Minerva Urology and Nephrology (formerly: Minerva Urologica e Nefrologica)
EDIZIONI MINERVA MEDICA

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Minerva Urology and Nephrology 2022 Jun 16
DOI: 10.23736/S2724-6051.22.04849-2

Article type: Original article

Article first published online: June 16, 2022
Manuscript accepted: May 19, 2022
Manuscript revised: April 15, 2022
Manuscript received: January 4, 2022

Adverse events related to antimuscarinics and beta-3-agonist: “real-life” data from the Eudra-Vigilance database.

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Keywords: EudraVigilance, Adverse Events, Antimuscarinics, Mirabegron, Beta-3-Agonist

ABSTRACT

BACKGROUND: Antimuscarinic (AM) and beta-3-agonist (B3A) treatment are the standard first line pharmacological treatment used to manage overactive bladder (OAB) patients. Aim of our study was to analyze real-life data of adverse events related to AMs and B3A reported on Eudra-Vigilance (EV) database.

METHODS: EV database is the system for managing and analyzing information on suspected adverse reactions to medicines which have been authorized or being studied in clinical trials in the European Economic Area (EEA). We recorded the number of AEs for antimuscarinic and beta-3-agonist per category and severity until January 2021.

RESULTS: Overall, 2313 AEs were reported for Oxybutinin, 5129 for Solifenacin, 2483 for Tolterodine, 3523 for Fesoterodine, 787 for Trospium, 621 for Propiverine and 7213 for Mirabegron. Urinary retention was higher for Fesoterodine (43%) and Tolterodine (23%) when compared to Solifenacin (10%), Mirabegron (11%) and Oxybutinin (4%). Cognitive disorder was uncommon for all the analyzed drugs analyzed. Regarding anticolinergic AEs: vision blurred, dry mouth and constipation were higher for AMs when compared to Mirabegron. Their prevalence was higher in female patients. Mirabegron presented a higher risk of hypertension (7%) when compared to Oxybutinin (2%, p<0,01), Solifenacin (2%, p<0,01), Tolterodine (2%, p<0,01) and Fesoterodine (1%, p<0,01); the rate of hypertension was higher in females (63%) than males (29%) (p<0,01). The risk of acute urinary retention was also significantly higher (15% vs 10%, p <0,01)) in older patients (>85 years)

CONCLUSIONS: Real life data is consistent with registry studies regarding the rate of AEs related to antimuscarinic and beta-3-agonist. However some differences were observed. Female patients present higher rates of AEs when compared to male patients. The risk of acute urinary retention was particularly evident in the octogenarians.

INTRODUCTION

AMs and B3A are the standard first line pharmacotherapy for OAB[1]. The International Continence Society defines OAB as a symptom complex characterized by urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with (OAB wet) or without (OAB dry) urinary incontinence, in the absence of other detectable disease[2]. International guidelines recommend AMs and B3A as the first line drugs options[3]. AMs are a group of anticholinergic drugs that competitively inhibit postganglionic muscarinic receptors. The Food and Drug Administration (FDA)-approved oxybutynin immediate release (IR) in 1975. Since then, five new AMs drugs have been approved[4]. In 2012, the FDA approved the first non-antimuscarinic oral medication, mirabegron, to treat patients with OAB symptoms[4]. Both AMs and B3A have been tested in several randomized clinical trials showing their efficacy to manage OAB but with a different safety profile[4].

Since 2012, researchers have been allowed to access adverse events (AEs) data in the European Union (EU) EudraVigilance (EV) database. EV is a freely accessible European database managed by European Medicines Agency (EMA) that collects and processes suspected adverse drug reactions. Pharmaceutical companies that hold the marketing authorization of a medicine, as well as medicines regulatory authorities in the European Economic Area (EEA), are legally required to submit reports of suspected side effects to EV. This includes reports received from healthcare professionals and patients. This excludes nonserious side effects occurring outside the EEA. The database is updated on a weekly fashion. So far, the EV database allows to evaluate the evolution of AM and B3A AEs through different years. The analysis of EV safety data from spontaneous reporting systems has a proven value for the detection and analysis of AEs of different medicines following their introduction in clinical practice[5]. Clinical trials have demonstrated that AMs and B3As are effective treatments in OAB patients with an acceptable but different safety

profile[3-5]. Evaluation of the different safety profile of B3A and AMs is still an issue particularly for the possible impact in the real life practice on the rate of drug's adherence. Possible differences between AEs reported in RCTs versus real life has been also reported[6,7]. These differences between the results of clinical trials and outcomes in real-life clinical practice may be explained by the restrictive selection criteria of RCTs, such as good prognosis and minimal comorbidities, the strict and scheduled follow-up and the possibility to start new treatments without any costs for the patients. Data in octogenarians are also lacking in clinical trials and they are particularly important considering that older patients receive potentially more toxic drugs, since most of them will have preexisting comorbidities.

With this knowledge in mind, we analyzed AEs reported in the EV database and hypothesized that elderly patients would present higher rates of some AEs.

MATERIAL & METHODS

We retrospectively evaluated publicly, and freely available AEs reported for AMs and B3As until January 2021 in the EV database (www.adrreports.eu). Data were extracted by EV database to large Microsoft Excel files and prepared for further investigations. In order to include all data available, we analyzed the number of individual cases. The AEs reports were assigned to reaction group categories utilized in the EV database. We also analyzed data for gender (females/males). We analyzed Solifenacin, Tolterodine, Fesoterodine, Oxybutinin, Trospium and Propiverine as AMs and Mirabegron as B3A. As well, seriousness of AEs events was recorded. A side effect is classified as "serious" if it results (I) in death, (II) in life-threating, (III) requires hospitalization or prolongation of existing hospitalization, (IV) results in persistent or significant disability/incapacity (as per reporter's opinion), (V) is a congenital anomaly/birth defect or (VI) results in some other medically

important conditions. According to EV database, they were also divided in resolving, resolving with sequelae, resolved, not resolved and fatal.

