>Classification:</u> cost description
31 <i>Kane et al</i> [57] 32 2009 33 US	To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by patients.	<u>Design:</u> retrospective cohort analysis <u>Follow Up:</u> 12 months <u>Sample Size:</u> 571 (A:375, NA:196)	<u>Measure:</u> number of infusions in 12 month period <u>Classification:</u> (≥8 infusions = adherent, <7 infusions = nonadherent) <u>Method of</u>	Outpatient costs ED costs Pharmacy costs Medical costs Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2004 <u>Cost of Nonadherence:</u> All cause: OC:\$6679 (\$8272.62), EDC:\$314 (\$388.92), MC:\$16129 (\$19977.40),	<u>Quality:</u> medium <u>Classification:</u> cost outcome description

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4			<u>Assessment:</u>		HC:\$6893 (\$8537.68)	
5			health claims data		Disease state specific:	
6					OC:\$3931 (\$4868.94),	
7					EDC:\$91 (\$112.71),	
8					PC:\$18751 (\$23225.01),	
9					MC:\$10243 (\$12686.99),	
10					HC:\$4494 (\$5566.27)	
11	<i>Mitra et al</i> [58]	To assess the	<u>Design:</u> retrospective,	<u>Measure:</u> MPR	Inpatient costs	<u>Type of Costs:</u> adjusted
12	2012	association between	observational cohort	<u>Classification:</u>	Outpatient	<u>Classification:</u> all cause and disease
13	US	adherence to oral 5-	study	(≥80% = adherent,	costs	state specific
14		aminosalicylates (5-	<u>Follow Up:</u> 12 months	<80% =	ED costs	<u>Currency Year:</u> USD, 2010
15		ASAs) and all cause	<u>Sample Size:</u> 1693	nonadherent)	Pharmacy	<u>Cost of Nonadherence:</u>
16		costs and health care	(A:476, NA:1216)	<u>Method of</u>	costs	All cause:
17		utilisation among		<u>Assessment:</u>	Ancillary costs	PC:\$1541.60 (\$1681.55)
18		patients with active		pharmacy claims	Non-pharmacy	Disease state specific:
19		ulcerative colitis.		data	costs	IC:\$28726.65 (\$31334.47),
20						OC:\$1145.67 (\$1249.67),
21						EDC:\$635.95 (\$693.68),
22						AC:\$4923.29 (\$5370.23),
23						NPC:\$14226.32 (\$15517.79)
24						
25						
26	<i>Wan et al</i> [59]	To examine the effect	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
27	2014	of adherence versus	cohort analysis	<u>Classification:</u>	Total	<u>Classification:</u> all cause and disease
28	US	non-adherence on	<u>Follow Up:</u> 360 days	(≥80% = adherent,	healthcare	state specific
29		healthcare costs in	<u>Sample Size:</u> 1646	<80% =	costs	<u>Currency Year:</u> USD, 2009
30		patients with	(A:674, NA:972)	nonadherent)	Inpatient costs	<u>Cost of Nonadherence:</u>
31		inflammatory bowel		<u>Method of</u>	Outpatient	All cause:
32		disease.		<u>Assessment:</u>	costs	TC:\$47411 (\$52341.27),
33				pharmacy claims	ED costs	THC:\$32522 (\$35903.96),
34				data	Pharmacy	IC:\$17634 (\$19467.76),
35					costs	OC:\$10909 (\$12043.43),
36						EDC:\$458 (\$505.63),
37						PC:\$18410 (\$20324.46)
38						Disease state specific:
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4					TC:\$33652 (\$37151.47),	
5					THC:\$18764 (\$20715.27),	
6					IC:\$12564 (\$13870.53),	
7					OC:\$5890 (\$6502.50),	
8					EDC:\$48 (\$52.99),	
9					PC:\$15150 (\$16725.45)	
10	Epilepsy					
11	<i>Davis et al</i> [60]	To assess the extent of	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
