PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	High adherence to the "Wise List" treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines
AUTHORS	Eriksen, Jaran; Gustafsson, Lars; Ateva, Kristina; Rahmner, Pia; Håkanson.Ovesjö, Marie-Louise; Jirlow, Malena; Juhasz-Haverinen, Maria; Lärfars, Gerd; Malmstrom, Rickard; Wettermarik, Björn; Andersén Karlsson, Eva

VERSION 1 - REVIEW

REVIEWER	Linda Amundstuen Reppe Associate professor Faculty of Health Nord University Trøndelag, Norway
REVIEW RETURNED	23-Oct-2016

GENERAL COMMENTS	The page numbers referred to are that of the manuscript. (Authors and affiliations at page 1). General comments The article is interesting, as is the concept of the Wise list. I think Box 1 and table 1 are especially valuable to the Readers, in order to understand the concept. The adherence to the Wise list is high, but not 100%. I think this should be addressed more thoroughly in the discussions section (the only thing mentioned specifically is over-treatment of PPIs). It is a bit difficult to understand exactly how you can be sure that a prescriber have or have not been adherent with the recommendations in the Wise list. I think the term “demographic data” in the methods section (page 7, lines 44-47) should be explained in more detail to give us an idea about this. For example, how do you know that PPIs are used unnecessary? This would require that you know the patients’ diagnosis. In addition, do you have information as to whether there are (good) reasons to deviate from the Wise list in specific cases? For example, do you know whether there might be contraindications to simvastatin that makes the prescriber choose another drug instead? If not, I think this should be discussed in the “limitations” part of the discussions. Also, is there a specific goal for the acceptable adherence? To someone not familiar with the Wise list, I think it is still difficult to grasp all the “multifaceted” organizational aspects of the concept. The list itself is nicely presented in box 1, and the financial incentives are described. However, “the communication strategy consisting of a branding and marketing strategy” could be exemplified in the discussions.

	I would prefer that the argumentation for focusing on the four specific pharmacotherapeutic areas (including references), were given in the methods section rather than in the results section (page 10). The authors mentions the importance of including e.g. the new biological drugs and expensive drugs in the recommendations. In the background (page 5 of the manuscript), it is mentioned that this is addressed in the Wise list. Are there any examples of "Wise pieces of advice" given in relation to these kinds of drug, or, can the authors give some examples as to exactly this challenge is addressed in the Wise list? Generally, I think the figure captions need some more information. For example, "Stockholm Healthcare Region" is mentioned in figure 3, but not in the other figure captions. Specific comments • Page 3, line 19: I think it would be clarifying to include "core and complementary" before "substances". • Page 3, line 23: The year 2001 appear here, whereas the description at page 8, line 12 says 2002. The figures also present numbers from 2002. The clinicians and experts contributing to the Wise list are described in several ways at different places in the text, which may be confusing: • Page 3, line38/39: "key opinion leaders and prescribers" • Page 5, line 32: "respected experts and clinicians" • Page 6, line 27: "trusted medical colleagues and pharmacotherapeutic experts" • Page 11, line 10: "key opinion leaders and prescribers" • Page 24, line 32: "respected drug experts" I would prefer a consistent use of the terms as to avoid confusion. • Page 5, lines 45-50: Reference number 15 is noted twice in two following sentences, whereas I remain unsure whether this is the reference for all the included text in these lines. Especially, a reference is needed for the last sentence. • Page 6, Box 1, lines 15-16: I would prefer the URL to be deleted or presented at the end of the box. • Page 6, Box 1, line 29: The word "clear"; I assume that whether criteria are clear or not, may be questioned. • Page 6, Box 1, lines 34-36: "This joint effort…". This point deviates from the other points in the bulleted list, as it includes information on the effects of the concept (trust and adherence) rather than the concept itself. I suggest that this is rephrased to give a more neutral description of the conflict of interest policy. Also, a more detailed description of this policy should be included in the box, in box 2 or in the methods section of the article. • Page 7, Box 2, line 7: I suggest you change the word "wise" with "rational". The term "operative resources" in the figure itself (page 24, appr. 25) should be defined more clearly. Together, the box and the figure does not describe who is cooperating. The "respected drug expert" is included, but not the clinicians. • Page 8, line 56-57: I think it should be specified exactly which values that are compared in the extremal quotient. I am a bit confused as to what is the difference, if any, between