Statistical Analysis

Data were extracted from the EV database and transferred to large Microsoft Excel files and prepared for further investigation. Number of AEs (percentages) were recorded for gender (males/females) and for age (≤65, 65-85, ≥85 years old). In the EV database patients are divided into the following age groups: ≥85 years old, between 65 and 85, and ≤65 years old. Further analysis of AEs was performed considering the different AEs groups by gender (males/females) and by age groups (≤65, 65-85, ≥85 years old). Pooled relative risk (PRR) were calculated to compare the three age classes: ≤65, 65-85, ≥85 years old. Following the methodology presented by Ruiz et al. we performed to estimate the PRR[8]. A p value of 0.05 was considered as threshold of significance.

RESULTS

Overall, the number of AEs reported for Oxybutynin was 2313, for Solifenacin 5129, for Tolterodine 2483, for Fesoterodine 3523, for Trospium 787, for Propiverine 621 and for Mirabegron 7213. Dry mouth was the most common AE for Oxybutinin with 175/2313 events (7%). Solifenacin most common AEs were dry mouth and urinary retention (respectively 500/5129 (9%) and 520/5129 events (10%)). Tolterodine most common AE was urinary retention 580/2843 events (23%). Fesoterodine most common AE was urinary retention 1525/3523 events (43%). Mirabegron most common AEs were hypertension with 529/7213 events (7%) and urinary retention with 805/7213 events(10%). Urinary retention was higher for Tolterodine (23%) and Fesoterodine (43%) when compared to other AMs and B3A (PRR 2,56-16,30 (95%CI 2,21-22,17, $p < 0,01$) (Table 3). Cognitive disorder was uncommon for all the drugs analyzed (Table 1). Regarding anticolinergic AEs: frequency of vision blurred, dry mouth and constipation were higher for AMs (respectively 51/2313 (2%), 175/2313 (1%) and 84/2313 (3%) for oxybutynin and 222/5129(4%), 500/5129 (9%),

297/5129 (5%) for solifenacin) when compared to Mirabegron (respectively 68/7213 (1%), 162/7213 (2%) and 243/7213 (3%)). Dry mouth prevalence was higher in female patients (respectively 110/175 (63%) for oxybutynin and 345/500 (69%) for solifenacin). Mirabegron presented a higher risk of hypertension (529/7213 events, 7%) when compared to Oxybutinin (41/2313 events, 2%), Tolterodine (42/2483 events, 2%), Fesoterodine (35/3523 events, 1%) and Solifenacin (51/5129 events, 2%) (PRR 4,34-7,38 (95%CI 3,18-10,37), $p < 0,01$) (Table 3) and it was more prevalent in female gender (333/529 events, 63%). When looking at older patients (>85 yrs old), urinary retention presents a high prevalence for all analyzed drugs (13/112 (12%) for Oxybutinin, 76/520 (15%) for solifenacin, 67/580 (12%) for Tolterodine, 223/1525 (15%) for Fesoterodine and 111/805 (15%) for mirabegron.

DISCUSSION

Our study has systematically analyzed the AEs until January 2021 reported for AMs and B3A using the EV database. AMs and B3A are commonly used in OAB in urological clinical practice[9-13]. Even if AMs are the mainstay in OAB oral medical treatment, they are associated with a high prevalence of bothersome AEs such as dry mouth and constipation[9] which can be a concern for older patients with OAB. Mirabegron is an oral beta-3-adrenoceptor that offers an option to AMs for patients with OAB as shown by significant improvements in key efficacy measures (eg. Incontinence and micturition frequency) for mirabegron versus placebo in phase III trials[10-12].

Overall, rates of AEs reported for mirabegron in phase III trials appeared similar to those for placebo whilst the incidence of dry mouth appeared to be lower than for AMs[13]. Mirabegron 50 mg was significantly better tolerated than most agents with lower rates of dry mouth, constipation and urinary retention[9,13,14]. Recent results from 44 randomized controlled trials (RCTs) involving 27309 patients showed that mirabegron 50 mg was as efficacious as AMs and provides a more favorable tolerability profile, including significantly

lower rates of dry mouth compared with AMs (OR 2,99 [95% IC: 0,68-13.75])[15]. Our analysis of EV database confirmed previous studies [13,14] with statistical significative differences between mirabegron and oxybutynin, solifenacin, fesoterodine and tolterodine. (Table 1). Dry mouth for mirabegron as AE in females had significative differences confronting it with all AMs drugs (oxybutynin, tolterodine, fesoterodine and solifenacin) (table 1), confirming literature data[9,13]. No significative differences were reported for dry mouth AEs in patients older >85 for all drugs (Table 3).

No significative differences were reported for 26 studies on blurred vision (n = 25796 patients) (OR 0,83 [95% IC 0,43 - 1,63)[9] and for 18 studies on hypertension (n = 20712) (OR = 0,97, 95%IC 0,76-1,25) between mirabegron and AMs. As expected, EV analysis data showed no differences on blurred vision comparing respectively mirabegron (1%) with AMs (less than 4%) while mirabegron presented a higher risk of hypertension (7%), particularly in females (63%) when compared to AMs (less than 2%) (PRR 4,34-7,38 (95%CI 3,18-10,37), p<0,01) (Table 3).

Risk of constipation for mirabegron was significantly lower in a metanalysis of 54 studies (n = 40854 patients) with nine types of AMs including solifenacin[9]. Our analysis of EV database showed no significative differences between constipation for solifenacin or mirabegron use (247 (5%) vs 243 (3%), p = 0,28), neither in males (79 (23%) vs 99 (41%), PRR 1,12 (0,84-1,50), p=0,44) neither in patients older than 85 years (43 (15%) vs 22 (9%), p= 0,07) confirming that study. In females group a significative statistical difference in constipation was reported between oxybutynin and solifenacin (0,59 (0,44-0,79), p<0,01). So in females, this least drug could be preferred on solifenacin in treatment choices.

In the elderly patients (>85 yrs), urinary retention presents a high incidence for all analyzed drugs (12-15%) while in literature Mirabegron has a significantly lower urinary retention rate compared with all AMs, including oxybutynin (metanalysis of 17 studies,

n=22137 patients)[9]. In addition, Wagg et al[16] evaluated the efficacy and tolerability of mirabegron in subgroups of patients aged >65 yr and >75 yr: over a 1-yr period, the incidence of the most common AEs, including urinary retention, was similar between both the doses of mirabegron as placebo and there appeared to be no loss of efficacy with age.