12	2008	refill non-adherence	claims analysis	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
13	US	with antiepileptic	<u>Follow Up:</u> 12 months	(≥80% = adherent,	ED costs	<u>Currency Year:</u> USD, 2003
14		drugs (AEDs) and the	<u>Sample Size:</u> 10892	<80% =	Pharmacy	<u>Cost of Nonadherence</u> ^{###} :
15		potential association	(A:6644, NA:4248)	nonadherent)	costs	TC:\$1466 (\$1865.56),
16		between AED non-		<u>Method of</u>	Other	IC:\$1799 (\$2289.32),
17		adherence and		<u>Assessment:</u>	pharmacy	EDC:\$260 (\$330.86),
18		healthcare costs in an		pharmacy claims	costs	PC:-\$71 (-\$90.35),
19		adult managed care		data		OtPC:-\$358 (-\$455.57)
20		population.				
21						
22						
23	<i>Ettinger et al</i> [61]	To assess the extent to	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
24	2009	which elderly patients	claims analysis	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
25	US	diagnosed with	<u>Follow Up:</u> 12 months	(≥80% = adherent,	ED costs	<u>Currency Year:</u> USD, 2003
26		epilepsy are non-	<u>Sample Size:</u> 1278	<80% =	Pharmacy	<u>Cost of Nonadherence:</u>
27		adherent to	(A:758, NA:520)	nonadherent)	costs	TC:\$17817 (\$22673.06),
28		antiepileptic drugs		<u>Method of</u>	Physician	IC:\$2714 (\$3453.71),
29		(AEDs) and the		<u>Assessment:</u>	Office visit	EDC:\$526 (\$669.36),
30		potential association		pharmacy claims	costs	PC:\$347 (\$441.58),
31		between AED non-		data	Ancillary costs	POC:\$3063 (\$3897.83),
32		adherence and seizure			Other	AC:\$8344 (\$10618.18),
33		recurrence, resource			pharmacy	OtPC:\$2822 (\$3591.14)
34		utilisation and annual			costs	
35		direct medical costs.				
36						
37						
38	<i>Faught et al</i> [62]	To study the impact of	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
39	2009	non-adherence to	observational open	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
40	US	antiepileptic drugs	cohort design	(≥80% = adherent,	Outpatient	<u>Currency Year:</u> USD, 2002
41						<u>Quality:</u> medium
42						<u>Classification:</u> cost
43						description
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3		(AEDs) on healthcare	<u>Follow Up:</u> 4.65 years	<80% =	costs	<u>Cost of Nonadherence</u> * :
4		utilisation and direct	<u>Sample Size:</u> 33658	nonadherent)	ED costs	TC:\$14417.64 (\$18713.91),
5		medical costs in a	(A:24907, NA:8751)	<u>Method of</u>	Pharmacy	IC:\$6682.28 (\$6873.51),
6		Medicaid population.		<u>Assessment:</u>	costs	OC:\$2172.40 (\$2819.75),
7				pharmacy claims	Other	EDC:\$405.96 (\$526.93),
8				data	pharmacy	PC:\$822.40 (\$1067.46),
9					costs	OtPC:\$4334.60 (\$5626.26)
10						
11	HIV/AIDS					
12	<i>Barnett et al</i> [63]	To characterise the	<u>Design:</u> retrospective	<u>Measure:</u>	Total costs	<u>Type of Costs:</u> unadjusted
13	2011	cost of HIV care	observational cohort	antiretroviral		<u>Classification:</u> disease state specific;
14	US	including combination	study	taking behaviour		viral load count
15		antiretroviral	<u>Follow Up:</u> 1 year	<u>Classification:</u>		<u>Currency Year:</u> USD, 2006
16		treatment.	<u>Sample Size:</u> 1896	(85% adherence		<u>Cost of Nonadherence</u> ** :
17			(not specified)	with 3		High viral load:
