

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Economic impact of medication nonadherence by disease groups: a systematic review
AUTHORS	Cutler, Rachelle; Fernandez-Llimos, Fernando; Frommer, Michael; Benrimoj, Charlie; Garcia Cardenas, Victoria

VERSION 1 – REVIEW

REVIEWER	Tatiana Dilla Eli Lilly, Spain I work for the pharmaceutical industry. I have no competing interest related to this review.
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	<p>This is an excellent systematic review of the economic impact of nonadherence to medication by disease groups.</p> <p>The only concern that should be addressed before publication is the need to remove some results from the methods section. Specifically these two sentences (in page 6, line 24 and line 29) should be part of the results:</p> <ul style="list-style-type: none">- The cost analysis of studies (figures 2 and 3) reported annual medication nonadherence costs incurred by the patient from a healthcare provider perspective.- The most utilized methods were medication possession ratio (MPR) and proportion of days covered (PDC).
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REVIEWER	Janice Blanchard George Washington United States
REVIEW RETURNED	29-May-2017

GENERAL COMMENTS	<p>p. 6 I would imagine in some cases costs are based on later outcome costs-such as unnecessary hospitalizations or ED visits. You mention “direct costs to the healthcare system” c line36-37 please expand or clarify the definition you used for costs.</p> <p>p.12 lines 35-40 again please define what each of these costs entail eg pharmacy costs are what?</p> <p>The whole results section is just a listing of costs by different groups and is a bit monotonous. Can you say a little more about these as a group perhaps? Eg did cardiovascular costs mainly reflect more hospitalizations for heart failure or higher numbers of myocardial infarctions? Please give more details.</p>
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	Discussion second paragraph-maybe put earlier that costs does not include avoidable costs in the intro or methods section. It makes me wonder what is each type of cost listed? What are the medical costs, pharmacy costs, etc? Not a lot of details so I was confused what the type of costs that are measured in each of these indicators.
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REVIEWER	Seth A. Berkowitz Massachusetts General Hospital/Harvard Medical School Boston, MA, USA
REVIEW RETURNED	21-Jun-2017

GENERAL COMMENTS	<p>I was asked to provide review of the methods of this paper. I think the methods are appropriate and this appears to be a well conducted systematic review. I do not note any concerns.</p> <p>The authors note that study heterogeneity does not permit meta-analysis, and this seems reasonable to me after looking at their included studies. I would also note that conceptually it is not clear to me that the results would be meta-analyzable, as it is not clear to me that there is a single 'effect' of non-adherence on healthcare costs. The effect will invariably differ based on what the treatments not being adhered to are, what conditions they are treating, and the structure of healthcare finance in the country being studied. Therefore I think a descriptive systematic review, without meta-analysis, is sufficient to present what is known on the topic, and provide the clinical condition specific breakdowns, as the authors have done.</p>
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REVIEWER	John E Zeber Central Texas VA / Baylor Scott & White Health
REVIEW RETURNED	11-Jul-2017

GENERAL COMMENTS	<p>This is naturally a long paper given its topic and breadth of literature in this area, yet generally seems to represent a useful review project. I do, however, have some rather significant concerns in terms of definitions, search terms, inclusion criteria and therefore the scope of the review and lessons to be learned. At a minimum, I would call for more clarity regarding these points, and/or a fuller defense in establishing the context the information you share. 1) From my own cursory search of just one of your condition categories (mental health), it seems like many potential cost of adherence papers were omitted, across a range of approaches (cost-effectiveness, hypothetical models etc.). Since I realize this broadens the conceptual study design here, such inclusions might not all be appropriate, yet it appears several omitted publications were directly on target; 2) Secondly, per above, I now wonder if your search terms were too limited or might be opened up in an effort to capture relevant papers – e.g., pharmacy, pharmacological treatment, economic or financial [costs], readmissions due to poor adherence, etc. 3) then, also relevant but perhaps heading towards either being tangential or greatly adding complexity, what about indirect studies targeting copayment changes to patients which in turn adversely affect adherence and raise overall costs, cost-effective of adherence intervention or comparing two drugs, or medication side effects that actually cause extra treatment costs?</p>
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I cannot advocate that every step in the very complex adherence decision – effect – treatment –costs chain be fully examined, but all these issues are tied in how “costs” are evaluated. I would again request at least consideration of these concerns, at a minimum significant discussion as one type of limitation to this (or any similar) study. Nevertheless, the breadth of information presented and summarized is impressive, and should contribute to our knowledge of this subject. More Clarification and thought would help systems or policy makers place results in context.