Antimuscarinic drug treatment is known to have side effects and, consequently, poor adherence in therapeutic regimens. In a systematic review of 2014, the long-term (greater than 6 months) median persistence rates of adherence to antimuscarinic drugs in daily clinical practice were 12.0% to 39.4% (with an outlier of 75.5%) at 12 months, 8.0% to 15.0% at 18 months and 6.0% to 12.0% at 24 months[17].

Analysis of seriousness of AEs confirm a higher rate of serious AEs for Oxybutinin (4374 (80%) on a total of 5441) (Table 6), for Tolterodine 5038 (89%) on a total of 5605 (Table 8) and for Fesoterodine 5959 (88%) on a total of 6731 (Table 9). These results confirmed literature data[17-20]. Lower percentages of serious AEs were reported for Solifenacin (2155 (20%) on a total of 10429) (Table 7) and for Mirabegron (2452 (17%) on a total of 14193) (Table 10). These least results on B3A confirm a 2020 metanalysis of Lozano-Ortega[21] which indicates that the safety and efficacy profile of mirabegron remains favorable compared with antimuscarinics among older adults. This includes safety outcomes typically associated with anticholinergic burden, which were less frequently observed in patients treated with mirabegron.

EV database does not provide data on the total prescriptions of each individual drug, duration of use, possible interruptions and patients' characteristics. Therefore comparison between AEs of each drug can be burdened by numerous bias. However EV database is an useful tool: it is a system for monitoring the safety of medicines. Its components facilitate electronic reporting of suspected adverse reactions related to medicines and the effective analysis of data. This enables the early detection of potential safety issues. The system contains different components that perform specific tasks in the process of

electronic reporting of suspected adverse drug reactions. The database contains more than 5 million individual cases, making it one of the world's largest pharmacovigilance databases. So notwithstanding its limitations, it is one of largest European database on safety profile of drugs and its analysis should be considered useful in understanding and managing AEs of any kind of drug. Furthermore our results confirm some data on OAB medication and particularly the age and gender effect on the rate of AEs.

We must acknowledge some limitation to our study. Our study presents the typical misleading interpretation of data common to all the pharmacovigilance databases. In fact, the frequency of AEs for a specific drug may be influenced by certain factors including the extent of use of the drug, publicity and nature of AEs. We have no information on the number of patients under treatment: data collection and reports in EV databases are also influenced by national policies and reports from different caregivers (physicians vs nurse vs biologists) may be also relevant. It is also assumable that caregivers were pushed to report only serious AEs as observed in our study. The lack of clinical data including comorbidities, cancer status, performance status and indication for treatment are also common limitations of the EV database[6,7].

Notwithstanding these limitations, our study firstly showed the rate of AES observed in AMs and B3A, confirming a different safety profile particularly in elderly patients or in females and the importance of a tailored medicine based on patients and drugs' characteristics to correctly manage OAB patients.

CONCLUSIONS

Analysis of the EV database is an opportunity to evaluate real life AEs in patients under treatment with AMs or B3A. Our analysis of EV database showed differences in AEs for gender and age. Female patients present higher rates of AEs when compared to male patients. Older patients present a significant risk of AUR for AMs which was not relevant for B3A. So Mirabegron could be considered best option in this kind of patients. Further

studies should evaluate the possible impact of AEs on OAB drug compliance and prescriptions.

Conflicts of interest.—

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Acknowledgments

Authors contribution:

Cosimo De Nunzio - substantial contributions to the conception and design of the work; drafting the work, final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Antonio Nacchia – substantial contributions to the the acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Carmen Gravina – substantial contributions to the the acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Beatrice Turchi – substantial contributions to the the acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Giacomo Gallo – substantial contributions to the interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Alberto Trucchi – substantial contributions to the interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ferdinando Di Giacomo – substantial contributions to the interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Giuseppe Disabato – substantial contributions to the interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Antonio Franco – substantial contributions to the interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Lorenzo Rovesti – substantial contributions to the interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Riccardo Lombardo – substantial contributions to the conception and design of the work; drafting the work, final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Antonio Cicione – substantial contributions to the conception and design of the work; drafting the work, final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Andrea Tubaro - substantial contributions to the conception and design of the work; drafting the work, final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Reaction Groups	Oxibutinin	Solifenacin	Tolterodine	Fesoterodine	Trospium	Propiverine	Mirabegron
Total AEs	**2313**	**5129**	**2483**	**3523**	**787**	**621**	**7213**
HYPERTENSION	41/2313 (2%)	51/5129 (2%)	42/2483 (2%)	35/3523 (1%)	7/787 (1%)	3/621 (<1%)	529/7213 (7%)
Male	6/41 (15%)	14/51 (27%)	9/42 (21%)	9/35 (26%)	2/7 (29%)	2/3 (67%)	155/529 (29%)
Female	35/41 (85%)	35/51 (67%)	32/42 (76%)	25/35 (74%)	5/7 (71%)	1/3 (33%)	333/529 (63%)
TACHYCARDIA	26/2313 (1%)	33/5129 (1%)	28/2483 (1%)	22/3523 (1%)	21/787 (2%)	11/621 (2%)	54/7213 (1%)
Male	16/26 (62%)	10/33 (30%)	8/28 (28%)	12/22 (55%)	10/21 (52%)	5/11 (45%)	22/54 (41%)
Female	10/26 (38%)	22/33 (66%)	20/28 (72%)	10/22 (45%)	8/21 (35%)	5/11 (45%)	25/54 (46%)
VISION BLURRED	51/2313 (2%)	222/5129 (4%)	52/2483 (1%)	75/3523 (2%)	20/787 (2%)	19/621 (3%)	68/7213 (1%)
Male	15/51 (29%)	56/222 (25%)	16/52 (30%)	23/75 (31%)	6/20 (27%)	5/19 (25%)	20/68 (29%)
Female	36/51 (71%)	156/222 (70%)	36/52 (70%)	51/75 (68%)	14/20 (73%)	12/19 (60%)	46/68 (68%)
CONSTIPATION	84/2313 (3%)	297/5129 (5%)	84/2483 (3%)	123/3523 (3%)	60/787 (7%)	24/621 (4%)	243/7213 (3%)
Male	26/84 (31%)	79/297 (27%)	32/84 (38%)	43/123 (35%)	26/60 (45%)	9/24 (29%)	99/243 (41%)
Female	58/84 (69%)	214/297 (72%)	50/84 (62%)	76/123 (62%)	33/60 (53%)	14/24 (60%)	142/243 (58%)
DRY MOUTH	175/2313 (7%)	500/5129 (9%)	152/2483 (6%)	236/3523 (7%)	81/787 (10%)	80/621 (10%)	162/7213 (2%)
Male	63/175 (36%)	145/500 (29%)	43/152 (28%)	78/236 (33%)	30/81 (35%)	29/80 (33%)	59/162 (36%)
Female	110/175 (63%)	345/500 (69%)	107/152 (72%)	150/236 (64%)	51/81 (65%)	50/80 (63%)	49/162 (30%)
COGNITIVE DISORDER	27/2313 (0,004%)	34/5129 (0,006%)	15/2483 (0,006%)	25/3523 (0,007%)	5/787 (0,006%)	5/621 (0,008%)	15/7213 (0,002%)
Male	4/27 (15%)	7/34 (21%)	7/15 (47%)	7/25 (40%)	2/5 (40%)	2/5 (40%)	7/15 (47%)
Female	15/27 (55%)	15/34 (44%)	6/15 (53%)	15/25 (60%)	3/5 (60%)	3/5 (60%)	7/15 (47%)
URINARY RETENTION	112/2313 (4%)	520/5129 (10%)	580/2483 (23%)	1525/3523 (43%)	58/787 (8%)	35/621 (5%)	805/7213 (10%)
Male	41/112 (37%)	246/520 (47%)	260/580 (45%)	1019/1525 (69%)	32/58 (55%)	23/35 (66%)	423/805 (52%)
Female	62/112 (55%)	248/520 (48%)	297/580 (51%)	424/1525 (28%)	24/58 (41%)	12/35 (34%)	362/805 (45%)