18				antiretroviral		TC:\$25824 (\$30067.54)
19				therapy regimen =		Low viral load:
20				adherent, all other		TC:\$20509.67 (\$23879.92)
21				use =		
22				nonadherent)		
23				<u>Method of</u>		
24				<u>Assessment:</u>		
25				pharmacy claims		
26				data		
27						
28						
29						
30	<i>Cooke et al</i> [64]	To measure adherence	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted
31	2014	to antiretroviral	claims analysis	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
32	US	therapy regimens in	<u>Follow Up:</u> 1 year	(≥90% = adherent,	costs	<u>Currency Year:</u> USD, 2011
33		commercially insured	<u>Sample Size:</u> 3528	<90% =	Inpatient costs	<u>Cost of Nonadherence:</u>
34		patients with HIV	(A:1737, NA:640)	nonadherent)	Outpatient	THC:\$18868 (\$20184.58),
35		infection and analyse		<u>Method of</u>	costs	IC:\$2700 (\$2888.40),
36		the clinical and		<u>Assessment:</u>	Pharmacy	OC:\$915 (\$978.85),
37		demographic factors		pharmacy claims	costs	PC:\$15253 (\$16317.33)
38		associated with ≥90%		data		
39		adherence.				
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	<i>Pruitt et al</i> [65] 2015 US	To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.	<u>Design:</u> retrospective cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 502 (A:56, NA:176)	<u>Measure:</u> MPR <u>Classification:</u> (≥90% = adherent, <90% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Other pharmacy costs Behavioural health inpatient costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2009 <u>Cost of Nonadherence*:</u> HIV: TC:\$15360 (\$16957.32), IC:\$3864 (\$4265.76), OC:\$3948 (\$4358.52), PC:\$4956 (\$5471.40), OtPC:\$1764 (\$1947.48), BHIC:\$840 (\$927.36) AIDS: TC:\$27648 (\$30523.08), IC:\$13008 (\$14360.76), OC:\$5880 (\$6491.52), PC:\$5640 (\$6226.56), OtPC:\$2580 (\$2848.32), BHIC:\$528 (\$582.96)	<u>Quality:</u> medium <u>Classification:</u> cost description
24 25 26 27 28 29 30 31 32 33 34 35 36 37	Parkinson's Disease <i>Davis et al</i> [66] 2010 US	To assess the extent to which patients diagnosed with Parkinson's disease are non-adherent with antiparkinson therapy and the potential association between non-adherence and all cause medical costs.	<u>Design:</u> retrospective administrative claims study <u>Follow Up:</u> 12 months <u>Sample Size:</u> 3119 (A:1211, NA:1908)	<u>Measure:</u> MPR <u>Classification:</u> (≥80% = adherent, <80% = nonadherent) <u>Method of Assessment:</u> pharmacy claims data	Total costs Pharmacy costs Medical costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> disease state specific <u>Currency Year:</u> USD, 2001 <u>Cost of Nonadherence:</u> TC:\$18511 (\$24262.36), PC:\$2684 (\$3537.36), MC:\$15827 (\$20859.12)	<u>Quality:</u> medium <u>Classification:</u> cost outcome description
38 39 40 41 42 43 44 45 46 47	<i>Delea et al</i> [67] 2011 US	To assess the associations between adherence to	<u>Design:</u> retrospective historical cohort study <u>Follow Up:</u> 12 months	<u>Measure:</u> PDC <u>Classification:</u> (≥80% =	Total costs Inpatient costs Pharmacy	<u>Type of Costs:</u> adjusted and unadjusted <u>Classification:</u> all cause and disease state specific	<u>Quality:</u> high <u>Classification:</u> cost description

