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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-

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

All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [12], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[12]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The cost analysis of studies (figures 2 and 3) reported annual medication nonadherence costs incurred by the patient from a healthcare provider perspective. The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. The most utilized methods were medication possession ratio (MPR) and proportion of days covered (PDC). Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [13]. All studies were classified in accordance with Drummond's distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis).

The Drummond checklist [14] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

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

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).

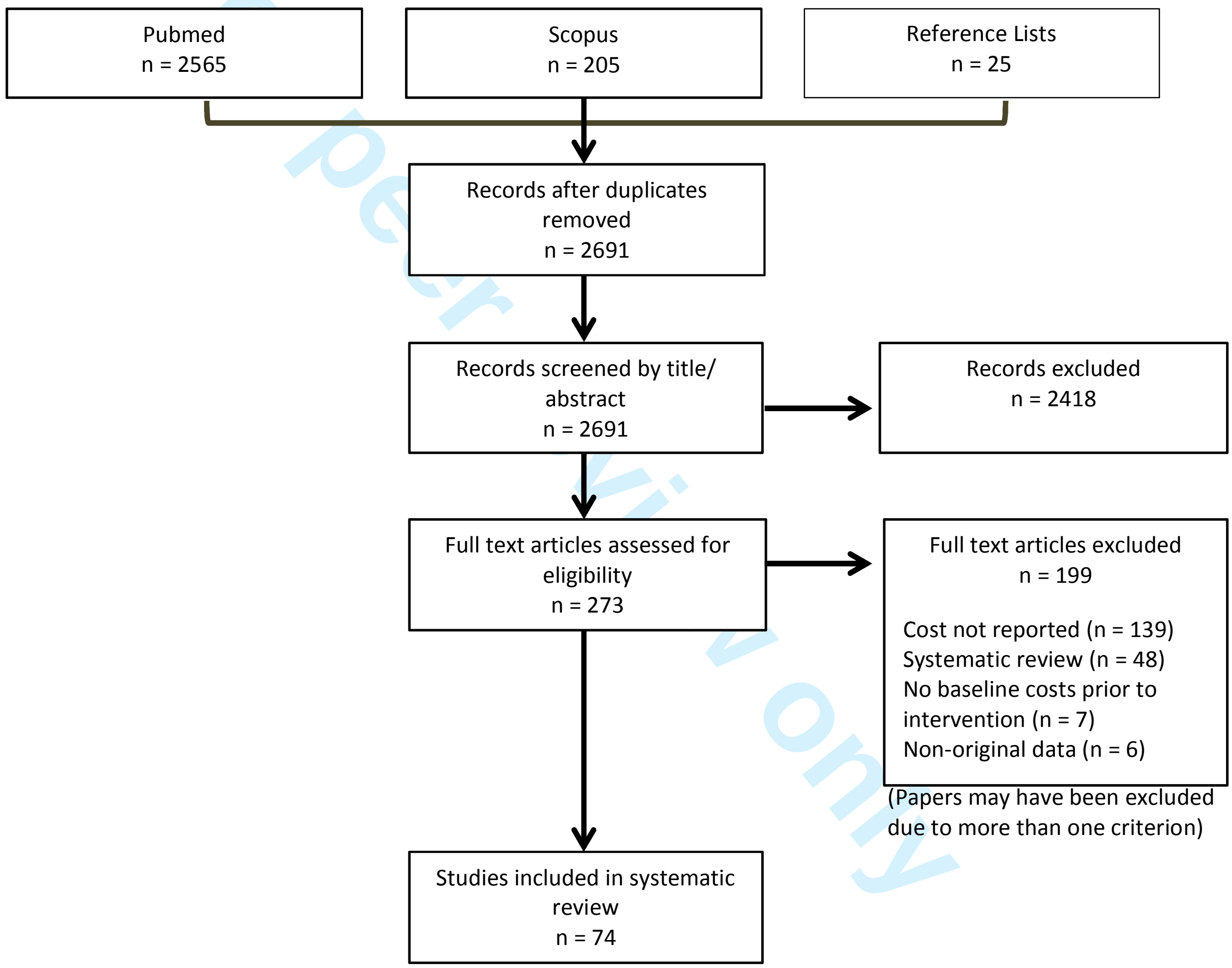

Figure 1: Flow diagram of references identified, retrieved and included in the systematic review

3.2 Characteristics of individual studies

Sixty-one studies (82%) were conducted in the Unites 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.

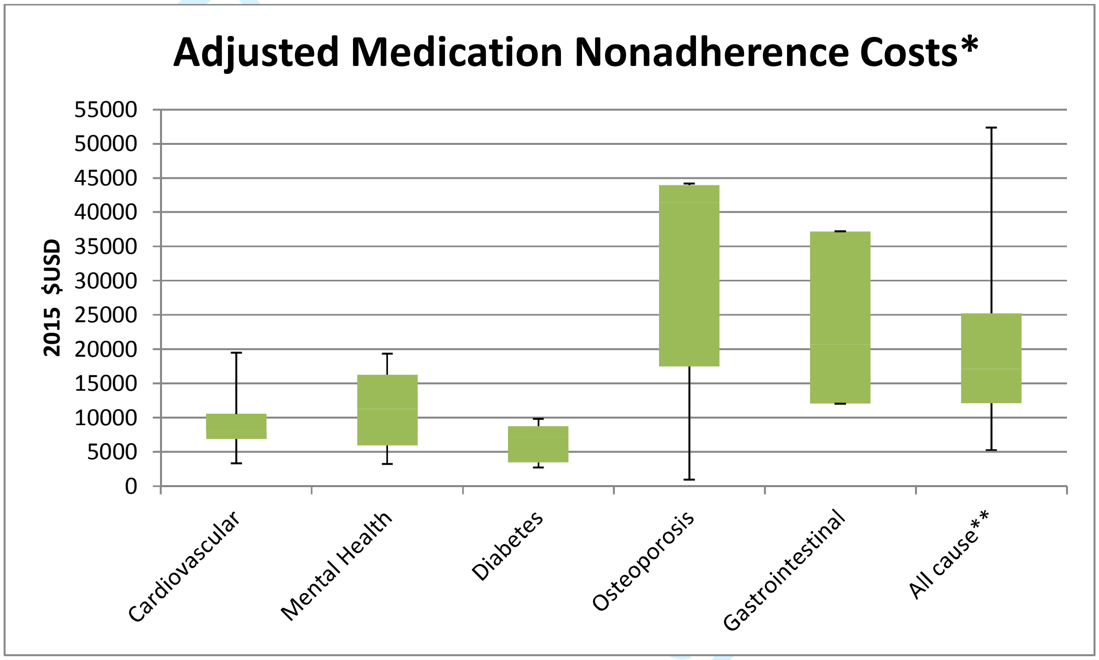

Figure 2: Annual Adjusted Medication Nonadherence Costs
*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.
** All cause costs: mixed disease state studies

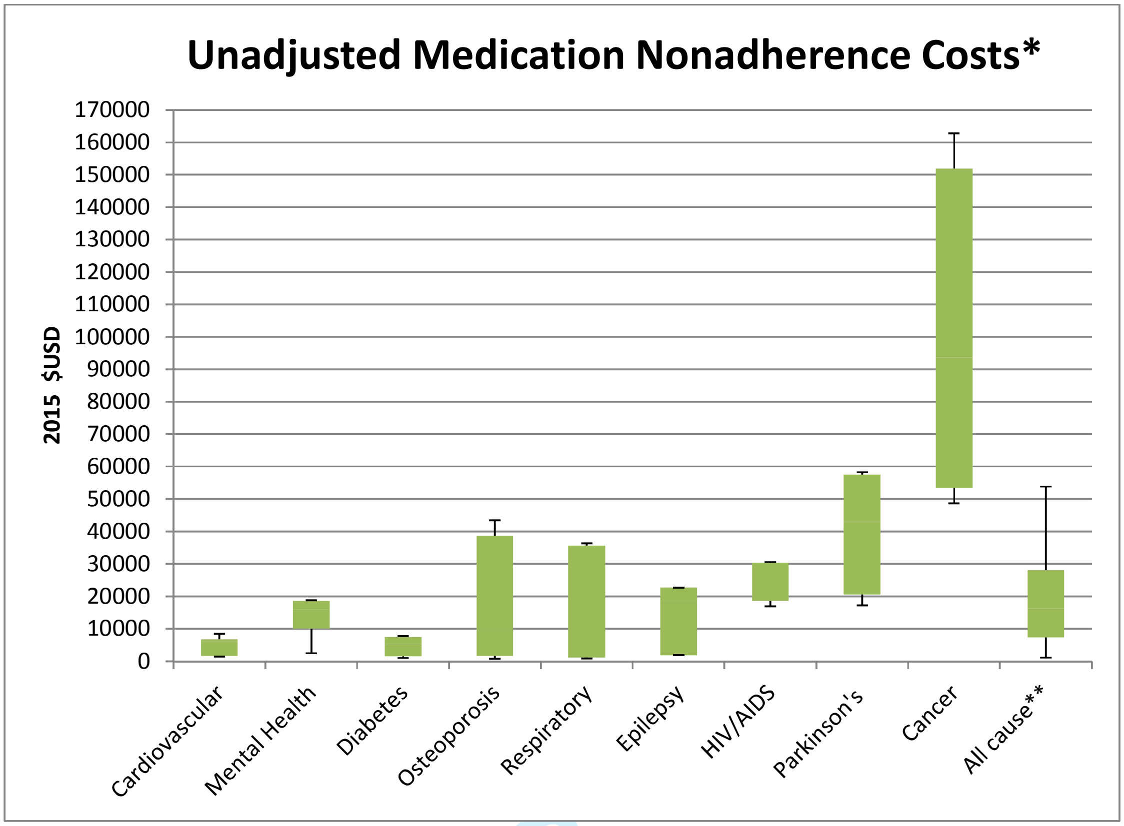

Figure 3: Annual Unadjusted Medication Nonadherence Costs

*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 nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

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

Cardiovascular Disease

Twelve studies measured the economic impact of medication nonadherence in cardiovascular disease [17 24 54 55 58 60 61 70 75 82 84 85]. Six studies reported adjusted costs [17 24 54 55 60 70] with annual costs being extrapolated for two of these[24 54]. Total healthcare costs and/or total costs were assessed in all of the studies with the major indicators measured including pharmacy costs[16,20,21,23,25], medical costs[15,16,20, 23,25] and outpatient costs[16, 21]. The annual economic cost of nonadherence ranged from $3,347 to $19,472. Sokol et al[60] 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.
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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 [58 61 75 82 84 85]. Rizzo et al[58] 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[75], 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[61 82], outpatient costs[61 82], pharmacy costs[61 84 85], medical costs[84 85] and hospitalization costs[84 85].

Mental Health

The analyses used to report the economic impact of medication nonadherence in mental health varied widely. Ten of 13 studies provided a total nonadherence cost estimate in mental health[16 18

20 45 52 59 67 80 87 88], with annual cost data being extrapolated for three of these[20 59 88]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged from $3,252 to $19,363 [16 18 52 53 67 80]. Bagalman et al[18] focused primarily on the indirect costs associated with nonadherence – short-term disability, workers compensation and paid time off costs – while all other studies addressed direct costs. The main indicators used to measure the direct economic impact of medication nonadherence were pharmacy costs[16 32 45 52 53 59 67 88], inpatient costs[32 53 59 87 88], outpatient costs[16 32 52 59 88] and hospitalization costs[15 16 52 88].

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

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

Diabetes mellitus:

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 the relationship between nonadherence and short term disability costs in addition to assessing direct costs[38].

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 [41 77]. Four out of 11 studies reported the adjusted cost of medication nonadherence in addition to reporting unadjusted costs [21 73 74 76]. Three studies further classified nonadherence through subgroup analysis, with Briesacher et al[21] using MPR 20% interval increases and the two studies conducted by Zhao et al[73 74] using PDC, with ≥80% classified as high adherence, 50-79% medium adherence and <50% low adherence . In the studies conducted by Zhao et al[73 74], 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[21] 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 [41 73 74].

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 [39].

Respiratory Disease:

All five studies reported the unadjusted cost of medication nonadherence. The methods of classifying adherence levels varied greatly among them[29 31 46 57 78]. Two studies used MPR[29 57], one the Morisky 4-Item scale[46], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[78] and one a 37 day gap in claims data[31]. Joshi et al[46] 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[29] reported a direct relationship between decreases in medication nonadherence level and total costs, whereas Quittner et al[57] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the lowest subgroup of adherence across all measures ranged from $804 to $36,259.

Gastrointestinal Disease:

Three of five studies reported the adjusted annual cost of medication nonadherence per patient utilizing the MPR method [37 50 65]. Of these, two reported the total cost ($12,085 and $37,151)[37 65] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the total cost nor total healthcare costs[23 47]. Carter et al[23] reported hospitalization costs to be $42,854 while Kane et al[47] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

Epilepsy:

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

HIV/AIDS:

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

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.

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 medication nonadherence, it further justifies the need to agree on consistent methods for estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used in 64% of studies, followed by PDC, which was used in 9%. These percentages were consistent with those found recently by Sattler et al [91]. Even though the measures of medication nonadherence may be comparable, the definition of MPR and the cut-off points to define nonadherence differed significantly. Dragomir et al[84] defined MPR as the total days' supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalization; Wu et al[70] removed the number of hospitalized days from the calculation; and Pittman et al[54] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Nonadherence could also be further classified into subcategories within MPR and PDC based on percentages. Twenty-eight studies defined nonadherence as MPR< 80%, and 19 studies categorized nonadherence into varying percentage subgroups. While Karve et al[92] validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent hospitalizations in patients across a broad array of chronic diseases, 71 of the 74 studies included in this review examined more than just hospitalization costs as an indicator metric. Further research is required to identify and standardise nonadherence thresholds using other outcomes such as laboratory, productivity and pharmacy measures.

Within the 74 studies covered, 30 different indicators were used to measure the cost of nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a meta-analysis was impossible. It is imperative that a standardized approach be established to measure and report the economic impact of medication nonadherence. The core outcome set must take into consideration the perspective of the intended audience and the proportion of nonadherence cost that is attributable to each outcome to determine an appropriate model[93]. The critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient costs, outpatient costs, emergency department visit costs, medical costs and hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes include short term disability costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs. We suggest that further analysis of the contribution of each outcome to the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future research.

Many studies have examined the relationship between nonadherence and economic outcomes using a cross-sectional analysis[44]. The implications of this are that potentially crucial confounders such as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for example, did greater adherence result in reduced costs and improved health outcomes, or was the patient healthier initially and more capable of being adherent? A longitudinal design is needed to overcome this limitation.

None of the studies included a full economic evaluation. An economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each[13]. While none of the studies taken separately could inform a choice between alternative courses of action, they did provide key evidence for decision makers about costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority of studies to model cost estimates. Three-quarters of the studies were classified as cost descriptions, providing a cost or outcome overview of the health consequences associated with nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall conclusions that are able to be drawn and emphasised the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al[94] highlighted the need for more information on the consequences of nonadherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Due to the advances in technology available to record and assess medication nonadherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the inclusion criteria[15 16 58 67 68 87]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between nonadherence and increasing healthcare costs.