Table 1: AEs of different AMs and B3A according to gender

Table 2: AEs (%) for AMs and B3A according to age

Reaction Groups							
Total AEs	**2313**	**5129**	**2483**	**3523**	**787**	**621**	**7213**
HYPERTENSION	41/2313 (2%)	51/5129 (2%)	42/2483 (2%)	35/3523 (1%)	7/787 (1%)	3/621 (<1%)	529/7213 (7%)
<65	20/41 (49%)	24/51 (49%)	11/42 (26%)	3/35 (9%)	0/7 (0%)	1/3 (33%)	126/529 (26%)
65 - 85	20/41 (49%)	22/51 (41%)	24/42 (57%)	21/35 (60%)	4/7 (57%)	1/3 (33%)	366/529 (67%)
>85	1/41 (2%)	5/51 (10%)	3/42 (7%)	2/35 (6%)	3/7 (43%)	1/3 (33%)	37/529 (7%)
TACHYCARDIA	26/2313 (1%)	33/5129 (1%)	28/2483 (1%)	22/3523 (1%)	21/787 (2%)	11/621 (2%)	54/7213 (1%)
<65	20/26 (77%)	19/33 (58%)	9/28 (32%)	6/22 (27%)	9/21 (46%)	6/11 (55%)	11/54 (21%)
65-85	2/26 (8%)	11/33 (33%)	10/28 (36%)	10/22 (45%)	5/21 (25%)	2/11 (19%)	36/54 (66%)
>85	4/26 (15%)	3/33 (9%)	3/28 (11%)	1/22 (5%)	2/21 (10%)	0/11 (0%)	7/54 (13%)
VISION BLURRED	51/2313 (2%)	222/5129 (4%)	52/2483 (1%)	75/3523 (2%)	20/787 (2%)	19/621 (3%)	68/7213 (1%)
<65	12/51 (36%)	96/222 (47%)	13/52 (25%)	14/75 (19%)	9/20 (45%)	13/19 (65%)	28/68 (41%)
65-85	18/51 (55%)	104/222 (48%)	23/52 (44%)	40/75 (53%)	9/20 (45%)	3/19 (15%)	34/68 (50%)
>85	2/51 (4%)	12/222 (5%)	10/52 (19%)	8/75 (11%)	0/20 (0%)	0/19 (0%)	6/68 (9%)
CONSTIPATION	84/2313 (3%)	297/5129 (5%)	84/2483 (3%)	123/3523 (3%)	60/787 (7%)	24/621 (4%)	243/7213 (3%)
<65	40/84 (48%)	76/297 (24%)	12/84 (14%)	18/123 (15%)	11/60 (19%)	3/24 (14%)	88/243 (36%)
65-85	37/84 (44%)	178/297 (61%)	41/84 (49%)	69/123 (56%)	22/60 (38%)	12/24 (50%)	133/243 (55%)
>85	7/84 (8%)	43/297 (15%)	14/84 (17%)	15/123 (12%)	7/60 (12%)	7/24 (30%)	22/243 (9%)
DRY MOUTH	175/2313 (7%)	500/5129 (9%)	152/2483 (6%)	236/3523 (7%)	81/787 (10%)	81/621 (10%)	162/7213 (2%)
<65	89/175 (49%)	207/500 (43%)	34/152 (22%)	50/236 (21%)	19/81 (23%)	6/81 (8%)	57/162 (33%)
65-85	79/175 (47%)	265/500 (51%)	74/152 (49%)	121/236 (51%)	38/81 (45%)	42/81 (51%)	89/162 (57%)
>85	7/175 (4%)	28/500 (6%)	23/152 (15%)	26/236 (10%)	8/81 (10%)	16/81 (20%)	16/162 (10%)
COGNITIVE DISORDER	27/2313 (0,004%)	34/5129 (0,006%)	15/2483 (0,006%)	25/3523 (0,007%)	5/787 (0,006%)	5/621 (0,008%)	15/7213 (0,002%)
<65	**15/27 (43%)**	**16/34 (47%)**	**0/15 (0%)**	**5/25 (20%)**	**0/5 (0%)**	**0/5 (0%)**	**7/15 (51%)**
65-85	**10/27 (40%)**	**17/34 (50%)**	**4/15 (26%)**	**10/25 (40%)**	**3/5 (60%)**	**3/5 (60%)**	**6/15 (36%)**
>85	**2/27 (7%)**	**1/34 (3%)**	**3/15 (20%)**	**6/25 (24%)**	**2/5 (40%)**	**2/5 (40%)**	**2/15 (13%)**
URINARY RETENTION	**112/2313 (4%)**	**520/5129 (10%)**	**580/2483 (23%)**	**1525/3523 (43%)**	**58/787 (8%)**	**35/621 (5%)**	**805/7213 (10%)**
<65	**53/112 (49%)**	**214/520 (40%)**	**143/580 (25%)**	**109/1525 (7%)**	**7/58 (13%)**	**7/35 (21%)**	**88/805 (10%)**
65-85	**46/112 (47%)**	**230/520 (45%)**	**265/580 (47%)**	**686/1525 (45%)**	**32/58 (59%)**	**18/35 (54%)**	**606/805 (75%)**
Age >85	**13/112 (12%)**	**76/520 (15%)**	**67/580 (12%)**	**223/1525 (15%)**	**8/58 (15%)**	**6/35 (18%)**	**111/805 (15%)**