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levodopa/carbidopa/e
ntacapone therapy and
healthcare utilisation
and costs.

Sample Size: 1215
(A:617, NA:598)

satisfactory, <80%
= unsatisfactory)
Method of
Assessment:
pharmacy claims
data

costs
Other costs

Currency Year: USD, 2005

Cost of Nonadherence:

Adjusted all cause:

TC:\$19686 (\$23625.30),

IC:\$5954 (\$7145.43),

PC:\$6391 (\$7669.88),

OtC:\$8795 (\$10554.94)

Adjusted disease state specific:

TC:\$8574 (\$10289.71),

IC:\$3705 (\$4446.39),

PC:\$3850 (\$4620.41),

OtC:\$1884 (\$2261)

Unadjusted all cause:

TC:\$19362 (\$23236.46),

IC:\$5463 (\$6556.18),

PC:\$6158 (\$7390.26),

OtC:\$7740 (\$9288.82)

Unadjusted disease state specific:

TC:\$9156 (\$10988.18),

IC:\$3238 (\$3885.94),

PC:\$3789 (\$4547.20),

OtC:\$2129 (\$2555.03)

Wei et al[68]
2014
US

To examine the
associations of
adherence to
antiparkinson drugs
with healthcare
utilisation and
economic outcomes.

Design: retrospective
cross-sectional study
Follow Up: 19 months
Sample Size: 7583 (90-
100%:3948, 80-
89%:1456, ≤79%:2179)

Measure: MPR
Classification:
(>90<100% = high,
>80<89% =
moderate, ≤79% =
low)
Method of
Assessment:
pharmacy claims
data

Total costs
Inpatient costs
Outpatient
costs
Pharmacy
costs

Type of Costs: unadjusted

Classification: disease state specific

Currency Year: USD, 2007

Cost of Nonadherence:

