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Analysis of the nervous and gastrointestinal events associated with solifenacin in older adults using the FDA adverse event reporting system

--Manuscript Draft--

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Abstract:	Background Antimuscarinics are the backbone of the pharmacological management of overactive bladder. Still, concerns have been raised over the nervous system (NS) adverse drug events (AEs) due to their dissimilarities to muscarinic receptor-subtype affinities. Objective This study aimed to identify the nervous system and gastrointestinal adverse drug events (ADEs) associated with solifenacin use in older adults (≥ 65 years). Methods A case/non-case analysis was performed on the reports submitted to the FDA Adverse Event Reporting System (FAERS) between 01/01/2004 and 30/06/2020. Cases were reports for solifenacin with ≥ 1 ADEs as preferred terms included in the Medical Dictionary of Regulatory Activities (MedDRA) system organ classes' nervous system' or 'gastrointestinal' disorders. Non-cases were all other remaining reports for solifenacin. The case/non-cases was compared between solifenacin and other bladder antimuscarinics. Frequentist approaches, including the proportional reporting ratio (PRR) and reporting odds ratio (ROR), were used to measure disproportionality. The empirical Bayesian Geometric Mean (EBGM) score and information component (IC) value were calculated using a Bayesian approach. A signal was defined as the lower limit of 95% confidence intervals of ROR ≥ 2, PRR ≥ 2, IC > 0, EBGM > 1, for ADEs with ≥ 4 reports. Results 107 MedDRA preferred terms (PTs) comprising 970 ADE reports were retrieved for nervous system disorders associated with solifenacin. For gastrointestinal disorders, 129 MedDRA PTs comprising 1817 ADE reports were retrieved. Statistically significant results were found for ‘altered state of consciousness’: ROR= 9.71 (2.13 - 44.35), PRR= 9.69 (2.12 - 44.2) and IC= 1.29 (0.93 - 1.66). Conclusions The disproportionality reporting of 'altered state of consciousness', a previously unidentified ADE, was unexpected. Further monitoring of this ADE is needed to ensure patient safety, as this could be linked to poor balance and falls in older adults.

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Response to Reviewers:	Analysis of the US FDA adverse event reporting system to identify adverse nervous system and gastrointestinal events associated with solifenacin Nishtala et.al Dear Editor Thank you for the opportunity to revise our paper and correct the typographical errors raised by the reviewer. Please see below, in blue, our response to comments. All page and line numbers refer to the manuscript file in the track changed copy. Reviewers' comments: There remain a few minor items to be considered or corrected: Page 3 of R1 line 27: you should write 'Alzheimer's disease', not Alzheimer's alone lines 32 to 35: because of your amendment there appears now the word 'consequently' twice in two consecutive sentences (a linguistic comment) line 34: instead of '...is often...', you should write '...might be...' Page 5 of R1 line 37: please reword '...what was unique about these compounds...'; the following wording is suggested '...it was unique for these compounds that they...' Line 40: '...no studies have reported the amount...' Page 6 of R1 Line 10 to 11: please double-check the sentence. Are the symbols > and < used correctly for the three terms 'memory impairmen', loss of consciousness' and cerebral infartion'? Please, double check with supplementary tables and figures. Page 7 of R1 line 38: re-consider the changed wording: '...serious ADEs may be underreporting.' (linguistic) We have corrected all typographical errors highlighted by the reviewer.
Additional Information:	
Question	**Response**
Is this work funded by the National Institutes of Health (NIH) or any of the NIH related PMC-participating or Europe PMC funders?	No
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Analysis of the US FDA adverse event reporting system to identify adverse nervous system and gastrointestinal events associated with solifenacin

Nishtala et.al

Dear Editor

Thank you for the opportunity to revise our paper and correct the typographical errors raised by the reviewer. Please see below, in blue, our response to comments. All page and line numbers refer to the manuscript file in the track changed copy.

Reviewers' comments:
There remain a few minor items to be considered or corrected:

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Analysis of the adverse nervous system and gastrointestinal events associated with solifenacin in older adults using the US FDA adverse event reporting system

Running title: Adverse effects of solifenacin

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Keywords: antimuscarinics; patient safety; pharmacovigilance; pharmacoepidemiology; elderly; reporting odds ratio

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Declarations:

Data Sharing

We agree to share all relevant raw data for this study with any researcher wishing to use them for non-commercial purposes.

Author Contributions

Study concept and design: Connie Nicholls and Prasad S Nishtala, Statistical analysis: Prasad S Nishtala, Te-yuan Chyou; Interpretation of data: All authors; Drafting of the manuscript: Connie Nicholls and Prasad S Nishtala, Critical revision of the manuscript for important intellectual content: All authors; Study supervision: Prasad S Nishtala.

Abstract

Background Antimuscarinics are the backbone of the pharmacological management of overactive bladder. Still, concerns have been raised over the nervous system (NS) adverse drug events (AEs) due to their dissimilarities to muscarinic receptor-subtype affinities.

Objective

This study aimed to identify the nervous system and gastrointestinal adverse drug events (ADEs) associated with solifenacin use in older adults (≥ 65 years).

Methods

A case/non-case analysis was performed on the reports submitted to the FDA Adverse Event Reporting System (FAERS) between 01/01/2004 and 30/06/2020. Cases were reports for solifenacin with ≥ 1 ADEs as preferred terms included in the Medical Dictionary of Regulatory Activities (MedDRA) system organ classes' nervous system' or 'gastrointestinal' disorders. Non-cases were all other remaining reports for solifenacin. The case/non-cases was compared between solifenacin and other bladder antimuscarinics. Frequentist approaches, including the proportional reporting ratio (PRR) and reporting odds ratio (ROR), were used to measure disproportionality. The empirical Bayesian Geometric Mean (EBGM) score and information component (IC) value were calculated using a Bayesian approach. A signal was defined as the lower limit of 95% confidence intervals of ROR ≥ 2, PRR ≥ 2, IC > 0, EBGM > 1, for ADEs with ≥ 4 reports.

Results

107 MedDRA preferred terms (PTs) comprising 970 ADE reports were retrieved for nervous system disorders associated with solifenacin. For gastrointestinal disorders, 129 MedDRA PTs comprising 1817 ADE reports were retrieved. Statistically significant results were found for ‘altered state of consciousness’: ROR= 9.71 (2.13 - 44.35), PRR= 9.69 (2.12 - 44.2) and IC= 1.29 (0.93 - 1.66).

Conclusions

The disproportionality reporting of *'altered state of consciousness'*, a previously unidentified ADE, was unexpected. Further monitoring of this ADE is needed to ensure patient safety, as this could be linked to poor balance and falls in older adults.

1. Introduction

Overactive bladder (OAB) is a condition that is highly prevalent in older adults, and it is estimated to occur in 30% of adults over 65 [1, 2]. In addition, certain medical conditions such as stroke, Parkinson's disease, and dementia are recognised as risk factors for OAB and are more common in older age. Therefore, if lifestyle interventions fail to treat the condition, antimuscarinic therapy is recommended as first-line medication to all ≥ 65 years of age.

Solifenacin is an efficacious treatment for an OAB [3]. However, adverse drug events (ADEs) occur with use. The summary of product characteristics (SmPC) for solifenacin lists gastrointestinal (GI) ADEs as the most prevalent. A meta-analysis conducted by Vouri et al. showed GI ADEs are very common with the use of all antimuscarinics, especially solifenacin, which had the second-highest rates of constipation (15.4%) and dry mouth (26%) in older adults when compared to other antimuscarinics [4]. Antimuscarinics have also raised concern over the nervous system (NS) ADEs. Studies suggest they can exacerbate cognitive impairment in dementia and possibly precipitate the disease in older adults [5].

Antimuscarinics cause NS ADEs by altering acetylcholine-mediated neurotransmission through interaction with muscarinic receptors in the brain [6]. Older adults are particularly susceptible to these alterations, as muscarinic neurons in the brain progressively decrease with age [7]. A meta-analysis of 31 studies revealed that blood-brain barrier (BBB) permeability increases naturally with ageing due to age-related diseases, such as stroke and Alzheimer's disease [8]. Greater BBB permeability increases the ability of drugs to penetrate the brain, including antimuscarinics like solifenacin, increasing the risk of NS ADEs. In addition, increased polypharmacy, co-morbidities, and natural age-related changes in pharmacokinetics and pharmacodynamics increase the susceptibility of older adults to ADEs [9].

Although older adults are vulnerable to ADEs, they are often excluded from clinical trials. Consequently, trials investigating the ADE profile for solifenacin fail to adequately uncover all ADEs related data for this age group, raising safety concerns. Therefore, the safety information for solifenacin might be inadequate or not updated in the drug labels to better advise patients of risk. Hence, post-marketing surveillance provides an opportunity to analyse ADEs on this vulnerable population. This study examines the NS and GI ADEs occurring in older adults when taking solifenacin by analysing post-market reports recorded on the food and drug administration adverse event reporting system (FAERS).

2. Method

2.1 Data source

The Elsevier Pharmapendium database was searched to derive the primary data for the study. The use of PharmaPendium for drug safety research is described elsewhere [10-12]. On 17/01/2021, there were 17,962,359 FAERS reports and 4,778 drugs with data in the Pharmapendium [13]. The database is curated and maintained by Elsevier, and using the FAERS data search functionality, post-market reports can be specifically searched and extracted for analyses. The AERs report number and case ID uniquely identify each FAERS report. In addition,

each report includes details such as indication, dose, frequency, route of administration, manufacturer, and role implicating the ADE(s) for the drug. Additional patient information is also included: age, sex, geographic location, the outcome of the event, occupation of the reporter, contaminant and interacting medications. The Ethical Implications of Research Activity Form to conduct this study was approved by the University of Bath.