Specific Comments: major

- Abstract – I recognize the word limitations and journal header requirements, but this does appear a bit choppy and could use context plus why this is a significant area of inquiry. Also, given there are other measures of adherence paper quality, maybe a little on Drummond would help; if no room, it was appropriate to note that here, then reserve details for methods. The summary of observed findings are well presented here, along with a brief discussion of state of literature on this topic.
- introduction – solid albeit short, I agree that evidence exists but not frequently in systematic format (though see my quick mental health search),and very few papers are evaluated for quality; as you imply, perhaps this is even more important for economic examinations, where methods might be less familiar to PubMed audiences. Even prior to reading the methods and conducting a limited search, I noted there are many other potential associated with medications (financial, quality of life, other) to consider. In addition to possibly addressing some of these issues related to my primary review, perhaps a brief example or two of what prior studies have observed regarding cost related to poor adherence. Then, besides more detail in the discussion, perhaps a statement or primer on what might be gained from study in terms of policy and clinical practice.
- Methods – aside from aforementioned issues, a couple other points for clarification: Did you look at other potential databases, as many systematic reviews do (CINAHL, PsychInfo)? – perhaps this might account for some omitted articles. How did appropriately examine non-English journals? It seems like you only focused on papers targeting impact of clear “interventions”, though not sure if this includes descriptive studies, models as previously mentioned and so on, as such studies certainly provide both factual information and additional insights.. If so, this requires more explanation and defense as to what defines a true intervention, versus observation of a clinical implementation or other real world efforts. In addition, more clarity is required regarding direct versus indirect costs, as in section 2.2 you state as “incurred by the patient from a healthcare provider perspective, which is a little confusing; plus one article I provided below captured another indirect cost, criminal justice / jail diversion, another potential significant total. Also, how are indirect costs calculated, based on author report, estimation, other source? As he is an expert in the field, the Drummond quality list seems comprehensive and very appropriate here (versus the Nichol quality tool). Why only consider articles after 1997, as it seems there has long been a research interest in adherence costs, and most systematic reviews explore a far longer time period. See other comments for additional search terms to consider, along with other conceptual or concrete cost categories and models to evaluate.

• Results – aside from primary concern of potentially relevant articles overlooked, I have few concerns about this section. A couple regarding the presentation include section 3.4 - be clear that costs = average per year patient, yes? Then are these tables only direct costs, as text below seems to suggest? Overall a good summary but readers could get lost in similar details, so perhaps a bit more effort to highlight key differences across conditions versus constant summary of # with adjusted costs etc., which could better be saved for a table. OK re: the meta-analysis and thank you for reporting that exploration effort. Returning to my main point, given personal experience in mental health adherence work, I conducted a quick search using a few search terms (adherence, cost) from just PubMed, and uncovered quite a few articles. If indeed these are not appropriate per your criteria, then per above more explanation and defense is needed, as these certainly seem on target to different degrees, especially few marked with ** below (also see included brief title list I attached). I assume that doing the same new additional search for your other disease categories would uncover useful publications. I also note the main summary table is well done, and helps mitigate the need to include as many text details referenced earlier.

Hartung D, Low A, Jindai K, Mansoor D, Judge M, Mendelson A, Kansagara D, Motu Apuaka M, Freeman M, Kondo K. Interventions to Improve Pharmacological Adherence Among Adults With Psychotic Spectrum Disorders and Bipolar Disorder: A Systematic Review. *Psychosomatics*. 2017 Mar - Apr;58(2):101-112.

** Dilokthornsakul P, Thooputra T, Patanaprathep O, Kongsakon R, Chaiyakunapruk N. Effects of medication adherence on hospitalizations and healthcare costs in patients with schizophrenia in Thailand. *SAGE Open Med*. 2016 Mar 8;4.

Druais S, Doutriaux A, Cognet M, Godet A, Lançon C, Levy P, Samalin L, Guillon P. Cost Effectiveness of Paliperidone Long-Acting Injectable Versus Other Antipsychotics for the Maintenance Treatment of Schizophrenia in France. *Pharmacoeconomics*. 2016 Apr;34(4):363-91.

** Predmore ZS, Mattke S, Horvitz-Lennon M. Improving antipsychotic adherence among patients with schizophrenia: savings for states. *Psychiatr Serv*. 2015 Apr 1;66(4):343-5.

** Robertson AG, Swanson JW, Van Dorn RA, Swartz MS. Treatment participation and medication adherence: effects on criminal justice costs of persons with mental illness. *Psychiatr Serv*. 2014 Oct;65(10):1189-91.

** King D, Knapp M, Patel A, Amaddeo F, Tansella M, Schene A, Koeter M, Angermeyer M, Becker T. The impact of non-adherence to medication in patients with schizophrenia on health, social care and societal costs. Analysis of the QUATRO study. *Epidemiol Psychiatr Sci*. 2014 Mar;23(1):61-70.