	prescriber categories and caregiver categories: o Page 8, lines 19-24: The term caregiver is used. o Page 9, lines 42-43: The term prescriber categories is used. In the next paragraphs, primary care and hospitals are focused on. o Page 9, 54-56: “For all other prescriber categories…” – is this the same at the caregiver category “others” in figure 2? Page 10, lines 55-56: Do you have a reference supporting the numbers of substances with market authorization? • Page 11, lines 48-49: “Another factor that might have contributed is the difference in pressure from the pharmaceutical industry”. However, the pressure to prescribe omeprazole was comparable to that to prescribe esomeprazole, for which the prescribing was low. Therefore, the first sentence confuses me. • Table 1: “since 2005” may be interpreted as the advice has been present in the Wise list all years since 2005. • Figure 3: There seems to be a black R on the wrong place of the 2002 column.

REVIEWER	Albert Figueras Fundació Institut Català de Farmacologia. Universitat Autònoma de Barcelona. Spain I declare that i have no competing interest that could influence my opinion, comments and suggestions in the present review.
REVIEW RETURNED	26-Oct-2016

GENERAL COMMENTS	This is an interesting research about the use of medicines in a context where the promotion of rational use of medicines has been implemented during the last decades. The Authors describe the "Wise list" concept and explore the consumption of medicines (whole consumption and consumption by group and specific active ingredient) along the last 15 years. The results presented in the manuscript suggest a very good outcome associated with the multifaceted approach described, including the Wise Pieces of Advice. This is an observational not controlled study, and the Authors acknowledge the limitations of their approach. Notwithstanding this limitation, it should be taken into account that it would be very difficult to design an experimental region-wide approach lasting 15 years. So, the design seems the best possible in this case. The results show high adherence to the proposed Wise list. These are good news in the present times, when pressure by pharmaceutical companies use to push poorly evaluated or unnecessary product into the pharmaceutical market. To my opinion, describing this experience is interesting in order to encourage other countries to set up similar systems adapted to their local particularities and needs. One of the questions behind the study is the constant growing of prescriptions (overprescription? overuse?) of certain therapeutic groups (e.g., proton pump inhibitors, antidepressants, statins). This is a Global problem that shoud be addressed Globally. Anyway, it is better that the increase of prescriptions is at the expense of reccomended products (as is the case in the Stockholm experience) instead of new, expensive and uncertain me-toos.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

General comments

1. The article is interesting, as is the concept of the Wise list. I think Box 1 and table 1 are especially valuable to the Readers, in order to understand the concept.
Response: Thank you for this comment.

2. The adherence to the Wise list is high, but not 100%. I think this should be addressed more thoroughly in the discussions section (the only thing mentioned specifically is over-treatment of PPIs).
Response: Thank you for raising this point, we agree that it warrants clarification. The Wise List recommendations include core and complementary medicines for common diseases, but do not include all possible treatment strategies for e.g. complicated cases, patients with allergies to medicines, cases with potential drug-drug interactions etc. The aim of the Wise List is to achieve >80% adherence (as is reflected in the financial incentive strategy). Physicians should be able to use their clinical judgment and deviate from the recommendations if deemed necessary. Complete adherence is therefore not wanted or advisable. This has now been clarified in the text on page 11:
"…a small bonus linked to their adherence to the Wise List if the adherence was more than 80% and if they reflected on their prescribing patterns in a "quality report".35 A higher target has not been set, as complete adherence is not considered suitable. This is because the Wise List does not include all possible treatment strategies for e.g. complicated cases, patients with allergies to medicines, or cases with potential drug-drug interactions. Physicians should have the possibility of using their clinical judgment and prescribe a substance not included on the Wise List if this is better for the patients. Therefore, complete adherence is neither wanted nor aimed for."