TC(90-100):\$36407 (\$41293.43),

TC(80-89):\$43417 (\$49244.29),

TC(≤79):\$45867 (\$52023.13),

IC(90-100):\$15294 (\$17346.71),

IC(80-89):\$21603 (\$24502.49),

IC(≤79):\$24727 (\$28045.78),

OC(90-100):\$10155 (\$11517.97),

Quality: medium

Classification: cost
description

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4					OC(80-89):\$11838 (\$13426.86),	
5					OC(≤79):\$12889 (\$14618.92),	
6					PC(90-100):\$10957 (\$12427.61),	
7					PC(80-89):\$9976 (\$11314.95),	
8					PC(≤79):\$8251 (\$9358.42)	
9	Musculoskeletal					
10	<i>Ivanova et al</i> [69]	To compare the rates	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted
11	2012	of severe relapse and	cohort study	<u>Classification:</u>	Total	<u>Classification:</u> all cause, disease state
12	US	total direct and	<u>Follow Up:</u> 2 years	(≥80% = adherent,	healthcare	specific and indirect
13		indirect costs over a 2	<u>Sample Size:</u> 648	<80% =	costs	<u>Currency Year:</u> USD, 2007
14		year period between	(A:448, NA:200)	nonadherent)	Inpatient costs	<u>Cost of Nonadherence</u> *:
15		US based employees		<u>Method of</u>	Outpatient	All cause:
16		with MS who were		<u>Assessment:</u>	costs	TC:\$8079 (\$9276.76),
17		adherent and non-		pharmacy claims	ED costs	THC:\$6022 (\$6830.25),
18		adherent to disease		data	Pharmacy	IC:\$1030.50 (\$1168.81),
19		modifying drugs.			costs	OC:\$3231 (\$3664.65),
20					Medical costs	EDC:\$143.50 (\$162.76),
21					Short term	PC:\$1617 (\$1834.03),
22					disability costs	MC:\$4405.50 (\$4996.79)
23					Absenteeism	Disease state specific:
24					cost	TC:\$3005 (\$3408.32),
25						IC:\$505 (\$572.78),
26						OC:\$1710 (\$1939.51),
27						EDC:\$37 (\$41.97),
28						PC:\$753 (\$854.07),
29						MC:\$2252 (\$2554.26)
30						Indirect:
31						STDC:\$1231 (\$1396.22),
32						AbC:\$826 (\$936.86)
33						
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37	<i>Tan et al</i> [70]	To assess the impact of	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Medical costs	<u>Type of Costs:</u> adjusted and unadjusted
38	2011	treatment adherence	cohort study	<u>Classification:</u>		<u>Classification:</u> disease state specific
39	US	on MS related	<u>Follow Up:</u> 12 months	(≥80% = adherent,		<u>Currency Year:</u> USD, 2007
40		hospitalizations	<u>Sample Size:</u> 2446	<80% =		<u>Cost of Nonadherence:</u>
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3		(inpatient), ER visits,	(A:1459, NA:987)	nonadherent)	Adjusted:	
4		MS relapses and		<u>Method of</u>	MC:\$4348 (\$5062.49)	
5		medical costs.		<u>Assessment:</u>	Unadjusted:	
6				pharmacy claims	MC:\$5179 (\$6030.04)	
7				data		
8						
9	Zhao et al[71]	To examine predictors	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> adjusted
10	2011	associated with	cohort analysis	<u>Classification:</u>	Inpatient costs	<u>Classification:</u> disease state specific
11	US	duloxetine adherence	<u>Follow Up:</u> 12 months	(≥80% = adherent,	Outpatient	<u>Currency Year:</u> USD, 2008
12		and its association with	<u>Sample Size:</u> 5435	<80% =	costs	<u>Cost of Nonadherence:</u> commercial:
13		healthcare costs	(A:1744, NA:3691)	nonadherent)	Pharmacy	TC:\$20323 (\$22609.12),
14		among fibromyalgia		<u>Method of</u>	costs	IC:\$4808 (\$5348.85),
15		patients.		<u>Assessment:</u>		OC:\$9822 (\$10926.87),
16				pharmacy claims		PC:\$5693 (\$6333.40)
17				data		<u>Medicare:</u>
18						TC:\$25282 (\$28125.96),
19						IC:\$8604 (\$9571.86),
20						OC:\$10068 (\$11200.54),
21						PC:\$6611 (\$7354.67)
22						
23						
24	Cancer					
25	Darkow et al[72]	Estimate the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted
26	2007	association between	observational cohort	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
27	US	treatment	analysis	(≥95% = very high,	costs	<u>Currency Year:</u> USD, 2004
28		interruptions and non-	<u>Follow Up:</u> 12 months	>90<95% = high,	Inpatient costs	<u>Cost of Nonadherence:</u>
29		adherence with	<u>Sample Size:</u> 267	>50<90% =	Outpatient	THC(≥95):\$42250 (\$52330.90),
30		imatinib and	(≥95%:120, 90-95%:25,	intermediate,	costs	THC(90-95):\$39236 (\$48597.76),
31		healthcare costs for US	50-90%:69, <50%:53)	<50% = low)	ED costs	THC(50-90):\$54770 (\$67838.19),
32		managed care patients.		<u>Method of</u>	Pharmacy	THC(<50):\$131357 (\$162698.93),
33				<u>Assessment:</u>	costs	IC(≥95):\$1156 (\$1431.82),
34				pharmacy claims	Medical costs	IC(90-95):\$1362 (\$1686.97),
35				data	Other	IC(50-90):\$19096 (\$23652.33),
36					pharmacy	IC(<50):\$81572 (\$101035.18),
37					costs	OC(≥95):\$9299 (\$11517.75),
38					Other costs	OC(90-95):\$11148 (\$13807.93),
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For peer review