** Hansen RA, Maciejewski M, Yu-Isenberg K, Farley JF. Adherence to antipsychotics and cardiometabolic medication: association with health care utilization and costs. *Psychiatr Serv*. 2012 Sep 1;63(9):920-8.

** Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. *Curr Med Res Opin*.

• Discussion – deferring for a minute the primary concern that a potentially limited inclusion criteria or omissions would at least affect the context of these findings if not the generalizability, I believe the discussion is also nicely presented and summarizes the information reviewed here. Also note that in first sentence here, there have been other systematic reviews, though more targeting overall risk factors or conceptual issues. Overall, one concern is that while thorough, there is a distinct possibility that potential exclusions (even if varying degree of being tangential) yield a product that is not representative of all-cost impact studies. Further clarifications in a revision will help enable readers to better interpret the extent of at that issue. I recognize some potential factors may well lie outside the scope of your intentions, such as the actual cost of medications side effects, the role of copayment policies that affect adherence, or the comparative economic benefit of non-pharmacological treatment options. However, all these probably should be taken into account as significant conceptual issues if not directly tested empirically. Given the variety of approaches, methods and adherence definitions, this raises a point about how accurate “costs due to adherence” can be truly estimated, and what we should do with this information. This is not primarily a study flaw, but recognition of topic complexity that should be better highlighted. Also, how can systems / states / clinics really understand the scope of problem and therefore how to target this issue? Note there have been review papers on the cost-effectiveness of adherence interventions, which are potentially more useful to health systems. So I am suggesting that a paragraph better documenting some limitations to help with context, while also raising how concerns about indirect costs and what systems or policy makers can utilize this review would be clearly useful. Otherwise, as noted, the discussion is quite comprehensive and thoughtful, including a comment that societal costs have not been adequately summarized accordingly.

minor points: [all minor, perhaps subject to journal's formatting requirements]

- though agreeing your brief bullets, especially some potential limitations, admit I often find these reader summaries too cursory for much merit.
- did a single reviewer determine article quality per Drummond, team consensus?
- though largely accurate, an early sentence about “medications being cost-effective” is more hopeful conjecture (without a citation as well) and often not the case.
- thanks for registration and other information on the protocol
- be sure to add commas after all e.g., and i.e.,
- suggest adding a sub-header when you move to presenting the specific conditions

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: This is an excellent systematic review of the economic impact of nonadherence to medication by disease groups.

- The need to remove some results from the methods section. Specifically these two sentences (in page 6, line 24 and line 29) should be part of the results

Response: We would like to thank the reviewer for pointing this out. The sentences regarding results have been removed from the methods section and correctly identified in the results section.

Section 3.4: The cost analysis of studies (figures 2 and 3) reported annual medication nonadherence costs incurred by the patient per year.

Reviewer #2:

- p. 6 I would imagine in some cases costs are based on later outcome costs-such as unnecessary hospitalizations or ED visits. You mention “direct costs to the healthcare system” c line36-37 please expand or clarify the definition you used for costs.

- p.12 lines 35-40 again please define what each of these costs entail eg pharmacy costs are what?

Response: We understand the reviewers concern regarding the lack of clarity in terminology used to classify. The terminology and indicator used to group costs is derived from the original studies classification of the cost. A glossary of terms was going to be included however many studies fail to define what exactly is incorporated in the cost reported and there is much heterogeneity between studies. This further supports the notion for a standardized model to be designed to measure the cost of medication nonadherence based on key defined cost categories. It is therefore not possible to provide clear definitions of each indicator due to the aforementioned reasons. We have endeavored to make this clearer via adding a paragraph to explain the definition of costs.

Section 2.2: 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.

Section 3.4: 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.

- The whole results section is just a listing of costs by different groups and is a bit monotonous. Can you say a little more about these as a group perhaps? Eg did cardiovascular costs mainly reflect more hospitalizations for heart failure or higher numbers of myocardial infarctions? Please give more details.

Response: An introductory paragraph summarizing key differences amongst disease groups has been included.

Section 3.5: 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.

- Discussion second paragraph-maybe put earlier that costs does not include avoidable costs in the intro or methods section. It makes me wonder what is each type of cost listed? What are the medical costs, pharmacy costs, etc? Not a lot of details so I was confused what the type of costs that are measured in each of these indicators

Response: Please see comments above regarding the definition of costs. The costs most likely do include avoidable costs however the classification of the original studies data has not grouped them into an avoidable cost category. Due to the restraints of claims and healthcare databases coding, it is most likely that avoidable costs such as unnecessary hospital admissions, physician office visits and healthcare resource utilization have been incorporated into the direct cost category. This is reported in the results section and the concern has been addressed in the discussion.

Section 4: 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.

Reviewer #3: I think the methods are appropriate and this appears to be a well conducted systematic review. I do not note any concerns.