Table 3: Pooled Relative Risks for AMs and B3A for gender

Reaction Groups	Oxibutinin versus Solifenacin	Oxibutinin versus Mirabegron	Solifenacin versus Mirabegron	Tolterodine versus Oxibutinin	Fesoterodine versus Oxibutinin	Fesoterodine versus Solifenacin	Fesoterodine versus Tolterodine	Mirabegron vs Fesoterodine	Mirabegron vs Tolterodine
Total AEs									
HYPERTENSION	0,56 (0,37-0,85), P=0,01	4,13 (3,02 – 5,66), P<0,01	7,38 (5,54 -9,83), p<0,01	0,95 (0,42-1,46), p=0,83	0,56 (0,36-0,87), p=0,01	0,56 (0,36-0,88), p=0,01	0,58 (0,37-0,91), p=0,01	7,38 (5,26-10,37), p<0,01	4,34 (3,18-5,92), p<0,01
Male	0,95 (0,36-2,47), p= 0,98	0,12 (0,05-0,35), p<0,01	0,12 (0,07-0,21), p=<0,01	1,39 (0,49-3,90), p=0,53	0,98 (0,35-2,76), p=0,97	0,93 (0,41-2,16), p=0,88	0,70 (0,28-1,77), p=0,46	8,41 (4,30-16,45), p<0,01	5,92 (3,03-11,59), p<0,01
Female	2,12 (1,33-3,38), p<0,01	0,31 (0,22-0,44), p<0,01	0,15 (0,10-0,21), p<0,01	0,88 (0,55-1,42), p=0,63	0,47 (0,28-0,78), p<0,01	1,04 (0,62-1,73), p=0,89	0,55 (0,33-0,93), p=0,02	6,20 (4,14-9,29), p<0,01	3,62 (2,26—5,20), p<0,01
TACHYCARDIA	0,57 (0,34-0,95) p=0,03	0,67 (0,41-1,06) p=0,09	1,16 (0,76-1,79) p=0,49	1,00 (0,59-1,71) p=0,99	0,55 (0,31-0,98) p=0,04	0,43 (0,25-0,74) p<0,01	0,55 (0,32-0,97) p=0,04	1,20 (0,73-1,97) p=0,47	0,66 (0,42-1,05) p=0,08
Male	3,54 (1,61-7,86), p<0,01	2,30 (1,21-4,37), p=0,01	0,65 (0,31-1,37), p=0,25	0,46 (0,20-1,09), p=0,08	0,90 (0,47-1,72), p=0,75	3,20 (1,50-6,76), p<0,01	1,94 (0,86-4,35), p=0,11	0,49 (0,27-0,88), p=0,02	0,95 (0,42-2,12), p=0,89
Female	1,01 (0,48-2,13), p=0,89	1,25 (0,60-2,59), p=0,55	1,24 (0,70-2,19), p=0,47	1,86 (0,87-3,97), p=0,11	0,66 (0,27-1,57), p=0,34	0,66 (0,31-1,40), p=0,28	2,84 (1,33-6,05), p<0,01	1,20 (0,57-2,52), p=0,61	0,42 (0,23-0,76), p<0,01
VISION BLURRED	1,96 (1,45-2,65) p<0,01	0,43 (0,29-0,61) p<0,01	0,21 (0,17-0,29) p<0,01	0,95 (0,65-1,39) p=0,79	0,96 (0,68-1,37) p=0,85	0,49 (0,37-0,67) p<0,01	1,01 (0,72-1,45) p=0,92	0,44 (0,32-0,61) p<0,01	0,45 (0,31-0,64) p<0,01
Male	0,59 (0,33-1,05), p=0,07	2,34 (1,20-4,56), p=0,01	3,93 (2,36-6,54), p<0,01	0,99 (0,49-2,00), p=0,98	1,01 (0,53-1,92), p=0,98	0,60 (0,37-0,97), p=0,04	1,01 (0,54-1,91), p=0,97	0,42 (0,23-0,77), p<0,01	0,43 (0,22-0,83), p=0,01
Female	0,51 (0,35-0,73), p<0,01	5,60 (3,25-9,66), p<0,01	4,75 (3,74-6,60), p<0,01	0,94 (0,54-1,48), p=0,77	0,93 (0,61-1,42), p=0,73	0,48 (0,35-0,65), p<0,01	0,99 (0,65-1,52), p=0,99	0,44 (0,30-0,65), p<0,01	0,4 (0,28-0,68), p<0,01
CONSTIPATION	1,56 (1,23-1,98) p<0,01	0,94 (0,73-1,20) p=0,60	0,60 (0,50-0,70) p<0,01	0,93 (0,69-1,25) p=0,64	0,96 (0,53-1,26) p=0,77	0,60 (0,49-0,74) p<0,01	1,23 (0,79-1,36) p=0,82	0,96 (0,78-1,19) p=0,74	0,99 (0,78-1,27) p=0,98
Male	0,73 (0,47-1,13), p=0,16	0,82 (0,53-1,26), p=0,36	1,12 (0,84-1,50), p=0,44	1,15 (0,69-1,92), p=0,60	1,08 (0,67-1,76), p=0,73	0,79 (0,55-1,15), p=0,22	0,61 (0,40-0,91), p=0,02	1,12 (0,79-1,60), p=0,53	1,07 (0,71-1,58), p=0,75
Female	0,59 (0,44-0,79), p<0,01	1,27 (0,94-1,72), p=0,12	2,12 (1,71-2,61), p<0,01	0,80 (0,55-1,17), p=0,25	0,86 (0,61-1,21), p=0,39	0,51 (0,40-0,67), p<0,01	1,07 (0,75-1,52), p=0,71	0,92 (0,70-1,21), p=0,53	0,98 (0,71-1,35), p=0,90
DRY MOUTH	1,30 (1,10-1,53) p<0,01	0,30 (0,24-0,37) p<0,01	0,23 (0,19-0,27) p<0,01	0,81 (0,66-0,99) p=0,05	0,88 (0,73-1,07) p=0,21	0,69 (0,59-0,79) p<0,01	1,09 (0,89-1,33) p=0,37	0,34 (0,28-0,41) p<0,01	0,37 (0,30-0,46) p<0,01
Male	0,96 (0,72-1,28), p=0,77	3,33 (2,34-4,73), p<0,01	3,54 (2,62-4,79), p<0,01	0,64 (0,34-0,93), p=0,02	0,81 (0,58-1,12), p=0,21	0,78 (0,59-1,03), p=0,08	1,27 (0,88-1,85), p=0,19	0,37 (0,26-0,52), p<0,01	0,47 (0,32-0,70), p<0,01
Female	0,84 (0,61-1,04), p=0,11	6,96 (4,99-9,72), p<0,01	9,86 (7,32-13,28), p<0,01	0,79 (0,54-1,16), p=0,23	1,70 (1,26-2,30), p<0,01	0,63 (0,53—0,77), p<0,01	0,99 (0,77-1,27), p=0,98	0,16 (0,12-0,22), p<0,01	0,22 (0,15-0,31), p<0,01
COGNITIVE DISORDER	0,57 (0,34-0,94) p=0,03	0,19 (0,10-0,33) p<0,01	0,31 (0,17-0,58) p<0,01	0,52 (0,28-0,97) p=0,04	0,63 (0,37-1,09) p=0,10	1,07 (0,64-1,79) p=0,79	1,17 (0,62-2,22) p=0,62	0,29 (0,15-0,56) p<0,01	0,34 (0,17-0,70) p<0,01
Male	1,76 (0,51-6,01), p=0,36	1,78 (0,52-6,08), p=0,35	1,41 (0,49-4,01), p=0,52	1,63 (0,48-5,56), p=0,43	1,15 (0,33-3,92), p=0,82	1,46 (0,51-4,14), p=0,48	0,70 (0,25-2,01), p=0,51	0,49 (0,17-1,39), p=0,18	0,34 (0,12-0,98), p=0,04
Female	2,21 (1,08-4,53), p=0,03	6,68 (2,72-16,36), p<0,01	3,01 (1,23-7,39), p=0,02	0,37 (0,14-0,96), p=0,04	0,66 (0,32—1,34), P=0,24	1,45 (0,71-2,97), P=0,30	1,76 (0,89-4,53), P=0,24	0,23 (0,09—0,55), P<0,01	0,40 (0,13-1,19), P=0,10
URINARY RETENTION	2,09 (1,71-2,55) p<0,01	2,30 (1,90-2,80) p<0,01	1,10 (0,99-1,22) p=0,07	2,56 (2,21-2,97) p<0,01	8,94 (7,43-10,25) p<0,01	4,27 (3,90-4,67) p<0,01	2,14 (1,98-2,33) p<0,01	0,26 (0,24-0,28) p<0,01	0,48 (0,43-0,53) p<0,01
Male	0,35 (0,25-0,49), p<0,01	0,29 (0,21-0,40), p<0,01	0,81 (0,70-0,93), p=0,01	5,90 (4,23-8,16), p<0,01	16,30 (11,98-22,17), p<0,01	6,05 (5,29-6,90), p<0,01	2,76 (2,43-3,13), p<0,01	0,28 (0,25-0,31), p<0,01	0,77 (0,67-0,90), p=0,01
Female	0,55 (0,42-0,73), p<0,01	0,54 (0,41-0,70), p<0,01	0,96 (0,82-1,12), p=0,60	4,43 (3,31-5,79), p<0,01	4,48 (3,39-5,21), p<0,01	2,48 (2,14-2,90), p<0,01	0,97 (0,84-1,11), p=0,68	0,41 (0,36-0,54), p<0,01	0,51 (0,43-0,67), p<0,01