OC(50-90):\$14631 (\$18121.97),
 OC(<50):\$33956 (\$42057.94),
 EDC(≥95):\$36 (\$44.59),
 EDC(90-95):\$568 (\$703.53),
 EDC(50-90):\$104 (\$128.81),
 EDC(<50):\$183 (\$226.66),
 PC(≥95):\$29056 (\$35988.80),
 PC(90-95):\$23693 (\$29346.18),
 PC(50-90):\$18330 (\$22703.56),
 PC(<50):\$8733 (\$10816.70),
 MC(≥95):\$10731 (\$13291.43),
 MC(90-95):\$13452 (\$16661.66),
 MC(50-90):\$34202 (\$42362.64),
 MC(<50):\$116892
 (\$144782.57),OtPC(≥95):\$2462
 (\$3049.44),
 OtPC(90-95):\$2091 (\$2589.92),
 OtPC(50-90):\$2238 (\$2771.99),
 OtPC(<50):\$5732 (\$7099.66),
 OtC(≥95):\$241 (\$298.50),
 OtC(90-95):\$374 (\$463.24),
 OtC(50-90):\$371 (\$459.52),
 OtC(<50):\$1181 (\$1462.79)

30 *Wu et al*[73]
 31 2010
 32 US

To examine the
 association between
 adherence with
 imatinib and direct
 healthcare costs and
 resource utilisation

Design: retrospective
 observational cohort
 analysis
Follow Up: 12 months
Sample Size: 592
 (A:350, NA:242)

Measure: MPR
Classification:
 (≥85% = high
 adherence, <85%
 = low adherence)
Method of
Assessment:
 pharmacy claims
 data

Total costs
 Inpatient costs
 Outpatient
 costs
 ED costs
 Pharmacy
 costs
 Other
 pharmacy
 costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence:
 TC:\$107341 (\$119415.73),
 IC:\$44498 (\$49503.55),
 OC:\$34097 (\$37932.55),
 EDC:\$248 (\$275.90),
 PC:\$22846 (\$25415.93),
 OtPC:\$5652 (\$6287.79)

Quality: medium
Classification: cost
 description

Addiction

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4	Leider et al[74]	To assess the economic	<u>Design:</u> retrospective	<u>Measure:</u> urine	Total	<u>Type of Costs:</u> unadjusted
5	2011	burden of chronic	claims based analysis	testing	healthcare	<u>Classification:</u> disease state specific
6	US	opioid users and to	<u>Follow Up:</u> 12 months	<u>Classification:</u>	costs	<u>Currency Year:</u> USD, 2008
7		determine whether	<u>Sample Size:</u> 2100	(positive test =	Inpatient costs	<u>Cost of Nonadherence:</u>
8		opioid regimen non-	(A:442, NA:1658)	nonadherent,	Outpatient	THC:\$26433 (\$29406.43),
9		adherence contributes		negative test =	costs	IC:\$6361 (\$7076.55),
10		to increased		adherent)	ED costs	OC:\$9734 (\$10828.97),
11		healthcare costs.		<u>Method of</u>	Pharmacy	EDC:\$421 (\$468.36),
12				<u>Assessment:</u>	costs	PC:\$7960 (\$8855.42),
13				health claims data	Medical costs	MC:\$1957 (\$2177.14)
14				<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> unadjusted
15				<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
16	Ruetsch et al[75]	To examine patient	<u>Design:</u> cross sectional,	(≥80% = adherent,	costs	<u>Currency Year:</u> USD, 2013
17	2017	characteristics and	retrospective analysis	<80% =	Inpatient costs	<u>Cost of Nonadherence:</u>
18	US	outcomes associated	health claims data	nonadherent)	Outpatient	THC:\$16555 (\$16995.62),
19		with nonadherence to	<u>Follow Up:</u> 12 months	<u>Method of</u>	costs	IC:\$5657 (\$5807.57),
20		buprenorphine and to	<u>Sample Size:</u> 477	<u>Assessment:</u>	ED costs	OC:\$5594 (\$5742.89),
21		identify specific	(A:172, NA:305)	health claims data	Pharmacy	EDC:\$1147 (\$1177.53),
22		patterns of			costs	PC:\$2365 (\$2427.95),
23		nonadherent			Physician	POC:\$1765 (\$1811.98),
24		behaviour.			office visit	MC:\$14190 (\$14567.68)
25					costs	
26					Medical costs	
27					Total	<u>Type of Costs:</u> adjusted and unadjusted
28					healthcare	<u>Classification:</u> disease state specific
29					costs	<u>Currency Year:</u> USD, 2010
30					Inpatient costs	<u>Cost of Nonadherence:</u>
31	Tkacz et al[76]	To estimate the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total	<u>Type of Costs:</u> adjusted and unadjusted
32	2014	healthcare service	cohort analysis	<u>Classification:</u>	healthcare	<u>Classification:</u> disease state specific
33	US	utilisation and costs	<u>Follow Up:</u> 12 months	(≥80% = adherent,	costs	<u>Currency Year:</u> USD, 2010
34		associated with	<u>Sample Size:</u> 455	<80% =	Inpatient costs	<u>Cost of Nonadherence:</u>
35		buprenorphine	(A:146, NA:309)	nonadherent)	Outpatient	Adjusted:
36		medication assisted		<u>Method of</u>	costs	THC:\$49051 (\$53503.88),
37		therapy adherence		<u>Assessment:</u>	ED costs	IC:\$26470 (\$28872.96),
38		among a sample of		pharmacy claims	Pharmacy	OC:\$14570 (\$15892.67),
39		opioid dependent		data	costs	EDC:\$4439 (\$4841.98),
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members.