The authors note that study heterogeneity does not permit meta-analysis, and this seems reasonable to me after looking at their included studies. I would also note that conceptually it is not clear to me that the results would be meta-analyzable, as it is not clear to me that there is a single 'effect' of non-adherence on healthcare costs. The effect will invariably differ based on what the treatments not being adhered to are, what conditions they are treating, and the structure of healthcare finance in the country being studied. Therefore I think a descriptive systematic review, without meta-analysis, is sufficient to present what is known on the topic, and provide the clinical condition specific breakdowns, as the authors have done.

We thank you for your valuable feedback.

Reviewer #4: I have some rather significant concerns in terms of definitions, search terms, inclusion criteria and therefore the scope of the review and lessons to be learned. At a minimum, I would call for more clarity regarding these points, and/or a fuller defense in establishing the context the information you share.

1. Abstract does appear a bit choppy and could use context plus why this is a significant area of inquiry. Also, given there are other measures of adherence paper quality, maybe a little on Drummond would help; if no room, it was appropriate to note that here, then reserve details for methods.

Response: The abstract has been reworked to help address the concerns of it being disjointed. Headings and the word limit are in alignment with journal requirements.

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

2. Introduction;

- In addition to possibly addressing some of these issues related to my primary review, perhaps a brief example or two of what prior studies have observed regarding cost related to poor adherence.

- perhaps a statement or primer on what might be gained from study in terms of policy and clinical practice.

Response: Thank you for this direction we have added a statement to the introduction to help provide clinical context and frame the paper in terms of policy and clinical practice.

Section 1: 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].

Section 1: Policymakers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[10]. 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.

3. Methods;

- Did you look at other potential databases, as many systematic reviews do (CINAHL, PsychInfo)? – perhaps this might account for some omitted articles. How did you appropriately examine non-English journals?

Response: A comprehensive search of PubMed and Scopus was conducted. There were no language restriction filters used. Where articles were identified in a language other than English a native speaker of the language read the paper in conjunction with reviewer RC to determine if it met the inclusion criteria. No non-English studies met the inclusion criteria. The exact search criteria utilized has been included as a supplementary file (eTable1).

- It seems like you only focused on papers targeting impact of clear “interventions”, though not sure if this includes descriptive studies, models as previously mentioned and so on, as such studies certainly provide both factual information and additional insights.. If so, this requires more explanation and defense as to what defines a true intervention, versus observation of a clinical implementation or other real world efforts.

All studies included in the review were required to quantify the cost of medication nonadherence in a dollar value. This included more than just intervention studies, with majority of studies being non-intervention retrospective analysis of healthcare claims data. Intervention studies were only included if they reported the cost of medication nonadherence in addition to baseline data so a comparison could be made. They were classified as intervention studies as per classification by the author in the original study. In many instances intervention studies were excluded as they did not report baseline data.

- In addition, more clarity is required regarding direct versus indirect costs, as in section 2.2 you state as “incurred by the patient from a healthcare provider perspective, which is a little confusing; plus one article I provided below captured another indirect cost, criminal justice / jail diversion, another potential significant total. Also, how are indirect costs calculated, based on author report, estimation, other source?

Response: Please see comments above regarding the classification of costs. Revisions to section 2.2 and 3.4 further clarify these concerns.

- Why only consider articles after 1997, as it seems there has long been a research interest in adherence costs, and most systematic reviews explore a far longer time period. There were no time constraints placed on the search strategy, the earliest included study that met all inclusion criteria was from 1997.

4. Results;

- Regarding the presentation include section 3.4 - be clear that costs = average per year patient, yes? Then are these tables only direct costs, as text below seems to suggest?

Response: You raise an important query. We have endeavored to make the wording clearer in the revision. Costs represent average per patient cost per year. The cost ranges incorporate both direct and indirect costs. Removal of text 'from a healthcare provider perspective' removes the ambiguity suggesting that only direct costs are reported.

Section 3.4: The cost analysis of studies (figures 2 and 3) reported annual medication nonadherence costs incurred by the patient per year.

- Overall a good summary but readers could get lost in similar details, so perhaps a bit more effort to highlight key differences across conditions versus constant summary of # with adjusted costs etc., which could better be saved for a table.

Response: Taking this into consideration an introductory paragraph summarizing key differences amongst disease groups has been included.

Section 3.5: 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.

- Returning to my main point, given personal experience in mental health adherence work, I conducted a quick search using a few search terms (adherence, cost) from just PubMed, and uncovered quite a few articles. If indeed these are not appropriate per your criteria, then per above more explanation and defense is needed, as these certainly seem on target to different degrees, especially few marked with ** below (also see included brief title list I attached). I assume that doing the same new additional search for your other disease categories would uncover useful publications.