Reaction Groups	PRR[1] Solifenacin vs Oxibutinin	PRR[2] Mirabegron vs Oxibutinin	PRR[3] Mirabegron vs Solifenacin	PRR[4] Tolterodine vs Oxibutinin	PRR[5] Fesoterodine vs Oxibutinin	PRR[6] Fesoterodine vs Solifenacin	PRR[7] Fesoterodine vs Tolterodine	PRR[8] Mirabegron vs Fesoterodine	PRR[9] Mirabegron vs Tolterodine
Total AEs									
HYPERTENSION	0,56 (0,37-0,85) P=0,01	4,13 (3,02 – 5,66) P<0,01	7,38 (5,54 -9,83) p<0,01	0,95 (0,42-1,46) p=0,83	0,56 (0,36-0,87) p=0,01	0,56 (0,36-0,88) p=0,01	0,58 (0,37-0,91) p=0,01	7,38 (5,26-10,37) p<0,01	4,34 (3,18-5,92) p<0,01
<65	0,96 (0,62-1,48) p=0,87	0,49 (0,34-0,69) p=0,01	0,49 (0,34-0,69) p=0,01	0,51 (0,27-1,07) p=0,07	0,09 (0,03 -0,33) p<0,01	0,18 (0,05-0,60) p=0,01	0,19 (0,05-0,69) p=0,01	20,50 (6,53-64,40) p<0,01	3,94 (2,13-7,29) p<0,01
65 - 85	0,88 (0,57 – 1,38) p=0,59	1,44 (1,05 -1,98) p=0,03	1,63 (1,18 -2,24) p<0,01	1,12 (0,62-2,02) p=0,71	0,69 (0,37-1,27) p=0,23	0,69 (0,37-1,27) p=0,23	0,61 (0,34-1,11) p=0,10	8,51 (5,49-13,19) p<0,01	5,27 (3,50-7,95) p<0,01
>85	4,02 (0,48– 3,07) p=0,19	2,87 (0,40-20,37) p=0,29	0,71 (0,29-1,73) p=0,46	2,79 (0,29-26,84) p=0,37	1,31 (0,12-14,47) p=0,82	0,26 (0,05-1,35) p=0,11	0,28 (0,05-1,45) p=0,13	9,02 (2,18-37,41) p<0,01	4,24 (1,31-13,76) p=0,02
TACHYCARDIA	0,57 (0,34-0,95) p=0,03	0,67 (0,41-1,06) p=0,09	1,16 (0,76-1,79) p=0,49	1,00 (0,59-1,71) p=0,99	0,55 (0,31-0,98) p=0,04	0,43 (0,25-0,74) p<0,01	0,55 (0,32-0,97) p=0,04	1,20 (0,73-1,97) p=0,47	0,66 (0,42-1,05) p=0,08
<65	0,75 (0,52-1,07) p=0,12	0,26 (0,15-0,47) p<0,01	0,36 (0,19-0,65) p<0,01	0,44 (0,20-0,96) p=0,04	0,19 (0,08-0,48) p<0,01	0,45 (0,18-1,14) p=0,10	0,47 (0,17-1,31) p=0,15	0,90 (0,33-2,42) p=0,83	0,42 (0,17-1,01) p=0,05
65-85	4,33 (1,05-17,86) p=0,04	8,67 (2,25-33,25) p<0,01	2,00 (1,19-3,36) p<0,01	4,66 (1,02-21,24) p=0,05	0,19 (0,08-0,49) p<0,01	1,32 (0,56-3,11) p=0,52	0,70 (0,29-1,69) p=0,43	1,73 (0,86-3,49) p=0,12	0,51 (0,30-0,86) p=0,01
>85	0,59 (0,14-2,41) p=0,46	0,70 (0,19-2,52) p=0,58	1,42 (0,40-5,13) p=0,59	0,70 (0,16-3,12) p=0,64	0,16 (0,02-1,47) p=0,11	0,13 (0,01-1,02) p=0,05	0,23 (0,02-2,26) p=0,21	3,42 (0,42-27,78) p=0,25	0,80 (0,21-3,10) p=0,75
VISION BLURRED	1,96 (1,45-2,65) p<0,01	0,43 (0,29-0,61) p<0,01	0,21 (0,17-0,29) p<0,01	0,95 (0,65-1,39) p=0,79	0,96 (0,68-1,37) p=0,85	0,49 (0,37-0,67) p<0,01	1,01 (0,72-1,45) p=0,92	0,44 (0,32-0,61) p<0,01	0,45 (0,31-0,64) p<0,01
<65	1,84 (1,10-3,08) p=0,02	1,75 (0,99-3,10) p=0,05	0,95 (0,69-1,31) p=0,77	1,01 (0,46-2,21) p=0,98	0,77 (0,35-1,65) p=0,50	0,21 (0,12-0,37) p<0,01	0,76 (0,36-1,61) p=0,47	0,98 (0,51-1,87) p=0,94	0,74 (0,38-1,43) p=0,37
65-85	1,33 (0,89-1,97) p=0,16	1,42 (0,91-2,20) p=0,12	1,07 (0,81-1,41) p=0,64	1,19 (0,64-2,20) p=0,58	1,46 (0,83-2,54) p=0,18	0,56 (0,39-0,80) p<0,01	1,23 (0,74-2,04) p=0,43	0,42 (0,26-0,65) p<0,01	0,50 (0,30-0,85) p=0,01
>85	1,38 (0,32-5,97) p=0,67	2,25 (0,47-10,69) p=0,31	1,63 (0,64-4,19) p=0,30	4,66 (1,02-21,23) p=0,05	2,62 (0,55-12,36) p=0,22	0,97 (0,40-2,37) p=0,95	0,56 (0,22-1,43) p=0,22	0,37 (0,13-1,06) p=0,04	0,21 (0,08-0,57) p<0,01
CONSTIPATION	1,56 (1,23-1,98) p<0,01	0,94 (0,73-1,20) p=0,60	0,60 (0,50-0,70) p<0,01	0,93 (0,69-1,25) p=0,64	0,96 (0,53-1,26) p=0,77	0,60 (0,49-0,74) p<0,01	1,23 (0,79-1,36) p=0,82	0,96 (0,78-1,19) p=0,74	0,99 (0,78-1,27) p=0,98