2.2 Definition of ADEs

ADEs were defined as per preferred terms (PTs) stated in the Medical Dictionary for Regulatory Activities (MedDRA v23.1) [14]. MedDRA classifies these PTs into a hierarchical system, mapping to higher-level terms (HLTs), higher grouped level terms (HGLTs), and system organ class (SOC).

2.3 Study design and participants

For this study, reports were extracted between 01/01/2004 and 30/06/2020 and restricted to adults aged 65 and 120. Cases were reports for solifenacin with at least one ADE included in the MedDRA SOC 'nervous system' or 'gastrointestinal disorders.' Non-cases were all other remaining reports for solifenacin. Cases/non-cases were extracted for the same ADEs using identical search parameters for seven other antimuscarinics: oxybutynin, tolterodine, propiverine, darifenacin, trospium, fesoterodine, and flavoxate.

2.4 Statistical analysis

The ratio of case/non-cases for ADEs associated with solifenacin was compared to the case/non-cases for all other antimuscarinics for the same study period. Signals were generated using the statistical analysis software 'R' (version 3.6.1) [15]. Disproportionality analyses were used to generate the proportional reporting ratio (PRR) and reporting odds ratio (ROR) [16]. The information component (IC) and Empirical Bayesian Geometric Mean (EBGM) for each ADE were calculated using the Bayesian approach. For example, a signal was determined if an ADE had ≥ 4 reports, and the lower limit of the 95% CI was ≥ 2 for ROR, ≥ 2 for PRR, > 0 for IC value, and >1 for EBGM value.

3. Results:

A total of 10,934 unique case reports were retrieved for all bladder antimuscarinic ADEs between 01/01/2004 and 30/06/2020 for adults ≥ 65 years. Of these, 3722 case reports were for ADEs associated with solifenacin, as shown in **Figure 1**. For NS disorders, this included 107 MedDRA PTs comprising 726 ADE reports (**Online resource 1)**. Additionally, 129 MedDRA PTs comprised 1211 ADE reports for GI disorders (**Online resource 2)**. The patients within the reports for solifenacin had an average age of 78 years, and 66% were female. Consumers submitted the majority (56.5%) of reports. Forty-four countries submitted reports (**Online resource 3)**, with the majority submitted by the United States (71.9%).

Three statistically significant signals were found for ‘altered state of consciousness’: ROR= 9.71 (2.13 - 44.35) (**Figure 2**), RR= 9.69 (2.12 - 44.2) and IC= 1.29 (0.93 - 1.66). Some NS ADEs achieved a ROR with a lower CI ≥ 1 that were not present in the product literature for solifenacin: 'loss of consciousness' 1.78 (1.11 – 2.86), 'memory impairment' 1.5 (1.02 – 2.20), and 'cerebral infarction' 8.74 (1.89 – 40.46). Two significant signals were

also found for ‘constipation’ EBGM= 1.34 (1.24 - 1.46) (**Figure 3**), IC= 0.47 (0.38 - 0.56). Other significant IC values can be seen in **Online resource 4** (GI) and **5** (NS).

4. Discussion

Our study investigated solifenacin's NS and GI safety in older adults and identified three signals related to the NS and two signals related to GI safety.

NS signals:

Reported outcomes relating to the NS included an altered state of consciousness that was severe. Eight out of the ten reports resulted in hospitalisation, disability, or were specified to be life-threatening. The ADE is not listed in solifenacin's SmPC. Previous studies in older adults taking solifenacin have not identified this ADE, possibly due to limited participants. A literature review identified that most had 75 participants or less, undermining the statistical power to detect infrequently occurring ADEs [7, 17-20]. The ADE was described in a case study that reported an older patient taking solifenacin who, in association with delirium and hallucinations, experienced disturbances in consciousness [21]. An altered level of consciousness could potentially cause falls and injury, which raises safety implications for patients if not communicated appropriately.

These findings suggest that solifenacin can elicit central nervous system (CNS) ADEs. Solifenacin is a lipophilic compound that can be highly distributed into tissues throughout the body, including the brain [22]. Interestingly, a study by Krauwinkel et al. revealed solifenacin to be highly protein-bound in the blood, averaging between 97.7-98.1% [17]. Extensive protein binding suggests that it may not cross the blood-brain barrier (BBB) since there would be a highly reduced free fraction of the drug available for transport into the brain. Furthermore, solifenacin is ionised at bodily pH, limiting transportation across the BBB via diffusion. However, like other antimuscarinics such as oxybutynin, solifenacin is a tertiary amine; therefore, it could cross the BBB and elicit CNS ADEs [23].

Studies examining pharmacokinetics that influence the distribution of solifenacin reveal that it results in significant brain penetration when administered to rats, likewise for oxybutynin and tolterodine [24]. Compared to the antimuscarinics with low brain penetration, it was unique for these compounds that they were not a substrate for the brain's primary efflux transporter P-GP. The findings indicate that all the tertiary amine antimuscarinics get transported across the BBB. However, solifenacin can accumulate due to a lack of efflux transport out of the brain via P-GP. After oral administration, no studies have reported the amount of solifenacin present in cerebrospinal fluid in humans. Assessing this would provide a more reliable indicator of the true level of solifenacin distribution to the brain. Despite this, the evidence indicates that the drug penetrates the BBB and elicits CNS ADEs.

Furthermore, Farrall et al. conducted a meta-analysis of 31 studies, showing that BBB permeability increases naturally with ageing [8]. Therefore, older adults are increasingly vulnerable to drug penetration into the brain. Additionally, diseases of old age can further increase BBB permeability [25]. Due to these factors, and with muscarinic neurons in the brain naturally degenerating with age, older adults are more susceptible to cognitive antimuscarinic ADEs [7].

The ADEs 'memory impairment', 'loss of consciousness' and 'cerebral infarction' produced RORs with a lower limit of 95% CI ≥1. These results are unexpected, as this ROR value could indicate an increased reporting of these ADEs, which are not known to be side effects of solifenacin. Previous studies assessing whether solifenacin affects cognitive function in older adults, including memory, have found no significant changes with solifenacin use [7, 18, 19, 26, 27]. However, the longest duration of these studies was 12 weeks, which may not be long enough to identify potential long-term impacts of solifenacin on a person's memory. Also, in a case-control study conducted by Park, the participants were older adults who had previously had a stroke, a disease known to cause cognitive impairment [7]. These participants had cognitive impairment pre-dating solifenacin use, a potential confounding factor. Suppose an initial degree of cognitive impairment was present. It may be difficult for assessors to judge if solifenacin worsened cognitive impairment further, a factor not accounted for in the studies analysis. Therefore, post-marketing data may better indicate solifenacin's long-term effect on memory. 'Cerebral infarction' and 'loss of consciousness' have not been reported in previous studies. Like the ADE's 'altered state of consciousness,' these could be rare NS ADEs, only identifiable through post-marketing surveillance. A potential increased relative risk of 'loss of consciousness' further supports that solifenacin can cause disturbances to consciousness. However, we recognise the term 'altered consciousness' is rather unspecific PT and LLT and must be put into context to other terms in the group of related PTs that can cause disturbances to consciousness and memory. Hence, we combined the MedDRA PT's altered consciousness, somnolence and lethargy to reflect the same group of adverse effects described in the product label. However, the combined PT group did not produce a signal. The disproportionality measures were ROR (1.43, 95%CI 1.12-1.82), PRR (1.41, 95%CI 1.12-1.79), IC (0.31, 95%CI 0.12-0.50) and EBGM (1.18, 95%CI 1.03-1.34). It highlights how signals derived from spontaneous reports may be discordant with safety information included in the label.

Linking ADEs to drugs through post-market surveillance cannot establish causality; however, such findings are important for signal detection. Despite the EGBM signal for 'altered state of consciousness' not showing significance, the disproportionality between this ADE reported for solifenacin and other antimuscarinics should not be ignored. Since this ADE is not listed in the SmPC, patients and healthcare professionals will be unaware it could compromise patient safety. Further research is needed to understand and confirm the association between an altered state of consciousness and solifenacin. Due to this event's rare nature, a case-control study would potentially offer a viable approach for identifying an association between taking solifenacin and this ADE. The FAERS database should be monitored for future reports of this ADE.

GI signals:

Interestingly, two out of four signal criteria were met for 'constipation'. This ADE's significance was expected since it was the second most reported GI ADE in multiple studies on older adults [17, 19, 20]. It was the second most reported GI ADE on the FAERS database, agreeing with these findings. It is listed as a 'common' ADE in solifenacin's SmPC, corroborating the literature and this study's findings. The finding of insignificant ROR and PRR values suggest no increased relative reporting of this ADE when taking solifenacin.

Similarly, the ADE' dry mouth' accumulated the most reports for GI ADEs on the Pharmapendium. Dry mouth is identified as a 'very common' ADE (occurring in ≥1/10 people). It is reported as the most common GI ADE in

many studies on older adults using solifenacin [17, 19, 20, 26]. In agreement with the literature, dry mouth accumulated the most GI ADEs for solifenacin. However, the statistical analysis showed no increased relative reporting risk. A reason could be other antimuscarinics have a similar ADE profile to solifenacin. A meta-analysis of 69 trials on 26,229 patients conducted by Kessler et al. examined ADEs associated with bladder antimuscarinics [28]. They found similar ADE profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, trospium chloride, with the only exception being oral oxybutynin [28]. Dry mouth was consistently the most reported ADE for all the antimuscarinics. An explanation for this could be the class of antimuscarinics having similar pharmacology and modes of action, eliciting similar ADEs. Having ADEs common to all the antimuscarinics can mask the signals [29].