Response: We would like to thank the reviewer for pointing out these very interesting works. The list of potentially omitted studies has been reviewed with potentially 1 out of the 14 listed being suitable for inclusion in the systematic review. This paper was omitted initially due to the lack of MeSH terms when the search was conducted. This article has now been included in the review as a manual search result taking total included studies to 75. Hartung et al was not included as it was published after the search was conducted. Dilokthornsakul et al, Druais et al and Predmore et al were not retrieved because there were no MeSH assigned when the search was conducted. Additionally Dilokthornsakul et al use cost in singular, where the query used for the systematic review utilized "costs" in plural. All were reviewed and excluded based on inclusion criteria. Pesa et al was not retrieved in the search strategy because it does not measure any costs associated with medication nonadherence rather it compares the cost of healthcare resource utilization between two antipsychotic medications. Upon review this study does not meet the inclusion criteria. Markowitz et al, King et al, Hansen et al, Damen et al and Marcus et al were all captured in the initial literature search and progressed to full text review. They were excluded based on criteria the 'paper does not report the cost of nonadherence'. Dilla et al and Sun et al were captured in the search strategy and progressed to full text review. They were excluded based on the criteria 'systematic reviews'. Hong et al was captured in the literature search however excluded at title/abstract screening as the paper did not clearly assess the economic impact of medication nonadherence.

Section 3.5.2: 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.

81. Robertson AG, Swanson JW, Van Dorn RA, et al. Treatment participation and medication adherence: effects on criminal justice costs of persons with mental illness. *Psychiatric services* (Washington, DC) 2014;65(10):1189-91 doi: 10.1176/appi.ps.201400247[published Online First: Epub Date]].

5. Discussion;

- Note that in first sentence here, there have been other systematic reviews, though more targeting overall risk factors or conceptual issues.

Response: Thank you for this point; in the revision this sentence has been reworded.

Section 4: 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.

- Overall, one concern is that while thorough, there is a distinct possibility that potential exclusions (even if varying degree of being tangential) yield a product that is not representative of all-cost impact studies. Further clarifications in a revision will help enable readers to better interpret the extent of that issue. I recognize some potential factors may well lie outside the scope of your intentions, such as the actual cost of medications side effects, the role of copayment policies that affect adherence, or the comparative economic benefit of non-pharmacological treatment options. However, all these probably should be taken into account as significant conceptual issues if not directly tested empirically.

Response: The systematic review examined all studies that quantified a cost value and attributed it to nonadherence. Classifications of these costs were as per report in the original study. The role of copayment policies and comparative economic benefit of non-pharmacological treatment options lied outside the scope of this review and thus were not assessed.

- Given the variety of approaches, methods and adherence definitions, this raises a point about how accurate "costs due to adherence" can be truly estimated, and what we should do with this information. This is not primarily a study flaw, but recognition of topic complexity that should be better highlighted.

Response: We acknowledge the complexity of elements of medication nonadherence and have thus added an additional statement to the discussion addressing this concern.

Section 4: 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.

- Also, how can systems / states / clinics really understand the scope of problem and therefore how to target this issue? Note there have been review papers on the cost-effectiveness of adherence interventions, which are potentially more useful to health systems. So I am suggesting that a paragraph better documenting some limitations to help with context, while also raising how concerns about indirect costs and what systems or policy makers can utilize this review would be clearly useful.

Response: We thank you for highlighting the lack of context in regards to how quantifying the cost of medication nonadherence can help policy makers. This has been amended in the revision.

Section 4: 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 [95] 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[96]. 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.

6. General comments;

- Did a single reviewer determine article quality per Drummond, team consensus?

Response: Team consensus was utilized to classify the quality and economic evaluation of studies. A sentence has been added to section 2.3 outlining this.

Section 2.3: 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) by team consensus (RC and VGC).

- General comments; be sure to add commas after all e.g., and i.e.,

- General comments; suggest adding a sub-header when you move to presenting the specific conditions

Response: Thank you for this feedback we have amended these in the revision.

VERSION 2 – REVIEW

REVIEWER	Janice Blanchard United States George Washington University
REVIEW RETURNED	10-Sep-2017

