PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-of-Illness of patient-reported Adverse Drug Events – A population-based cross-sectional survey
AUTHORS	Gyllensten, Hanna; Rehnberg, Clas; Jönsson, Anna; Petzold, Max; Carlsten, Anders; Andersson Sundell, Karolina

VERSION 1 - REVIEW

REVIEWER	Walter P Wodchis Associate Professor Institute of Health Policy Management and Evaluation University of Toronto Canada
REVIEW RETURNED	21-Feb-2013

GENERAL COMMENTS	This article addresses an important and understudied challenge in health care – the prevalence and impact of adverse drug events. The authors have conducted a large population based survey to study patient self-reported adverse drug events in Sweden and in this paper have attempted to measure the cost-burden associated with this public health and health care issue. There are a number of significant limitations to the study, some of which the authors have considered but others have not been adequately addressed. The grammatical construction of many sentences and paragraphs are not clear and make parts of the manuscript very difficult to read and understand. I think the key finding is the last sentence to the discussion . “We have also found…studies.” The key finding is that very sick people have higher incidence of ADEs and higher costs. The fact is that these people have many medications and are then at higher risk for ADEs. The higher costs may not relate at all to the incidence of ADEs in this study design. They may be entirely attributable to concurrent illnesses. Ideally the study would have compared similar individuals with and without ADEs, either through a matching or propensity-adjusted analysis. That could have provided an estimate of the attributable ADE costs.

	Points to be addressed. P4 The rationale and reporting of drug dependence as a key construct of ADE is not explained . Similarly the meaning of untreated indications is not described. While the reader is referred to other publications for more details about the survey some key information must be reported here to be able to assess the validity of the current study. 1. P5. Last paragraph: the questions relating to 'experienced ADEs and other measures in the questionnaire should be better described – how can we know that the ADR costs are 'attributable' ? what was the question posed to the survey respondents? 2. P6. Direct costs. The sentences "Costs of medicine…" is unclear – how did the survey measure medicine use resulting from ADRs or STEs. 3. P6. Direct costs: Were reduced costs for medications withdrawn from patients considered? 4. Again in the results – how would patients know whether they had experienced an ADE? 5. The discussion needs to highlight that the ADE costs reported here are those for patients who experienced ADEs because for the most part they are very sick and on many medications – the costs are not because of ADEs but among people who experience ADEs. The ADR results, if better justified are more likely to be attributable. 6. I am unsure of the validity of the extrapolations in Figure 3, if important it should be better justified and the implications should be highlighted in the discussion and conclusions. 7. P18. Line 4 ' not identified in the register'. … were these new medications that were reported by patients but not found in the registers? What do you mean by 'not identified in the register'? 8. Figure 4. Please include the scale (minimum Maximum) in the HRQOL and provide an interpretation in the methods section or results…. What does 2.0 mean as an average HRQOL score? 9. Why is drug dependence an ADE? I haven't seen this included before in ADE. The literature review is sparse and a bit dated. A more recent review of cost studies examining costs of ADRs is available (including using administrative data). The literature on ADEs is likely to be less fruitful but a more current search and additional research to be considered in the discussion would be useful . Grammatical issues that require rewriting .

	Introduction p.4 lines 24-30. “The distribution of cost items…[in the healthcare system the development of the …]” particularly the second clause is difficult to understand but the whole sentence needs to be restructured. p. 12 Sensitivity analyses – some sentences, particularly the 3rd sentence are difficult to understand “Because of skewed data..” p19. Lines 42+ last paragraph. P20 lines 31… “Therefore we report…” the meaning is not clear P 20 entire second paragraph is problematic “The strengths of this study… “ including text on p21.

REVIEWER	Dr Anthony R Cox Lecturer in Clinical Pharmacy College of Medical and Dental Sciences University of Birmingham Birmingham UK
REVIEW RETURNED	08-Apr-2013