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						
*Aubert et al***[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.	Design: Retrospective cohort study Follow Up: 3 years Sample Size: 10227 (A:3512, NA:6715)	Measure: MPR Classification: MPR < 80 = non-compliant Method of Assessment: pharmacy claims data	Total Healthcare costs Medical Costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence: THC:$5289.61 ($6865.90), MC:$4908.09 ($6370.60)	Quality: medium Classification: cost description
*Casciano et al***[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.	Design: Retrospective, observational, quasi-experimental study Follow Up: 18months Sample Size: 13289 (A:2852, NA:4184, NE:6253)	Measure: PDC Classification: PDC <80 = low adherence , 0 = no warfarin exposure Method of Assessment: pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2005 Cost of Nonadherence*: TC:$16612.44($19936.70), IC:$9382.56 ($11260.10), OC:$8605.92 ($10328), PC:$2388.24 ($2866.20), MC:$15235.80($18285)	Quality: medium Classification: cost description
*Dilokthornsakul et al***[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	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 393 (A:168, NA:219, OA:6)	Measure: MPR Classification: MPR < 80 = undersupply, MPR >120 = oversupply Method of Assessment: pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC:$1157 ($1433.06), IC:$1019 ($1262.13), OC:$138 ($170.93)	Quality: high Classification: 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) 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)	Quality: medium Classification: cost description
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) Unadjusted Hospitalised patients: THC:$14725 ($14566.40), PC:$3374 ($3337.66), MC:$2475 ($2448.34), HC:$8876 ($8780.40) Predicted disease state specific:	Quality: medium Classification: cost description

					HC:$2669 ($2640.25) Predicted hospitalised patient: HC$9214 ($9114.76)	
Pittman et al ***[6]*** 2011 US	To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.	Design: Retrospective cohort study Follow Up: 18 months Sample Size: 381422 (A:258013, MA:65795, LA:57614)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence 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, 2009 Cost of Nonadherence*: all cause: THC(>80):$6798.67 ($7505.66), THC(60-79):$7072.67 ($7808.16), THC(<59):$7401.33 ($8170.99), PC(>80):$1767.33 ($1951.11), PC(60-79):$1789.33 ($1975.40), PC(<59):$1937.33 ($2138.79), MC(>80):$4472.67 ($4937.78), MC(60-79):$4840.67 ($5344.05, MC(<59):$5138.67 ($5673.04) Disease state specific: PC(>80):$558.67 ($616.77), PC(60-79):$442.67 ($488.70), PC(<59):$325.33 ($359.16), MC(>80):$1596.67 ($1762.71), MC(60-79):$1722 ($1901.07), MC(<59):$1792.67 ($1979.09)	Quality: medium Classification: cost description
Pittman et al ***[7]*** 2010 US	To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 625620(A:467006, MA:96226, LA:62388)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence	Total Healthcare Costs Outpatient Costs ED Costs Pharmacy Costs Hospitalization	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: Adjusted: THC(>80):$7261 ($8077.79), THC(60-79):$7530 ($8377.05), THC(<59):$7370 ($8199.05), OC(>80):$3390 ($3771.34), OC(60-79):$3705 ($4121.77),	Quality: medium Classification: cost description

	costs of care.		<u>Method of Assessment:</u> 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-	<u>Design:</u> Retrospective cohort study <u>Follow Up:</u> 12 months <u>Sample Size:</u> 7211(P:2668, NC:3101, NP:649, T:793)	<u>Measure:</u> ordinary least square regression analysis <u>Classification:</u> >80% = persistent, ≥30<80% = non-compliance, <30%	Total Healthcare Costs	<u>Type of Costs:</u> unadjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 1994 <u>Cost of Nonadherence:</u> All cause: THC(>80):$341 ($509.66), THC(30-80):$694 ($1037.26),	<u>Quality:</u> low <u>Classification:</u> 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

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),

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),

	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),

					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

	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

					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

Becker et al ***[14]*** 2007 US	Examine treatment outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries.	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505)	Measure: prescription refill rate Classification: 75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, <25% = negligible adherence Method of Assessment: pharmacy claims data	Total Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2006 Cost of Nonadherence*: TC(75-100):$13564 ($15792.91), TC(50-74):$13772 ($16035.09), TC(25-49):$15792 ($18387.03), TC(<25):$16156 ($18810.84)	Quality: low Classification: cost description
Eaddy et al ***[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.	Design: Retrospective database analysis Follow Up: 1 year Sample Size: 7864 (<80%:2655, 80-125%:5065, >125%:144)	Measure: continuous multiple interval medications available Classification: <80% = partially compliant, 80-125% = compliant, >125% = overly compliant Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs Pharmacy costs Medical costs Physician office visit costs Other costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence*: IC:$37380 ($4906.39), OC:$504 ($654.19), PC:$1872 ($2429.83), MC:$6228 ($8083.86), POC:$1944 ($2523.29) OtC:$12 ($15.58)	Quality: medium Classification: cost description
Gilmer et al ***[16]*** 2004	To evaluate the relationship between	Design: Retrospective database analysis	Measure: cumulative	Total costs Outpatient	Type of Costs: adjusted Classification: disease state specific	Quality: medium Classification: cost

US	adherence to treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.	Follow Up: 1 year Sample Size: 1619 (<49%:388, 50-79%:259, 80-100%:664, >110%:308)	possession ratio Classification: <49% = nonadherent, 50-79% = partially adherent, 80-100% = adherent, >110% = excess medication fillers Method of Assessment: pharmacy claims data	costs Pharmacy costs Hospitalization costs	Currency Year: USD, 1999 Cost of Nonadherence: 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.	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	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:	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

	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 Method of Assessment: health insurance data	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	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

	with schizophrenia.		Assessment: survey		ESC:£1603 ($3241.47)	
*Offord et al**[21]*** 2013 US	To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term antipsychotic adherence, healthcare utilisation and costs.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 1462 (A:589, NA:873)	Measure: time to discontinuation Classification: adherent vs. nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Pharmacy costs Hospitalization costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: TC:$15400 ($17132.34) OC:$5773 ($6422.40), PC:$3777 ($4201.87), HC:$5850 ($6508.06) Disease state specific: TC:$5358 ($5960.72) OC:$858 ($954.52), PC:$1549 ($1723.25), HC:$2952 ($3284.07)	Quality: medium Classification: cost description
*Offord et al**[22]*** 2013 US	To examine the impact of medication adherence on healthcare utilisation among Medicare insured schizophrenia patients.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 354 (A:126, NA:228)	Measure: MPR Classification: MPR ≥ 70= high adherence, MPR < 70 = low adherence Method of Assessment: pharmacy claims data	Inpatient costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: IC:$9053 ($10071.37), PC:$4267 ($4746.99), Disease state specific: IC:$2468 ($2745.62), PC:$1085 ($1207.05)	Quality: low Classification: cost description
*Robinson et al**[23]*** 2006 US	To determine if the type of antidepressant drug is related to adherence and assess the 6 month health care costs among newly diagnosed	Design: Retrospective claims analysis Follow Up: 6 months Sample Size: 60386 (A:11526, NA:8860)	Measure: Antidepressant medication management measures Classification: meeting less than	Total costs Inpatient costs Outpatient costs ED visit costs Pharmacy	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2004 Cost of Nonadherence*: all cause: TC:$12658 ($15678.21) IC:$3006 ($3723.24),	Quality: medium Classification: cost description

	patients.		<3 medication management measures = nonadherent Method of Assessment: pharmacy claims data, Medicaid data, observational assessment	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/schizoaffective 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

			data			
Diabetes						
*An et al***[26]** 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.	Design: Prospective cohort study Follow Up: 3 years Sample Size: 608 (A:472, NA:136)	Measure: MPR Classification: MPR≥90% = adherent, MPR<90% = nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence*: TC:$1657.11 ($1884.14) OC: $1413.99 ($1608.20), HC: $243.11 ($276.12)	Quality: medium Classification: cost description
*Egede et al***[27]** 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**[28]** 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	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),	Quality: medium Classification: cost description

			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)	
*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	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

					Unadjusted disease state specific: HC:$6919 ($8569.88), PC:$785 ($972.30), MC:$5192 ($6430.82), STDC:$1717 ($2126.68)	
*Hansen et al***[30]** 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.	Design: Retrospective, cohort study Follow Up: 2 years Sample Size: 108592 (A:63830, NA:44762)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total Healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific Currency Year: USD, 2005 Cost of Nonadherence#: 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)	Quality: medium Classification: cost description
*Hong et al***[31]** 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.	Design: Retrospective, cohort study Follow Up: 3 years Sample Size: 40082 (A:11800, NA:28282)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: KRW, 2007 Cost of Nonadherence: TC:₩765453 ($1142.31), HC:₩397549 ($593.28)	Quality: medium Classification: cost description
*Jha et al***[32]** 2012	How often do previously non-	Design: Retrospective, observational claims	Measure: MPR Classification:	Total costs ED costs	Type of Costs: adjusted Classification: disease state specific	Quality: high Classification: cost

US	adherent patients become adherent and vice versa? Are changes in adherence associated with increased or decreased hospitalizations or 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?	analysis Follow Up: unclear Sample Size: 135639 (A:99976, NA:36553)	MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Hospitalization costs	Currency Year: USD, 2011 Cost of Nonadherence***: TC:$4680000000 ($5006563305.49), EDC:$735000000 ($786287185.80), HC:$3950000000 ($4225625012.11)	outcome description
*White et al**[33]*** 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),	Quality: low Classification: cost analysis

					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**[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	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

					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**[35]*** 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	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)	Quality: medium Classification: cost description

					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 a**[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	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

					PC:$213 ($222.23), POC:$44 ($45.91)	
*Halpern et al**[37]*** 2011 US	To examine the associations of adherence to osteoporosis therapies with occurrence of closed fracture, all cause medical costs and all cause hospitalizations.	Design: Retrospective analysis Follow Up: 540 days Sample Size: 21655 (≥80%:8759, ≥50<80%:5237, <50%:7659)	Measure: MPR Classification: (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence Method of Assessment: pharmacy claims data	Medical costs	Type of Costs: unadjusted Classification: all cause Currency Year: USD, 2006 Cost of Nonadherence: commercial: 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)	Quality: medium Classification: cost outcome description
*Hazel-Fernandez et al**[38]*** 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),	Quality: medium Classification: cost outcome description

					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)	
*Huybrechts et al**[39]*** 2006 US	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> (≥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
Kjellberget al[40] 2016 Denmark	To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of	<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> (≥70% = compliant, <70% = noncompliant) <u>Method of</u>	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),	<u>Quality:</u> high <u>Classification:</u> cost outcome description

	noncompliance with health care resource use and cost.		Assessment: pharmacy claims data		MC:€3471 ($4369.20), Disease state specific: TC:€754 ($949.12), MC:€426 ($536.24),	
*Modi et al**[41]*** 2015 US	To evaluate compliance with osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 27913 (A:23430, NA:34483)	Measure: MPR Classification: (≥80% = compliant, <80% = noncompliant) Method of Assessment: healthcare claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2011 Cost of Nonadherence: 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)	Quality: medium Classification: cost outcome description
*Olsen et al**[42]*** 2013 Denmark	To assess the association between refill compliance and all cause health care costs.	Design: Retrospective observational study Follow Up: 2 years Sample Size: 47176 (not specified)	Measure: MPR Classification: (≥80% = optimal compliance, >50<80% = suboptimal compliance, <50% = low compliance Method of Assessment:	Fracture costs	Type of Costs: unadjusted Classification: fracture site specific Currency Year: DKK, 2010 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)	Quality: medium Classification: cost analysis

			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)	
Sunyecz et al ***[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.	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), PC:$918 ($1101.70), RC:$184 ($220.82)	Quality: low Classification: cost description
Zhao et al ***[44]*** 2014 US	To examine the association between teriparatide adherence and healthcare utilisation and costs	Design: Retrospective cohort study Follow Up: 36 months Sample Size: 824 (≥80:362, 50-80%:219,	Measure: PDC Classification: (≥80% = high, 50-80% = medium, <50% = low)	Total healthcare costs Inpatient costs Outpatient	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence*: Adjusted:	Quality: medium Classification: 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)	
Zhao et al ***[45]*** 2013 US	To examine the association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebrop	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	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),	Quality: medium Classification: cost description

	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)	
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)	
Diehl et al ***[47]*** 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 ***[48]*** 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

			questionnaire		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)	
*Miravitlles et al***[49]** 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).	Design: multicentre, retrospective, observational study Follow Up: 18 months Sample Size: 1365 (A:246, NA:1119)	Measure: GOLD 2007 Guidelines Classification: (adherent, nonadherent) Method of Assessment: 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	Type of Costs: unadjusted Classification: disease state specific Currency Year: EUR, 2009 Cost of Nonadherence: 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)	Quality: medium Classification: cost description
*Quittner et al***[50]** 2014 US	To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.	Design: retrospective, cohort study Follow Up: 2 years Sample Size: 3287 (≥80%: 663, 50-80%: 949, <50%: 1675)	Measure: MPR Classification: (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence) Method of Assessment: pharmacy claims	Total healthcare costs	Type of Costs: unadjusted Classification: all cause and disease state specific 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:	Quality: medium Classification: cost description

			data		THC(≥80):$23764 ($25422.22), THC(50-80):$33132.50 ($35444.44), THC(<50):$33894 ($36259.07)	
Gastrointestinal Disease						
Carter et al ***[51]*** 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 ***[52]*** 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
Kane et al ***[53]*** 2009 US	To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by	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 =	Outpatient costs ED costs Pharmacy costs Medical costs Hospitalization	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2004 Cost of Nonadherence: All cause: OC:$6679 ($8272.62),	Quality: medium Classification: cost outcome description

	patients.		nonadherent) Method of Assessment: health claims data	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)	
Mitra et al **[54]** 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.	Design: retrospective, observational cohort study Follow Up: 12 months Sample Size: 1693 (A:476, NA:1216)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Ancillary costs Non-pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence: 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)	Quality: high Classification: cost description
Wan et al **[55]** 2014 US	To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.	Design: retrospective cohort analysis Follow Up: 360 days Sample Size: 1646 (A:674, NA:972)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2009 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),	Quality: high Classification: cost description

					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 ***[56]*** 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 ***[57]*** 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 ***[58]***	To study the impact of	Design: retrospective	Measure: MPR	Total costs	Type of Costs: unadjusted	Quality: medium

2009 US	non-adherence to antiepileptic drugs (AEDs) on healthcare utilisation and direct medical costs in a Medicaid population.	observational open cohort design Follow Up: 4.65 years Sample Size: 33658 (A:24907, NA:8751)	Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Other pharmacy costs	Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence*: TC:$14417.64 ($18713.91), IC:$6682.28 ($6873.51), OC:$2172.40 ($2819.75), EDC:$405.96 ($526.93), PC:$822.40 ($1067.46), OtPC:$4334.60 ($5626.26)	Classification: cost description
HIV/AIDS						
Barnett et al ***[59]*** 2011 US	To characterise the cost of HIV care including combination antiretroviral treatment.	Design: retrospective observational cohort study Follow Up: 1 year Sample Size: 1896 (not specified)	Measure: antiretroviral taking behaviour Classification: (85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent) Method of Assessment: pharmacy claims data	Total costs	Type of Costs: unadjusted Classification: disease state specific; viral load count Currency Year: USD, 2006 Cost of Nonadherence**: High viral load: TC:$25824 ($30067.54) Low viral load: TC:$20509.67 ($23879.92)	Quality: medium Classification: cost description
Cooke et al ***[60]*** 2014 US	To measure adherence to antiretroviral therapy regimens in commercially insured patients with HIV infection and analyse the clinical and demographic factors	Design: retrospective claims analysis Follow Up: 1 year Sample Size: 3528 (A:1737, NA:640)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) Method of Assessment: pharmacy claims	Total healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2011 Cost of Nonadherence: THC:$18868 ($20184.58), IC:$2700 ($2888.40), OC:$915 ($978.85), PC:$15253 ($16317.33)	Quality: medium Classification: cost description

	associated with ≥90% adherence.		data			
Pruitt et al ***[61]*** 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.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 502 (A:56, NA:176)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Other pharmacy costs Behavioural health inpatient costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2009 Cost of Nonadherence*: 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)	Quality: medium Classification: cost description
Parkinson's Disease						
Davis et al ***[62]*** 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.	Design: retrospective administrative claims study Follow Up: 12 months Sample Size: 3119 (A:1211, NA:1908)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2001 Cost of Nonadherence: TC:$18511 ($24262.36), PC:$2684 ($3537.36), MC:$15827 ($20859.12)	Quality: medium Classification: cost outcome description
Delea et al ***[63]***	To assess the	Design: retrospective	Measure: PDC	Total costs	Type of Costs: adjusted and unadjusted	Quality: high

2011 US	associations between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilisation and costs.	historical cohort study Follow Up: 12 months Sample Size: 1215 (A:617, NA:598)	Classification: (≥80% = satisfactory, <80% = unsatisfactory) Method of Assessment: pharmacy claims data	Inpatient costs Pharmacy costs Other costs	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), OC:$8795 ($10554.94) Adjusted disease state specific: TC:$8574 ($10289.71), IC:$3705 ($4446.39), PC:$3850 ($4620.41), OC:$1884 ($2261) Unadjusted all cause: TC:$19362 ($23236.46), IC:$5463 ($6556.18), PC:$6158 ($7390.26), OC:$7740 ($9288.82) Unadjusted disease state specific: TC:$9156 ($10988.18), IC:$3238 ($3885.94), PC:$3789 ($4547.20), OC:$2129 ($2555.03)	Classification: cost description
Wei et al ***[64]*** 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	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),	Quality: medium Classification: cost description

			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						
*Ivanova et al***[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.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 648 (A:448, NA:200)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Short term disability costs Absenteeism cost	Type of Costs: unadjusted Classification: all cause, disease state specific and indirect Currency Year: USD, 2007 Cost of Nonadherence*: 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)	Quality: high Classification: cost outcome description
*Tan et al***[66]** 2011	To assess the impact of treatment adherence	Design: retrospective cohort study	Measure: MPR Classification:	Medical costs	Type of Costs: adjusted and unadjusted Classification: disease state specific	Quality: medium Classification: cost

US	on MS related hospitalizations (inpatient), ER visits, MS relapses and medical costs.	Follow Up: 12 months Sample Size: 2446 (A:1459, NA:987)	(≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data		Currency Year: USD, 2007 Cost of Nonadherence: Adjusted: MC:$4348 ($5062.49) Unadjusted: MC:$5179 ($6030.04)	description
*Zhao et al**[67]*** 2011 US	To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 5435 (A:1744, NA:3691)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: commercial: TC:$20323 ($22609.12), IC:$4808 ($5348.85), OC:$9822 ($10926.87), PC:$5693 ($6333.40) Medicare: TC:$25282 ($28125.96), IC:$8604 ($9571.86), OC:$10068 ($11200.54), PC:$6611 ($7354.67)	Quality: medium Classification: cost analysis
Cancer						
*Darkow et al**[68]*** 2007 US	Estimate the association between treatment interruptions and non-adherence with imatinib and healthcare costs for US managed care patients.	Design: retrospective observational cohort analysis Follow Up: 12 months Sample Size: 267 (≥95%:120, 90-95%:25, 50-90%:69, <50%:53)	Measure: MPR Classification: (≥95% = very high, >90<95% = high, >50<90% = intermediate, <50% = low) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other pharmacy	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC(≥95):$42250 ($52330.90), THC(90-95):$39236 ($48597.76), THC(50-90):$54770 ($67838.19), THC(<50):$131357 ($162698.93), IC(≥95):$1156 ($1431.82), IC(90-95):$1362 ($1686.97), IC(50-90):$19096 ($23652.33), IC(<50):$81572 ($101035.18),	Quality: high Classification: cost description

				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)	
Wu et al[69] 2010 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						
Leider et al[70] 2011	To assess the economic burden of chronic	Design: retrospective claims based analysis	Measure: urine testing	Total healthcare	Type of Costs: unadjusted Classification: disease state specific	Quality: medium Classification: cost

US	opioid users and to determine whether opioid regimen non-adherence contributes to increased healthcare costs.	Follow Up: 12 months Sample Size: 2100 (A:442, NA:1658)	Classification: (positive test = nonadherent, negative test = adherent) Method of Assessment: health claims data	costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs	Currency Year: USD, 2008 Cost of Nonadherence: THC:$26433 ($29406.43), IC:$6361 ($7076.55), OC:$9734 ($10828.97), EDC:$421 ($468.36), PC:$7960 ($8855.42), MC:$1957 ($2177.14)	analysis
*Tkacz et al**[71]*** 2014 US	To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent members.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 455 (A:146, NA:309)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence: 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), OC:$14173 ($15459.63), EDC:$4058 ($4426.39), PC:$3557 ($3879.91)	Quality: medium Classification: cost description
Metabolic conditions other than diabetes mellitus						
*Lee et al**[72]*** 2011 US	To assess the relationship between medication adherence and healthcare costs among US patients on	Design: retrospective cohort study Follow Up: 12 months Sample Size: 4923 (A:1372, NA:1304)	Measure: MPR Classification: (≥80% = high adherent, <80% = low adherent)	Total costs Inpatient costs Outpatient costs ED costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence:	Quality: medium Classification: cost description

	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

Spain	hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.	Sample Size: 87 (A:21, NA:66)	(>75% = adherent, ≤75% = nonadherent) Method of Assessment: pharmacy and hospital claims data	Cost of Nonadherence[####]: All cause: HC:€6275.80 ($8893.94)	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, 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 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[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-

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

Costs were defined as any indicator associated with medication nonadherence that was quantified with a monetary value in the original study. This included direct costs (those costs borne by the healthcare system, community and patients' families in addressing the illness), indirect costs (mainly productivity losses to society caused by the health problem or disease) and avoidable costs (those costs incurred for patients suffering complications, resulting from suboptimal medicines use, and patients with the same disease who experienced no complications). The indicators were grouped for analysis based on the original studies classification of the cost. All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [18], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[18]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [19]. All studies were classified in accordance with Drummond's distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or

effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).

