## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Anticholinergic and sedative drug burden in community-dwelling older people: a national database study |
| **AUTHORS** | Byrne, Catherine; Walsh, Caroline; Cahir, Caitriona; Ryan, Cristín; Williams, David; Bennett, Kathleen |

## VERSION 1 – REVIEW

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| **REVIEWER** | Robert Vander Stichele<br>Department of Pharmacology, Ghent University, Belgium<br>None Declared |
| **REVIEW RETURNED** | 06-Mar-2018 |

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| **GENERAL COMMENTS** | This is a description of the dynamic group of anticholinergic and sedative (AC-S)drugs (non)users among the elderly GMS population of Ireland.<br><br>In addition, the impact of demographics and polypharmacy on AC-S use is explored.<br><br>The article is well written and focusses on the Drug Burden Index approach as one method to measure AC or AC-S exposure.<br><br>It provides a interesting list of AC-S medications relevant for Ireland; together with a proposal for minimal effective dosage in the older adult for each of (or most of) the AC-S.<br><br>There are a few minor comments that can be left to the discretion of the authors to respond to.<br><br>1) There is no systematic evaluation of AS medication that is specific to Ireland (and not available in the original DBI list or other lists.<br>In addition, there could be some discussion of AC medication not available in Ireland and popular in other major countries, and the reasons for that (regulatory or economic).<br><br>In my understanding the DBI is meant to evaluate an individual medication list at a given point in time, at the dosage schedule at that time.<br>The method applied here to establish the daily dosage is averaging use over one year (including gaps in prescribing by non-adherence, or as needed use, or change in dosages over time).<br><br>The method of determining polypharmacy level over one year is also one method for application on data over one year and not cross-sectional data. The method probably inflates a little the level of polypharmacy. |

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| | Combined with a very low threshold for AC-S use, it is no wonder that there is more then 20 fold Odds ratio with extreme polypharmacy.<br><br>The results and conclusions remain valid, but some relativation may be helpful.<br><br>So, maybe consider to remove the term "cross-sectional from the title.<br><br>Data on the coverage of GSM population versus total Irish population in the elderly and very old could be given in the introduction. |

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| **REVIEWER** | Arduino A Mangoni<br>Flinders University, Adelaide, Australia<br>None declared |
| **REVIEW RETURNED** | 29-Mar-2018 |

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| **GENERAL COMMENTS** | This is a well written pharmacoepidemiology manuscript describing the exposure to DBI medications in older adults in Ireland.<br><br>Minor comment:<br><br>I note a significant imbalance in exposure to drugs with sedative vs. anticholinergic effects. The discussion should emphasise this aspect and compare the findings to other similar studies conducted in other jurisdictions. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer 1: There are a few minor comments that can be left to the discretion of the authors to respond to.

1) There is no systematic evaluation of AS medication that is specific to Ireland (and not available in the original DBI list or other lists). In addition, there could be some discussion of AC medication not available in Ireland and popular in other major countries, and the reasons for that (regulatory or economic).

Response: As stated in the manuscript, there is no complete list of DBI medications available in the literature to use for screening purposes. In one of the original DBI studies in the USA (Hilmer 2009), a list of DBI medications taken by study participants was provided. However, this was not a complete list as it only included medications taken by study participants, rather than all medications screened. We used this list as a basis for the development of our master DBI list, together with reference to the British National Formulary, Martindale and SmPCs, as referenced in the methods section of our paper. Our master DBI list includes all DBI medications, available in Ireland and most other European countries, based on our definition of a medication with clinically significant anticholinergic or sedative effects. This master DBI list is a complete list to use for screening purposes, rather than one that only includes DBI medications taken by study participants. Therefore, most of the DBI medications on our master DBI list are not specific to Ireland but likely to be available in other countries. A review of AC medications not available in Ireland but available elsewhere, and reasons for this is beyond the scope of this paper, but we have included this as a possible limitation in the discussion.

Changes made to the manuscript:

1. Two additional supplementary tables have been included:

a) A supplementary table (Table S2) showing the DBI medications listed in the original DBI study in the USA (Hilmer 2009) but not included in our master DBI list, with reasons for this.

b) A supplementary table (Table S3) showing the DBI medications included in our master list, but not listed in the original DBI study in the USA (Hilmer 2009).