<65	0,20 (0,15-0,27) p<0,01	0,76 (0,58-1,01) p=0,06	1,42 (1,10-1,84) p=0,01	0,23 (0,15-0,73) p<0,01	0,30 (0,17-0,51) p<0,01	0,34 (0,21-0,58) p<0,01	1,05 (0,51-2,19) p=0,88	2,39 (1,44-3,96) p<0,01	2,52 (1,38-4,61) p<0,01
65-85	1,02 (0,78-1,33) p=0,90	0,88 (0,67-1,16) p=0,36	0,86 (0,73-1,03) p=0,10	1,03 (0,66-1,60) p=0,89	1,22 (0,82-1,81) p=0,31	0,56 (0,43-0,74) p<0,01	1,25 (0,85-1,84) p=0,25	0,94 (0,71-1,26) p=0,68	1,11 (0,79-1,58) p=0,53
>85	1,74 (0,81-3,72) p=0,16	1,08 (0,48-2,43) p=0,86	0,62 (0,38-1,01) p=0,05	1,86 (0,75-4,61) p=0,18	1,41 (0,57-3,44) p=0,46	0,51 (0,28-0,91) p=0,02	0,77 (0,38-1,61) p=0,49	0,71 (0,37-1,38) p=0,32	0,54 (0,28-1,06) p=0,07
DRY MOUTH	1,30 (1,10-1,53) p<0,01	0,30 (0,24-0,37) p<0,01	0,23 (0,19-0,27) p<0,01	0,81 (0,66-0,99) p=0,05	0,88 (0,73-1,07) p=0,21	0,69 (0,59-0,79) p<0,01	1,09 (0,89-1,33) p=0,37	0,34 (0,28-0,41) p<0,01	0,37 (0,30-0,46) p<0,01
<65	0,86 (0,71-1,03) p=0,11	0,73 (0,57-0,95) p=0,02	0,85 (0,67-1,07) p=0,17	0,36 (0,24-0,52) p<0,01	0,37 (0,26-0,52) p<0,01	0,36 (0,26-0,46) p<0,01	1,04 (0,69-1,60) p=0,87	0,57 (0,38-0,81) p<0,01	0,58 (0,38-0,88) p=0,01
65-85	1,17 (0,98-1,41) p=0,09	1,23 (0,99-1,53) p=0,06	1,05 (0,89-1,23) p=0,56	0,87 (0,64-1,19) p=0,39	1,00 (0,76-1,33) p=0,95	0,66 (0,54-0,82) p<0,01	1,15 (0,86-1,53) p=0,32	0,37 (0,27-0,47) p<0,01	0,41 (0,31-0,56) p<0,01
>85	1,16 (0,51-2,63) p=0,71	2,47 (1,04-5,85) p=0,04	2,12 (1,17-3,81) p=0,01	3,06 (1,31-7,12) p=0,01	2,43 (1,06-5,61) p=0,04	0,51 (0,28-0,91) p=0,02	0,80 (0,45-1,39) p=0,43	0,30 (0,16-0,56) p<0,01	0,24 (0,13-0,45) p<0,01
COGNITIVE DISORDER	0,57 (0,34-0,94) p=0,03	0,19 (0,10-0,33) p<0,01	0,31 (0,17-0,58) p<0,01	0,52 (0,28-0,97) p=0,04	0,63 (0,37-1,09) p=0,10	1,07 (0,64-1,79) p=0,79	1,17 (0,62-2,22) p=0,62	0,29 (0,15-0,56) p<0,01	0,34 (0,17-0,70) p<0,01
<65	0,90 (0,56-1,45) p=0,66	0,84 (0,44-1,59) p=0,59	0,93 (0,49-1,76) p=0,83	0,03 (0,01-0,50) p=0,01	0,22 (0,08-0,96) p=0,01	0,42 (0,16-1,16) p=0,10	7,75 (0,43-140,17) p=0,17	0,68 (0,22-2,15) p=0,52	5,16 (0,30-90,40) p=0,26
65-86	1,43 (0,79-2,57) p=0,23	1,08 (0,49-2,38) p=0,85	0,76 (0,37-1,52) p=0,43	0,37 (0,11-1,19) p=0,09	0,66 (0,27-1,58) p=0,35	0,81 (0,37-1,75) p=0,59	1,76 (0,55-5,61) p=0,34	0,29 (0,11-0,81) p=0,02	0,52 (0,15-1,83) p=0,31
>85	0,40 (0,04-4,15) p=0,44	1,80 (0,28-11,51) p=0,53	4,53 (0,44-46,23) p=0,20	1,40 (0,23-8,36) p=0,71	0,21 (0,04-1,08) p=0,06	8,74 (1,05-72,53) p=0,04	1,41 (0,35-5,63) p=0,62	0,13 (0,03-0,81) p=0,03	0,23 (0,04-1,37) p=0,11
URINARY RETENTION	2,09 (1,71-2,55) p<0,01	2,30 (1,90-2,80) p<0,01	1,10 (0,99-1,22) p=0,07	2,56 (2,21-2,97) p<0,01	8,94 (7,43-10,25) p<0,01	4,27 (3,90-4,67) p<0,01	2,14 (1,98-2,33) p<0,01	0,26 (0,24-0,28) p<0,01	0,48 (0,43-0,53) p<0,01
<65	0,97 (0,77-1,21) p=0,76	0,25 (0,19-0,33) p<0,01	0,28 (0,22-0,35) p<0,01	2,51 (1,84-3,43) p<0,01	1,77 (1,30-2,42) p<0,01	0,74 (0,59-0,93) p=0,01	0,54 (0,42-0,69) p<0,01	0,39 (0,30-0,52) p<0,01	0,21 (0,16-0,28) p<0,01
65-85	1,08 (0,85-1,37) p=0,55	1,83 (1,46-2,30) p<0,01	1,70 (0,53-1,89) p<0,01	5,37 (3,94-7,30) p<0,01	9,79 (7,30-13,14) p<0,01	4,34 (3,79-5,01) p<0,01	1,70 (1,49-1,93) p<0,01	0,43 (0,39-0,48) p<0,01	0,79 (0,69-0,90) p<0,01
Age >85	1,28 (0,74-2,23) p=0,37	1,05 (0,61-1,80) p=0,86	0,83 (0,64-1,09) p=0,19	4,80 (2,66-8,67) p<0,01	7,45 (4,27-13,01) p<0,01	4,27 (3,30-5,52) p<0,01	2,35 (1,79-3,07) p<0,01	0,24 (0,19-0,30) p<0,01	0,57 (0,42-0,77) p<0,01