THE STUDY	Definitions I have some concern about definitions used. ADE does not include suspicion of an association with the drug. The following are two definitions of adverse event: “Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment” Meyboom HB, Lindquist M, Egberts ACG. An ABC of drug-related Problems. Drug Safety 2000;22(6):415-423 “Any untoward occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relation to the treatment.” Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. The Lancet 2000;356:1255-1259 The distinction is important because an adverse effect includes some attribution of the adverse outcome to a drug, whereas an adverse event is an outcome that happens after a drug is used regardless of any lack of causality. The definition used in the opening sentence of the paper may lead to confusion as to whether ADEs or ADRs are being studied. This is further compounded when the paper goes on to say “All reported ADEs were carefully examined and cross-examined to exclude responses not indicated a suspected symptom or drug”. If this is the case, than the paper is looking at suspected adverse drug reactions, not suspected adverse

	drug events. If the paper was examining ADEs then all events patients reported following drug use should be considered ADEs. If the patients were asked in the survey only to give events which they believed were drug related, then the study is not examining ADEs, but suspected ADRs. This confusion continues throughout the paper, including the discussion. The paper needs to clarify the definitions it uses. Page 6 of 44: Methods: Participants and data collection: The study obtains ADEs from the use of a questionnaire mailed to a random sample of Swedish citizens. The study's methods section states "All reported ADRs were carefully examined and cross-examined to exclude responses not indicating a suspected symptom or drug". While it is noted that the word "suspected" is used, it would be useful to know the process of this examination. What did "carefully examined and cross-examined" mean? Was a causality assessment tool used (such as Naranjo?) or was this decision based on clinical knowledge of one of the study authors? Was the cross-examination carried out by another individual? How were differences of opinion decided upon? Please note this needs to be discussed in light of the previous discussion about definitions of what constitutes an ADE or ADE. Page 6 of 44: Methods: Direct Costs: Costs of medicines is noted as a direct cost: "Direct costs resulting from ADRs or STEs included the costs for prescription drugs and healthcare use caused by either ADRs or STEs". How was such a causal link between the use of these prescription drugs and the ADR or STE arrived at? The paper states that it was the "cost of any medicine reported in the survey for treating an ADR or STE", so patients identified it? In the results section (Table 3) there is a prescription drug costs for those respondents without an ADE. Clearly this cost cannot be associated with an ADR or STE in those with not ADE, so is the cost of prescription drugs in those with an ADR or STE may just be a marker than those patients who report ADEs are higher users of prescribed drug therapy? In Table 1 it is noted that women were statistically more likely to report an ADE than men. There is other research suggesting a female susceptibility to ADRs, or do the authors suspect this is due to a responder bias or because of increased susceptibility? Page 22 of 44. Discussion: A comment is made about the STEs, that they are as common and as costly as ADRs. This is a perhaps more complicated problem than it initially appears, since not all STEs are preventable. Not all patients derive benefit from the drugs they take, which the number needed to treat (NNT) shows. Are all non-responders to a drug STEs? If this is a cost, it is a cost we accept when deciding to prescribe.
GENERAL COMMENTS	This is an interesting Cost of Illness study, from a societal perspective, examining ADEs in Sweden. It also attempts to measure the direct costs of ADRs and sub-therapeutic effects. It is an interesting addition to the literature on the harms of drugs.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Walter P Wodchis
Associate Professor
Institute of Health Policy Management and Evaluation University of Toronto Canada

* This article addresses an important and understudied challenge in health care – the prevalence and impact of adverse drug events. The authors have conducted a large population based survey to study patient self-reported adverse drug events in Sweden and in this paper have attempted to measure the cost-burden associated with this public health and health care issue. There are a number of significant limitations to the study, some of which the authors have considered but others have not been adequately addressed. The grammatical construction of many sentences and paragraphs are not clear and make parts of the manuscript very difficult to read and understand.

I think the key finding is the last sentence to the discussion. “We have also found…studies.” The key finding is that very sick people have higher incidence of ADEs and higher costs. The fact is that these people have many medications and are then at higher risk for ADEs. The higher costs may not relate at all to the incidence of ADEs in this study design. They may be entirely attributable to concurrent illnesses.

Ideally the study would have compared similar individuals with and without ADEs, either through a matching or propensity-adjusted analysis. That could have provided an estimate of the attributable ADE costs.
Response: We agree that the high overall COI identified for respondents with ADE is not a measure of costs caused by ADEs, but we were unable to include detailed questions on ADE-related resource use for all ADE categories in the survey. Thus we selected to focus on costs and resource use resulting from ADRs and STEs specifically, and therefore we can only report direct costs resulting from ADRs and STEs as caused by (two subcategories of) ADEs. We can only speculate that at least some of the reported extensive healthcare use for respondents with ADEs may be caused by their drug-use complication. Moreover, some of the respondents with ADRs and STEs did report that they had experienced sick-leave, informal care and lost leisure time resulting from their ADE, although the survey question did not enable quantifying this resource use as costs.