The Drummond checklist [20] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

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

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 Unites 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.

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[23 24 26 28 30 31 33 36-38 41 42 46 48 49 54 55 57 60-64 69-77 82 91-94] and 11 studies (15%) reported nonadherence costs to be less than adherence costs[22 25 35 43 58 62 65 80 87 89 90]. Four reported fluctuating findings based on varying nonadherence cost subcategories[32 47 66 88] and two studies reported conflicting findings between adjusted and unadjusted costs [78 79]. Sunyecz et al[67], Eisenberg et al[40] and Joe et al[86] 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[46] reported all cause total nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

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

3.5 Cost of medication nonadherence via disease group

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

3.5.1 Cardiovascular Disease

Twelve studies measured the economic impact of medication nonadherence in cardiovascular disease [11 23 30 60 61 64 66 75 80 88 90 91]. Six studies reported adjusted costs [11 23 30 60 61 75] with annual costs being extrapolated for two of these[30 60]. Total healthcare costs and/or total costs were assessed in all of the studies with the major indicators measured including pharmacy costs[11 30 60 61 75], medical costs[11 23 30 60 75] and outpatient costs[30 61]. The annual economic cost of nonadherence ranged from $3,347 to $19,472. Sokol et al[11] 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 [64 66 80 88 90 91]. Rizzo et al[64] 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[80], 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[66 88], outpatient costs[66 88], pharmacy costs[66 90 91], medical costs[90 91] and hospitalization costs[90 91].

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[22 24 26 51 58 65 72 81 86 93 94], with annual cost data being extrapolated for four of these[26 65 81 94]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged from $3,252 to $19,363 [22 24 58 59 72 86]. Bagalman et al[24] focused primarily on the indirect costs associated with nonadherence – short-term disability, workers compensation and paid time off costs while Robertson et al[81] 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 costs[22 38 51 58 59 65 72 94], inpatient costs[38 59 65 93 94], outpatient costs[22 38 58 65 94] and hospitalization costs[21 22 58 94].

The total unadjusted cost for medication nonadherence ranged from $2,512 to $25,920 as reported in four studies [51 65 81 94]. Becker et al[26] used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%,

<25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al[93] outlined the predicted cost of nonadherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

3.5.3 Diabetes mellitus:

Nine studies reported some cost measurement of the impact of medication nonadherence with reference to the health system and the individual[39 44 46 50 73 75 87 89 92]. One study estimated that the total US cost attributable to nonadherence in diabetes was slightly over $5 billion[50]. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819 [46 50 73 75 92]. One study reported total costs in relation to subgroup analysis based on MPR level[73], and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients[75].

A further three studies reported unadjusted cost findings[39 87 89] and four studies reported unadjusted costs in addition to adjusted values[44 46 73 92]. 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 [39 89].

The most prominent indicators used to determine costs were pharmacy costs[39 44 46 73 75 92], outpatient costs[39 46 75 89 92], inpatient costs[46 75 92] and hospitalization costs[50 87 89]. All studies assessed the direct costs associated with medication nonadherence. One study evaluated the relationship between nonadherence and short term disability costs in addition to assessing direct costs[44].

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 [47 83]. Four out of 11 studies reported the adjusted cost of medication nonadherence in addition to reporting unadjusted costs [27 78 79 82]. Three studies further classified nonadherence through subgroup analysis, with Briesacher et al[27] using MPR 20% interval increases and the two studies conducted by Zhao et al[78 79] using PDC, with ≥80% classified as high adherence, 50-79% medium adherence and <50% low adherence . In the studies conducted by Zhao et al[78 79], 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[27] 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 [47 78 79].

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 [45].

3.5.5 Respiratory Disease:

All five studies reported the unadjusted cost of medication nonadherence. The methods of classifying adherence levels varied greatly among them[35 37 52 63 84]. Two studies used MPR[35 63], one the Morisky 4-Item scale[52], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[84] and one a 37 day gap in claims data[37]. Joshi et al[52] 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[35] reported a direct relationship between decreases in medication nonadherence level and total costs, whereas Quittner et al[63] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the lowest subgroup of adherence across all measures ranged from $804 to $36,259.

3.5.6 Gastrointestinal Disease:

Three of five studies reported the adjusted annual cost of medication nonadherence per patient utilizing the MPR method [43 56 70]. Of these, two reported the total cost ($12,085 and $37,151)[43 70] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the total cost nor total healthcare costs[29 53]. Carter et al[29] reported hospitalization costs to be $42,854 while Kane et al[53] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

3.5.7 Epilepsy:

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

3.5.8 HIV/AIDS:

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

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 [33 36 71]. Wei et al[71] 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[36].

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[49], one assessed only the medical costs[68] and one examined the direct costs in commercial and Medicare supplemental patient populations[77]. Zhao et al[77] reported the adjusted annual cost in the commercial population to be $22,609, and in the Medicare supplemental group, $28,126. Ivanova et al[49] 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[32 74]. One study reported total annual costs of $119,416[74], while the other gave a subgroup analysis based on classified adherence levels[32]. 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[55] while the unadjusted cost ranged from $29,406 to $52,213 [55 69]. Leider et al[55] reported the main contributors to this cost to be outpatient costs ($10,829) and pharmacy costs ($8,855), whereas Tkacz et al[69] reported them to be inpatient costs ($28,873 and $28,407) and outpatient costs ($15,893 and $15,460).

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[54]. 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:

Only Candrilli et al[28] 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[30 46 49 60 63 65 94]. Ten studies reported on economic indicators without giving total cost or total healthcare cost[21 44 45 53 54 56 59 80 85 94], and one study reported on costs per episode of nonadherence[85] .

The adjusted cost of medication nonadherence was reported in 10 studies with an estimated range 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 nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[60] 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 [21 40 45 49 53 54 57 63-65 67 80 85 94]. A further four studies reported adjusted and unadjusted costs[36 44 46 92]. 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 required statistical parameters in particular standard deviation[95]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.

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

medication nonadherence thus enabling greater planning in terms of health policy to help counteract costs.

The economic, clinical and humanistic consequences of medication nonadherence will continue to grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to adequately address the determinants of adherence through utilization of effective health interventions. Haynes et al [96] highlights that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments". Improving medication adherence provides an opportunity for major cost savings to healthcare systems. Moving forward health policy needs to recognize the link between adherence and health system efficacy and the opportunity it presents to allocate health budget spending more appropriately. Predictions of population health outcomes through utilization of treatment efficacy data need to be used in conjunction with adherence rates to inform planning and project evaluation[5]. 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.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [97], 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 medication nonadherence, it further justifies the need to agree on consistent methods for estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used in 65% of studies, followed by PDC, which was used in 9%. These percentages were consistent with those found recently by Sattler et al [98]. Even though the measures of medication nonadherence may be comparable, the definition of MPR and the cut-off points to define nonadherence differed significantly. Dragomir et al[90] defined MPR as the total days' supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalization; Wu et al[75] removed the number of hospitalized days from the calculation; and Pittman et al[60] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Nonadherence could also be further classified into subcategories within MPR and PDC based on percentages. Twenty-eight studies defined nonadherence as MPR< 80%, and 19 studies categorized nonadherence into varying percentage subgroups. While Karve et al[99] validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent hospitalizations in patients across a broad array of chronic diseases, 72 of the 75 studies included in this review examined more than just hospitalization costs as an indicator metric. Further research is required to identify and standardise nonadherence thresholds using other outcomes such as laboratory, productivity and pharmacy measures.

Within the 75 studies covered, 34 different indicators were used to measure the cost of nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a meta-analysis was impossible. It is imperative that a standardized approach be established to measure and report the economic impact of medication nonadherence. The core outcome set must take into consideration the perspective of the intended audience and the proportion of nonadherence cost that is attributable to each outcome to determine an appropriate model[100]. The critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient costs, outpatient costs, emergency department visit costs, medical costs and hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes include short term disability costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs. We suggest that further analysis of the contribution of each outcome to the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future research.

Many studies have examined the relationship between nonadherence and economic outcomes using a cross-sectional analysis[50]. The implications of this are that potentially crucial confounders such as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for example, did greater adherence result in reduced costs and improved health outcomes, or was the patient healthier initially and more capable of being adherent? A longitudinal design is needed to overcome this limitation.

None of the studies included a full economic evaluation. An economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each[19]. While none of the studies taken separately could inform a choice between alternative courses of action, they did provide key evidence for decision makers about costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority of studies to model cost estimates. Three-quarters of the studies were classified as cost descriptions, providing a cost or outcome overview of the health consequences associated with nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall conclusions that are able to be drawn and emphasised the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al[101] highlighted the need for more information on the consequences of nonadherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Of the seventy five included studies, sixty two of the studies were conducted in the United States. Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and disease states. Comparison of costs between healthcare systems is difficult as no two are the same and as healthcare is generally more expensive in the United States cost estimates may not reflect average values. Thus caution needs to be taken when interpreting results however findings help to represent the significance of the economic burden medication nonadherence plays. Analysis of studies not conducted in the United States support the finding that generally medication nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.

Due to the advances in technology available to record and assess medication nonadherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the inclusion criteria[21 22 64 72 73 93]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between nonadherence and increasing healthcare costs.

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.

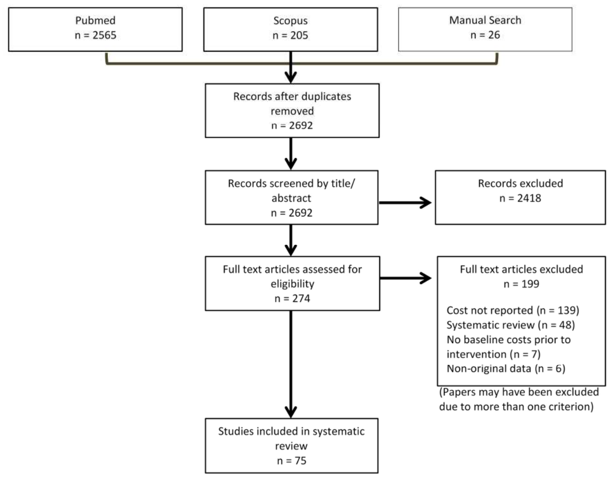

Figure 1: PRISMA Flow Diagram

209x297mm (300 x 300 DPI)

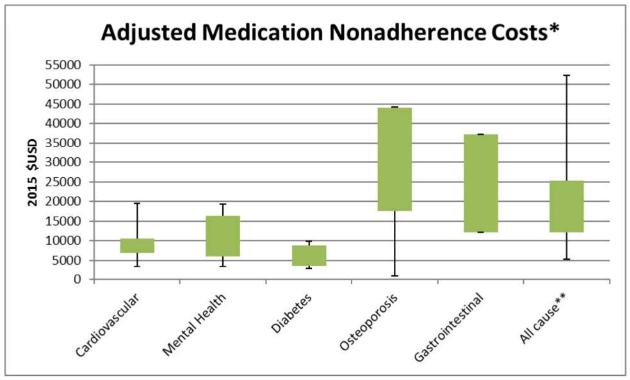

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year *Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.** All cause costs: mixed disease state studies

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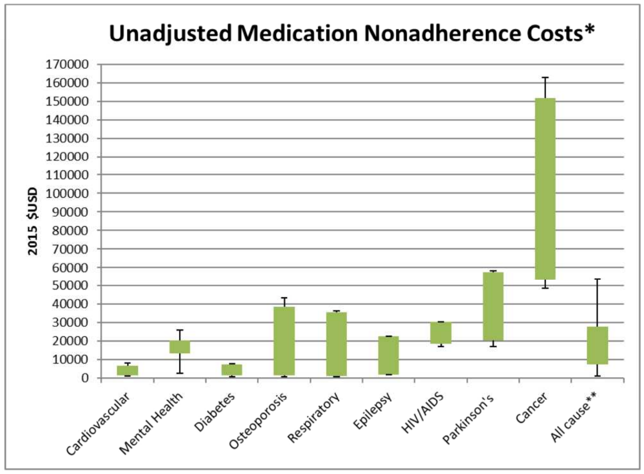

Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year *Disease groups with three or more studies were included. Epilepsy only included three studies limiting the range of costs.** All cause costs: mixed disease state studies

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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						
*Aubert et al***[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.	Design: Retrospective cohort study Follow Up: 3 years Sample Size: 10227 (A:3512, NA:6715)	Measure: MPR Classification: MPR < 80 = non-compliant Method of Assessment: pharmacy claims data	Total Healthcare costs Medical Costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence: THC:$5289.61 ($6865.90), MC:$4908.09 ($6370.60)	Quality: medium Classification: cost description
*Casciano et al***[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.	Design: Retrospective, observational, quasi-experimental study Follow Up: 18months Sample Size: 13289 (A:2852, NA:4184, NE:6253)	Measure: PDC Classification: PDC <80 = low adherence , 0 = no warfarin exposure Method of Assessment: pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2005 Cost of Nonadherence*: TC:$16612.44($19936.70), IC:$9382.56 ($11260.10), OC:$8605.92 ($10328), PC:$2388.24 ($2866.20), MC:$15235.80($18285)	Quality: medium Classification: cost description
*Dilokthornsakul et al***[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	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 393 (A:168, NA:219, OA:6)	Measure: MPR Classification: MPR < 80 = undersupply, MPR >120 = oversupply Method of Assessment: pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC:$1157 ($1433.06), IC:$1019 ($1262.13), OC:$138 ($170.93)	Quality: high Classification: 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) 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)	Quality: medium Classification: cost description
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) Unadjusted Hospitalised patients: THC:$14725 ($14566.40), PC:$3374 ($3337.66), MC:$2475 ($2448.34), HC:$8876 ($8780.40) Predicted disease state specific:	Quality: medium Classification: cost description

					HC:$2669 ($2640.25) Predicted hospitalised patient: HC$9214 ($9114.76)	
*Pittman et al***[6]** 2011 US	To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.	Design: Retrospective cohort study Follow Up: 18 months Sample Size: 381422 (A:258013, MA:65795, LA:57614)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence 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, 2009 Cost of Nonadherence*: all cause: THC(>80):$6798.67 ($7505.66), THC(60-79):$7072.67 ($7808.16), THC(<59):$7401.33 ($8170.99), PC(>80):$1767.33 ($1951.11), PC(60-79):$1789.33 ($1975.40), PC(<59):$1937.33 ($2138.79), MC(>80):$4472.67 ($4937.78), MC(60-79):$4840.67 ($5344.05, MC(<59):$5138.67 ($5673.04) Disease state specific: PC(>80):$558.67 ($616.77), PC(60-79):$442.67 ($488.70), PC(<59):$325.33 ($359.16), MC(>80):$1596.67 ($1762.71), MC(60-79):$1722 ($1901.07), MC(<59):$1792.67 ($1979.09)	Quality: medium Classification: cost description
*Pittman et al***[7]** 2010 US	To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 625620(A:467006, MA:96226, LA:62388)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence	Total Healthcare Costs Outpatient Costs ED Costs Pharmacy Costs Hospitalization	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: Adjusted: THC(>80):$7261 ($8077.79), THC(60-79):$7530 ($8377.05), THC(<59):$7370 ($8199.05), OC(>80):$3390 ($3771.34), OC(60-79):$3705 ($4121.77),	Quality: medium Classification: cost description

	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 ß-	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)	
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),

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),

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),

					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	<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

	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

					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

*Becker et al**[14]*** 2007 US	Examine treatment outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries.	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505)	Measure: prescription refill rate Classification: 75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, <25% = negligible adherence Method of Assessment: pharmacy claims data	Total Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2006 Cost of Nonadherence*: TC(75-100):$13564 ($15792.91), TC(50-74):$13772 ($16035.09), TC(25-49):$15792 ($18387.03), TC(<25):$16156 ($18810.84)	Quality: low Classification: cost description
*Eaddy et al**[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.	Design: Retrospective database analysis Follow Up: 1 year Sample Size: 7864 (<80%:2655, 80-125%:5065, >125%:144)	Measure: continuous multiple interval medications available Classification: <80% = partially compliant, 80-125% = compliant, >125% = overly compliant Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs Pharmacy costs Medical costs Physician office visit costs Other costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence*: IC:$3780 ($4906.39), OC:$504 ($654.19), PC:$1872 ($2429.83), MC:$6228 ($8083.86), POC:$1944 ($2523.29) OtC:$12 ($15.58)	Quality: medium Classification: cost description
*Gilmer et al**[16]*** 2004	To evaluate the relationship between	Design: Retrospective database analysis	Measure: cumulative	Total costs Outpatient	Type of Costs: adjusted Classification: disease state specific	Quality: medium Classification: cost