Positive IC values (lower 95% CI >0) were found for multiple GI and NS ADEs, suggesting a stronger association than expected compared to other antimuscarinics [30]. Some significant associations were expected, such as dry mouth, dyspepsia, and somnolence, as listed in the SmPC. Somnolence was also detected in a study conducted by Wesnes et al., consistent with the findings of this study and the product literature that solifenacin could cause fatigue [18]. This finding further supports that solifenacin can cause disturbances in consciousness. Errors of classification of ADEs to PTs could have occurred here, as somnolence is defined as "a feeling of wanting to sleep", and at what point would these symptoms be classed as an 'altered state of consciousness'? Potential misclassification like this could significantly impact statistical results and is why the findings for 'altered state of consciousness' should not be overlooked. Monitoring for future reporting for the ADEs with significant ICs would be recommended, as this is an example of early signal detection [30].

There are limitations of this study associated with using the FAERS database. First, causality regarding signals cannot be assumed. Second, voluntary submission of reports and potential selective reporting of only serious ADEs may be underreported. Third, although reports were systematically deduplicated during analysis, some duplicate reports can remain where multiple sources may have reported a particular ADE case. Finally, reporting through SRS is often incomplete, including a lack of patient information such as medical and family history, and is likely to introduce bias in these findings.

Additionally, the incident rate in a population cannot be calculated, as the level of solifenacin exposure in the population is unknown. Methodological limitations to this study include not examining the impact of concomitant medications of ADEs on reports. Also, dependent or temporal relationships with ADEs were not measured. NS ADEs can often be cumulative or dose-dependent, impacting results. Finally, signals must be interpreted with caution for ADEs for solifenacin, which have ROR with a wide CI, indicating a small sample size.

Despite the several shortcomings of the SRS database, they are useful for hypotheses generation, which can then be investigated in large scale pharmacoepidemiology studies. In addition, the SRS offers safety information on a large and wide spectrum of populations covering the entire life cycle of the drug. Therefore, they are particularly attractive for pursuing pharmacovigilance activities at a low cost.

5. Conclusions

Certainty surrounding solifenacin's ability to elicit nervous system ADEs is unclear. The disproportionality reporting of 'altered state of consciousness, a previously unidentified ADE, was unexpected. This ADE needs further monitoring and research to ensure patient safety, as this could be linked to poor balance and falls in older adults. The GI adverse effects reported with solifenacin are similar to those described in the SmPC.

6. Compliance with Ethical Standards

Conflict of Interest: All authors declare no conflict of interest.

Funding: No funding was received to conduct this study.

Ethical approval: The study was approved by the Departments Ethics Officer of the University of Bath. The study used publicly available data for its analysis.

Informed consent: Formal consent is not required for this type of study.

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Analysis of the adverse nervous system and gastrointestinal events associated with solifenacin in older adults using the US FDA adverse event reporting system

Running title: Adverse effects of solifenacin

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Declarations:

Data Sharing

We agree to share all relevant raw data for this study with any researcher wishing to use them for non-commercial purposes.

Author Contributions

Study concept and design: Connie Nicholls and Prasad S Nishtala, Statistical analysis: Prasad S Nishtala, Te-yuan Chyou; Interpretation of data: All authors; Drafting of the manuscript: Connie Nicholls and Prasad S Nishtala, Critical revision of the manuscript for important intellectual content: All authors; Study supervision: Prasad S Nishtala.

Abstract

Background Antimuscarinics are the backbone of the pharmacological management of overactive bladder. Still, concerns have been raised over the nervous system (NS) adverse drug events (AEs) due to their dissimilarities to muscarinic receptor-subtype affinities.

Objective

This study aimed to identify the nervous system and gastrointestinal adverse drug events (ADEs) associated with solifenacin use in older adults (≥ 65 years).

Methods

A case/non-case analysis was performed on the reports submitted to the FDA Adverse Event Reporting System (FAERS) between 01/01/2004 and 30/06/2020. Cases were reports for solifenacin with ≥ 1 ADEs as preferred terms included in the Medical Dictionary of Regulatory Activities (MedDRA) system organ classes' nervous system' or 'gastrointestinal' disorders. Non-cases were all other remaining reports for solifenacin. The case/non-cases was compared between solifenacin and other bladder antimuscarinics. Frequentist approaches, including the proportional reporting ratio (PRR) and reporting odds ratio (ROR), were used to measure disproportionality. The empirical Bayesian Geometric Mean (EBGM) score and information component (IC) value were calculated using a Bayesian approach. A signal was defined as the lower limit of 95% confidence intervals of ROR ≥ 2, PRR ≥ 2, IC > 0, EBGM > 1, for ADEs with ≥ 4 reports.

Results

107 MedDRA preferred terms (PTs) comprising 970 ADE reports were retrieved for nervous system disorders associated with solifenacin. For gastrointestinal disorders, 129 MedDRA PTs comprising 1817 ADE reports were retrieved. Statistically significant results were found for 'altered state of consciousness': ROR= 9.71 (2.13 - 44.35), PRR= 9.69 (2.12 - 44.2) and IC= 1.29 (0.93 - 1.66).

Conclusions

The disproportionality reporting of *'altered state of consciousness'*, a previously unidentified ADE, was unexpected. Further monitoring of this ADE is needed to ensure patient safety, as this could be linked to poor balance and falls in older adults.

1. Introduction

Overactive bladder (OAB) is a condition that is highly prevalent in older adults, and it is estimated to occur in 30% of adults over 65 [1, 2]. In addition, certain medical conditions such as stroke, Parkinson's disease, and dementia are recognised as risk factors for OAB and are more common in older age. Therefore, if lifestyle interventions fail to treat the condition, antimuscarinic therapy is recommended as first-line medication to all ≥ 65 years of age.

Solifenacin is an efficacious treatment for an OAB [3]. However, adverse drug events (ADEs) occur with use. The summary of product characteristics (SmPC) for solifenacin lists gastrointestinal (GI) ADEs as the most prevalent. A meta-analysis conducted by Vouri et al. showed GI ADEs are very common with the use of all antimuscarinics, especially solifenacin, which had the second-highest rates of constipation (15.4%) and dry mouth (26%) in older adults when compared to other antimuscarinics [4]. Antimuscarinics have also raised concern over the nervous system (NS) ADEs. Studies suggest they can exacerbate cognitive impairment in dementia and possibly precipitate the disease in older adults [5].

Antimuscarinics cause NS ADEs by altering acetylcholine-mediated neurotransmission through interaction with muscarinic receptors in the brain [6]. Older adults are particularly susceptible to these alterations, as muscarinic neurons in the brain progressively decrease with age [7]. A meta-analysis of 31 studies revealed that blood-brain barrier (BBB) permeability increases naturally with ageing due to age-related diseases, such as stroke and Alzheimer's disease [8]. Greater BBB permeability increases the ability of drugs to penetrate the brain, including antimuscarinics like solifenacin, increasing the risk of NS ADEs. In addition, increased polypharmacy, co-morbidities, and natural age-related changes in pharmacokinetics and pharmacodynamics increase the susceptibility of older adults to ADEs [9].

Although older adults are vulnerable to ADEs, they are often excluded from clinical trials. Consequently, trials investigating the ADE profile for solifenacin fail to adequately uncover all ADEs related data for this age group, raising safety concerns. ~~Consequently~~Therefore, the safety information for solifenacin might be~~is often~~ inadequate or not updated in the drug labels to better advise patients of risk. Hence, post-marketing surveillance provides an opportunity to analyse ADEs on this vulnerable population. This study examines the NS and GI ADEs occurring in older adults when taking solifenacin by analysing post-market reports recorded on the food and drug administration adverse event reporting system (FAERS).

2. Method

2.1 Data source

The Elsevier Pharmapendium database was searched to derive the primary data for the study. The use of PharmaPendium for drug safety research is described elsewhere [10-12]. On 17/01/2021, there were 17,962,359 FAERS reports and 4,778 drugs with data in the Pharmapendium [13]. The database is curated and maintained by Elsevier, and using the FAERS data search functionality, post-market reports can be specifically searched and extracted for analyses. The AERs report number and case ID uniquely identify each FAERS report. In addition,

each report includes details such as indication, dose, frequency, route of administration, manufacturer, and role implicating the ADE(s) for the drug. Additional patient information is also included: age, sex, geographic location, the outcome of the event, occupation of the reporter, contaminant and interacting medications. The Ethical Implications of Research Activity Form to conduct this study was approved by the University of Bath.

2.2 Definition of ADEs

ADEs were defined as per preferred terms (PTs) stated in the Medical Dictionary for Regulatory Activities (MedDRA v23.1) [14]. MedDRA classifies these PTs into a hierarchical system, mapping to higher-level terms (HLTs), higher grouped level terms (HGLTs), and system organ class (SOC).

2.3 Study design and participants

For this study, reports were extracted between 01/01/2004 and 30/06/2020 and restricted to adults aged 65 and 120. Cases were reports for solifenacin with at least one ADE included in the MedDRA SOC 'nervous system' or 'gastrointestinal disorders.' Non-cases were all other remaining reports for solifenacin. Cases/non-cases were extracted for the same ADEs using identical search parameters for seven other antimuscarinics: oxybutynin, tolterodine, propiverine, darifenacin, trospium, fesoterodine, and flavoxate.