Thus we have now complemented the results with two propensity score sensitivity analyses, for self-reported overall healthcare costs and indirect costs estimated from self-reported productivity loss, respectively, based on ADE exposure (page 14, 2nd paragraph on page 21, 2nd paragraph on page 25).

* Points to be addressed.
* P4 The rationale and reporting of drug dependence as a key construct of ADE is not explained . Similarly the meaning of untreated indications is not described.
Response: We have included a section to clarify the terminology and definitions used (pages 5-6, new section on ADE definitions).

* While the reader is referred to other publications for more details about the survey some key information must be reported here to be able to assess the validity of the current study.
* 1. P5. Last paragraph: the questions relating to ‘experienced ADEs and other measures in the questionnaire should be better described – how can we know that the ADR costs are ‘attributable’? what was the question posed to the survey respondents?
Response: We have included the questions used for retrieving self-reported healthcare and drug use resulting from ADRs or STEs in the Methods section (page 7, 1st paragraph).

* 2. P6. Direct costs. The sentences “Costs of medicine…” is unclear – how did the survey measure medicine use resulting from ADRs or STEs.
Response: We have included the question used for retrieving self-reported drug use resulting from ADRs or STEs in the methods section (page 7, 1st paragraph).

* 3. P6. Direct costs: Were reduced costs for medications withdrawn from patients considered?
Response: We did not reduce costs resulting from ADRs or STEs based on withdrawn medications resulting from ADRs or STEs, since the cost for the initial drug (the drug causing the event) were paid. Thus it is not included in the cost for drugs use resulting from ADRs or STEs. However, the overall costs for prescription drugs will be decreased since the withdrawal will affect the total prescription drug cost during 2010. We have clarified this in the Methods section (page 8, 3rd paragraph).

* 4. Again in the results – how would patients know whether they had experienced an ADE?
Response: Previous research has identified patients themselves as important actors in reporting adverse events, also due to drug use. Moreover, the general public is today expected to monitor drug use and report suspected ADRs. Thus we believe that the self-reported ADEs reported in our survey adds a relevant aspect to the knowledge of drug use outcomes, although it needs to be acknowledged that the events were self-reported and not assessed for causality by any experienced clinician. We did examine the reports carefully and excluded some clear misunderstandings (e.g. drug dependence from cardiac medicines).

We have reinforced in the methods and results sections that the study is based on self-reported ADEs (1st paragraph on page 5, page 8, 3rd paragraph on page 9, page 16, and page 20). Moreover, we have commented on this in the Discussion section (page 24).

* 5. The discussion needs to highlight that the ADE costs reported here are those for patients who experienced ADEs because for the most part they are very sick and on many medications – the costs are not because of ADEs but among people who experience ADEs. The ADR results, if better justified are more likely to be attributable.
Response: Yes, those reporting ADEs were more extensive users of prescription drugs, healthcare resource use, transportation services, and informal care, compared to other respondents. Moreover, they had more short-term sick-leave and disability pension than other respondents. Much of this increase in resource use will be due to co-morbidities, and will be involved in causing the ADE, but some respondents also reported that they had experienced sick-leave, informal care and lost leisure time resulting from ADEs. Only the healthcare and drug use costs reported as resulting from ADRs or STEs were attributable costs, estimated based on resource use reported by the respondents. We have clarified this in the Discussion section (page 23, 1st paragraph).

* 6. I am unsure of the validity of the extrapolations in Figure 3, if important it should be better justified and the implications should be highlighted in the discussion and conclusions.
Response: We have excluded the extrapolation to annual costs and the sensitivity analysis based on extrapolation since the denominator (annual prevalence of self-reported ADEs) was unclear (page 3, page 12, page 14, 2nd paragraph on page 22, 2nd paragraph on page 23, and 2nd paragraph on page 25).

* 7. P18. Line 4 ‘ not identified in the register’. … were these new medications that were reported by patients but not found in the registers? What do you mean by ‘not identified in the register’?
Response: We have clarified in the Direct costs section (page 8, 3rd paragraph).

* 8. Figure 4. Please include the scale (minimum Maximum) in the HRQOL and provide an interpretation in the methods section or results…. What does 2.0 mean as an average HRQOL score?