GENERAL COMMENTS	<p>This is an important topic. However there are several areas in which I find the manuscript very difficult to follow. I also think the authors should have restricted their review to more recent studies. Specific comments as follows:</p> <p>1. Introduction</p> <p>First paragraph is very awkward. Please consider rewording this sentence “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” Also typo “emphasising”</p> <p>Paragraph 2 contains important information but is repetitive-please shorten</p> <p>Paragraph 3 also awkward and long. Please consider rewording the sentence “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.”</p>
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	<p>2.1 Methods-I do wonder why no date restrictions were used? Please provide justification as this can lead to the inclusion of many outdated references.</p> <p>Results The results are helpful but as written it is presented in a really hard to read format.</p> <p>Discussion p. 18 Awkward sentence. Please consider rewording “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.”</p> <p>p. 20 Awkward sentence: 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].” This sentence could be reworded-it is quite hard to really understand what the writer is trying to say and I am not sure this is truly a downside. What outputs and inputs should these studies examine?</p> <p>p. 21 I would also add the bias of having so many studies in the United States that prescription medication costs and healthcare costs may be higher in the US.</p> <p>p. 21-This last paragraph is exactly why I think the authors should have used a more narrow timeframe for study inclusion.</p>
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REVIEWER	John E Zeber Baylor Scott & White / Central Texas VA
REVIEW RETURNED	30-Aug-2017

GENERAL COMMENTS	<p>Overall, the authors have done a solid job of addressing comments, and concerns, from all the reviewers; this includes some common critiques (e.g., presentation of numerical / cost results). The response table was also helpful in providing this information, along with a tracked changes version of the manuscript. The paper by its nature, remains very long, yet this revision has helped some with readability and allowing readers to summarize primary findings. Some additional comments below.</p> <ul style="list-style-type: none"> • Abstract and the introduction do read better, while providing additional information as overall context. • Not sure why you did not include other databases as mentioned, as there often can be found other relevant papers; this replication wouldn't take that much more effort. The other explanations or method details seem adequate (e.g., definition of indirect costs), though I believe some readers at least may have a difficult time understanding certain criteria and definitions, even those familiar and interested in the topic. I still suggest clarifying that no time period was placed upon studies but that the first eligible one was not published until 1997. This does seem a little odd that noting relevant was done before then, given the lengthy run of adherence work. • Results now a bit clearer though still may be a bit “dry” for audiences, yet presents the salient information.
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	<p>But without focusing more on the specific list of reasons my own search of several potential articles were omitted, it just re-asserts the question of how firm and logical the inclusion criteria were. For one thing, it should be noted that updating a literature review upon revision to add a newer relevant article is not that significant a chore, and if wholly appropriate, I definitely suggest adding the new 2017 paper. Then, not necessarily disagreeing with one or more of the exclusions, mine was a very quick search that seemed to reveal several articles that indeed appeared on point. So noting that other readers may also either see or wonder about other articles, I admit that remains my one true concern about this paper, quality of overall presentation and goal notwithstanding. The topic itself is so broad with multiple definitions and methodological approaches as the authors noted. I read and understand your detailed follow-up review of these papers (again, perhaps only a sample of ones you found initially or others), and thank you for that nice effort. But this was to illustrate a point, and I still believe that there needs to be at least a statement that e.g., “numerous other papers do discuss non-adherence costs but either addressed tangential issues or did not present primary relevant data”. This issue with missing MeSH terms is quite valid but also raises another larger concern about how many systematic review studies are missing postnatally relevant articles.</p> <ul style="list-style-type: none"> • Overall, the discussion has also now nicely incorporated some broader conceptual issues and practical implications for health systems that were suggested, while appropriately noting some of my points were not pertinent. I appreciate the thoroughness of the revision and responses, even though we might still disagree on inclusion criteria and scope of this review.
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VERSION 2 – AUTHOR RESPONSE

Reviewer #2:

1. Introduction

- First paragraph is very awkward. Please consider rewording this sentence “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” Also typo “emphasising”

Response: We would like to thank the reviewer for identifying these issues. This paragraph has been reworded to assist with readability and the spelling mistake rectified.

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].

- Paragraph 2 contains important information but is repetitive-please shorten
This paragraph has been reworded to assist with readability and remove repetition.

Response: 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 [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[4].

- Paragraph 3 also awkward and long. Please consider rewording the sentence “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.”

Response: This paragraph has been reworded and split into two paragraphs to assist with readability. 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

- I do wonder why no date restrictions were used? Please provide justification as this can lead to the inclusion of many outdated references.

Response: In accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used. Cochrane states ‘Date restrictions should be applied only if it is known that relevant studies could only have been reported during a specific time period, for example if the intervention was only available after a certain time point’.

Additionally analysis of the earlier studies included demonstrates that they follow the same pattern of association between medication nonadherence and increasing healthcare costs. With all cost data in the review being standardized to \$US2015 values it allows more meaningful comparisons between studies to be made no matter their date of publication.

3. Results

- The results are helpful but as written it is presented in a really hard to read format.

Response: We understand that the results section may be dry and difficult to read in the text format. However the written text is required to provide more detailed content and analysis within disease groups. In order to help improve readability of results; the following measures have been taken:

1. A summary paragraph has been included prior to individual disease group analysis to draw key comparisons between disease group findings.
2. An additional table eTable 3 has been developed to highlight the cost comparisons between disease groups for adjusted and unadjusted costs.
3. Figures 2 and 3 graphically represent the total cost comparisons of adjusted and unadjusted costs across disease groups.