2.4 Statistical analysis

The ratio of case/non-cases for ADEs associated with solifenacin was compared to the case/non-cases for all other antimuscarinics for the same study period. Signals were generated using the statistical analysis software 'R' (version 3.6.1) [15]. Disproportionality analyses were used to generate the proportional reporting ratio (PRR) and reporting odds ratio (ROR) [16]. The information component (IC) and Empirical Bayesian Geometric Mean (EBGM) for each ADE were calculated using the Bayesian approach. For example, a signal was determined if an ADE had ≥ 4 reports, and the lower limit of the 95% CI was ≥ 2 for ROR, ≥ 2 for PRR, > 0 for IC value, and >1 for EBGM value.

3. Results:

A total of 10,934 unique case reports were retrieved for all bladder antimuscarinic ADEs between 01/01/2004 and 30/06/2020 for adults ≥ 65 years. Of these, 3722 case reports were for ADEs associated with solifenacin, as shown in **Figure 1**. For NS disorders, this included 107 MedDRA PTs comprising 726 ADE reports (**Online resource 1)**. Additionally, 129 MedDRA PTs comprised 1211 ADE reports for GI disorders (**Online resource 2)**. The patients within the reports for solifenacin had an average age of 78 years, and 66% were female. Consumers submitted the majority (56.5%) of reports. Forty-four countries submitted reports (**Online resource 3)**, with the majority submitted by the United States (71.9%).

Three statistically significant signals were found for 'altered state of consciousness': ROR= 9.71 (2.13 - 44.35) (**Figure 2**), RR= 9.69 (2.12 - 44.2) and IC= 1.29 (0.93 - 1.66). Some NS ADEs achieved a ROR with a lower CI ≥ 1 that were not present in the product literature for solifenacin: 'loss of consciousness' 1.78 (1.11 – 2.86), 'memory impairment' 1.5 (1.02 – 2.20), and 'cerebral infarction' 8.74 (1.89 – 40.46). Two significant signals were

also found for 'constipation' EBGM= 1.34 (1.24 - 1.46) (**Figure 3**), IC= 0.47 (0.38 - 0.56). Other significant IC values can be seen in **Online resource 4** (GI) and **5** (NS).

4. Discussion

Our study investigated solifenacin's NS and GI safety in older adults and identified three signals related to the NS and two signals related to GI safety.

NS signals:

Reported outcomes relating to the NS included an altered state of consciousness that was severe. Eight out of the ten reports resulted in hospitalisation, disability, or were specified to be life-threatening. The ADE is not listed in solifenacin's SmPC. Previous studies in older adults taking solifenacin have not identified this ADE, possibly due to limited participants. A literature review identified that most had 75 participants or less, undermining the statistical power to detect infrequently occurring ADEs [7, 17-20]. The ADE was described in a case study that reported an older patient taking solifenacin who, in association with delirium and hallucinations, experienced disturbances in consciousness [21]. An altered level of consciousness could potentially cause falls and injury, which raises safety implications for patients if not communicated appropriately.

These findings suggest that solifenacin can elicit central nervous system (CNS) ADEs. Solifenacin is a lipophilic compound that can be highly distributed into tissues throughout the body, including the brain [22]. Interestingly, a study by Krauwinkel et al. revealed solifenacin to be highly protein-bound in the blood, averaging between 97.7-98.1% [17]. Extensive protein binding suggests that it may not cross the blood-brain barrier (BBB) since there would be a highly reduced free fraction of the drug available for transport into the brain. Furthermore, solifenacin is ionised at bodily pH, limiting transportation across the BBB via diffusion. However, like other antimuscarinics such as oxybutynin, solifenacin is a tertiary amine; therefore, it could cross the BBB and elicit CNS ADEs [23].

Studies examining pharmacokinetics that influence the distribution of solifenacin reveal that it results in significant brain penetration when administered to rats, likewise for oxybutynin and tolterodine [24]. Compared to the antimuscarinics with low brain penetration, it~~what~~ was unique for~~about~~ these compounds ~~was~~ that they were not a substrate for the brain's primary efflux transporter P-GP. The findings indicate that all the tertiary amine antimuscarinics get transported across the BBB. However, solifenacin can accumulate due to a lack of efflux transport out of the brain via P-GP. After oral administration, no studies have ~~been~~ reported ~~to establish~~ the amount of solifenacin present in cerebrospinal fluid in humans. Assessing this would provide a more reliable indicator of the true level of solifenacin distribution to the brain. Despite this, the evidence indicates that the drug penetrates the BBB and elicits CNS ADEs.

Furthermore, Farrall et al. conducted a meta-analysis of 31 studies, showing that BBB permeability increases naturally with ageing [8]. Therefore, older adults are increasingly vulnerable to drug penetration into the brain. Additionally, diseases of old age can further increase BBB permeability [25]. Due to these factors, and with muscarinic neurons in the brain naturally degenerating with age, older adults are more susceptible to cognitive antimuscarinic ADEs [7].

The ADEs "memory impairment", "loss of consciousness" and "cerebral infarction" produced RORs with a lower limit of 95% CI ≥1. These results are unexpected, as this ROR value could indicate an increased reporting of these ADEs, which are not known to be side effects of solifenacin. Previous studies assessing whether solifenacin affects cognitive function in older adults, including memory, have found no significant changes with solifenacin use [7, 18, 19, 26, 27]. However, the longest duration of these studies was 12 weeks, which may not be long enough to identify potential long-term impacts of solifenacin on a person's memory. Also, in a case-control study conducted by Park, the participants were older adults who had previously had a stroke, a disease known to cause cognitive impairment [7]. These participants had cognitive impairment pre-dating solifenacin use, a potential confounding factor. Suppose an initial degree of cognitive impairment was present. It may be difficult for assessors to judge if solifenacin worsened cognitive impairment further, a factor not accounted for in the studies analysis. Therefore, post-marketing data may better indicate solifenacin's long-term effect on memory. 'Cerebral infarction' and 'loss of consciousness' have not been reported in previous studies. Like the ADE's 'altered state of consciousness,' these could be rare NS ADEs, only identifiable through post-marketing surveillance. A potential increased relative risk of 'loss of consciousness' further supports that solifenacin can cause disturbances to consciousness. However, we recognise the term 'altered consciousness' is rather unspecific PT and LLT and must be put into context to other terms in the group of related PTs that can cause disturbances to consciousness and memory. Hence, we combined the MedDRA PT's 'altered consciousness, somnolence and lethargy to reflect the same group of adverse effects described in the product label. However, the combined PT group did not produce a signal. The disproportionality measures were ROR (1.43, 95%CI 1.12-1.82), PRR (1.41, 95%CI 1.12-1.79), IC (0.31, 95%CI 0.12-0.50) and EBGM (1.18, 95%CI 1.03-1.34). It highlights how signals derived from spontaneous reports may be discordant with safety information included in the label.

Linking ADEs to drugs through post-market surveillance cannot establish causality; however, such findings are important for signal detection. Despite the EGBM signal for 'altered state of consciousness' not showing significance, the disproportionality between this ADE reported for solifenacin and other antimuscarinics should not be ignored. Since this ADE is not listed in the SmPC, patients and healthcare professionals will be unaware it could compromise patient safety. Further research is needed to understand and confirm the association between an altered state of consciousness and solifenacin. Due to this event's rare nature, a case-control study would potentially offer a viable approach for identifying an association between taking solifenacin and this ADE. The FAERS database should be monitored for future reports of this ADE.

GI signals:

Interestingly, two out of four signal criteria were met for 'constipation'. This ADE's significance was expected since it was the second most reported GI ADE in multiple studies on older adults [17, 19, 20]. It was the second most reported GI ADE on the FAERS database, agreeing with these findings. It is listed as a 'common' ADE in solifenacin's SmPC, corroborating the literature and this study's findings. The finding of insignificant ROR and PRR values suggest no increased relative reporting of this ADE when taking solifenacin.

Similarly, the ADE 'dry mouth' accumulated the most reports for GI ADEs on the Pharmapendium. Dry mouth is identified as a 'very common' ADE (occurring in ≥1/10 people). It is reported as the most common GI ADE in

many studies on older adults using solifenacin [17, 19, 20, 26]. In agreement with the literature, dry mouth accumulated the most GI ADEs for solifenacin. However, the statistical analysis showed no increased relative reporting risk. A reason could be other antimuscarinics have a similar ADE profile to solifenacin. A meta-analysis of 69 trials on 26,229 patients conducted by Kessler et al. examined ADEs associated with bladder antimuscarinics [28]. They found similar ADE profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, trospium chloride, with the only exception being oral oxybutynin [28]. Dry mouth was consistently the most reported ADE for all the antimuscarinics. An explanation for this could be the class of antimuscarinics having similar pharmacology and modes of action, eliciting similar ADEs. Having ADEs common to all the antimuscarinics can mask the signals [29].

Positive IC values (lower 95% CI >0) were found for multiple GI and NS ADEs, suggesting a stronger association than expected compared to other antimuscarinics [30]. Some significant associations were expected, such as dry mouth, dyspepsia, and somnolence, as listed in the SmPC. Somnolence was also detected in a study conducted by Wesnes et al., consistent with the findings of this study and the product literature that solifenacin could cause fatigue [18]. This finding further supports that solifenacin can cause disturbances in consciousness. Errors of classification of ADEs to PTs could have occurred here, as somnolence is defined as "a feeling of wanting to sleep", and at what point would these symptoms be classed as an 'altered state of consciousness'? Potential misclassification like this could significantly impact statistical results and is why the findings for 'altered state of consciousness' should not be overlooked. Monitoring for future reporting for the ADEs with significant ICs would be recommended, as this is an example of early signal detection [30].