PC:\$3581 (\$3906.09)
 Unadjusted:
 THC:\$47868 (\$52213.49),
 IC:\$26043 (\$28407.20),
 OC:\$14173 (\$15459.63),
 EDC:\$4058 (\$4426.39),
 PC:\$3557 (\$3879.91)

Metabolic conditions other than diabetes mellitus

Lee et al[77]
 2011
 US

To assess the relationship between medication adherence and healthcare costs among US patients on dialysis given cinacalcet to manage secondary hypoparathyroidism.

Design: retrospective cohort study
Follow Up: 12 months
Sample Size: 4923 (A:1372, NA:1304)

Measure: MPR
Classification: (≥80% = high adherent, <80% = low adherent)
Method of Assessment: pharmacy claims data

Total costs
 Inpatient costs
 Outpatient costs
 ED costs
 Pharmacy costs
 Other pharmacy costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2010
Cost of Nonadherence:
 All cause:
 PC:\$5556 (\$6060.38)
 Disease state specific:
 TC:\$126996 (\$138524.78),
 IC:\$14844 (\$16191.55),
 OC:\$101854 (\$111100.37),
 EDC:\$734 (\$800.63),
 PC:\$3244 (\$3538.49),
 OtPC:\$9564 (\$10432.23)

Quality: medium
Classification: cost description

Blood

Candrilli et al[78]
 2011
 US

To investigate the relationships among hydroxyurea adherence, healthcare utilisation and healthcare costs.

Design: retrospective longitudinal study
Follow Up: 12 months
Sample Size: 312 (A:110, NA:202)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment:

Total costs
 Inpatient costs
 ED costs
 Pharmacy costs
 Physician office visit

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2008
Cost of Nonadherence:
 All cause:
 TC:\$ 20436 (\$22734.83),

Quality: medium
Classification: cost description

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pharmacy claims data	costs	IC:\$9780 (\$10880.15), EDC:\$837 (\$931.15), PC:\$2579 (\$2869.11), POC:\$3483 (\$3874.80), AC:\$3911 (\$4350.95)
	Ancillary costs	Disease state specific: TC:\$12097 (\$13457.78), IC:\$7315 (\$8137.86), EDC:\$552 (\$614.09), PC:\$158 (\$175.77), POC:\$1865 (\$2074.79), AC:\$2466 (\$2743.40)

All						
<i>Alvarez Payero et al</i> ^[79]	To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.	<u>Design:</u> retrospective observational study <u>Follow Up:</u> 1527 days <u>Sample Size:</u> 87 (A:21, NA:66)	<u>Measure:</u> pharmacy records <u>Classification:</u> (>75% = adherent, ≤75% = nonadherent) <u>Method of Assessment:</u> pharmacy and hospital claims data	Hospitalization costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause <u>Currency Year:</u> EUR, 2012 <u>Cost of Nonadherence</u> ^{####} : All cause: HC:€6275.80 (\$8893.94)	<u>Quality:</u> low <u>Classification:</u> cost outcome description