2. Addition to the Discussion, Strengths and limitations section, 2nd paragraph, last sentence:

“Finally, the master DBI list provided in this study (Supplementary Table S1) was based on medications and dosages relevant to prescribing in Ireland. Therefore, there may be medications available in other countries that are not on this list, and there may be medications on this list that are not available in other countries. The minimum effective dosages applied refer to prescribing in Ireland. Therefore, whilst the master DBI list provided could be used as a starting point in other countries, adaption to the local setting in terms of availability of drugs and dosage is necessary.”

2) In my understanding the DBI is meant to evaluate an individual medication list at a given point in time, at the dosage schedule at that time. The method applied here to establish the daily dosage is averaging use over one year (including gaps in prescribing by non-adherence, or as needed use, or change in dosages over time).

Response: Thank you for the comment. Several different study designs have been used to evaluate DBI exposure, including population-based studies using pharmacy claims data that averaged DBI over a fixed period (Gnjidic 2014, Nishtala 2014). We acknowledge that most DBI studies conducted previously employed smaller cohorts, were not based on pharmacy claims data, and assessed DBI exposure of participants at a given time point. The method applied in the current study for determining DBI exposure was based on the method used in a previous population-based study using pharmacy claims data, which averaged DBI use over one year (Nishtala 2014), as referenced in the methods section of the current paper. Furthermore, to evaluate DBI exposure over one year we evaluated DBI exposure on a monthly basis and then summed over the year. The average level of DBI exposure was similar across all months.

3) The method of determining polypharmacy level over one year is also one method for application on data over one year and not cross-sectional data. The method probably inflates a little the level of polypharmacy.

Response: The method for determining polypharmacy is based on the method used in previous published population-based studies using pharmacy claims data (Cahir 2010, Byrne 2017), as referenced in the methods section of the current paper. We agree it may slightly inflate the level of polypharmacy as suggested.

4) Combined with a very low threshold for AC-S use, it is no wonder that there is more than 20 fold Odds ratio with extreme polypharmacy.

Response: Thank you. We agree with the reviewer’s comment.

5) The results and conclusions remain valid, but some relativation may be helpful. So, maybe consider to remove the term "cross-sectional from the title.

Response: Thank you. We have removed the term “cross-sectional” from the title.

7) Data on the coverage of GSM population versus total Irish population in the elderly and very old could be given in the introduction.

Response: We provide data on the coverage of the GMS population vs total Irish population in the elderly and very old in the first paragraph of the methods section of our paper. We prefer to leave this information in the methods section of the manuscript rather than in the introduction.

Reviewer 2: Minor comment

I note a significant imbalance in exposure to drugs with sedative vs. anticholinergic effects. The discussion should emphasise this aspect and compare the findings to other similar studies conducted in other jurisdictions.

Response: Thank you for the suggestion. An additional paragraph has been included in the Discussion, 3rd paragraph, to address this:

"In the present study, exposure to medications with sedative effects was considerably higher in older people compared to exposure to medications with anticholinergic effects. This is likely to be due to the frequent use of anxiolytic/hypnotic drugs, antidepressants and opioid analgesics. Similar patterns of use have been noted in cohorts of older people living in Finland (Gnjidic 2012), Australia (Wilson 2010, Gnjidic 2012), and the USA (Cao 2008). However, older aged people in Ireland appear have considerably higher rates of use of codeine products and tramadol than their counterparts in Finland, according to a national population study in Finland of similar design to the present study (Gnjidic 2014)."

FORMATTING AMENDMENTS

1. Figure File Format - Please provide another copy of your figures with better qualities and please ensure that Figures are of better quality or not pix-elated when zoom in. NOTE: They can be in TIFF or JPG format and make sure that they have a resolution of at least 300 dpi. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable.

2. No Figure Legend- Please include Figure legends at the end of your main manuscript.

3. Patient and Public Involvement statement - Kindly rename your sub- heading from "Patient Involvement" to Patient and Public Involvement statement"

4. Please mention the author 'Cahir, Caitriona' in your CONTRIBUTORSHIP STATEMENT both in your main document and in ScholarOne.

Response: Thank you. We have attended to the above formatting amendments in our revised manuscript.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Robert Vander Stichele<br>Ghent University, Department of Pharmacology, Belgium<br>None declared |
| **REVIEW RETURNED** | 25-May-2018 |

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| **GENERAL COMMENTS** | The authors have responded well to the comments, and provided insight to researchers from other countries about their classification of anticholinergics and sedatives in a more universal way. |