There are limitations of this study associated with using the FAERS database. First, causality regarding signals cannot be assumed. Second, voluntary submission of reports and potential selective reporting of only serious ADEs may be underreported~~ing~~. Third, although reports were systematically deduplicated during analysis, some duplicate reports can remain where multiple sources may have reported a particular ADE case. Finally, reporting through SRS is often incomplete, including a lack of patient information such as medical and family history, and is likely to introduce bias in these findings.

Additionally, the incident rate in a population cannot be calculated, as the level of solifenacin exposure in the population is unknown. Methodological limitations to this study include not examining the impact of concomitant medications of ADEs on reports. Also, dependent or temporal relationships with ADEs were not measured. NS ADEs can often be cumulative or dose-dependent, impacting results. Finally, signals must be interpreted with caution for ADEs for solifenacin, which have ROR with a wide CI, indicating a small sample size.

Despite the several shortcomings of the SRS database, they are useful for hypotheses generation, which can then be investigated in large scale pharmacoepidemiology studies. In addition, the SRS offers safety information on a large and wide spectrum of populations covering the entire life cycle of the drug. Therefore, they are particularly attractive for pursuing pharmacovigilance activities at a low cost.

5. Conclusions

Certainty surrounding solifenacin's ability to elicit nervous system ADEs is unclear. The disproportionality reporting of 'altered state of consciousness, a previously unidentified ADE, was unexpected. This ADE needs further monitoring and research to ensure patient safety, as this could be linked to poor balance and falls in older adults. The GI adverse effects reported with solifenacin are similar to those described in the SmPC.

6. Compliance with Ethical Standards

Conflict of Interest: All authors declare no conflict of interest.

Funding: No funding was received to conduct this study.

Ethical approval: The study was approved by the Departments Ethics Officer of the University of Bath. The study used publicly available data for its analysis.

Informed consent: Formal consent is not required for this type of study.

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Figure 1: Mapping of solifenacin-associated all adverse drug events at different MedDRA levels. HLGT, high-level group term; HLT, high-level term; n, number of reports; PT, preferred term; SOC, system organ class.

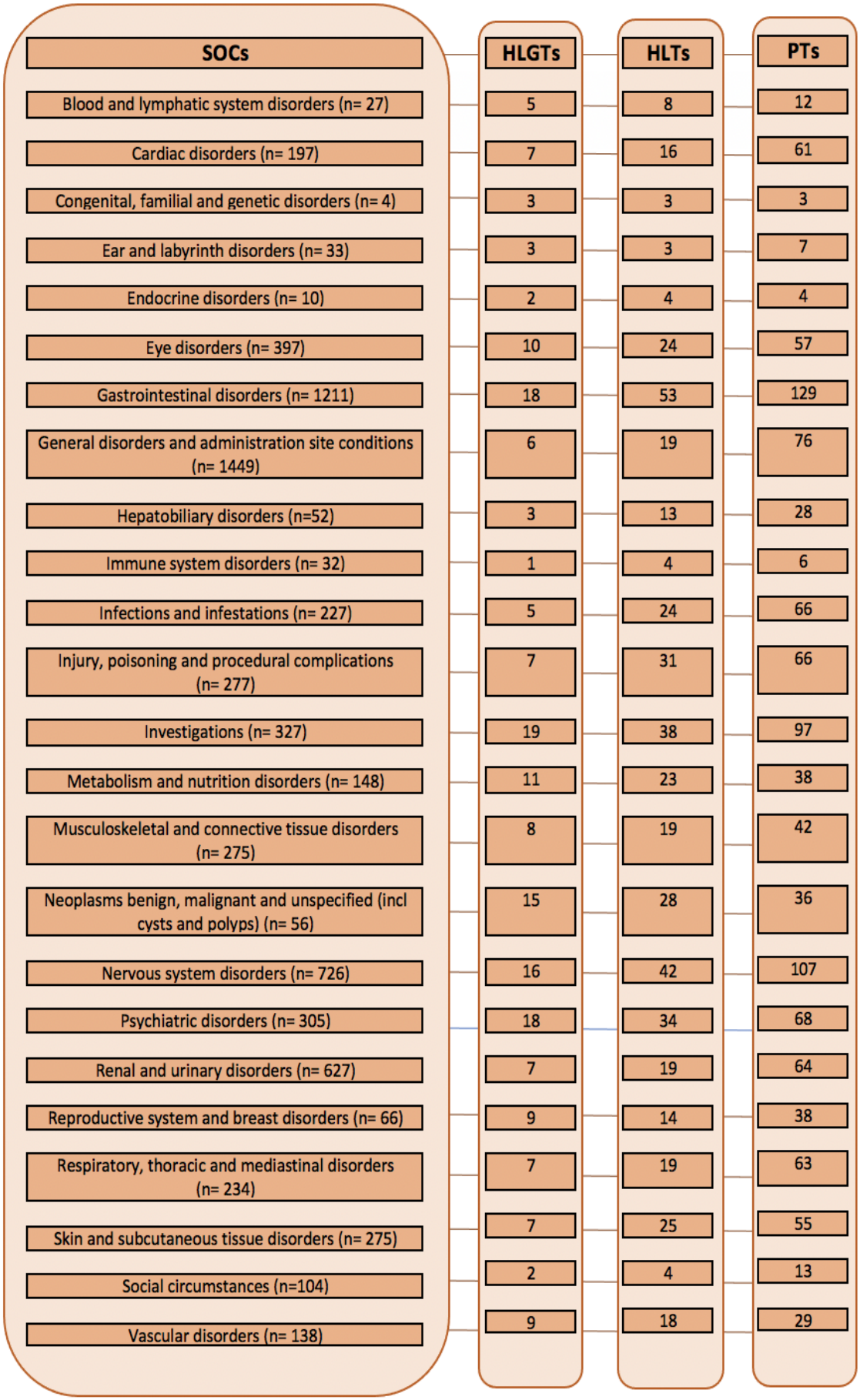

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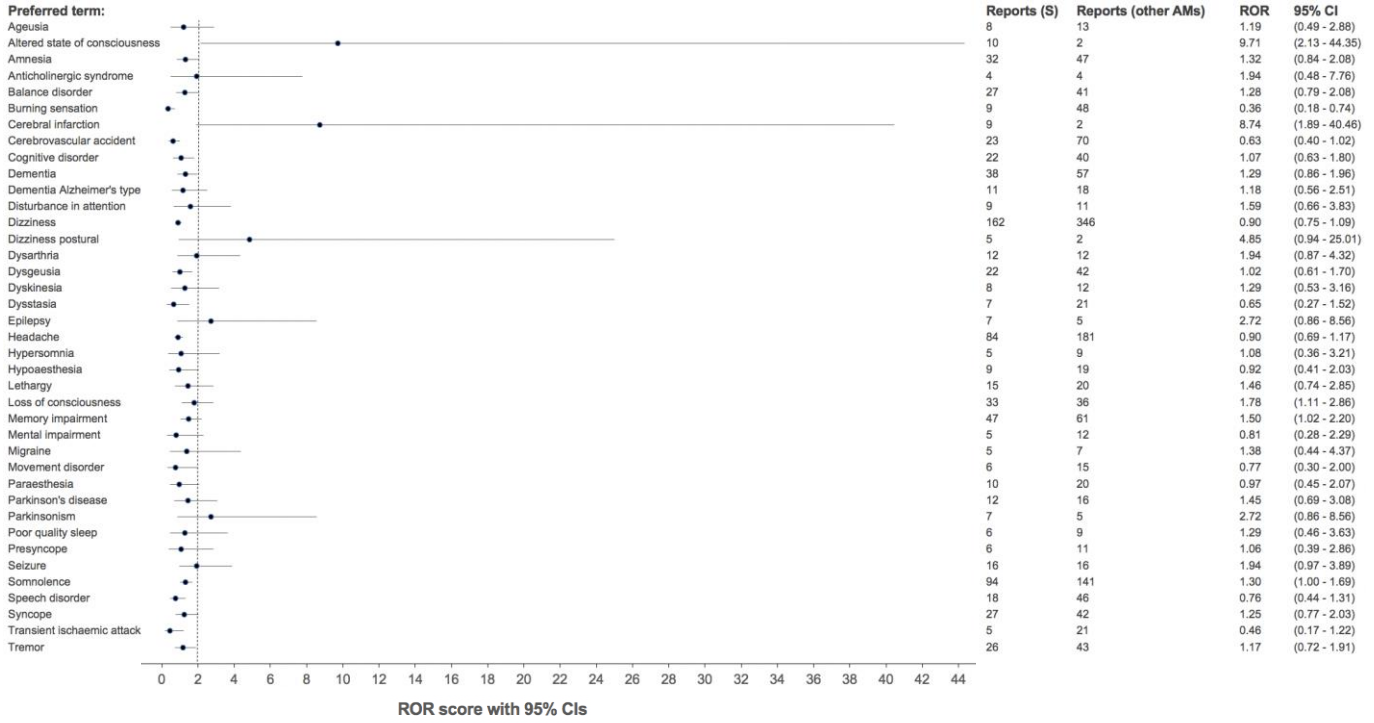
Figure 2: Forest plots of the ROR and EBGM scores with 95% CIs for solifenacin- associated nervous system adverse events (classed as Medical Dictionary of Regulatory Activities preferred terms). ADE, adverse drug event; AMs; antimuscarinics; CI, confidence interval; EBGM, Empirical Bayesian geometric mean; ROR, reporting odds ratio; S, solifenacin.