US	adherence to treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.	Follow Up: 1 year Sample Size: 1619 (<49%:388, 50-79%:259, 80-100%:664, >110%:308)	possession ratio Classification: <49% = nonadherent, 50-79% = partially adherent, 80-100% = adherent, >110% = excess medication fillers Method of Assessment: pharmacy claims data	costs Pharmacy costs Hospitalization costs	Currency Year: USD, 1999 Cost of Nonadherence: 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.	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	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:	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

	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 Method of Assessment: health insurance data	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	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

	with schizophrenia.		Assessment: survey		ESC:£1603 ($3241.47)	
*Offord et al**[21]*** 2013 US	To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term antipsychotic adherence, healthcare utilisation and costs.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 1462 (A:589, NA:873)	Measure: time to discontinuation Classification: adherent vs. nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Pharmacy costs Hospitalization costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: TC:$15400 ($17132.34) OC:$5773 ($6422.40), PC:$3777 ($4201.87), HC:$5850 ($6508.06) Disease state specific: TC:$5358 ($5960.72) OC:$858 ($954.52), PC:$1549 ($1723.25), HC:$2952 ($3284.07)	Quality: medium Classification: cost description
*Offord et al**[22]*** 2013 US	To examine the impact of medication adherence on healthcare utilisation among Medicare insured schizophrenia patients.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 354 (A:126, NA:228)	Measure: MPR Classification: MPR ≥ 70= high adherence, MPR < 70 = low adherence Method of Assessment: pharmacy claims data	Inpatient costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: IC:$9053 ($10071.37), PC:$4267 ($4746.99), Disease state specific: IC:$2468 ($2745.62), PC:$1085 ($1207.05)	Quality: low Classification: cost description
*Robertson et al**[23]** 2014 US*	To examine the impact of the combination of treatment utilization and medication possession on arrest and incarceration outcomes and on	Design: Retrospective cohort study Follow Up:90 days Sample Size:1376 (90/90:637, 60/90:240, 30/90:174, 0/90:316)	Measure: MPR Classification: MPR ≥80% = adherent Method of Assessment: Medicaid claims	Total costs Inpatient costs Outpatient costs Emergency department costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD,2005 Cost of Nonadherence*: TC(90/90):$28068 ($33495.65), TC(60/90):$21720 ($25920.11), TC(30/90):$21084 ($25161.12),	Quality: medium Classification: cost description

costs.	data	Pharmacy costs Target case management costs Psychiatric assessment costs Arrest costs Incarceration costs	TC(0/90):$12516 ($14936.28), IC(90/90):$12168 ($14520.99), IC(60/90):$10068 ($12014.90), IC(30/90):$11376 ($13575.84), IC(0/90):$5592 ($6673.35), OC(90/90):$6468 ($7718.75), OC(60/90):$4152 ($4954.89), OC(30/90):$2916 ($3479.88), OC(0/90):$2136 ($2549.05), EDC(90/90):$96 ($114.56), 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]** 2006 US	To determine if the type of antidepressant drug is related to adherence and assess the 6 month health care costs among newly diagnosed patients.	Design: Retrospective claims analysis Follow Up: 6 months Sample Size: 60386 (A:11526, NA:8860)	Measure: Antidepressant medication management measures Classification: meeting less than <3 medication management measures = nonadherent Method of Assessment: pharmacy claims data, Medicaid data, observational assessment	Total costs Inpatient costs Outpatient costs ED visit costs Pharmacy costs Physician office visit costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2004 Cost of Nonadherence*: 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)	Quality: medium Classification: cost description
Svarstad et al **[25]** 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/schizoaffective 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 **[26]** 2003	To evaluate the economic impact of	Design: Retrospective database analysis	Measure: MPR Classification:	Total costs Pharmacy	Type of Costs: adjusted Classification: disease state specific	Quality: medium Classification: cost

US	antidepressant treatment adherence among patients treated for depression	Follow Up: 6 months Sample Size: 14190 (A:5638, NA:8552)	MPR≥70% = adherent, MPR<70% = nonadherent Method of Assessment: pharmacy claims data	costs Medical costs	Currency Year: USD, 1999 Cost of Nonadherence: TC:$11815 ($16290.09) PC:$1123 ($1548.35), MC:$10692 ($14741.74)	description
Diabetes						
*An et al***[27]** 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.	Design: Prospective cohort study Follow Up: 3 years Sample Size: 608 (A:472, NA:136)	Measure: MPR Classification: MPR≥90% = adherent, MPR<90% = nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence*: TC:$1657.11 ($1884.14) OC: $1413.99 ($1608.20), HC: $243.11 ($276.12)	Quality: medium Classification: cost description
*Egede et al***[28]** 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**[29]** 2015	To examine healthcare costs associated with	Design: Retrospective, observational cohort	Measure: MPR Classification:	Total costs Inpatient costs	Type of Costs: adjusted and unadjusted Classification: all cause and disease	Quality: medium Classification: cost

Canada	adherence to oral antihyperglycemic agents and the effects of depression and anxiety disorders on these in older adults with type 2 diabetes	analysis Follow Up: 1 year Sample Size: 301 (A:224, NA:77)	MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Outpatient costs Pharmacy costs Physician office visit costs	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), 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)	description
*Hagen et al**[30]*** 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	Healthcare costs Pharmacy costs Medical costs Short term	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific Currency Year: USD, 2003 Cost of Nonadherence: Adjusted all cause:	Quality: medium Classification: cost description

			Method of Assessment: 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)	
*Hansen et al***[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.	Design: Retrospective, cohort study Follow Up: 2 years Sample Size: 108592 (A:63830, NA:44762)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total Healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific Currency Year: USD, 2005 Cost of Nonadherence[#]: 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)	Quality: medium Classification: cost description
*Hong et al***[32]** 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and	Design: Retrospective, cohort study Follow Up: 3 years Sample Size: 40082 (A:11800, NA:28282)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% =	Total costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: KRW, 2007 Cost of Nonadherence: TC:₩765453 ($1142.31),	Quality: medium Classification: cost description

	subsequent health outcomes.		nonadherent Method of Assessment: pharmacy claims data		HC:₩397549 ($593.28)	
*Jha et al**[33]*** 2012 US	How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or decreased hospitalizations or 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?	Design: Retrospective, observational claims analysis Follow Up: unclear Sample Size: 135639 (A:99976, NA:36553)	Measure: MPR Classification: MPR≥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≥95%, MPR>75%<95%,	Total costs Pharmacy 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

	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 a****[37]*** 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	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),	Quality: medium Classification: cost description

				costs	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)	
*Halpern et al**[38]*** 2011 US	To examine the associations of adherence to osteoporosis therapies with occurrence of closed fracture, all cause medical costs and all cause hospitalizations.	Design: Retrospective analysis Follow Up: 540 days Sample Size: 21655 (≥80%:8759, ≥50<80%:5237, <50%:7659)	Measure: MPR Classification: (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence Method of Assessment: pharmacy claims data	Medical costs	Type of Costs: unadjusted Classification: all cause Currency Year: USD, 2006 Cost of Nonadherence: commercial: 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)	Quality: medium Classification: cost outcome description
*Hazel-Fernandez et al**[39]*** 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),	Quality: medium Classification: cost outcome description

					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)	
Huybrechts et al ***[40]*** 2006 US	To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.	Design: Retrospective cohort study Follow Up: 5 years Sample Size: 38120 (A:9530, NA:28590)	Measure: MPR Classification: (≥80% = compliant, <50% = noncompliant) Method of Assessment: pharmacy claims	Total costs Medical costs Institutional costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2000 Cost of Nonadherence: TC:$7200 ($9706.44), MC:$1476 ($1989.84), InstC:$5736 ($7732.80)	Quality: low Classification: cost description

			data			
*Kjellberget al***[41]** 2016 Denmark	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.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 38234 (A:26806, NA:11428)	Measure: MPR Classification: (≥70% = compliant, <70% = noncompliant) Method of Assessment: pharmacy claims data	Total costs Medical costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: Euro, 2011 Cost of Nonadherence: all cause: TC:€4933 ($6209.58), MC:€3471 ($4369.20), Disease state specific: TC:€754 ($949.12), MC:€426 ($536.24),	Quality: high Classification: cost outcome description
*Modi et al***[42]** 2015 US	To evaluate compliance with osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 27913 (A:23430, NA:34483)	Measure: MPR Classification: (≥80% = compliant, <80% = noncompliant) Method of Assessment: healthcare claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2011 Cost of Nonadherence: 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)	Quality: medium Classification: cost outcome description
*Olsen et al***[43]** 2013 Denmark	To assess the association between refill compliance and	Design: Retrospective observational study Follow Up: 2 years	Measure: MPR Classification: (≥80% = optimal	Fracture costs	Type of Costs: unadjusted Classification: fracture site specific Currency Year: DKK, 2010	Quality: medium Classification: cost analysis

	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)	
*Sunyecz 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

					PC:$918 ($1101.70), RC:$184 ($220.82)	
*Zhao et al***[45]** 2014 US	To examine the association between teriparatide adherence and healthcare utilisation and costs among hip fracture patients.	Design: Retrospective cohort study Follow Up: 36 months Sample Size: 824 (≥80:362, 50-80%:219, <50%:243)	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	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence*: 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), 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)	Quality: medium Classification: cost description
*Zhao et al***[46]**	To examine the	Design: Retrospective	Measure: PDC	Total	Type of Costs: adjusted and unadjusted	Quality: medium

2013 US	association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty (KV) patients.	observational cohort study Follow Up: 36 months Sample Size: 1568 (≥80: 783, 50-80%: 382, <50%: 403)	Classification: (≥80% = high, 50-80% = medium, <50% = low) Method of Assessment: pharmacy claims data	healthcare costs Inpatient costs Outpatient costs Pharmacy costs	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), 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)	Classification: cost description
Respiratory Disease						
*Delea et al**[47]*** 2008	To assess the association between	Design: Retrospective longitudinal cohort	Measure: MPR Classification:	Total costs Outpatient	Type of Costs: unadjusted Classification: disease state specific	Quality: medium Classification: cost

US	adherence with fluticasone propionate/salmeterol combination product in a single inhaler and asthma care utilisation and costs in asthma patients in typical US clinical practice	study Follow Up: 24 months Sample Size: 12907 (≥75: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652)	(≥75, 50-75%, 25-50%, <25%) Method of Assessment: pharmacy claims data	costs ED costs Other costs	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), 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)	description
*Diehl et al**[48]*** 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**[49]*** 2006	Examine the association of	Design: quantitative analysis	Measure: Morisky scale	Total productivity	Type of Costs: unadjusted Classification: disease state specific	Quality: medium Classification: cost

US	medication adherence with workplace productivity and health related quality of life in asthma patients.	Follow Up: Sample Size: 385 (high:150, medium:73, low: 162)	Classification: (0= high adherence, 1-2 = medium adherence, >2 = low adherence) Method of Assessment: questionnaire	cost Absenteeism costs Presenteeism costs	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), 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
Miravitlles et al ***[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).	Design: multicentre, retrospective, observational study Follow Up: 18 months Sample Size: 1365 (A:246, NA:1119)	Measure: GOLD 2007 Guidelines Classification: (adherent, nonadherent) Method of Assessment: 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	Type of Costs: unadjusted Classification: disease state specific Currency Year: EUR, 2009 Cost of Nonadherence: 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)	Quality: medium Classification: cost description
Quittner et al ***[51]*** 2014 US	To evaluate associations of adherence to	Design: retrospective, cohort study Follow Up: 2 years	Measure: MPR Classification: (≥80% = high	Total healthcare costs	Type of Costs: unadjusted Classification: all cause and disease state specific	Quality: medium Classification: 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

*Kane et al**[54]*** 2009 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 Assessment: health claims data	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), 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)	Quality: medium Classification: cost outcome description
*Mitra et al**[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.	Design: retrospective, observational cohort study Follow Up: 12 months Sample Size: 1693 (A:476, NA:1216)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Ancillary costs Non-pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence: 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)	Quality: high Classification: cost description
*Wan et al**[56]*** 2014 US	To examine the effect of adherence versus non-adherence on healthcare costs in	Design: retrospective cohort analysis Follow Up: 360 days Sample Size: 1646	Measure: MPR Classification: (≥80% = adherent, <80% =	Total costs Total healthcare costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2009	Quality: high Classification: 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

	potential association between AED non-adherence and seizure recurrence, resource utilisation and annual direct medical costs.		pharmacy claims data	costs Ancillary costs Other pharmacy costs	PC:$347 ($441.58), POC:$3063 ($3897.83), AC:$8344 ($10618.18), OtPC:$2822 ($3591.14)	
Faught et al ***[59]*** 2009 US	To study the impact of non-adherence to antiepileptic drugs (AEDs) on healthcare utilisation and direct medical costs in a Medicaid population.	Design: retrospective observational open cohort design Follow Up: 4.65 years Sample Size: 33658 (A:24907, NA:8751)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) 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, 2002 Cost of Nonadherence*: TC:$14417.64 ($18713.91), IC:$6682.28 ($6873.51), OC:$2172.40 ($2819.75), EDC:$405.96 ($526.93), PC:$822.40 ($1067.46), OtPC:$4334.60 ($5626.26)	Quality: medium Classification: cost description
HIV/AIDS						
Barnett et al ***[60]*** 2011 US	To characterise the cost of HIV care including combination antiretroviral treatment.	Design: retrospective observational cohort study Follow Up: 1 year Sample Size: 1896 (not specified)	Measure: antiretroviral taking behaviour Classification: (85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent) Method of Assessment: pharmacy claims data	Total costs	Type of Costs: unadjusted Classification: disease state specific; viral load count Currency Year: USD, 2006 Cost of Nonadherence**: High viral load: TC:$25824 ($30067.54) Low viral load: TC:$20509.67 ($23879.92)	Quality: medium Classification: cost description
Cooke et al ***[61]***	To measure adherence	Design: retrospective	Measure: MPR	Total	Type of Costs: unadjusted	Quality: medium

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 Follow Up: 1 year Sample Size: 3528 (A:1737, NA:640)	Classification: (≥90% = adherent, <90% = nonadherent) Method of Assessment: pharmacy claims data	healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Classification: disease state specific Currency Year: USD, 2011 Cost of Nonadherence: THC:$18868 ($20184.58), IC:$2700 ($2888.40), OC:$915 ($978.85), PC:$15253 ($16317.33)	Classification: cost description
Pruitt et al **[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.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 502 (A:56, NA:176)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Other pharmacy costs Behavioural health inpatient costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2009 Cost of Nonadherence*: 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)	Quality: medium Classification: cost description
Parkinson's Disease						
Davis et al **[63]** 2010 US	To assess the extent to which patients diagnosed with Parkinson's disease are	Design: retrospective administrative claims study Follow Up: 12 months	Measure: MPR Classification: (≥80% = adherent, <80% =	Total costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2001 Cost of Nonadherence:	Quality: medium Classification: cost outcome description

	non-adherent with antiparkinson therapy and the potential association between non-adherence and all cause medical costs.	Sample Size: 3119 (A:1211, NA:1908)	nonadherent) Method of Assessment: pharmacy claims data		TC:$18511 ($24262.36), PC:$2684 ($3537.36), MC:$15827 ($20859.12)	
*Delea et al**[64]*** 2011 US	To assess the associations between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilisation and costs.	Design: retrospective historical cohort study Follow Up: 12 months Sample Size: 1215 (A:617, NA:598)	Measure: PDC Classification: (≥80% = satisfactory, <80% = unsatisfactory) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Pharmacy costs Other costs	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
*Wei et al**[65]*** 2014	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

US	adherence to antiparkinson drugs with healthcare utilisation and economic outcomes.	<u>Follow Up:</u> 19 months <u>Sample Size:</u> 7583 (90-100%:3948, 80-89%:1456, ≤79%:2179)	(>90<100% = high, >80<89% = moderate, ≤79% = low) <u>Method of Assessment:</u> pharmacy claims data	Outpatient costs Pharmacy costs	<u>Currency Year:</u> USD, 2007 <u>Cost of Nonadherence:</u> 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), 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)	description
Musculoskeletal						
Ivanova et al ***[66]*** 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),	<u>Quality:</u> high <u>Classification:</u> cost outcome description

					PC:$753 ($854.07), MC:$2252 ($2554.26) Indirect: STDC:$1231 ($1396.22), AbC:$826 ($936.86)	
*Tan et al**[67]*** 2011 US	To assess the impact of treatment adherence on MS related hospitalizations (inpatient), ER visits, MS relapses and medical costs.	Design: retrospective cohort study Follow Up: 12 months Sample Size: 2446 (A:1459, NA:987)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Medical costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence: Adjusted: MC:$4348 ($5062.49) Unadjusted: MC:$5179 ($6030.04)	Quality: medium Classification: cost description
*Zhao et al**[68]*** 2011 US	To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 5435 (A:1744, NA:3691)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: commercial: TC:$20323 ($22609.12), IC:$4808 ($5348.85), OC:$9822 ($10926.87), PC:$5693 ($6333.40) Medicare: TC:$25282 ($28125.96), IC:$8604 ($9571.86), OC:$10068 ($11200.54), PC:$6611 ($7354.67)	Quality: medium Classification: cost analysis
Cancer						
*Darkow et al**[69]*** 2007 US	Estimate the association between treatment interruptions and non-adherence with	Design: retrospective observational cohort analysis Follow Up: 12 months Sample Size: 267	Measure: MPR Classification: (≥95% = very high, >90<95% = high, >50<90% =	Total healthcare costs Inpatient costs Outpatient	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC(≥95):$42250 ($52330.90),	Quality: high Classification: cost description

	imatinib and healthcare costs for US managed care patients.	(≥95%:120, 90-95%:25, 50-90%:69, <50%:53)	intermediate, <50% = low) <u>Method of Assessment:</u> pharmacy claims data	costs ED costs Pharmacy costs Medical costs Other pharmacy costs Other costs	THC(90-95):$39236 ($48597.76), THC(50-90):$54770 ($67838.19), THC(<50):$131357 ($162698.93), IC(≥95):$1156 ($1431.82), IC(90-95):$1362 ($1686.97), IC(50-90):$19096 ($23652.33), IC(<50):$81572 ($101035.18), 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), 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)	
*Wu et al**[70]***	To examine the	<u>Design:</u> retrospective	<u>Measure:</u> MPR	Total costs	<u>Type of Costs:</u> unadjusted	<u>Quality:</u> medium