3. It is a bit difficult to understand exactly how you can be sure that a prescriber has or has not been adherent with the recommendations in the Wise list. I think the term "demographic data" in the methods section (page 7, lines 44-47) should be explained in more detail to give us an idea about this. For example, how do you know that PPIs are used unnecessary? This would require that you know the patients' diagnosis.
Response: The demographic data mentioned on page 7 includes age, sex, and the area where the patient lives. This has been clarified in the text:
"…register contains patient demographics (age, sex and area of residence of the patient) as well as information..."

However, this does not help in understanding whether a prescriber has been adherent to the Wise List or not. The adherence is measured by looking at all prescriptions within an ATC code at the 5th level. An example is A02BC which includes all PPIs. Within this group there are five registered substances in Sweden, of which only one is recommended on the Wise List. We cannot see the diagnosis of a patient prescribed PPI in the Stockholm area, but we can see whether the prescribed PPI is the PPI that is on the list or not, which is what we consider adherence. This has been clarified in the text on page 8:
"Note that the calculated adherence rate is not linked to data on diagnosis of the patient, but shows the amount of the substances prescribed for each specific ATC group of substances on the Wise List. E.g. for ATC A02BC (PPI), if a substance recommended on the Wise List is prescribed it is considered adherent to the Wise List recommendation."

The case of over-use of PPI is based on the fact that the number of DDDs prescribed in Stockholm for PPI is equivalent to 4.5% of the population constantly using PPI. This is a much higher proportion of

the population than that of diagnoses that need PPI treatment. This is explained in the results section on page 10 and the discussion on page 12.

4. In addition, do you have information as to whether there are (good) reasons to deviate from the Wise list in specific cases? For example, do you know whether there might be contraindications to simvastatin that makes the prescriber choose another drug instead? If not, I think this should be discussed in the "limitations" part of the discussions. Also, is there a specific goal for the acceptable adherence?
Response:
There might be very good reasons to deviate from the recommendations in the Wise List, as explained above under comment #2. The aim is to achieve >80% adherence. This has been clarified in the text (see comment #2 above).

5. To someone not familiar with the Wise list, I think it is still difficult to grasp all the "multifaceted" organizational aspects of the concept. The list itself is nicely presented in box 1, and the financial incentives are described. However, "the communication strategy consisting of a branding and marketing strategy" could be exemplified in the discussions.
Response: Thank you for this comment. We have clarified this in the discussion on page 11:
"The branding and marketing strategy is based on principles of social marketing. Core values of the brand Wise List have been defined as a shortlist of the best medicines, set up by respected experts and clinicians, for the best treatment of the most common diseases. This is in contrast to the marketing material provided by pharmaceutical industry. The Wise List has been promoted to prescribers and patients by traditional marketing methods such as ads in print, direct mail marketing like postcards, brochures, letters, and fliers and at oral presentations among stakeholders. The core value of the product has been consistent over the years and so also the key message in the marketing campaigns."

6. I would prefer that the argumentation for focusing on the four specific pharmacotherapeutic areas (including references), were given in the methods section rather than in the results section (page 10).
Response: Thank you for this comment. In the current methods section (page 8) we have explained why we selected these four therapeutic areas. The text in the results section (on page 10) further details the wise pieces of advice that we found related to these four areas, which was part of the results we set out to study. We therefore feel that this information belongs in the results section and we also think that the text would be more complicated to follow if we moved the pieces of text to the methods section.