Response: We have included the scales for EQ-5D-5L and EQ-VAS in the Methods section (page 10, 1st paragraph). Moreover, we have clarified the use of health profile results in the figure (page 21).

* 9. Why is drug dependence an ADE? I haven't seen this included before in ADE.
Response: Since we aimed to study ADEs in the general public we believe drug dependence is relevant to include (it is possible that it is less so in hospitalized patients). It has previously been suggested that there is abuse and/or dependence from prescription drugs such as sedatives, tranquilizers, opioids, and amphetamines (e.g. Huang B et al. Prevalence, correlates, and comorbidity of nonmedical prescription drug use and drug use disorders in the United States: Results of the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006 Jul;67(7):1062-73.). In accordance with the DSM-IV, drug dependence may be viewed as a maladaptive pattern of use of an addictive drug leading to clinically significant impairment or distress, and thus be viewed as "an injury resulting from medical intervention related to a drug". In our study, we included drug dependence that was assigned to either a prescription drug classified as a narcotic drug in Sweden, or one of five additional registered drugs with evidence on addictive properties: caffeine, codeine, nicotine, pregabalin and dextropropoxyphene.

* The literature review is sparse and a bit dated. A more recent review of cost studies examining costs of ADRs is available (including using administrative data). The literature on ADEs is likely to be less fruitful but a more current search and additional research to be considered in the discussion would be useful.
Response: We have updated the reference list with some recent publications, including e.g. a recent review of studies measuring the costs of drug-related morbidity written by our research group (Gyllensten et al 2012) and a review of studies measuring the ambulatory care ADE prevalence (Taché et al. 2011).

* Grammatical issues that require rewriting.
* Introduction p.4 lines 24-30. "The distribution of cost items…[in the healthcare system the development of the …]" particularly the second clause is difficult to understand but the whole sentence needs to be restructured.
Response: We have restructured the paragraph (page 4, 2nd paragraph).

* p. 12 Sensitivity analyses – some sentences, particularly the 3rd sentence are difficult to understand "Because of skewed data.."
Response: We have clarified the paragraph (page 14).

* p19. Lines 42+ last paragraph.
Response: Since this extrapolation is now excluded, the paragraph is deleted (now page 22, 2nd paragraph).

* P20 lines 31… "Therefore we report…" the meaning is not clear P 20 entire second paragraph is problematic "The strengths of this study… " including text on p21.
Response: We have clarified the paragraph (now page 23, 2nd paragraph).

Thank you for useful comments and suggestions for improvement of the manuscript!

Reviewer: Dr Anthony R Cox
Lecturer in Clinical Pharmacy
College of Medical and Dental Sciences
University of Birmingham
Birmingham
UK

* Definitions
* I have some concern about definitions used. ADE does not include suspicion of an association with the drug. The following are two definitions of adverse event:

“Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment”

Meyboom HB, Lindquist M, Egberts ACG. An ABC of drug-related Problems. Drug Safety 2000;22(6):415-423

“Any untoward occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relation to the treatment.”

Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. The Lancet 2000;356:1255-1259

The distinction is important because an adverse effect includes some attribution of the adverse outcome to a drug, whereas an adverse event is an outcome that happens after a drug is used regardless of any lack of causality. The definition used in the opening sentence of the paper may lead to confusion as to whether ADEs or ADRs are being studied. This is further compounded when the paper goes on to say “All reported ADEs were carefully examined and cross-examined to exclude responses not indicated a suspected symptom or drug”. If this is the case, than the paper is looking at suspected adverse drug reactions, not suspected adverse drug events.

If the paper was examining ADEs then all events patients reported following drug use should be considered ADEs. If the patients were asked in the survey only to give events which they believed were drug related, then the study is not examining ADEs, but suspected ADRs.

This confusion continues throughout the paper, including the discussion. The paper needs to clarify the definitions it uses.
Response: We have included a section to clarify the terminology and definitions used (pages5-6, new section on ADE definitions).