2010 US	association between adherence with imatinib and direct healthcare costs and resource utilisation	observational cohort analysis Follow Up: 12 months Sample Size: 592 (A:350, NA:242)	Classification: (≥85% = high adherence, <85% = low adherence) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Other pharmacy costs	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)	Classification: cost description
Addiction						
*Leider et al***[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.	Design: retrospective claims based analysis Follow Up: 12 months Sample Size: 2100 (A:442, NA:1658)	Measure: urine testing Classification: (positive test = nonadherent, negative test = adherent) Method of Assessment: health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: THC:$26433 ($29406.43), IC:$6361 ($7076.55), OC:$9734 ($10828.97), EDC:$421 ($468.36), PC:$7960 ($8855.42), MC:$1957 ($2177.14)	Quality: medium Classification: cost analysis
*Tkacz et al***[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.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 455 (A:146, NA:309)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence: 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),	Quality: medium Classification: cost description

					OC:$14173 ($15459.63), EDC:$4058 ($4426.39), PC:$3557 ($3879.91)	
Metabolic conditions other than diabetes mellitus						
*Lee et al**[73]*** 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 ($10432.23)	Quality: medium Classification: cost description
Blood						
*Candrilli et al**[74]*** 2011 US	To investigate the relationships among hydroxyurea adherence, healthcare utilisation and healthcare costs.	Design: retrospective longitudinal study Follow Up: 12 months Sample Size: 312 (A:110, NA:202)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs ED costs Pharmacy costs Physician office visit costs Ancillary costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: All cause: TC:$ 20436 ($22734.83), IC:$9780 ($10880.15), EDC:$837 ($931.15), PC:$2579 ($2869.11), POC:$3483 ($3874.80),	Quality: medium Classification: cost description

					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						
*Alvarez Payero et al***[75]** 2014 Spain	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.	Design: retrospective observational study Follow Up: 1527 days Sample Size: 87 (A:21, NA:66)	Measure: pharmacy records Classification: (>75% = adherent, ≤75% = nonadherent) Method of Assessment: pharmacy and hospital claims data	Hospitalization costs	Type of Costs: unadjusted Classification: all cause Currency Year: EUR, 2012 Cost of Nonadherence[####]: All cause: HC:€6275.80 ($8893.94)	Quality: low Classification: 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

[*]: 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.	
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 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].

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 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-

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

Costs were defined as any indicator associated with medication nonadherence that was quantified with a monetary value in the original study. This included direct costs (those costs borne by the healthcare system, community and patients' families in addressing the illness), indirect costs (mainly productivity losses to society caused by the health problem or disease) and avoidable costs (those costs incurred for patients suffering complications, resulting from suboptimal medicines use, and patients with the same disease who experienced no complications). The indicators were grouped for analysis based on the original studies classification of the cost. All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [19], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[19]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [20]. All studies were classified in accordance with Drummond's distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or

effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).

The Drummond checklist [21] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

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

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 Unites 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], prescription refill rates[22 27] and medication supplies[10]. The main characteristics of the included studies are summarized in eTable 2.

3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high[33 37 40 50 51 57 71 75 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 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% to 87.5% (mean 62.63%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [71]. 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 utilization of Drummond's distinguishing characteristics of healthcare evaluations criteria[20] 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 59 cost description studies (74% 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 $52,341, 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 (46%), medical costs (29%), emergency department costs (27%), and hospitalization costs (18%) (eTable 2). Avoidable costs (e.g., unnecessary hospitalizations, physician office visits and healthcare resource utilization) were not well defined with majority of studies failing to quantify these costs.

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, 39 studies (49%) reported nonadherence costs to be greater than adherence costs[24 25 27 29 31 32 34 37-39 42 43 47 49 50 55 56 58 61-65 70-78 84 86 87 96-99] and 11 studies (15%) reported nonadherence costs to be less than adherence costs[23 26 36 44 59 63 66 81 92 94 95]. Four reported fluctuating findings based on varying nonadherence cost subcategories[33 48 67 93] and two studies reported conflicting findings between adjusted and unadjusted costs [79 80]. Higher all cause total nonadherence costs and lower disease group specific nonadherence costs were reported in four studies[41 68 85 91], whereas Hansen et al[47] reported all cause total nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

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

3.5 Cost of medication nonadherence via disease group

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

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 costs[23 39 52 59 60 66 73 99], inpatient costs[39 60 66 98 99], outpatient costs[23 39 59 66 99] and hospitalization costs[22 23 59 99].

The total unadjusted cost for medication nonadherence ranged from $2,512 to $25,920 as reported in four studies [52 66 82 99]. Becker et al[27] used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%, <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al[98] outlined the predicted cost of nonadherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

3.5.3 Diabetes mellitus:

Eleven studies reported a cost measurement of the impact of medication nonadherence with reference to the health system and the individual[40 45 47 51 74 76 83 84 92 94 97]. One study estimated that the total US cost attributable to nonadherence in diabetes was slightly over $5 billion[51]. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819 [47 51 74 76 84 97]. One study reported total costs in relation to subgroup analysis based on MPR level[74], and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients[76]. Curtis et al[84] utilized a diabetic population to report all cause costs, with nonadherence costs being higher than adherence costs across all outcome indicators bar pharmacy costs.

A further four studies reported unadjusted cost findings[40 83 92 94] with an additional four studies reporting unadjusted costs in in combination with adjusted values[45 47 74 97]. 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 [40 94].

The most prominent indicators used to determine costs were pharmacy costs[40 45 47 74 76 83 84 97], outpatient costs[40 47 76 84 94 97], inpatient costs[47 76 97] and hospitalization costs[51 92 94]. All studies assessed the direct costs associated with medication nonadherence. One study evaluated the relationship between nonadherence and short term disability costs in addition to assessing direct costs[45].

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 ≥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 lowest subgroup of adherence across all measures ranged from $804 to $36,259. Contrastingly Davis et al[85] utilized adjusted costs across four sub classifications of PDC adherence ranges to demonstrate that nonadherence costs were lower than adherence costs in all costing outcomes reported except hospitalization costs .

3.5.6 Gastrointestinal Disease:

Three of five studies reported the adjusted annual cost of medication nonadherence per patient utilizing the MPR method [44 57 71]. Of these, two reported the total cost ($12,085 and $37,151)[44 71] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the total cost nor total healthcare costs[30 54]. Carter et al[30] reported hospitalization costs to be $42,854 while Kane et al[54] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

3.5.7 Epilepsy:

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

3.5.8 HIV/AIDS:

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

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

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

medication nonadherence thus enabling greater planning in terms of health policy to help counteract increasing avoidable costs.

The economic, clinical and humanistic consequences of medication nonadherence will continue to grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to adequately address the determinants of adherence through utilization of effective health interventions. Haynes et al [101] highlights that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments”. Improving medication adherence provides an opportunity for major cost savings to healthcare systems. Predictions of population health outcomes through utilization of treatment efficacy data need to be used in conjunction with adherence rates to inform planning and project evaluation[4]. 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.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [102], 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 medication nonadherence, it further justifies the need to agree on consistent methods for estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used in 63% of studies, followed by PDC, which was used in 11%. These percentages were consistent with those found recently by Sattler et al [103]. Even though the measures of medication nonadherence may be comparable, the definition of MPR and the cut-off points to define nonadherence differed significantly. Dragomir et al[95] defined MPR as the total days’ supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalization; Wu et al[76] removed the number of hospitalized days from the calculation; and Pittman et al[61] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Nonadherence could also be further classified into subcategories within MPR and PDC based on percentages. Thirty studies defined nonadherence as MPR< 80%, and 12 studies categorized nonadherence into varying percentage subgroups. While Karve et al[104] validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent hospitalizations in patients across a broad array of chronic diseases, 76 of the 79 studies included in this review examined more than just hospitalization costs as an indicator metric. Further research is required to identify and standardize nonadherence thresholds using other outcomes such as laboratory, productivity and pharmacy measures.

Within the 79 studies covered, 35 different indicators were used to measure the cost of nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a meta-analysis was impossible. It is imperative that a standardized approach be established to measure and report the economic impact of medication nonadherence. The core outcome set must take into consideration the perspective of the intended audience and the proportion of nonadherence cost that is attributable to each outcome to determine an appropriate model[105]. The critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient costs, outpatient costs, emergency department visit costs, medical costs and hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes include short term disability costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs. We suggest that further analysis of the contribution of each outcome to the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future research.

Many studies have examined the relationship between nonadherence and economic outcomes using a cross-sectional analysis[51]. The implications of this are that potentially crucial confounders such as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for example, did greater adherence result in reduced costs and improved health outcomes, or was the patient healthier initially and more capable of being adherent? A longitudinal design is needed to overcome this limitation.

Economic evaluations inform decisions on how to best make use of scarce societal health resources through offering an organized consideration of the range of possible alternative courses of action and the evidence of the likely effects of each[20]. While none of the studies taken separately could inform a choice between alternative courses of action, they did provide key evidence for decision makers about costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority of studies to model cost estimates. Three-quarters of the studies were classified as cost descriptions, providing a cost or outcome overview of the health consequences associated with nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall conclusions that are able to be drawn and emphasized the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al[106] highlighted the need for more information on the consequences of nonadherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Of the seventy nine included studies, sixty six of the studies were conducted in the United States. Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and disease groups. Comparison of costs between healthcare systems is difficult as no two are the same and as healthcare is generally more expensive in the United States cost estimates may not reflect average values. Thus caution needs to be taken when interpreting results however findings help to represent the significance of the economic burden medication nonadherence plays. Analysis of studies not conducted in the United States support the finding that generally medication nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.

Due to the advances in technology available to record and assess medication nonadherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the inclusion criteria[22 23 65 73 74 98]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between nonadherence and increasing healthcare costs.

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.

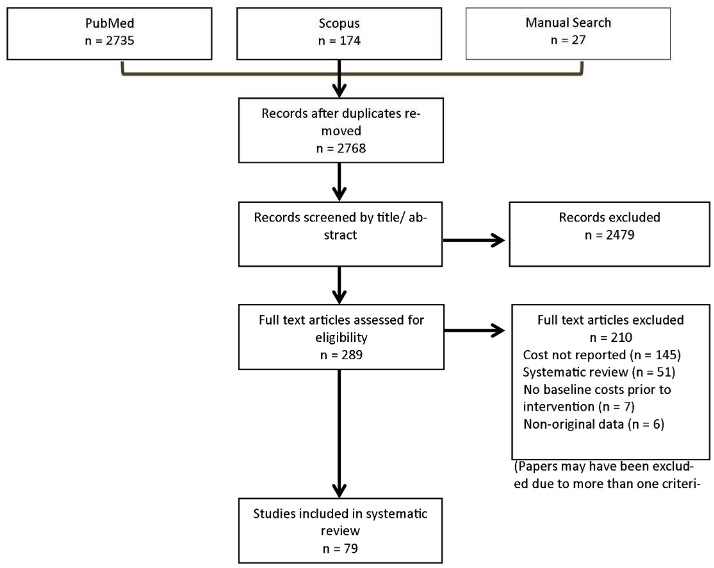

Figure 1: Flow diagram of references identified, retrieved and included in the systematic review

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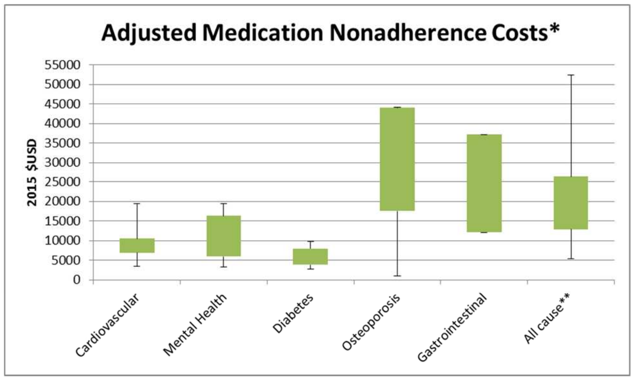

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year
*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.
** All cause costs: mixed disease state studies

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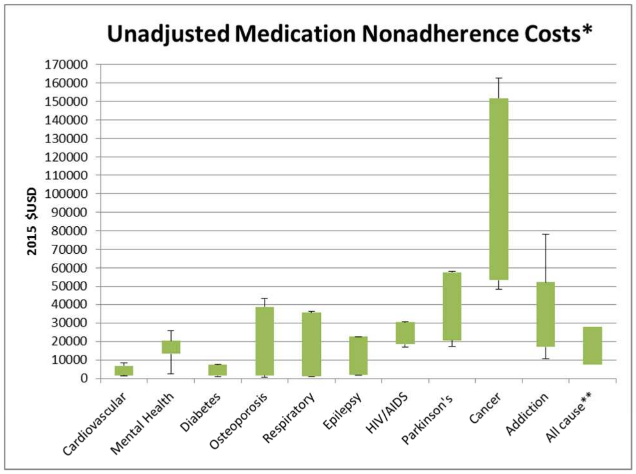

Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year
*Disease groups with three or more studies were included. Epilepsy and Addiction only included three studies limiting the range of costs.
** All cause costs: mixed disease state studies

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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						
Aubert et al ***[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.	Design: Retrospective cohort study Follow Up: 3 years Sample Size: 10227 (A:3512, NA:6715)	Measure: MPR Classification: MPR < 80 = non-compliant Method of Assessment: pharmacy claims data	Total Healthcare costs Medical Costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence: THC:$5289.61 ($6865.90), MC:$4908.09 ($6370.60)	Quality: medium Classification: cost description
Casciano et al ***[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.	Design: Retrospective, observational, quasi-experimental study Follow Up: 18months Sample Size: 13289 (A:2852, NA:4184, NE:6253)	Measure: PDC Classification: PDC <80 = low adherence , 0 = no warfarin exposure Method of Assessment: pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2005 Cost of Nonadherence*: TC:$16612.44($19936.70), IC:$9382.56 ($11260.10), OC:$8605.92 ($10328), PC:$2388.24 ($2866.20), MC:$15235.80($18285)	Quality: medium Classification: cost description
Dilokthornsakul et al ***[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	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 393 (A:168, NA:219, OA:6)	Measure: MPR Classification: MPR < 80 = undersupply, MPR >120 = oversupply Method of Assessment: pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC:$1157 ($1433.06), IC:$1019 ($1262.13), OC:$138 ($170.93)	Quality: high Classification: 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 hospitalized 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) Unadjusted Hospitalized 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 hospitalized patient: HC:$11715 ($11283.13)	Quality: medium Classification: cost description
*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 hospitalized 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) Unadjusted Hospitalized patients: THC:$14725 ($14566.40), PC:$3374 ($3337.66), MC:$2475 ($2448.34), HC:$8876 ($8780.40) Predicted disease state specific:	Quality: medium Classification: cost description

					HC:$2669 ($2640.25) Predicted hospitalized patient: HC$9214 ($9114.76)	
*Pittman et al**[6]*** 2011 US	To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.	Design: Retrospective cohort study Follow Up: 18 months Sample Size: 381422 (A:258013, MA:65795, LA:57614)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence 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, 2009 Cost of Nonadherence*: all cause: THC(>80):$6798.67 ($7505.66), THC(60-79):$7072.67 ($7808.16), THC(<59):$7401.33 ($8170.99), PC(>80):$1767.33 ($1951.11), PC(60-79):$1789.33 ($1975.40), PC(<59):$1937.33 ($2138.79), MC(>80):$4472.67 ($4937.78), MC(60-79):$4840.67 ($5344.05, MC(<59):$5138.67 ($5673.04) Disease state specific: PC(>80):$558.67 ($616.77), PC(60-79):$442.67 ($488.70), PC(<59):$325.33 ($359.16), MC(>80):$1596.67 ($1762.71), MC(60-79):$1722 ($1901.07), MC(<59):$1792.67 ($1979.09)	Quality: medium Classification: cost description
*Pittman et al**[7]*** 2010 US	To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 625620(A:467006, MA:96226, LA:62388)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence	Total Healthcare Costs Outpatient Costs ED Costs Pharmacy Costs Hospitalization	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: Adjusted: THC(>80):$7261 ($8077.79), THC(60-79):$7530 ($8377.05), THC(<59):$7370 ($8199.05), OC(>80):$3390 ($3771.34), OC(60-79):$3705 ($4121.77),	Quality: medium Classification: cost description

	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 ß-	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 <u>Method of Assessment:</u> 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.	<u>Design:</u> Retrospective cohort observational study <u>Follow Up:</u> 12 months <u>Sample Size:</u> 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)	<u>Measure:</u> medication supply <u>Classification:</u> 1-19%, 20-39%, 40-59%, 60-79%, 80-100% <u>Method of Assessment:</u> pharmacy claims data	Total Costs Pharmacy Costs Medical Costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 1998 <u>Cost of Nonadherence:</u> 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),	<u>Quality:</u> medium <u>Classification:</u> 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),