7. The authors mention the importance of including e.g. the new biological drugs and expensive drugs in the recommendations. In the background (page 5 of the manuscript), it is mentioned that this is addressed in the Wise list. Are there any examples of "Wise pieces of advice" given in relation to these kinds of drug, or, can the authors give some examples as to exactly this challenge is addressed in the Wise list?
Response: Thank you, this point is important to clarify. The latest editions of the Wise List contain recommendations for new biological medicines, e.g. use of TNF inhibitors for inflammatory bowel disease and rheumatologic diseases. It also contains recommendations for the use of expensive new oral anticoagulants in thromboemolic prophylaxis. This has been clarified in the discussion on page 12:
"The Wise List already contains recommendations for some new expensive biological medicines, e.g. TNF inhibitors for us in inflammatory bowel disease and rheumatologic diseases." And "In fact, a recent study of ours demonstrated that the most important factor influencing use of anticoagulants,

warfarin or a New Oral Anticoagulants, in Stockholm during the last five years was whether the substance was included as a Wise List recommendation.48”

8. Generally, I think the figure captions need some more information. For example, “Stockholm Healthcare Region” is mentioned in figure 3, but not in the other figure captions.
Response: Thank you for this comment. We have now updated all figure captions to include both the healthcare region and the fact that all prescriptions for the therapeutic area are included, e.g. figure 4: “Figure 4. Prescribing pattern for proton pump inhibitors (PPI) in Stockholm Healthcare Region between 2002 and 2015 showing all PPI prescriptions dispensed to the inhabitants in the region each year. The letter “R” signifies that the drug was recommended in the Wise List that year. DDD/TID = Defined daily dose/1000 inhabitants per day.”

Specific comments

Response: We thank the reviewer for bringing up these points. Our responses are listed below.

• Page 3, line 19: I think it would be clarifying to include “core and complementary” before “substances”.
Response: This has now been added.

• Page 3, line 23: The year 2001 appear here, whereas the description at page 8, line 12 says 2002. The figures also present numbers from 2002.
Response: We have now corrected this to 2002.

The clinicians and experts contributing to the Wise list are described in several ways at different places in the text, which may be confusing:
• Page 3, line38/39: “key opinion leaders and prescribers”
• Page 5, line 32: “respected experts and clinicians”
• Page 6, line 27: “trusted medical colleagues and pharmacotherapeutic experts”
• Page 11, line 10: “key opinion leaders and prescribers”
• Page 24, line 32: “respected drug experts”
I would prefer a consistent use of the terms as to avoid confusion.
Response: We have decided to only use the term “respected experts and clinicians” and have changed this throughout the manuscript. We have also modified the figure in Box 2.

• Page 5, lines 45-50: Reference number 15 is noted twice in two following sentences, whereas I remain unsure whether this is the reference for all the included text in these lines. Especially, a reference is needed for the last sentence.
Response: This has now been corrected. A reference has been added to the English version of the Wise List 2015 where the way the Wise List considers introduction of new medicines and environmental impact of medicines is described.

• Page 6, Box 1, lines 15-16: I would prefer the URL to be deleted or presented at the end of the box.
Response: The URL has been deleted.

• Page 6, Box 1, line 29: The word “clear”; I assume that whether criteria are clear or not, may be questioned.
Response: The word “clear” has been deleted from the sentence.

• Page 6, Box 1, lines 34-36: “This joint effort…”. This point deviates from the other points in the bulleted list, as it includes information on the effects of the concept (trust and adherence) rather than the concept itself. I suggest that this is rephrased to give a more neutral description of the conflict of interest policy. Also, a more detailed description of this policy should be included in the box, in box 2 or in the methods section of the article.
Response: The point has now been changed to: “Is a joint effort across discipline and institutions and includes a policy for conflict of interest with annually renewed declarations. This policy contains rules and regulations for definitions of conflict of interest and how to handle them25”

• Page 7, Box 2, line 7: I suggest you change the word “wise” with “rational”.
Response: This has been changed.