* Page 6 of 44: Methods: Participants and data collection: The study obtains ADEs from the use of a questionnaire mailed to a random sample of Swedish citizens. The study’s methods section states “All reported ADRs were carefully examined and cross-examined to exclude responses not indicating a suspected symptom or drug”. While it is noted that the word “suspected” is used, it would be useful to know the process of this examination. What did “carefully examined and cross-examined” mean? Was a causality assessment tool used (such as Naranjo?) or was this decision based on clinical knowledge of one of the study authors? Was the cross-examination carried out by another individual? How were differences of opinion decided upon? Please note this needs to be discussed in light of the previous discussion about definitions of what constitutes an ADE or ADE.
Response: The ADEs were self-reported and not formally assessed for causality by any experienced clinician. One researcher, a pharmacist (Katja M Hakkarainen), did the initial examination of reported ADEs. The first author, HG, also a pharmacist with clinical experience, did an independent examination of 10% of reported ADEs. Cases were discussed in the research group to reach consensus, and re-categorization was made accordingly to the consensus decision. Reported ADEs were excluded if not presenting an actual event (e.g. reporting a drug-related problem without a clinical consequence). Moreover, reported drug dependence was excluded if not resulting from an addictive drug (e.g. drug dependence from cardiac medicines).

We have clarified, in the Methods section, the description of the examination (page 7, 1st paragraph).

* Page 6 of 44: Methods: Direct Costs: Costs of medicines is noted as a direct cost: “Direct costs resulting from ADRs or STEs included the costs for prescription drugs and healthcare use caused by either ADRs or STEs”. How was such a causal link between the use of these prescription drugs and the ADR or STE arrived at? The paper states that it was the “cost of any medicine reported in the survey for treating an ADR or STE”, so patients identified it?
Response: Yes, the patients reported the drug use resulting from ADRs or STEs. We have included the question used for retrieving self-reported drug use resulting from ADRs or STEs in the Methods section (page 7, 1st paragraph).

* In the results section (Table 3) there is a prescription drug costs for those respondents without an ADE. Clearly this cost cannot be associated with an ADR or STE in those with not ADE, so is the cost of prescription drugs in those with an ADR or STE may just be a marker than those patients who report ADEs are higher users of prescribed drug therapy?
Response: Yes, those reporting ADEs were more extensive users of prescription drugs, healthcare resource use, transportation services, and informal care, compared to other respondents. Moreover, they had more short-term sick-leave and disability pension than other respondents. Much of this increase in resource use will be due to co-morbidities, and will be involved in causing the ADE, but some respondents also reported that they had experienced sick-leave, informal care and lost leisure time resulting from ADEs. We have clarified this in the Discussion section (page 23, 1st paragraph).

* In Table 1 it is noted that women were statistically more likely to report an ADE than men. There is other research suggesting a female susceptibility to ADRs, or do the authors suspect this is due to a responder bias or because of increased susceptibility?
Response: We cannot draw conclusions on this matter from our survey responses, although we believe that is an important question to address in future research since self-reported outcomes is likely to gain significance in the future (e.g. through the development of Patient-Reported Outcomes, person-centered care and development of the spontaneous ADR-reports).

* Page 22 of 44. Discussion: A comment is made about the STEs, that they are as common and as costly as ADRs. This is a perhaps more complicated problem than it initially appears, since not all STEs are preventable. Not all patients derive benefit from the drugs they take, which the number needed to treat (NNT) shows. Are all non-responders to a drug STEs? If this is a cost, it is a cost we accept when deciding to prescribe.
Response: Yes, all non-responders would be classified as STEs in this study, If the individual him or herself had expected a better effect of their medicine. We have clarified this in the section on the terminology and definitions used (page 5, 2nd paragraph). Moreover, we have commented on this in the Discussion section (page 26, 2nd paragraph)

* This is an interesting Cost of Illness study, from a societal perspective, examining ADEs in Sweden. It also attempts to measure the direct costs of ADRs and sub-therapeutic effects. It is an interesting addition to the literature on the harms of drugs.
Response: Thank you for your constructive and helpful comments!

Comment to editor
In addition to the adjustments based on reviewer comments, we have also made minor changes to table 4 due to reclassification of the preventability of one reported ADE that was made after submitting the initial manuscript (page 19).

VERSION 2 – REVIEW

REVIEWER	Walter P. Wodchis, PhD Associate Professor, IHPME, University of Toronto Research Scientist, Toronto Rehabilitation Institute Adjunct Scientist, Institute for Clinical Evaluative Sciences address: Institute of Health Policy Management & Evaluation University of Toronto
REVIEW RETURNED	15-May-2013

- The reviewer completed the checklist but made no further comments.