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),

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),

					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.					
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)	
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
*Becker et al**[14]***	Examine treatment	Design: Retrospective	Measure:	Total Costs	Type of Costs: unadjusted	Quality: low

2007 US	outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries.	cohort study <u>Follow Up:</u> 2 years <u>Sample Size:</u> 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505)	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		<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>Classification:</u> cost description
*Eaddy et al***[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 <u>Method of Assessment:</u> pharmacy claims data	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
*Gilmer et al***[16]** 2004 US	To evaluate the relationship between adherence to	<u>Design:</u> Retrospective database analysis <u>Follow Up:</u> 1 year	<u>Measure:</u> cumulative possession ratio	Total costs Outpatient 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

	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 Method of Assessment: pharmacy claims data	Pharmacy costs Hospitalization costs	Cost of Nonadherence: TC:$8168 ($11261.74), OC:$3464 ($4776.04), PC:$1542 ($2126.05), HC:$3413 ($4705.72)	
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

			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 Method of Assessment: health insurance data	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 with schizophrenia.	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:	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), ESC:£1603 ($3241.47)	Quality: medium Classification: cost analysis

			survey			
*Offord et al***[21]** 2013 US	To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term antipsychotic adherence, healthcare utilisation and costs.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 1462 (A:589, NA:873)	Measure: time to discontinuation Classification: adherent vs. nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Pharmacy costs Hospitalization costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: TC:$15400 ($17132.34) OC:$5773 ($6422.40), PC:$3777 ($4201.87), HC:$5850 ($6508.06) Disease state specific: TC:$5358 ($5960.72) OC:$858 ($954.52), PC:$1549 ($1723.25), HC:$2952 ($3284.07)	Quality: medium Classification: cost description
*Offord et al***[22]** 2013 US	To examine the impact of medication adherence on healthcare utilisation among Medicare insured schizophrenia patients.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 354 (A:126, NA:228)	Measure: MPR Classification: MPR ≥ 70= high adherence, MPR < 70 = low adherence Method of Assessment: pharmacy claims data	Inpatient costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: IC:$9053 ($10071.37), PC:$4267 ($4746.99), Disease state specific: IC:$2468 ($2745.62), PC:$1085 ($1207.05)	Quality: low Classification: cost description
*Robertson et al[***23***]* *2014* *US*	To examine the impact of the combination of treatment utilization and medication possession on arrest and incarceration outcomes and on costs.	Design: Retrospective cohort study Follow Up:90 days Sample Size:1376 (90/90:637, 60/90:240, 30/90:174, 0/90:316)	Measure: MPR Classification: MPR ≥80% = adherent Method of Assessment: Medicaid claims data	Total costs Inpatient costs Outpatient costs Emergency department costs Pharmacy	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD,2005 Cost of Nonadherence*: TC(90/90):$28068 ($33495.65), TC(60/90):$21720 ($25920.11), TC(30/90):$21084 ($25161.12), TC(0/90):$12516 ($14936.28),	Quality: medium Classification: cost description

				costs Target case management costs Psychiatric assessment costs Arrest costs Incarceration costs	IC(90/90):$12168 ($14520.99), IC(60/90):$10068 ($12014.90), IC(30/90):$11376 ($13575.84), IC(0/90):$5592 ($6673.35), OC(90/90):$6468 ($7718.75), OC(60/90):$4152 ($4954.89), OC(30/90):$2916 ($3479.88), OC(0/90):$2136 ($2549.05), EDC(90/90):$96 ($114.56), 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

2006 US	type of antidepressant drug is related to adherence and assess the 6 month health care costs among newly diagnosed patients.	claims analysis Follow Up: 6 months Sample Size: 60386 (A:11526, NA:8860)	Antidepressant medication management measures Classification: meeting less than <3 medication management measures = nonadherent Method of Assessment: pharmacy claims data, Medicaid data, observational assessment	Inpatient costs Outpatient costs ED visit costs Pharmacy costs Physician office visit costs	Classification: all cause and disease state specific Currency Year: USD, 2004 Cost of Nonadherence*: 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)	Classification: cost description
Svarstad et al **[25]** 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/schizoaffective 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 **[26]** 2003 US	To evaluate the economic impact of antidepressant	Design: Retrospective database analysis Follow Up: 6 months	Measure: MPR Classification: MPR≥70% =	Total costs Pharmacy costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 1999	Quality: medium Classification: cost description

	treatment adherence among patients treated for depression	Sample Size: 14190 (A:5638, NA:8552)	adherent, MPR<70% = nonadherent Method of Assessment: pharmacy claims data	Medical costs	Cost of Nonadherence: TC:$11815 ($16290.09) PC:$1123 ($1548.35), MC:$10692 ($14741.74)	
Diabetes						
*An et al**[27]*** 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.	Design: Prospective cohort study Follow Up: 3 years Sample Size: 608 (A:472, NA:136)	Measure: MPR Classification: MPR≥90% = adherent, MPR<90% = nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence*: TC:$1657.11 ($1884.14) OC: $1413.99 ($1608.20), HC: $243.11 ($276.12)	Quality: medium Classification: cost description
Buysman et al[28] 2017 US	To examine the impact of real world adherence on glycaemic control in type 2 diabetes patients treated with canagliflozin.	Design: Retrospective database analysis Follow Up: 12 months Sample Size: 2261 (A:1215, NA:1046)	Measure: PDC Classification: PDC≥80% = highly adherent, PDC<80% = less than highly adherent Method of Assessment: healthcare claims data	Pharmacy costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2014 Cost of Nonadherence: all cause: PC: $7225 ($7297.39) Disease state specific: PC: $4660 ($4706.69)	Quality: low Classification: cost description
Curtis et al[29] 2017 US	Examine the association between adherence to glucose lowering agents and	Design: Retrospective analysis Follow Up: 3 years Sample Size: 228074	Measure: PDC Classification: PDC≥80% = adherent,	Total costs Outpatient costs Pharmacy	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2014 Cost of Nonadherence:	Quality: medium Classification: cost description

	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

					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	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	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) Unadjusted disease state specific: HC:$6919 ($8569.88), PC:$785 ($972.30), MC:$5192 ($6430.82), STDC:$1717 ($2126.68)	Quality: medium Classification: cost description
Hansen et al ***[33]*** 2010	To compare all cause total health care costs	Design: Retrospective, cohort study	Measure: MPR Classification:	Total Healthcare	Type of Costs: adjusted and unadjusted Classification: all cause and disease	Quality: medium Classification: cost

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.	Follow Up: 2 years Sample Size: 108592 (A:63830, NA:44762)	MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	costs Inpatient costs Outpatient costs Pharmacy costs	state specific Currency Year: USD, 2005 Cost of Nonadherence[#]: 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
Hong et al ***[34]*** 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.	Design: Retrospective, cohort study Follow Up: 3 years Sample Size: 40082 (A:11800, NA:28282)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: KRW, 2007 Cost of Nonadherence: TC:₩765453 ($1142.31), HC:₩397549 ($593.28)	Quality: medium Classification: cost description
Jha et al ***[35]*** 2012 US	How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or	Design: Retrospective, observational claims analysis Follow Up: unclear Sample Size: 135639 (A:99976, NA:36553)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment:	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

	decreased hospitalizations or 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?		pharmacy claims data			
*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

					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**[37]*** 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	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

					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**[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	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

					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 a**[39]*** 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	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), PC:\$213 (\$222.23), POC:\$44 (\$45.91)	Quality: medium Classification: cost description
*Halpern et al**[40]*** 2011 US	To examine the associations of adherence to osteoporosis therapies	Design: Retrospective analysis Follow Up: 540 days Sample Size: 21655	Measure: MPR Classification: (≥80% = high adherence,	Medical costs	Type of Costs: unadjusted Classification: all cause Currency Year: USD, 2006 Cost of Nonadherence: commercial:	Quality: medium Classification: 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

					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)	
*Huybrechts et al***[42]** 2006 US	To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.	Design: Retrospective cohort study Follow Up: 5 years Sample Size: 38120 (A:9530, NA:28590)	Measure: MPR Classification: (≥80% = compliant, <50% = noncompliant) Method of Assessment: pharmacy claims data	Total costs Medical costs Institutional costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2000 Cost of Nonadherence: TC:$7200 ($9706.44), MC:$1476 ($1989.84), InstC:$5736 ($7732.80)	Quality: low Classification: cost description
*Kjellberge al***[43]** 2016 Denmark	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.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 38234 (A:26806, NA:11428)	Measure: MPR Classification: (≥70% = compliant, <70% = noncompliant) Method of Assessment: pharmacy claims data	Total costs Medical costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: Euro, 2011 Cost of Nonadherence: all cause: TC:€4933 ($6209.58), MC:€3471 ($4369.20), Disease state specific: TC:€754 ($949.12), MC:€426 ($536.24),	Quality: high Classification: cost outcome description
*Modi et al***[44]** 2015	To evaluate compliance with	Design: Retrospective cohort study	Measure: MPR Classification:	Total costs Inpatient costs	Type of Costs: unadjusted Classification: all cause and disease	Quality: medium Classification: cost

US	osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance	Follow Up: 1 year Sample Size: 27913 (A:23430, NA:34483)	(≥80% = compliant, <80% = noncompliant) Method of Assessment: healthcare claims data	Outpatient costs ED costs Pharmacy costs Medical costs Other costs	state specific Currency Year: USD, 2011 Cost of Nonadherence: 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)	outcome description
Olsen et al ***[45]*** 2013 Denmark	To assess the association between refill compliance and all cause health care costs.	Design: Retrospective observational study Follow Up: 2 years Sample Size: 47176 (not specified)	Measure: MPR Classification: (≥80% = optimal compliance, >50<80% = suboptimal compliance, <50% = low compliance Method of Assessment: pharmacy claims data	Fracture costs	Type of Costs: unadjusted Classification: fracture site specific Currency Year: DKK, 2010 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)	Quality: medium Classification: cost analysis

					Other fracture: FC(50-80):-kr19261.50 (-$2377.93), FC(<50):kr684067.50 ($84451.66)	
Sunyecz et al ***[46]*** 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), PC:$918 ($1101.70), RC:$184 ($220.82)	Quality: low Classification: cost description
Zhao et al ***[47]*** 2014 US	To examine the association between teriparatide adherence and healthcare utilisation and costs among hip fracture patients.	Design: Retrospective cohort study Follow Up: 36 months Sample Size: 824 (≥80:362, 50-80%:219, <50%:243)	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	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence[*]: 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),	Quality: medium Classification: cost description

					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)	
*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	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 β_2-adrenergic agonist and COPD exacerbation rates and costs in commercially insured population	<u>Design:</u> Observational cohort study <u>Follow Up:</u> 12 months <u>Sample Size:</u> 13657 (≥80%: 1898, ≥50<80%: 1971, ≥30 <50%: 2443, <30% :7345)	<u>Measure:</u> PDC <u>Classification:</u> (≥80 = adherent, ≥50<80% = mildly nonadherent, ≥30 <50% = moderately nonadherent, <30% highly nonadherent) <u>Method of Assessment:</u> commercially insured healthcare claims data	Total costs Outpatient costs Pharmacy costs Hospitalization costs	<u>Type of Costs:</u> adjusted <u>Classification:</u> all cause and disease state specific <u>Currency Year:</u> USD, 2014 <u>Cost of Nonadherence*:</u> 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),	<u>Quality:</u> medium <u>Classification:</u> cost description

					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

	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

			questionnaire		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)	
*Miravitlles et al**[53]*** 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).	Design: multicentre, retrospective, observational study Follow Up: 18 months Sample Size: 1365 (A:246, NA:1119)	Measure: GOLD 2007 Guidelines Classification: (adherent, nonadherent) Method of Assessment: 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	Type of Costs: unadjusted Classification: disease state specific Currency Year: EUR, 2009 Cost of Nonadherence: 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)	Quality: medium Classification: cost description
*Quittner et al**[54]*** 2014 US	To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.	Design: retrospective, cohort study Follow Up: 2 years Sample Size: 3287 (≥80%: 663, 50-80%: 949, <50%: 1675)	Measure: MPR Classification: (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence) Method of Assessment: pharmacy claims data	Total healthcare costs	Type of Costs: unadjusted Classification: all cause and disease state specific 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),	Quality: medium Classification: cost description

					THC(50-80):$33132.50 ($35444.44), THC(<50):$33894 ($36259.07)	
Gastrointestinal Disease						
*Carter et al***[55]** 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***[56]** 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
*Kane et al***[57]** 2009 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

			Assessment: health claims data		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)	
Mitra et al ***[58]*** 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.	Design: retrospective, observational cohort study Follow Up: 12 months Sample Size: 1693 (A:476, NA:1216)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Ancillary costs Non-pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence: 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)	Quality: high Classification: cost description
Wan et al ***[59]*** 2014 US	To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.	Design: retrospective cohort analysis Follow Up: 360 days Sample Size: 1646 (A:674, NA:972)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2009 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:	Quality: high Classification: cost description

					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**[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	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

	(AEDs) on healthcare utilisation and direct medical costs in a Medicaid population.	Follow Up: 4.65 years Sample Size: 33658 (A:24907, NA:8751)	<80% = nonadherent) Method of Assessment: pharmacy claims data	costs ED costs Pharmacy costs Other pharmacy costs	Cost of Nonadherence*: TC:$14417.64 ($18713.91), IC:$6682.28 ($6873.51), OC:$2172.40 ($2819.75), EDC:$405.96 ($526.93), PC:$822.40 ($1067.46), OtPC:$4334.60 ($5626.26)	
HIV/AIDS						
Barnett et al ***[63]*** 2011 US	To characterise the cost of HIV care including combination antiretroviral treatment.	Design: retrospective observational cohort study Follow Up: 1 year Sample Size: 1896 (not specified)	Measure: antiretroviral taking behaviour Classification: (85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent) Method of Assessment: pharmacy claims data	Total costs	Type of Costs: unadjusted Classification: disease state specific; viral load count Currency Year: USD, 2006 Cost of Nonadherence**: High viral load: TC:$25824 ($30067.54) Low viral load: TC:$20509.67 ($23879.92)	Quality: medium Classification: cost description
Cooke et al ***[64]*** 2014 US	To measure adherence to antiretroviral therapy regimens in commercially insured patients with HIV infection and analyse the clinical and demographic factors associated with ≥90% adherence.	Design: retrospective claims analysis Follow Up: 1 year Sample Size: 3528 (A:1737, NA:640)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) 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, 2011 Cost of Nonadherence: THC:$18868 ($20184.58), IC:$2700 ($2888.40), OC:$915 ($978.85), PC:$15253 ($16317.33)	Quality: medium Classification: cost description

*Pruitt et al**[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.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 502 (A:56, NA:176)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Other pharmacy costs Behavioural health inpatient costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2009 Cost of Nonadherence*: 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)	Quality: medium Classification: cost description
Parkinson's Disease						
*Davis et al**[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.	Design: retrospective administrative claims study Follow Up: 12 months Sample Size: 3119 (A:1211, NA:1908)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2001 Cost of Nonadherence: TC:$18511 ($24262.36), PC:$2684 ($3537.36), MC:$15827 ($20859.12)	Quality: medium Classification: cost outcome description
*Delea et al**[67]*** 2011 US	To assess the associations between adherence to	Design: retrospective historical cohort study Follow Up: 12 months	Measure: PDC Classification: (≥80% =	Total costs Inpatient costs Pharmacy	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific	Quality: high Classification: cost description

	levodopa/carbidopa/entacapone 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

					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						
*Ivanova et al**[69]*** 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.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 648 (A:448, NA:200)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Short term disability costs Absenteeism cost	Type of Costs: unadjusted Classification: all cause, disease state specific and indirect Currency Year: USD, 2007 Cost of Nonadherence*: 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)	Quality: high Classification: cost outcome description
*Tan et al**[70]*** 2011 US	To assess the impact of treatment adherence on MS related hospitalizations	Design: retrospective cohort study Follow Up: 12 months Sample Size: 2446	Measure: MPR Classification: (≥80% = adherent, <80% =	Medical costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence:	Quality: medium Classification: cost description

	(inpatient), ER visits, MS relapses and medical costs.	(A:1459, NA:987)	nonadherent) Method of Assessment: pharmacy claims data		Adjusted: MC:$4348 ($5062.49) Unadjusted: MC:$5179 ($6030.04)	
*Zhao et al***[71]** 2011 US	To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 5435 (A:1744, NA:3691)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: commercial: TC:$20323 ($22609.12), IC:$4808 ($5348.85), OC:$9822 ($10926.87), PC:$5693 ($6333.40) Medicare: TC:$25282 ($28125.96), IC:$8604 ($9571.86), OC:$10068 ($11200.54), PC:$6611 ($7354.67)	Quality: medium Classification: cost analysis
Cancer						
*Darkow et al***[72]** 2007 US	Estimate the association between treatment interruptions and non-adherence with imatinib and healthcare costs for US managed care patients.	Design: retrospective observational cohort analysis Follow Up: 12 months Sample Size: 267 (≥95%:120, 90-95%:25, 50-90%:69, <50%:53)	Measure: MPR Classification: (≥95% = very high, >90<95% = high, >50<90% = intermediate, <50% = low) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other pharmacy costs Other costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC(≥95):$42250 ($52330.90), THC(90-95):$39236 ($48597.76), THC(50-90):$54770 ($67838.19), THC(<50):$131357 ($162698.93), IC(≥95):$1156 ($1431.82), IC(90-95):$1362 ($1686.97), IC(50-90):$19096 ($23652.33), IC(<50):$81572 ($101035.18), OC(≥95):$9299 ($11517.75), OC(90-95):$11148 ($13807.93),	Quality: high Classification: cost description

					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)	
*Wu et al**[73]*** 2010 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						
*Leider et al***[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.	Design: retrospective claims based analysis Follow Up: 12 months Sample Size: 2100 (A:442, NA:1658)	Measure: urine testing Classification: (positive test = nonadherent, negative test = adherent) Method of Assessment: health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: THC:$26433 ($29406.43), IC:$6361 ($7076.55), OC:$9734 ($10828.97), EDC:$421 ($468.36), PC:$7960 ($8855.42), MC:$1957 ($2177.14)	Quality: medium Classification: cost analysis
Ruetsch et al[75] 2017 US	To examine patient characteristics and outcomes associated with nonadherence to buprenorphine and to identify specific patterns of nonadherent behaviour.	Design: cross sectional, retrospective analysis health claims data Follow Up: 12 months Sample Size: 477 (A:172, NA:305)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Physician office visit costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2013 Cost of Nonadherence: 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)	Quality: medium Classification: cost description
*Tkacz et al***[76]** 2014 US	To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 455 (A:146, NA:309)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence: Adjusted: THC:$49051 ($53503.88), IC:$26470 ($28872.96), OC:$14570 ($15892.67), EDC:$4439 ($4841.98),	Quality: medium Classification: cost description

	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

			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)	
All						
Alvarez Payero et al **[79]** 2014 Spain	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.	Design: retrospective observational study Follow Up: 1527 days Sample Size: 87 (A:21, NA:66)	Measure: pharmacy records Classification: (>75% = adherent, ≤75% = nonadherent) Method of Assessment: pharmacy and hospital claims data	Hospitalization costs	Type of Costs: unadjusted Classification: all cause Currency Year: EUR, 2012 Cost of Nonadherence[####]: All cause: HC:€6275.80 ($8893.94)	Quality: low Classification: 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 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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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

[1]Some 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

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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-

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

Costs were defined as any indicator associated with medication nonadherence that was quantified with a monetary value in the original study. This included direct costs (those costs borne by the healthcare system, community and patients' families in addressing the illness), indirect costs (mainly productivity losses to society caused by the health problem or disease) and avoidable costs (those costs incurred for patients suffering complications, resulting from suboptimal medicines use, and patients with the same disease who experienced no complications). The indicators were grouped for analysis based on the original studies classification of the cost. All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [19], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[19]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [20]. All studies were classified in accordance with Drummond’s distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or

effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).