4. Discussion

- p. 18 awkward sentence. Please consider rewording “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.”

Response: This sentence has been removed from the discussion as it provides no extra value to the content of the paragraph and is only reiterating previous statements.

- p. 20 awkward sentence: 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].” This sentence could be reworded-it is quite hard to really understand what the writer is trying to say and I am not sure this is truly a downside. What outputs and inputs should these studies examine?

Response: We agree that not having included any studies that conducted a full economic evaluation is not necessarily a bad thing. We have therefore restructured this sentence to demonstrate and make clearer to the reader that while no individual study in the review conducted a full economic evaluation when you examine the studies as a whole they provide valuable insight into how addressing medication nonadherence can positively affect healthcare budgets.

Economic evaluations inform decisions on how to make best 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.

- p. 21 I would also add the bias of having so many studies in the United States that prescription medication costs and healthcare costs may be higher in the US.

Response: Thank you for identifying that due to the large portion of included studies being conducted in the US it could bias the results due to their generally higher costs of healthcare. We too agree that this could have an implication on the applicability of findings to other healthcare systems and have thus highlighted this in paragraph 10 of the discussion.

- p. 21-This last paragraph is exactly why I think the authors should have used a more narrow timeframe for study inclusion.

Response: While we understand your concerns, we do not feel that the lack of date restriction filters will significantly influence the overall findings derived from the systematic review. In accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used. Cochrane states 'Date restrictions should be applied only if it is known that relevant studies could only have been reported during a specific time period, for example if the intervention was only available after a certain time point'.

Additionally analysis of the earlier studies included demonstrates that they follow the same pattern of association between medication nonadherence and increasing healthcare costs. With all cost data in the review being standardized to \$US2015 values it allows more meaningful comparisons between studies to be made no matter their date of publication.

Reviewer #4:

1. Methods

- Not sure why you did not include other databases as mentioned, as there often can be found other relevant papers; this replication wouldn't take that much more effort.

Response: While we understand the reviewers concerns over the included databases we believe that PubMed and Scopus provide a comprehensive enough coverage of the medication nonadherence topic area. PubMed, which is not a single database but comprises Medline and PubMed Central, and Scopus are the two major databases in medicines related literature. Their coverage of medication adherence topics is so comprehensive, that the added value (measured as unique records retrieved) of non-medication-related databases like CINHALL (Health allied) or Psycinfo (Psychology) would not provide significant added value. Additionally the search has now been updated in PubMed and Scopus as at Sept 2017, to include more recent publications.

- The other explanations or method details seem adequate (e.g., definition of indirect costs), though I believe some readers at least may have a difficult time understanding certain criteria and definitions, even those familiar and interested in the topic.

Response: Due to the heterogeneity in the definitions utilized in the included studies, it is difficult to provide exact definitions of each of these details. Transparency has tried to be used to demonstrate this variation amongst studies with categorization of studies resulting from how they are categorized in the original study. As outlined in paragraph 2 of section 2.2 extracted information and paragraph 2 of section 3.4 medication nonadherence costs.

- I still suggest clarifying that no time period was placed upon studies but that the first eligible one was not published until 1997. This does seem a little odd that noting relevant was done before then, given the lengthy run of adherence work.

Response: A sentence has been added clarifying this.

Publication years ranged from 1997 to 2017, no date restriction filters were utilized with the earliest eligible study published in 1997.

2. Results

- Now a bit clearer though still may be a bit "dry" for audiences, yet presents the salient information. But without focusing more on the specific list of reasons my own search of several potential articles were omitted, it just re-asserts the question of how firm and logical the inclusion criteria were.

Response: We understand that the results section may be dry and difficult to read in the text format. However the written text is required to provide more detailed content and analysis within disease groups. In order to help improve readability of results, the following measures have been taken:

1. A summary paragraph has been included prior to individual disease group analysis to draw key comparisons between disease group findings.
2. An additional table eTable 3 has been developed to highlight the cost comparisons between disease groups for adjusted and unadjusted costs.
3. Figures 2 and 3 graphically represent the total cost comparisons of adjusted and unadjusted costs across disease groups.

The inclusion criteria were applied systematically across all studies retrieved in the literature search and screened for inclusion. The main reason studies were omitted from inclusion in the systematic review were that they failed to provide original cost/monetary data for the outcomes and link that to a measure of medication nonadherence.

- For one thing, it should be noted that updating a literature review upon revision to add a newer relevant article is not that significant a chore, and if wholly appropriate, I definitely suggest adding the new 2017 paper.

Response: The literature search has been updated as at Sept 2017, resulting in the inclusion of four additional studies.