Reporting odds-ratio of nervous system ADE:



EBGM score of nervous system ADE:

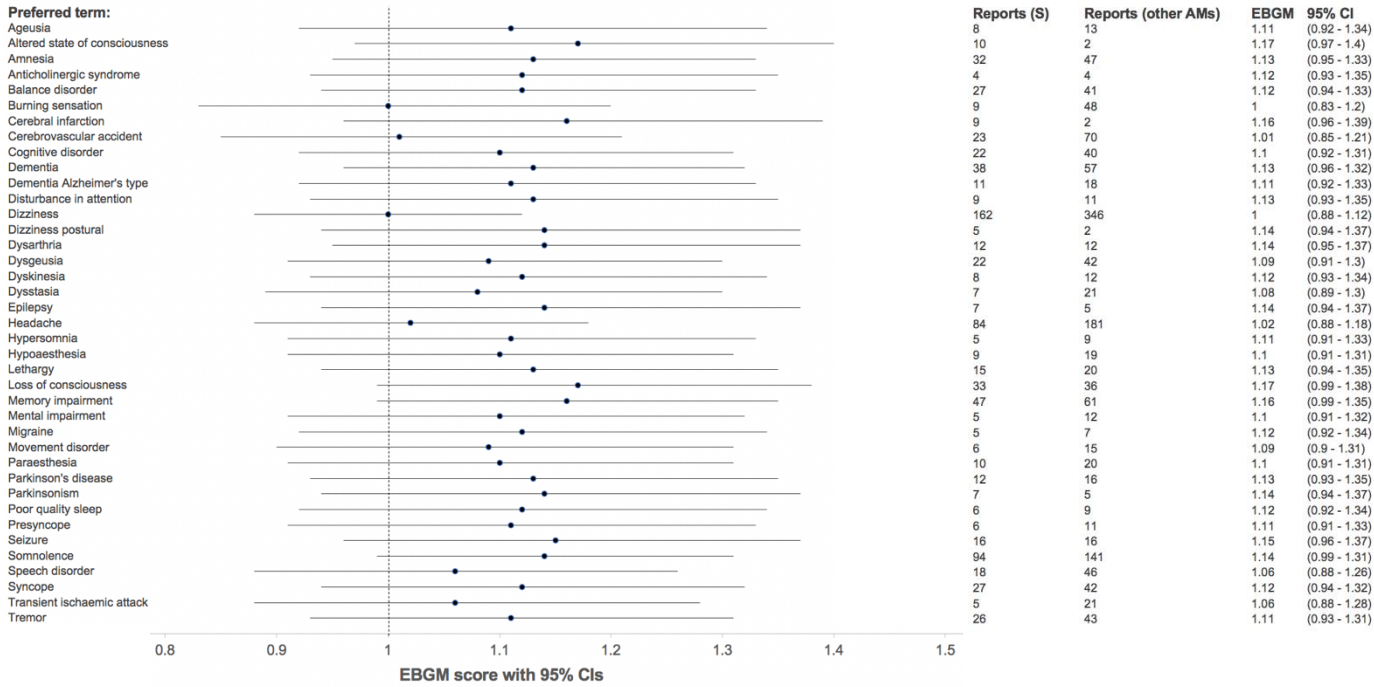


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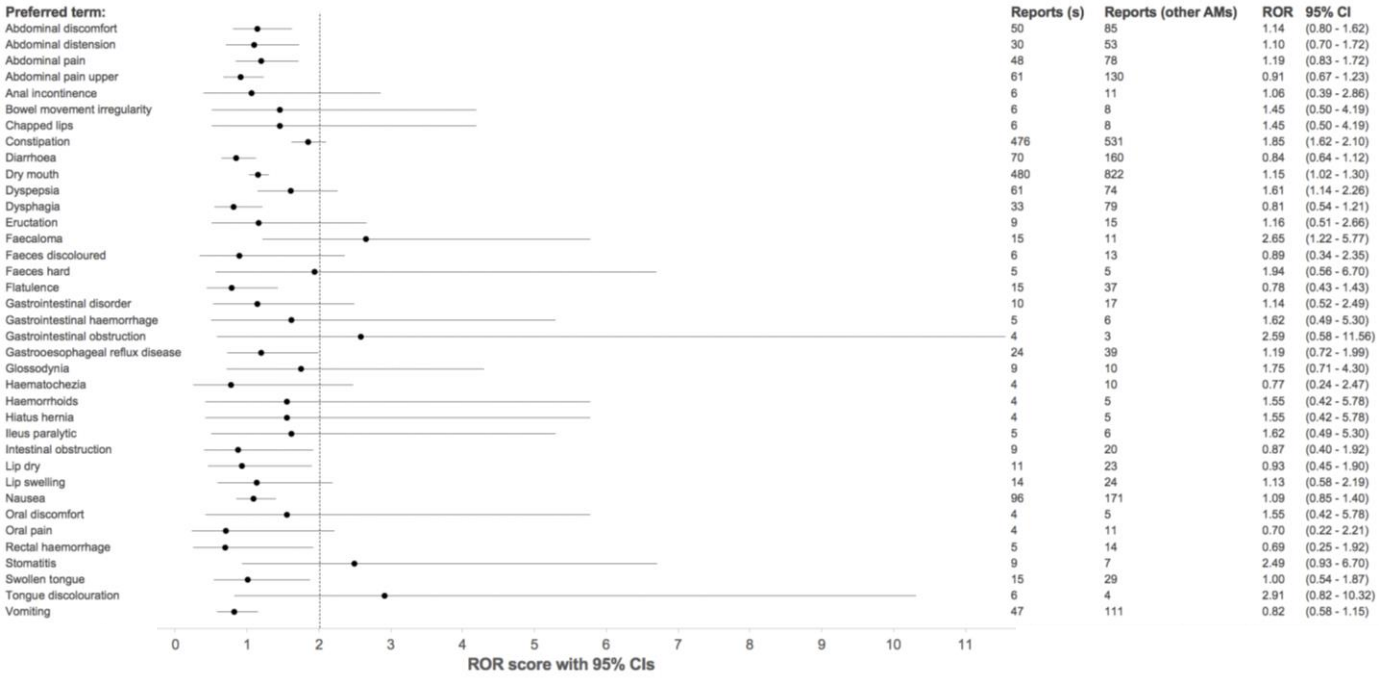
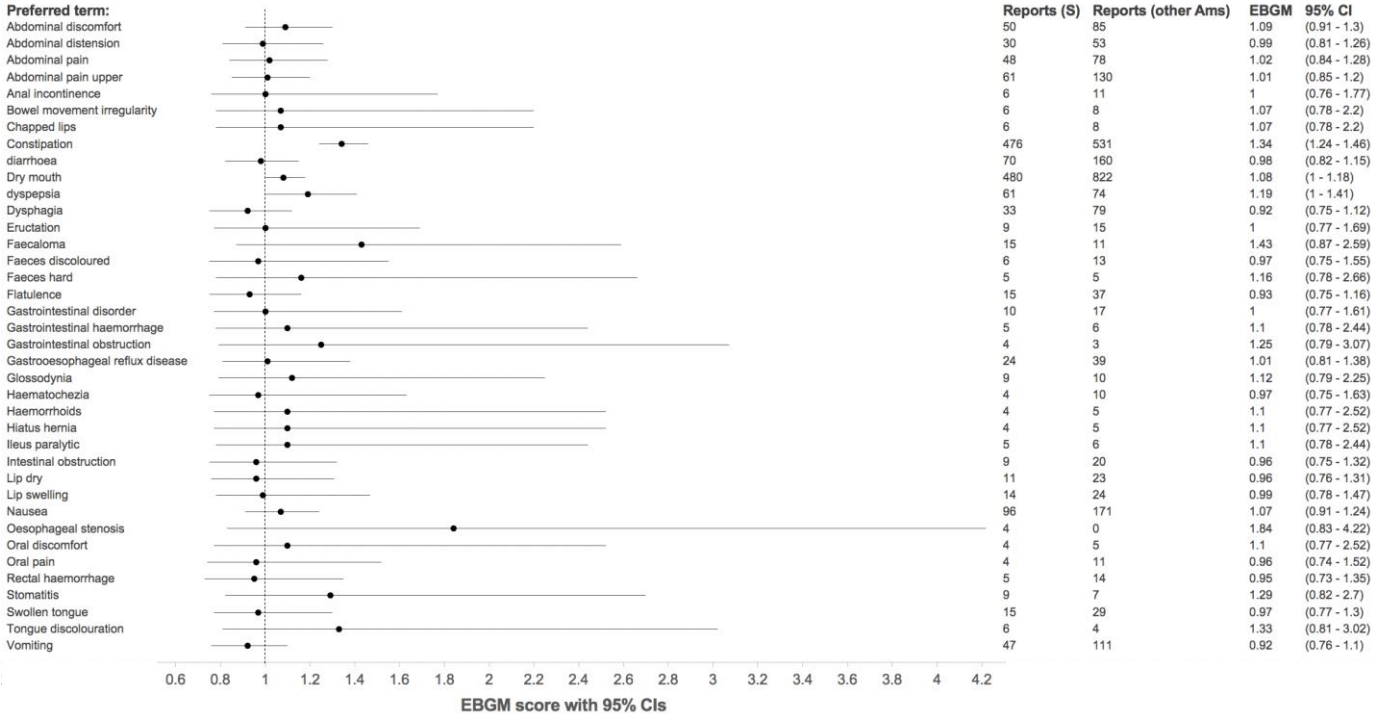
Figure 3: Forest plots of the ROR and EBGM scores with 95% CIs for solifenacin- associated gastrointestinal adverse events (classed as Medical Dictionary of Regulatory Activities preferred terms). ADE, adverse drug event; AMs; antimuscarinics; CI, confidence interval; EBGM, Empirical Bayesian geometric mean; ROR, reporting odds ratio; S, solifenacin.