The Drummond checklist [21] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as high quality if at least 75% of Drummond's criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

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

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

3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high[33 37 40 50 51 57 71 75 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 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% to 87.5% (mean 62.63%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [71]. 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 utilization of Drummond's distinguishing characteristics of healthcare evaluations criteria[20] 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 59 cost description studies (74% 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 $52,341, 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 (46%), medical costs (29%), emergency department costs (27%), and hospitalization costs (18%) (eTable 2). Avoidable costs (e.g., unnecessary hospitalizations, physician office visits and healthcare resource utilization) were not well defined with majority of studies failing to quantify these costs.

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, 39 studies (49%) reported nonadherence costs to be greater than adherence costs[24 25 27 29 31 32 34 37-39 42 43 47 49 50 55 56 58 61-65 70-78 84 86 87 96-99] and 11 studies (15%) reported nonadherence costs to be less than adherence costs[23 26 36 44 59 63 66 81 92 94 95]. Four reported fluctuating findings based on varying nonadherence cost subcategories[33 48 67 93] and two studies reported conflicting findings between adjusted and unadjusted costs [79 80]. Higher all cause total nonadherence costs and lower disease group specific nonadherence costs were reported in four studies[41 68 85 91], whereas Hansen et al[47] reported all cause total nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

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

3.5 Cost of medication nonadherence via disease group

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

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 costs[23 39 52 59 60 66 73 99], inpatient costs[39 60 66 98 99], outpatient costs[23 39 59 66 99] and hospitalization costs[22 23 59 99].

The total unadjusted cost for medication nonadherence ranged from $2,512 to $25,920 as reported in four studies [52 66 82 99]. Becker et al[27] used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%, <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al[98] outlined the predicted cost of nonadherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

3.5.3 Diabetes mellitus:

Eleven studies reported a cost measurement of the impact of medication nonadherence with reference to the health system and the individual[40 45 47 51 74 76 83 84 92 94 97]. One study estimated that the total US cost attributable to nonadherence in diabetes was slightly over $5 billion[51]. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819 [47 51 74 76 84 97]. One study reported total costs in relation to subgroup analysis based on MPR level[74], and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients[76]. Curtis et al[84] utilized a diabetic population to report all cause costs, with nonadherence costs being higher than adherence costs across all outcome indicators bar pharmacy costs.

A further four studies reported unadjusted cost findings[40 83 92 94] with an additional four studies reporting unadjusted costs in in combination with adjusted values[45 47 74 97]. 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 [40 94].

The most prominent indicators used to determine costs were pharmacy costs[40 45 47 74 76 83 84 97], outpatient costs[40 47 76 84 94 97], inpatient costs[47 76 97] and hospitalization costs[51 92 94]. All studies assessed the direct costs associated with medication nonadherence. One study evaluated the relationship between nonadherence and short term disability costs in addition to assessing direct costs[45].

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 ≥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 lowest subgroup of adherence across all measures ranged from $804 to $36,259. In contrast Davis et al[85] utilized adjusted costs across four sub-classifications of PDC adherence ranges to demonstrate that nonadherence costs were lower than adherence costs in all costing outcomes reported except hospitalization costs .

3.5.6 Gastrointestinal Disease:

Three of five studies reported the adjusted annual cost of medication nonadherence per patient utilizing the MPR method [44 57 71]. Of these, two reported the total cost ($12,085 and $37,151)[44 71] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the total cost nor total healthcare costs[30 54]. Carter et al[30] reported hospitalization costs to be $42,854 while Kane et al[54] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

3.5.7 Epilepsy:

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

3.5.8 HIV/AIDS:

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

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

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

medication nonadherence thus enabling greater planning in terms of health policy to help counteract increasing avoidable costs.

The economic, clinical and humanistic consequences of medication nonadherence will continue to grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to adequately address the determinants of adherence through utilization of effective health interventions. Haynes et al [101] highlights that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments". Improving medication adherence provides an opportunity for major cost savings to healthcare systems. Predictions of population health outcomes through utilization of treatment efficacy data need to be used in conjunction with adherence rates to inform planning and project evaluation[4]. 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.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [102], 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 medication nonadherence, it further justifies the need to agree on consistent methods for estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used in 63% of studies, followed by PDC, which was used in 11%. These percentages were consistent with those found recently by Sattler et al [103]. Even though the measures of medication nonadherence may be comparable, the definition of MPR and the cut-off points to define nonadherence differed significantly. Dragomir et al[95] defined MPR as the total days' supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalization; Wu et al[76] removed the number of hospitalized days from the calculation; and Pittman et al[61] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Nonadherence could also be further classified into subcategories within MPR and PDC based on percentages. Thirty studies defined nonadherence as MPR< 80%, and 12 studies categorized nonadherence into varying percentage subgroups. While Karve et al[104] validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent hospitalizations in patients across a broad array of chronic diseases, 76 of the 79 studies included in this review examined more than just hospitalization costs as an indicator metric. Further research is required to identify and standardize nonadherence thresholds using other outcomes such as laboratory, productivity and pharmacy measures.

Within the 79 studies covered, 35 different indicators were used to measure the cost of nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a meta-analysis was impossible. It is imperative that a standardized approach be established to measure and report the economic impact of medication nonadherence. The core outcome set must take into consideration the perspective of the intended audience and the proportion of nonadherence cost that is attributable to each outcome to determine an appropriate model[105]. The critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient costs, outpatient costs, emergency department visit costs, medical costs and hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes include short term disability costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs. We suggest that further analysis of the contribution of each outcome to the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future research.

Many studies have examined the relationship between nonadherence and economic outcomes using a cross-sectional analysis[51]. The implications of this are that potentially crucial confounders such as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for example, did greater adherence result in reduced costs and improved health outcomes, or was the patient healthier initially and more capable of being adherent? A longitudinal design is needed to overcome this limitation.

Economic evaluations inform decisions on how to best make use of scarce societal health resources through offering an organized consideration of the range of possible alternative courses of action and the evidence of the likely effects of each[20]. While none of the studies taken separately could inform a choice between alternative courses of action, they did provide key evidence for decision makers about costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority of studies to model cost estimates. Three-quarters of the studies were classified as cost descriptions, providing a cost or outcome overview of the health consequences associated with nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall conclusions that are able to be drawn and emphasized the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al[106] highlighted the need for more information on the consequences of nonadherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Of the seventy nine included studies, sixty six of the studies were conducted in the United States. Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and disease groups. Comparison of costs between healthcare systems is difficult as no two are the same and as healthcare is generally more expensive in the United States cost estimates may not reflect average values. Thus caution needs to be taken when interpreting results however findings help to represent the significance of the economic burden medication nonadherence plays. Analysis of studies not conducted in the United States support the finding that generally medication nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.

Due to the advances in technology available to record and assess medication nonadherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the inclusion criteria[22 23 65 73 74 98]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between nonadherence and increasing healthcare costs.

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.

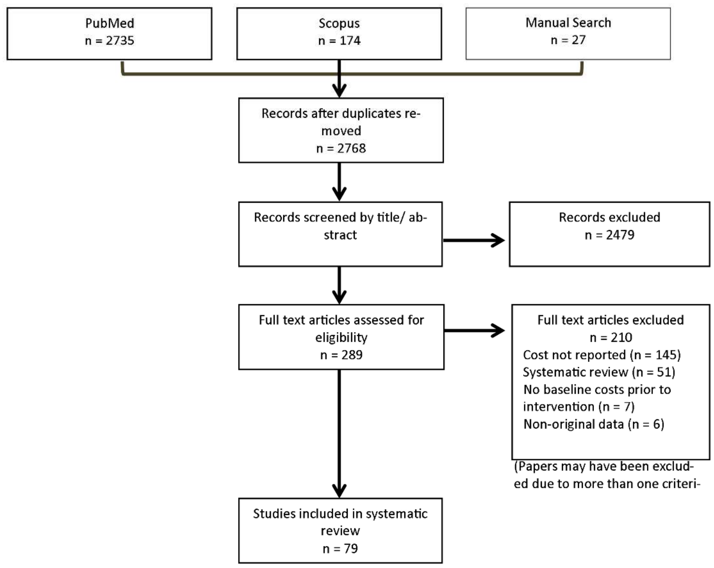

Figure 1: Flow diagram of references identified, retrieved and included in the systematic review

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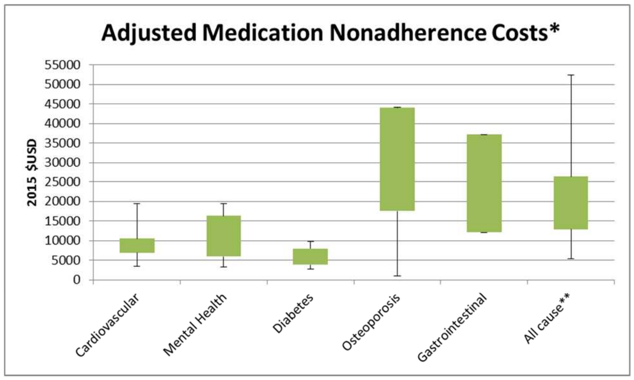

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year
*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.
** All cause costs: mixed disease state studies

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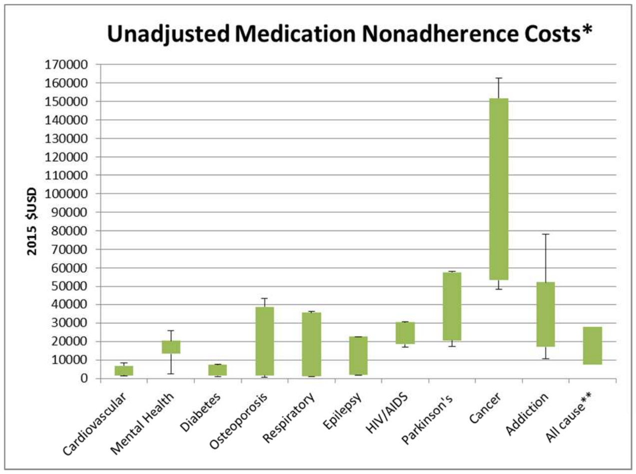

Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year
*Disease groups with three or more studies were included. Epilepsy and Addiction only included three studies limiting the range of costs.
** All cause costs: mixed disease state studies

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eTable 1 Search Strategy[1]

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						
Aubert et al[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.	Design: Retrospective cohort study Follow Up: 3 years Sample Size: 10227 (A:3512, NA:6715)	Measure: MPR Classification: MPR < 80 = non-compliant Method of Assessment: pharmacy claims data	Total Healthcare costs Medical Costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence: THC:$5289.61 ($6865.90), MC:$4908.09 ($6370.60)	Quality: medium Classification: cost description
Casciano et al[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.	Design: Retrospective, observational, quasi-experimental study Follow Up: 18months Sample Size: 13289 (A:2852, NA:4184, NE:6253)	Measure: PDC Classification: PDC <80 = low adherence , 0 = no warfarin exposure Method of Assessment: pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2005 Cost of Nonadherence*: TC:$16612.44($19936.70), IC:$9382.56 ($11260.10), OC:$8605.92 ($10328), PC:$2388.24 ($2866.20), MC:$15235.80($18285)	Quality: medium Classification: cost description
Dilokthornsakul et al[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	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 393 (A:168, NA:219, OA:6)	Measure: MPR Classification: MPR < 80 = undersupply, MPR >120 = oversupply Method of Assessment: pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC:$1157 ($1433.06), IC:$1019 ($1262.13), OC:$138 ($170.93)	Quality: high Classification: 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 hospitalized 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) Unadjusted Hospitalized 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 hospitalized patient: HC:$11715 ($11283.13)	Quality: medium Classification: cost description
*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 hospitalized 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) Unadjusted Hospitalized patients: THC:$14725 ($14566.40), PC:$3374 ($3337.66), MC:$2475 ($2448.34), HC:$8876 ($8780.40) Predicted disease state specific:	Quality: medium Classification: cost description

					HC:$2669 ($2640.25) Predicted hospitalized patient: HC$9214 ($9114.76)	
*Pittman et al**[6]*** 2011 US	To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.	Design: Retrospective cohort study Follow Up: 18 months Sample Size: 381422 (A:258013, MA:65795, LA:57614)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence 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, 2009 Cost of Nonadherence*: all cause: THC(>80):$6798.67 ($7505.66), THC(60-79):$7072.67 ($7808.16), THC(<59):$7401.33 ($8170.99), PC(>80):$1767.33 ($1951.11), PC(60-79):$1789.33 ($1975.40), PC(<59):$1937.33 ($2138.79), MC(>80):$4472.67 ($4937.78), MC(60-79):$4840.67 ($5344.05, MC(<59):$5138.67 ($5673.04) Disease state specific: PC(>80):$558.67 ($616.77), PC(60-79):$442.67 ($488.70), PC(<59):$325.33 ($359.16), MC(>80):$1596.67 ($1762.71), MC(60-79):$1722 ($1901.07), MC(<59):$1792.67 ($1979.09)	Quality: medium Classification: cost description
*Pittman et al**[7]*** 2010 US	To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 625620(A:467006, MA:96226, LA:62388)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence	Total Healthcare Costs Outpatient Costs ED Costs Pharmacy Costs Hospitalization	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: Adjusted: THC(>80):$7261 ($8077.79), THC(60-79):$7530 ($8377.05), THC(<59):$7370 ($8199.05), OC(>80):$3390 ($3771.34), OC(60-79):$3705 ($4121.77),	Quality: medium Classification: cost description

	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 ß-	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)	
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),

	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),

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),

					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.					
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)	
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
*Becker et al**[14]***	Examine treatment	Design: Retrospective	Measure:	Total Costs	Type of Costs: unadjusted	Quality: low

2007 US	outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries.	cohort study Follow Up: 2 years Sample Size: 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505)	prescription refill rate Classification: 75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, <25% = negligible adherence Method of Assessment: pharmacy claims data		Classification: disease state specific Currency Year: USD, 2006 Cost of Nonadherence*: TC(75-100):$13564 ($15792.91), TC(50-74):$13772 ($16035.09), TC(25-49):$15792 ($18387.03), TC(<25):$16156 ($18810.84)	Classification: cost description
Eaddy et al **[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.	Design: Retrospective database analysis Follow Up: 1 year Sample Size: 7864 (<80%:2655, 80-125%:5065, >125%:144)	Measure: continuous multiple interval medications available Classification: <80% = partially compliant, 80-125% = compliant, >125% = overly compliant Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs Pharmacy costs Medical costs Physician office visit costs Other costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence*: IC:$3780 ($4906.39), OC:$504 ($654.19), PC:$1872 ($2429.83), MC:$6228 ($8083.86), POC:$1944 ($2523.29) OtC:$12 ($15.58)	Quality: medium Classification: cost description
Gilmer et al **[16]** 2004 US	To evaluate the relationship between adherence to	Design: Retrospective database analysis Follow Up: 1 year	Measure: cumulative possession ratio	Total costs Outpatient costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 1999	Quality: medium Classification: cost description

	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 Method of Assessment: pharmacy claims data	Pharmacy costs Hospitalization costs	Cost of Nonadherence: TC:$8168 ($11261.74), OC:$3464 ($4776.04), PC:$1542 ($2126.05), HC:$3413 ($4705.72)	
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