- Then, not necessarily disagreeing with one or more of the exclusions, mine was a very quick search that seemed to reveal several articles that indeed appeared on point. So noting that other readers may also either see or wonder about other articles, I admit that remains my one true concern about this paper, quality of overall presentation and goal notwithstanding.

Response: The complete list of inclusion/exclusion criteria that were applied to the studies from the literature search has been included in the methodology. Further clarity in the initial exclusion criteria has been added through specifying that monetary values must have been stated.

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.

- The topic itself is so broad with multiple definitions and methodological approaches as the authors noted. I read and understand your detailed follow-up review of these papers (again, perhaps only a sample of ones you found initially or others), and thank you for that nice effort. But this was to illustrate a point, and I still believe that there needs to be at least a statement that e.g., "numerous other papers do discuss non-adherence costs but either addressed tangential issues or did not present primary relevant data".

Response: We agree that given the breadth of studies reporting on medication nonadherence and costs, greater clarity was required in the specific requirements as to why certain seemingly valid studies failed to meet the inclusion criteria. A statement has been added to the results section demonstrating the salient issue that while many studies do address costs and nonadherence they are outside the scope of this review.

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.

- This issue with missing MeSH terms is quite valid but also raises another larger concern about how many systematic review studies are missing postnatally relevant articles.

Response: We agree that issues with missing MeSH terms is a larger concern about how many systematic reviews are missing postnatally relevant studies , however this is outside the scope of this review.

VERSION 3 – REVIEW

REVIEWER	Janice Blanchard George Washington University
REVIEW RETURNED	27-Oct-2017

GENERAL COMMENTS	<p>This was a revision. The authors appear to have addressed the reviewer comments-I would recommend some minor revisions prior to publication. Please see below:</p> <p>Introduction first sentence third paragraph.</p> <p>1, First sentence “Addressing the eonomi impact...” does not make sense. I would just drop as next sentence seems to introduce the paragraph sufficiently.</p> <p>2. Section 3.2. after 2017 should have a semicolon between 2017 and no date restrictions instead of comma. I would however eliminate the part after the comma and instead just add a sentence (or even footnote) stating why they did not use date restrictions. The author has addressed this in the reviewer table so can just add this justification to the text.</p> <p>3. p. 15 “Contrastingly” would be better as “In contrast,” sub classifications should have a dash between the two words.</p> <p>4. Reviewer comments. The author should add in their justification of why no date restrictions to the context of the paper. Other comments seem to have been adequately addressed.</p>
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REVIEWER	John E Zeber Baylor Scott & White / Central Texas VA
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	<p>No further issues noted, and thanks to the authors for responding to not only my additional comments but that of another reviewer. While I don't agree that other databases would not necessarily yield more relevant publications, I respect their explanation and fact they extended the review to include a few more articles. Still offering the results section can seem a little dry and repetitive in presentation, undoubtedly many readers will benefit from such details. Overall, a very comprehensive and well-done synthesis.</p>
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VERSION 3 – AUTHOR RESPONSE

Reviewer #2:

1. Introduction

- First sentence “Addressing the economic impact...” does not make sense. I would just drop as next sentence seems to introduce the paragraph sufficiently.

Response: We would like to thank the reviewer for identifying this issue. This sentence has been removed from the introduction as recommended by the reviewer.

2. Results

- Section 3.2. after 2017 should have a semicolon between 2017 and no date restrictions instead of comma. I would however eliminate the part after the comma and instead just add a sentence (or even footnote) stating why they did not use date restrictions. The author has addressed this in the reviewer table so can just add this justification to the text.

Response: The justification as to why no date restrictions were used has been added to the results section 3.2 as well as a footnote added to eTable 1: Search Strategy.

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.

- p. 15 “Contrastingly” would be better as “In contrast,” sub classifications should have a dash between the two words.

Response: We thank the reviewer for identifying these concerns, the recommendations have been adopted.

3. Reviewer Comments

- The author should add in their justification of why no date restrictions to the context of the paper. Other comments seem to have been adequately addressed.

Response: The justification as to why no date restrictions were used has been added to the results section 3.2 as well as a footnote added to eTable 1: Search Strategy.

Reviewer #4:

Comment: No further issues noted, and thanks to the authors for responding to not only my additional comments but that of another reviewer. While I don't agree that other databases would not necessarily yield more relevant publications, I respect their explanation and fact they extended the review to include a few more articles. Still offering the results section can seem a little dry and repetitive in presentation, undoubtedly many readers will benefit from such details. Overall, a very comprehensive and well-done synthesis.

Response: We thank the reviewer for the considerable time and effort they devoted to reviewing this systematic review. We wish to express our appreciation for your in-depth comments, suggestions, and corrections, which have greatly improved the manuscript.