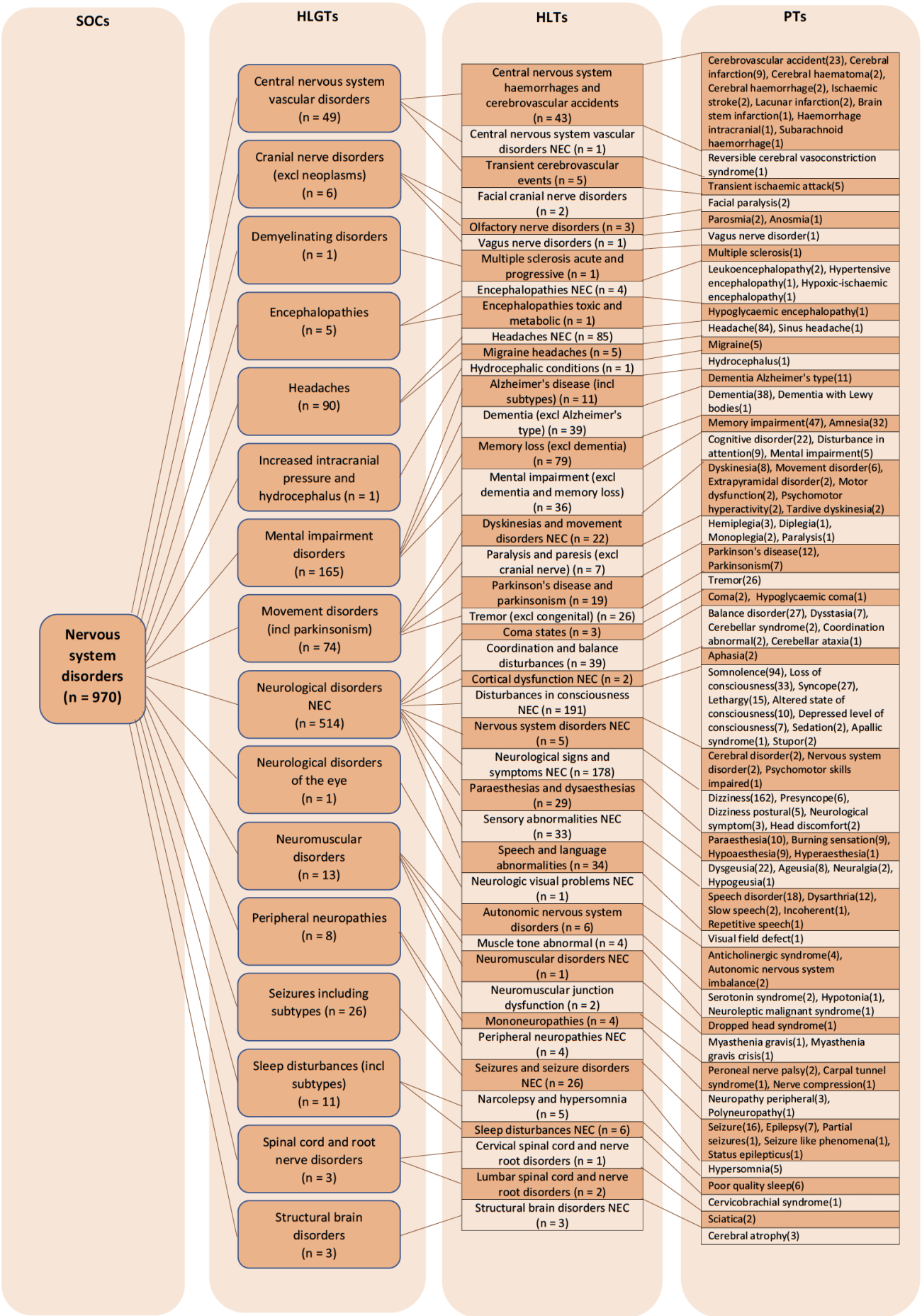
Reporting odds-ratio of gastrointestinal ADE:



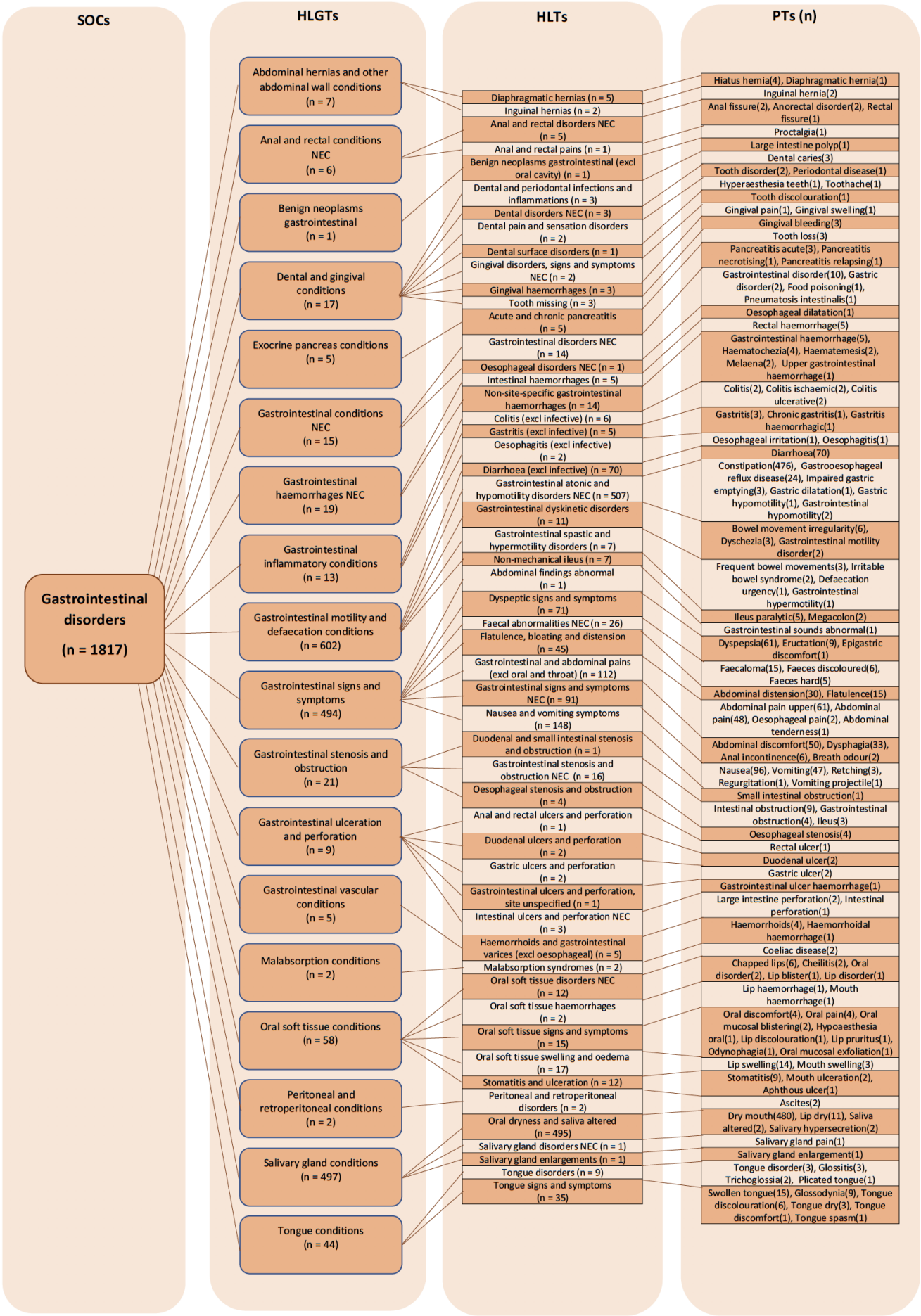
EBGM score of gastrointestinal ADE:



Click here to access/download;Table;supplementary figures and tables.docx



Supplementary Figure 1: Mapping of solifenacin-associated nervous system adverse drug events at different MedDRA levels. HLGT, high-level group term; HLT, high-level term; n, number of reports; PT, preferred term; SOC, system organ class.



Supplementary Figure 2: Mapping of solifenacin-associated gastrointestinal adverse drug events at different MedDRA levels. HLGT, high-level group term; HLT, high-level term; n, number of reports; PT, preferred term; SOC, system organ class.

Supplementary Table 1: Number and percentage of reports submitted in this study according to the location of the report.

Location	Number of reports	Percentage (%)
Armnia	1	0.03
Australia	7	0.19
Austria	2	0.05
Belgium	6	0.16
Brazil	12	0.32
Bulgaria	2	0.05
Canada	20	0.54
China	7	0.19
Country not specified	71	1.91
Croatia	2	0.05
Czechia	3	0.08
Denmark	3	0.08
Egypt	1	0.03
Finland	2	0.05
France	119	3.20
Germany	28	0.75
Greece	3	0.08
Hong kong	1	0.03
Hungary	2	0.05
Indonesia	2	0.05
Iran	3	0.08
Ireland	6	0.16
Israel	2	0.05
Italy	3	0.08
Japan	416	11.18
Netherlands	27	0.73
New Caledonia	1	0.03
Norway	2	0.05
Philippines	1	0.03
Poland	18	0.48
Portugal	1	0.03
Romania	2	0.05
Russia	3	0.08
Russian Federation	1	0.03
Singapore	1	0.03
South Africa	10	0.27
South Korea	5	0.13
Spain	24	0.64
Sweden	16	0.43
Switzerland	6	0.16
Taiwan	2	0.05
Turkey	2	0.05
United Kingdom	201	5.40
United States	2675	71.87

Supplementary Table 2: PRR and IC values with 95% CIs for solifenacin- associated gastrointestinal adverse events (classed as Medical Dictionary of Regulatory Activities preferred terms). A: Unique report number of the ADE for solifenacin. B: All remaining unique ADE reports for solifenacin. C: Unique report number of the ADE for all other bladder antimuscarinics. D: Number of unique remaining ADE reports for all bladder antimuscarinics (not including ADE of interest or solifenacin reports). ADE, adverse drug event; CI, confidence interval; IC, information component; INF, information not found; PRR, proportional reporting ratio.