The term “operative resources” in the figure itself (page 24, appr. 25) should be defined more clearly. Together, the box and the figure do not describe who is cooperating. The “respected drug expert” is included, but not the clinicians.
Response: The operative resources consist of a budget for staff, continuous medical education of our 200 experts, infrastructure, printing, distribution and marketing of the Wise List. This has been changed in the legend to Box 2:
“Operative resources include an annual budget for staff, continuous medical education of our 200 experts, infrastructure, printing, distribution and marketing of the Wise List.”
Both the respected expert and clinicians are included, and the figure has been updated accordingly.

• Page 8, line 56-57: I think it should be specified exactly which values that are compared in the extremal quotient.
Response: The adherence rates have been compared between the health centres, and this has now been added to the methods section.

I am a bit confused as to what is the difference, if any, between prescriber categories and caregiver categories:
o Page 8, lines 19-24: The term caregiver is used.
o Page 9, lines 42-43: The term prescriber categories is used. In the next paragraphs, primary care and hospitals are focused on.
o Page 9, 54-56: “For all other prescriber categories…” – is this the same at the caregiver category “others” in figure 2?
Response: In the examples above the two terms have been used interchangeably, which we agree looks confusing. We have now changed this to “prescribers” and “prescriber categories” throughout the manuscript.

Page 10, lines 55-56: Do you have a reference supporting the numbers of substances with market authorization?
Response: The reference is as follows: http://nsl.mpa.se/index_english.htm It has been added to the manuscript.

• Page 11, lines 48-49: “Another factor that might have contributed is the difference in pressure from the pharmaceutical industry”. However, the pressure to prescribe omeprazole was comparable to that to prescribe esomeprazole, for which the prescribing was low. Therefore, the first sentence confuses me.
Response: In this case we wanted to express that there were increasing numbers of prescriptions for PPI despite the pressure from the industry, but we agree that the formulation was confusing. We have therefore removed it and instead added:
“This marketing pressure from the pharmaceutical industry could have contributed to the failure in reducing PPI prescriptions, but despite increasing numbers of prescriptions, the vast majority

remained omeprazole, as recommended by the Wise List."

• Table 1: "since 2005" may be interpreted as the advice has been present in the Wise list all years since 2005.
Response: We agree, and have now removed this from the table text.

• Figure 3: There seems to be a black R on the wrong place of the 2002 column.
Response: This has now been corrected.

Reviewer: 2

This is an interesting research about the use of medicines in a context where the promotion of rational use of medicines has been implemented during the last decades. The Authors describe the "Wise list" concept and explore the consumption of medicines (whole consumption and consumption by group and specific active ingredient) along the last 15 years. The results presented in the manuscript suggest a very good outcome associated with the multifaceted approach described, including the Wise Pieces of Advice.

This is an observational not controlled study, and the Authors acknowledge the limitations of their approach. Notwithstanding this limitation, it should be taken into account that it would be very difficult to design an experimental region-wide approach lasting 15 years. So, the design seems the best possible in this case.

The results show high adherence to the proposed Wise list. These are good news in the present times, when pressure by pharmaceutical companies use to push poorly evaluated or unnecessary product into the pharmaceutical market. To my opinion, describing this experience is interesting in order to encourage other countries to set up similar systems adapted to their local particularities and needs.

One of the questions behind the study is the constant growing of prescriptions (overprescription? overuse?) of certain therapeutic groups (e.g., proton pump inhibitors, antidepressants, statins). This is a Global problem that should be addressed Globally. Anyway, it is better that the increase of prescriptions is at the expense of recommended products (as is the case in the Stockholm experience) instead of new, expensive and uncertain me-toos.

Response: Thank you very much for these encouraging comments. We hope that others will also find the Stockholm experience useful in relation to work promoting rational use of medicines.

VERSION 2 – REVIEW

REVIEWER	Linda Amundstuen Reppe Nord University, Norway
REVIEW RETURNED	25-Jan-2017

GENERAL COMMENTS	The Authors have made some important changes to the manuscript. I am particularly satisfied with the clarification of the assessment of adherence and what this actually means. I also think the reasons for the goal of 80% adherence is better explained than in the first draft of the manuscript. I still think the concept of the wise list and the achievement of adherence is very interesting, and many regions and countries can learn from this article.