A: adherent, NA: nonadherent, MA: moderate adherence, LA: low adherence, NC: noncompliance, NP: nonpersistent, P: persistent, T: turbulent, NE: no exposure, CHF: chronic heart failure, THC: total healthcare costs, TC: total costs, IC: inpatient costs, OC: outpatient costs, EDC: emergency department visit costs, PC: pharmacy costs, MC: medical costs, HC: hospitalization costs, POC: physician office visit costs, NPC: non-pharmacy costs, AC: ancillary costs, OtPC: other pharmacy costs, PAC: psychiatric assessment costs, TCMC: targeted case management costs, ArC: arrest costs, InC: incarceration costs, RC: radiology costs, SC: services costs, InstC: institutional costs, ESC: external services costs, MSC: medical services costs, PCC: primary care costs, MTC: medical test costs, FC: fracture costs, LC: laboratory costs, IntC: interdisciplinary costs, BHIC: behavioural health inpatient costs, STDC: short term disability costs, WCC: workers compensation costs, PTOC: paid time off costs, TPC: total productivity costs, AbC: absenteeism costs, PrC: presenteeism costs, ACC: acute care

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3 costs, OtC: other costs, com: commercial patients, med: Medicare supplemental patients, USD: United States dollar, GBP: Great British Pound, EUR: Euro,
4 DKK: Danish krone, CAD: Canadian dollar, KRW: South Korean won
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7 *: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group;
8 #: extrapolated annual cost and subgroups averaged; ##: cost represents losses in workplace productivity; ###: negative value as costs modelled against
9 adherent group; ####: cost per episode of nonadherence
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eTable 3: Total cost or total healthcare cost comparison across disease groups

Disease State	Min adj cost per annum per person	Max adj cost per annum per person	Median adj cost per annum per person	Mean adj cost per annum per person	No. adj studies	Min unadj cost per annum per person	Max unadj cost per annum per person	Median unadj cost per annum per person	Mean unadj cost per annum per person	No. unadj studies	Total studies ¹
Cardiovascular Disease	3347	19472	8080	9204	6	1433	8377.05	5951	4701	7	12
Mental Health	3253	19363	11262	11052	6	2512	25920	17211	16486	7	14
Diabetes Mellitus	2741	9819	6907	6310	7	1142	7950	5534	4934	8	11
Osteoporosis	949	44190	41402	32866	4	669	43404	9921	18190	10	11
Respiratory Disease	5701	7124	6689	6505	1	804	36259	11546	16124	5	6
Gastrointestinal Disease	12085	37151	20715	23317	3					2	5
Epilepsy					0	1866	22673	18714	14418	3	3
HIV/AIDS					0	16957	30523	23880	24322	3	3
Parkinson's Disease				10290*	1	10988	52023	36753	34129	3	3
Musculoskeletal conditions				25368*	2				3408.32*	2	3
Cancer					0	48598	162699	93627	99638	2	2
Addiction				53504*	1	16996	52213	29406	32872	3	3
Metabolic conditions other than diabetes mellitus					0				138525*	1	1
Blood conditions				13458*	1					0	1
All causes	5271	52341	17132	21257	14	1037	53793	16308	19352	10	30**

Costs reported in \$US2015 dollars

¹Some studies included both adjusted and unadjusted costs

*Single total cost/total healthcare cost reported

** In addition to disease-specific studies of the economic impact of medication nonadherence, studies reported the all-causes costs, encompassing cost drivers such as comorbidities. Alvarez Payero et al reported all cause costs only.

Do not report total cost/total healthcare cost

Single total cost/total healthcare cost reported



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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