Gastrointestinal ADE	IC	IC 95% CI (Lower)	IC 95% CI (Upper)	PRR	PRR 95% CI (Lower)	PRR 95% CI (Upper)	A	B	C	D
Abdominal discomfort	0.12	-0.19	0.44	1.14	0.81	1.61	50	3672	85	7127
Abdominal distension	0.09	-0.32	0.50	1.10	0.70	1.71	30	3692	53	7159
Abdominal pain	0.16	-0.16	0.48	1.19	0.83	1.70	48	3674	78	7134
Abdominal pain upper	-0.09	-0.39	0.20	0.91	0.67	1.23	61	3661	130	7082
Anal incontinence	0.05	-0.88	0.98	1.06	0.39	2.86	6	3716	11	7201
Bowel movement irregularity	0.33	-0.54	1.20	1.45	0.50	4.19	6	3716	8	7204
Chapped lips	0.33	-0.54	1.20	1.45	0.50	4.19	6	3716	8	7204
Constipation	0.47	0.38	0.56	1.74	1.54	1.95	476	3246	531	6681
diarrhoea	-0.16	-0.44	0.12	0.85	0.64	1.12	70	3652	160	7052
Dry mouth	0.12	0.02	0.21	1.13	1.02	1.26	480	3242	822	6390
dyspepsia	0.41	0.14	0.67	1.60	1.14	2.24	61	3661	74	7138
Dysphagia	-0.21	-0.62	0.20	0.81	0.54	1.21	33	3689	79	7133
Eructation	0.14	-0.60	0.88	1.16	0.51	2.65	9	3713	15	7197
Faecaloma	0.76	0.29	1.24	2.64	1.21	5.75	15	3707	11	7201
Faeces discoloured	-0.11	-1.06	0.85	0.89	0.34	2.35	6	3716	13	7199
Faeces hard	0.55	-0.34	1.45	1.94	0.56	6.69	5	3717	5	7207
Flatulence	-0.24	-0.85	0.38	0.79	0.43	1.43	15	3707	37	7175
Gastrointestinal disorder	0.12	-0.59	0.83	1.14	0.52	2.49	10	3712	17	7195
Gastrointestinal haemorrhage	0.42	-0.52	1.35	1.61	0.49	5.29	5	3717	6	7206
Gastrointestinal obstruction	0.75	-0.18	1.67	2.58	0.58	11.54	4	3718	3	7209
Gastrooesophageal reflux disease	0.16	-0.29	0.62	1.19	0.72	1.98	24	3698	39	7173
Glossodynia	0.48	-0.21	1.16	1.74	0.71	4.29	9	3713	10	7202
Haematochezia	-0.25	-1.45	0.94	0.78	0.24	2.47	4	3718	10	7202
Haemorrhoids	0.38	-0.67	1.44	1.55	0.42	5.77	4	3718	5	7207
Hiatus hernia	0.38	-0.67	1.44	1.55	0.42	5.77	4	3718	5	7207
Ileus paralytic	0.42	-0.52	1.35	1.61	0.49	5.29	5	3717	6	7206
Intestinal obstruction	-0.13	-0.92	0.65	0.87	0.40	1.91	9	3713	20	7192
Lip dry	-0.07	-0.77	0.63	0.93	0.45	1.90	11	3711	23	7189
Lip swelling	0.11	-0.49	0.71	1.13	0.59	2.18	14	3708	24	7188
Nausea	0.08	-0.15	0.31	1.09	0.85	1.39	96	3626	171	7041
Oesophageal stenosis	1.55	1.52	1.59	Inf	Inf	Inf	4	3718	0	7212
Oral discomfort	0.38	-0.67	1.44	1.55	0.42	5.77	4	3718	5	7207
Oral pain	-0.35	-1.56	0.86	0.70	0.22	2.21	4	3718	11	7201
Rectal haemorrhage	-0.37	-1.46	0.71	0.69	0.25	1.92	5	3717	14	7198
Stomatitis	0.72	0.10	1.35	2.49	0.93	6.68	9	3713	7	7205
Swollen tongue	0.00	-0.59	0.59	1.00	0.54	1.87	15	3707	29	7183
Tongue discolouration	0.82	0.09	1.55	2.91	0.82	10.29	6	3716	4	7208
Vomiting	-0.19	-0.54	0.15	0.82	0.58	1.15	47	3675	111	7101

Supplementary Table 3: PRR and IC values with 95% CIs for solifenacin- associated nervous system adverse events (classed as Medical Dictionary of Regulatory Activities preferred terms). A: Unique report number of the ADE for solifenacin. B: All remaining unique ADE reports for solifenacin. C: Unique report number of the ADE for all other bladder antimuscarinics. D: Number of unique remaining ADE reports for all bladder antimuscarinics (not including ADE of interest or solifenacin reports). ADE, adverse drug event; CI, confidence interval; IC, information component; PRR, proportional reporting ratio.

Nervous system ADE	IC	IC 95% CI (Lower)	IC 95% CI (Upper)	PRR	PRR 95% CI (Lower)	PRR 95% CI (Upper)	A	B	C	D
Ageusia	0.16	-0.62	0.95	1.19	0.49	2.87	8	3714	13	7199
Altered state of consciousness	1.29	0.93	1.66	9.69	2.12	44.20	10	3712	2	7210
Amnesia	0.25	-0.13	0.63	1.32	0.84	2.06	32	3690	47	7165
Anticholinergic syndrome	0.55	-0.44	1.55	1.94	0.48	7.74	4	3718	4	7208
Balance disorder	0.22	-0.20	0.64	1.28	0.79	2.07	27	3695	41	7171
Burning sensation	-1.11	-1.97	-0.24	0.36	0.18	0.74	9	3713	48	7164
Cerebral infarction	1.27	0.86	1.67	8.72	1.88	40.34	9	3713	2	7210
Cerebrovascular accident	-0.46	-0.97	0.05	0.64	0.40	1.02	23	3699	70	7142
Cognitive disorder	0.06	-0.42	0.54	1.07	0.63	1.79	22	3700	40	7172
Dementia	0.23	-0.12	0.59	1.29	0.86	1.94	38	3684	57	7155
Dementia Alzheimer's type	0.16	-0.51	0.83	1.18	0.56	2.50	11	3711	18	7194
Disturbance in attention	0.40	-0.30	1.10	1.59	0.66	3.82	9	3713	11	7201
Dizziness	-0.09	-0.27	0.09	0.91	0.76	1.09	162	3560	346	6866
Dizziness postural	1.07	0.39	1.75	4.84	0.94	24.96	5	3717	2	7210
Dysarthria	0.55	-0.02	1.13	1.94	0.87	4.31	12	3710	12	7200
Dysgeusia	0.01	-0.47	0.50	1.01	0.61	1.70	22	3700	42	7170
Dyskinesia	0.23	-0.54	1.01	1.29	0.53	3.16	8	3714	12	7200
Dysstasia	-0.45	-1.37	0.48	0.65	0.27	1.52	7	3715	21	7191
Epilepsy	0.78	0.09	1.47	2.71	0.86	8.54	7	3715	5	7207
Headache	-0.10	-0.35	0.15	0.90	0.70	1.16	84	3638	181	7031
Hypersomnia	0.07	-0.94	1.08	1.08	0.36	3.21	5	3717	9	7203
Hypoaesthesia	-0.08	-0.86	0.69	0.92	0.42	2.03	9	3713	19	7193
Lethargy	0.33	-0.22	0.88	1.45	0.74	2.84	15	3707	20	7192
Loss of consciousness	0.49	0.14	0.84	1.78	1.11	2.84	33	3689	36	7176
Memory impairment	0.35	0.05	0.66	1.49	1.02	2.18	47	3675	61	7151
Mental impairment	-0.21	-1.27	0.85	0.81	0.28	2.29	5	3717	12	7200
Migraine	0.29	-0.67	1.26	1.38	0.44	4.36	5	3717	7	7205
Movement disorder	-0.25	-1.23	0.72	0.78	0.30	2.00	6	3716	15	7197
Paraesthesia	-0.03	-0.76	0.70	0.97	0.45	2.07	10	3712	20	7192
Parkinson's disease	0.33	-0.28	0.95	1.45	0.69	3.07	12	3710	16	7196
Parkinsonism	0.78	0.09	1.47	2.71	0.86	8.54	7	3715	5	7207
Poor quality sleep	0.23	-0.66	1.13	1.29	0.46	3.63	6	3716	9	7203
Presyncope	0.05	-0.88	0.98	1.06	0.39	2.86	6	3716	11	7201
Seizure	0.55	0.06	1.05	1.94	0.97	3.87	16	3706	16	7196
Somnolence	0.23	0.01	0.46	1.29	1.00	1.67	94	3628	141	7071
Speech disorder	-0.28	-0.84	0.29	0.76	0.44	1.31	18	3704	46	7166
Syncope	0.20	-0.22	0.62	1.25	0.77	2.02	27	3695	42	7170
Transient ischaemic attack	-0.82	-1.96	0.31	0.46	0.17	1.22	5	3717	21	7191
Tremor	0.15	-0.29	0.58	1.17	0.72	1.90	26	3696	43	7169