	I have only a few specific comments: 1. The year 2001 still appear in the abstract (page 3, lines 29-30), as well as in the results section (page 9, lines 34/35) when describing the adherence of the recommendations for core medicines. In the Methods section (page 7, lines 54/55) and (page 8/lines 15/16) the year 2002 is given as a baseline. Also, in figure 2, the year 2001 is given. The graphichs in this figure, however, seem to start in the year 2003? The other figures describes data from 2002. I am a bit confused as to what it the first year of data on the adherence. 2. Page 7, line 26/27: A Reference to Box 1 is given. I Wonder whether a reference to Table 1 (too) might be advisable? 3. Figure 1 still has no information on which country/region the study is done in. If the numbers in bullet point 1 is checked, clarified and corrected I will recommend that the manuscript is accepted.

VERSION 2 – AUTHOR RESPONSE

Thank you for the comments regarding the revised manuscript. Here are our responses to each of them:

Comment 1. The year 2001 still appear in the abstract (page 3, lines 29-30), as well as in the results section (page 9, lines 34/35) when describing the adherence of the recommendations for core medicines. In the Methods section (page 7, lines 54/55) and (page 8/lines 15/16) the year 2002 is given as a baseline. Also, in figure 2, the year 2001 is given. The graphics in this figure, however, seem to start in the year 2003? The other figures describe data from 2002. I am a bit confused as to what it the first year of data on the adherence.
Response: Thank you for this comment. The year differs in these sections as all subsets of data were not available from the beginning. Please see our explanation to each specific point above:
a) The year 2001 still appear in the abstract (page 3, lines 29-30), as well as in the results section (page 9, lines 34/35) when describing the adherence of the recommendations for core medicines.
• Response: This should in fact be 2000, the year when the first joint list of treatment recommendations in Stockholm was launched. This has been changed in the abstract and in the results section. The reason was already explained in the first paragraph under “data sources” on page 7.
b) In the Methods section (page 7, lines 54/55) and (page 8/lines 15/16) the year 2002 is given as a baseline.
• Response: This is correct, and the reason for selecting this year was already explained in the text mentioned in the comment. However, we have clarified this in the third paragraph on page 8: “Adherence to recommendations was measured based on all dispensed prescriptions in Stockholm Healthcare Region each year between 2000 (the year the first joint list of treatment recommendations in Stockholm was launched) and 2015. Adherence to guidelines in different pharmacotherapeutic areas were studied from 2002 (when prescriber work place ID was added to the Swedish Prescribed Drug Register, and a national regulation for mandatory generic substitution was introduced in Sweden) to 2015.”
c) Also, in figure 2, the year 2001 is given.
• Response: This was an error and has now been changed to 2003, in accordance with comment d) below.
d) The graphics in this figure, however, seem to start in the year 2003?
• Response: This is correct, as data on prescriber category were available from 2003. This was already explained in the second paragraph on page 8.
e) The other figures describe data from 2002.

• Response: This is correct, as explained under comment b) above.

Comment 2. Page 7, line 26/27: A Reference to Box 1 is given. I Wonder whether a reference to Table 1 (too) might be advisable?
Response: Thank you for pointing this out. We agree and have added a reference to Table 1 in the text on page 7.

Comment 3. Figure 1 still has no information on which country/region the study is done in.
Response: Thank you for pointing out this omission. The first sentence in the legend for Figure 1 has been changed to: “Number of substances included in the Stockholm Healthcare Region’s Wise List over time.”

VERSION 3 – REVIEW

REVIEWER	Linda Amundstuen Reppe Nord University,Norway
REVIEW RETURNED	10-Feb-2017

GENERAL COMMENTS	I appreciate the authors' clarifications and explanations to my comments, and have no further comments. I wish the Authors good luck publishing this manuscript.