			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 Method of Assessment: health insurance data	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 with schizophrenia.	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:	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), ESC:£1603 ($3241.47)	Quality: medium Classification: cost analysis

			survey			
*Offord et al***[21]** 2013 US	To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term antipsychotic adherence, healthcare utilisation and costs.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 1462 (A:589, NA:873)	Measure: time to discontinuation Classification: adherent vs. nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Pharmacy costs Hospitalization costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: TC:$15400 ($17132.34) OC:$5773 ($6422.40), PC:$3777 ($4201.87), HC:$5850 ($6508.06) Disease state specific: TC:$5358 ($5960.72) OC:$858 ($954.52), PC:$1549 ($1723.25), HC:$2952 ($3284.07)	Quality: medium Classification: cost description
*Offord et al***[22]** 2013 US	To examine the impact of medication adherence on healthcare utilisation among Medicare insured schizophrenia patients.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 354 (A:126, NA:228)	Measure: MPR Classification: MPR ≥ 70= high adherence, MPR < 70 = low adherence Method of Assessment: pharmacy claims data	Inpatient costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: IC:$9053 ($10071.37), PC:$4267 ($4746.99), Disease state specific: IC:$2468 ($2745.62), PC:$1085 ($1207.05)	Quality: low Classification: cost description
Robertson et al[**23**] *2014* *US*	To examine the impact of the combination of treatment utilization and medication possession on arrest and incarceration outcomes and on costs.	Design: Retrospective cohort study Follow Up:90 days Sample Size:1376 (90/90:637, 60/90:240, 30/90:174, 0/90:316)	Measure: MPR Classification: MPR ≥80% = adherent Method of Assessment: Medicaid claims data	Total costs Inpatient costs Outpatient costs Emergency department costs Pharmacy	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD,2005 Cost of Nonadherence*: TC(90/90):$28068 ($33495.65), TC(60/90):$21720 ($25920.11), TC(30/90):$21084 ($25161.12), TC(0/90):$12516 ($14936.28),	Quality: medium Classification: cost description

				costs Target case management costs Psychiatric assessment costs Arrest costs Incarceration costs	IC(90/90):$12168 ($14520.99), IC(60/90):$10068 ($12014.90), IC(30/90):$11376 ($13575.84), IC(0/90):$5592 ($6673.35), OC(90/90):$6468 ($7718.75), OC(60/90):$4152 ($4954.89), OC(30/90):$2916 ($3479.88), OC(0/90):$2136 ($2549.05), EDC(90/90):$96 ($114.56), 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

2006 US	type of antidepressant drug is related to adherence and assess the 6 month health care costs among newly diagnosed patients.	claims analysis Follow Up: 6 months Sample Size: 60386 (A:11526, NA:8860)	Antidepressant medication management measures Classification: meeting less than <3 medication management measures = nonadherent Method of Assessment: pharmacy claims data, Medicaid data, observational assessment	Inpatient costs Outpatient costs ED visit costs Pharmacy costs Physician office visit costs	Classification: all cause and disease state specific Currency Year: USD, 2004 Cost of Nonadherence*: 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)	Classification: cost description
Svarstad et al ***[25]*** 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/schizoaffective 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 ***[26]*** 2003 US	To evaluate the economic impact of antidepressant	Design: Retrospective database analysis Follow Up: 6 months	Measure: MPR Classification: MPR≥70% =	Total costs Pharmacy costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 1999	Quality: medium Classification: cost description

	treatment adherence among patients treated for depression	Sample Size: 14190 (A:5638, NA:8552)	adherent, MPR<70% = nonadherent Method of Assessment: pharmacy claims data	Medical costs	Cost of Nonadherence: TC:$11815 ($16290.09) PC:$1123 ($1548.35), MC:$10692 ($14741.74)	
Diabetes						
*An et al**[27]*** 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.	Design: Prospective cohort study Follow Up: 3 years Sample Size: 608 (A:472, NA:136)	Measure: MPR Classification: MPR≥90% = adherent, MPR<90% = nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence*: TC:$1657.11 ($1884.14) OC: $1413.99 ($1608.20), HC: $243.11 ($276.12)	Quality: medium Classification: cost description
Buysman et al[28] *2017* *US*	To examine the impact of real world adherence on glycaemic control in type 2 diabetes patients treated with canagliflozin.	Design: Retrospective database analysis Follow Up: 12 months Sample Size: 2261 (A:1215, NA:1046)	Measure: PDC Classification: PDC≥80% = highly adherent, PDC<80% = less than highly adherent Method of Assessment: healthcare claims data	Pharmacy costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2014 Cost of Nonadherence: all cause: PC: $7225 ($7297.39) Disease state specific: PC: $4660 ($4706.69)	Quality: low Classification: cost description
Curtis et al[29] *2017* *US*	Examine the association between adherence to glucose lowering agents and	Design: Retrospective analysis Follow Up: 3 years Sample Size: 228074	Measure: PDC Classification: PDC≥80% = adherent,	Total costs Outpatient costs Pharmacy	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2014 Cost of Nonadherence:	Quality: medium Classification: cost description

	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

					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	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	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) Unadjusted disease state specific: HC:$6919 ($8569.88), PC:$785 ($972.30), MC:$5192 ($6430.82), STDC:$1717 ($2126.68)	Quality: medium Classification: cost description
Hansen et al ***[33]*** 2010	To compare all cause total health care costs	Design: Retrospective, cohort study	Measure: MPR Classification:	Total Healthcare	Type of Costs: adjusted and unadjusted Classification: all cause and disease	Quality: medium Classification: cost

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.	Follow Up: 2 years Sample Size: 108592 (A:63830, NA:44762)	MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	costs Inpatient costs Outpatient costs Pharmacy costs	state specific Currency Year: USD, 2005 Cost of Nonadherence[#]: 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
Hong et al[34] 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.	Design: Retrospective, cohort study Follow Up: 3 years Sample Size: 40082 (A:11800, NA:28282)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total costs Hospitalization costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: KRW, 2007 Cost of Nonadherence: TC:₩765453 ($1142.31), HC:₩397549 ($593.28)	Quality: medium Classification: cost description
Jha et al[35] 2012 US	How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or	Design: Retrospective, observational claims analysis Follow Up: unclear Sample Size: 135639 (A:99976, NA:36553)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment:	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

	decreased hospitalizations or 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?		pharmacy claims data			
*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

					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**[37]*** 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	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

					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**[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	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

					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 a**[39]*** 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	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), PC:$213 ($222.23), POC:$44 ($45.91)	Quality: medium Classification: cost description
*Halpern et al**[40]*** 2011 US	To examine the associations of adherence to osteoporosis therapies	Design: Retrospective analysis Follow Up: 540 days Sample Size: 21655	Measure: MPR Classification: (≥80% = high adherence,	Medical costs	Type of Costs: unadjusted Classification: all cause Currency Year: USD, 2006 Cost of Nonadherence: commercial:	Quality: medium Classification: 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

					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)	
Huybrechts et al ***[42]*** 2006 US	To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.	Design: Retrospective cohort study Follow Up: 5 years Sample Size: 38120 (A:9530, NA:28590)	Measure: MPR Classification: (≥80% = compliant, <50% = noncompliant) Method of Assessment: pharmacy claims data	Total costs Medical costs Institutional costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2000 Cost of Nonadherence: TC:$7200 ($9706.44), MC:$1476 ($1989.84), InstC:$5736 ($7732.80)	Quality: low Classification: cost description
Kjellberge al ***[43]*** 2016 Denmark	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.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 38234 (A:26806, NA:11428)	Measure: MPR Classification: (≥70% = compliant, <70% = noncompliant) Method of Assessment: pharmacy claims data	Total costs Medical costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: Euro, 2011 Cost of Nonadherence: all cause: TC:€4933 ($6209.58), MC:€3471 ($4369.20), Disease state specific: TC:€754 ($949.12), MC:€426 ($536.24),	Quality: high Classification: cost outcome description
Modi et al ***[44]*** 2015	To evaluate compliance with	Design: Retrospective cohort study	Measure: MPR Classification:	Total costs Inpatient costs	Type of Costs: unadjusted Classification: all cause and disease	Quality: medium Classification: cost

US	osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance	Follow Up: 1 year Sample Size: 27913 (A:23430, NA:34483)	(≥80% = compliant, <80% = noncompliant) Method of Assessment: healthcare claims data	Outpatient costs ED costs Pharmacy costs Medical costs Other costs	state specific Currency Year: USD, 2011 Cost of Nonadherence: 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)	outcome description
Olsen et al ***[45]*** 2013 Denmark	To assess the association between refill compliance and all cause health care costs.	Design: Retrospective observational study Follow Up: 2 years Sample Size: 47176 (not specified)	Measure: MPR Classification: (≥80% = optimal compliance, >50<80% = suboptimal compliance, <50% = low compliance Method of Assessment: pharmacy claims data	Fracture costs	Type of Costs: unadjusted Classification: fracture site specific Currency Year: DKK, 2010 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)	Quality: medium Classification: cost analysis

					Other fracture: FC(50-80):-kr19261.50 (-$2377.93), FC(<50):kr684067.50 ($84451.66)	
*Sunyecz et al**[46]*** 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), PC:$918 ($1101.70), RC:$184 ($220.82)	Quality: low Classification: cost description
*Zhao et al**[47]*** 2014 US	To examine the association between teriparatide adherence and healthcare utilisation and costs among hip fracture patients.	Design: Retrospective cohort study Follow Up: 36 months Sample Size: 824 (≥80:362, 50-80%:219, <50%:243)	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	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence*: 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),	Quality: medium Classification: cost description

					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)	
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	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 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 (≥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

					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	<u>Design:</u> Retrospective longitudinal cohort study <u>Follow Up:</u> 24 months <u>Sample Size:</u> 12907 (≥75: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652)	<u>Measure:</u> MPR <u>Classification:</u> (≥75, 50-75%, 25-50%, <25%) <u>Method of Assessment:</u> pharmacy claims data	Total costs Outpatient costs ED costs Other 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(≥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),	<u>Quality:</u> medium <u>Classification:</u> 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)	
*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

			questionnaire		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)	
*Miravitlles et al***[53]** 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).	Design: multicentre, retrospective, observational study Follow Up: 18 months Sample Size: 1365 (A:246, NA:1119)	Measure: GOLD 2007 Guidelines Classification: (adherent, nonadherent) Method of Assessment: 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	Type of Costs: unadjusted Classification: disease state specific Currency Year: EUR, 2009 Cost of Nonadherence: 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)	Quality: medium Classification: cost description
*Quittner et al***[54]** 2014 US	To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.	Design: retrospective, cohort study Follow Up: 2 years Sample Size: 3287 (≥80%: 663, 50-80%: 949, <50%: 1675)	Measure: MPR Classification: (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence) Method of Assessment: pharmacy claims data	Total healthcare costs	Type of Costs: unadjusted Classification: all cause and disease state specific 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),	Quality: medium Classification: cost description

					THC(50-80):$33132.50 ($35444.44), THC(<50):$33894 ($36259.07)	
Gastrointestinal Disease						
*Carter et al***[55]** 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***[56]** 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
*Kane et al***[57]** 2009 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

			Assessment: health claims data		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)	
Mitra et al ***[58]*** 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.	Design: retrospective, observational cohort study Follow Up: 12 months Sample Size: 1693 (A:476, NA:1216)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Ancillary costs Non-pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence: 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)	Quality: high Classification: cost description
Wan et al ***[59]*** 2014 US	To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.	Design: retrospective cohort analysis Follow Up: 360 days Sample Size: 1646 (A:674, NA:972)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2009 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:	Quality: high Classification: cost description

					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 ***[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	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

	(AEDs) on healthcare utilisation and direct medical costs in a Medicaid population.	Follow Up: 4.65 years Sample Size: 33658 (A:24907, NA:8751)	<80% = nonadherent) Method of Assessment: pharmacy claims data	costs ED costs Pharmacy costs Other pharmacy costs	Cost of Nonadherence*: TC:$14417.64 ($18713.91), IC:$6682.28 ($6873.51), OC:$2172.40 ($2819.75), EDC:$405.96 ($526.93), PC:$822.40 ($1067.46), OtPC:$4334.60 ($5626.26)	
HIV/AIDS						
*Barnett et al**[63]*** 2011 US	To characterise the cost of HIV care including combination antiretroviral treatment.	Design: retrospective observational cohort study Follow Up: 1 year Sample Size: 1896 (not specified)	Measure: antiretroviral taking behaviour Classification: (85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent) Method of Assessment: pharmacy claims data	Total costs	Type of Costs: unadjusted Classification: disease state specific; viral load count Currency Year: USD, 2006 Cost of Nonadherence**: High viral load: TC:$25824 ($30067.54) Low viral load: TC:$20509.67 ($23879.92)	Quality: medium Classification: cost description
*Cooke et al**[64]*** 2014 US	To measure adherence to antiretroviral therapy regimens in commercially insured patients with HIV infection and analyse the clinical and demographic factors associated with ≥90% adherence.	Design: retrospective claims analysis Follow Up: 1 year Sample Size: 3528 (A:1737, NA:640)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) 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, 2011 Cost of Nonadherence: THC:$18868 ($20184.58), IC:$2700 ($2888.40), OC:$915 ($978.85), PC:$15253 ($16317.33)	Quality: medium Classification: cost description

*Pruitt et al**[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.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 502 (A:56, NA:176)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Other pharmacy costs Behavioural health inpatient costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2009 Cost of Nonadherence*: 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)	Quality: medium Classification: cost description
Parkinson's Disease						
*Davis et al**[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.	Design: retrospective administrative claims study Follow Up: 12 months Sample Size: 3119 (A:1211, NA:1908)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2001 Cost of Nonadherence: TC:$18511 ($24262.36), PC:$2684 ($3537.36), MC:$15827 ($20859.12)	Quality: medium Classification: cost outcome description
*Delea et al**[67]** 2011 US	To assess the associations between adherence to	Design: retrospective historical cohort study Follow Up: 12 months	Measure: PDC Classification: (≥80% =	Total costs Inpatient costs Pharmacy	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific	Quality: high Classification: cost description

	levodopa/carbidopa/entacapone 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

					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						
*Ivanova et al**[69]*** 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.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 648 (A:448, NA:200)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Short term disability costs Absenteeism cost	Type of Costs: unadjusted Classification: all cause, disease state specific and indirect Currency Year: USD, 2007 Cost of Nonadherence*: 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)	Quality: high Classification: cost outcome description
*Tan et al**[70]*** 2011 US	To assess the impact of treatment adherence on MS related hospitalizations	Design: retrospective cohort study Follow Up: 12 months Sample Size: 2446	Measure: MPR Classification: (≥80% = adherent, <80% =	Medical costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence:	Quality: medium Classification: cost description

	(inpatient), ER visits, MS relapses and medical costs.	(A:1459, NA:987)	nonadherent) Method of Assessment: pharmacy claims data		Adjusted: MC:$4348 ($5062.49) Unadjusted: MC:$5179 ($6030.04)	
Zhao et al ***[71]*** 2011 US	To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 5435 (A:1744, NA:3691)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: commercial: TC:$20323 ($22609.12), IC:$4808 ($5348.85), OC:$9822 ($10926.87), PC:$5693 ($6333.40) Medicare: TC:$25282 ($28125.96), IC:$8604 ($9571.86), OC:$10068 ($11200.54), PC:$6611 ($7354.67)	Quality: medium Classification: cost analysis
Cancer						
Darkow et al ***[72]*** 2007 US	Estimate the association between treatment interruptions and non-adherence with imatinib and healthcare costs for US managed care patients.	Design: retrospective observational cohort analysis Follow Up: 12 months Sample Size: 267 (≥95%:120, 90-95%:25, 50-90%:69, <50%:53)	Measure: MPR Classification: (≥95% = very high, >90<95% = high, >50<90% = intermediate, <50% = low) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other pharmacy costs Other costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC(≥95):$42250 ($52330.90), THC(90-95):$39236 ($48597.76), THC(50-90):$54770 ($67838.19), THC(<50):$131357 ($162698.93), IC(≥95):$1156 ($1431.82), IC(90-95):$1362 ($1686.97), IC(50-90):$19096 ($23652.33), IC(<50):$81572 ($101035.18), OC(≥95):$9299 ($11517.75), OC(90-95):$11148 ($13807.93),	Quality: high Classification: cost description

					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)	
Wu et al ***[73]*** 2010 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						
*Leider et al**[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.	Design: retrospective claims based analysis Follow Up: 12 months Sample Size: 2100 (A:442, NA:1658)	Measure: urine testing Classification: (positive test = nonadherent, negative test = adherent) Method of Assessment: health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: THC:$26433 ($29406.43), IC:$6361 ($7076.55), OC:$9734 ($10828.97), EDC:$421 ($468.36), PC:$7960 ($8855.42), MC:$1957 ($2177.14)	Quality: medium Classification: cost analysis
Ruetsch et al[75] 2017 US	To examine patient characteristics and outcomes associated with nonadherence to buprenorphine and to identify specific patterns of nonadherent behaviour.	Design: cross sectional, retrospective analysis health claims data Follow Up: 12 months Sample Size: 477 (A:172, NA:305)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Physician office visit costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2013 Cost of Nonadherence: 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)	Quality: medium Classification: cost description
*Tkacz et al**[76]*** 2014 US	To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 455 (A:146, NA:309)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence: Adjusted: THC:$49051 ($53503.88), IC:$26470 ($28872.96), OC:$14570 ($15892.67), EDC:$4439 ($4841.98),	Quality: medium Classification: cost description

	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

			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)	
All						
*Alvarez Payero et al***[79]** 2014 Spain	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.	Design: retrospective observational study Follow Up: 1527 days Sample Size: 87 (A:21, NA:66)	Measure: pharmacy records Classification: (>75% = adherent, ≤75% = nonadherent) Method of Assessment: pharmacy and hospital claims data	Hospitalization costs	Type of Costs: unadjusted Classification: all cause Currency Year: EUR, 2012 Cost of Nonadherence####: All cause: HC:€6275.80 ($8893.94)	Quality: low Classification: 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 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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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

[1]Some 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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