Table 4: PRR of AEs comparing AMs and B3A

PRR1 confronted AEs of Oxibutinin versus Solifenacin, PRR2 confronted AEs of Oxibutinin vs Mirabegron, PRR3 confronted AEs of Solifenacin vs Mirabegron, PRR4 confronted AEs of Tolterodine vs Oxibutinin, PRR5 confronted AEs of Fesoterodine vs Oxibutinin, PRR6 confronted AEs of Fesoterodine vs Solifenacin, PRR7 confronted AEs of Fesoterodine vs Tolterodine, PRR8 confronted AEs of Mirabegron vs Fesoterodine, PRR9 confronted AEs of Mirabegron vs Tolterodine

Table 5 : PRR of AEs per age

Reaction Groups	Oxybutinin	Solifenacin	Tolterodine	Fesoterodine	Mirabegron
HYPERTENSION					
PRR 1	0,16 (0,01-0,36) p<0,01	0,21 (0,09-0,50) p<0,01	0,27 (0,08-0,91) p=0,03	0,66 (0,12-3,75) p=0,67	0,29 (0,21-0,41) p<0,01
PRR 2	0,16 (0,01-0,36) p<0,01	0,23 (0,09-0,55) p<0,01	0,11 (0,04-0,36) p<0,01	0,09 (0,02-0,35) p<0,01	0,10 (0,07-0,13) p<0,01
PRR 3	1,01 (0,64-1,56) p=0,99	0,92 (0,60-1,41) p= 0,69	2,35 (1,34-4,13) p<0,01	7,00 (2,31-21,22) p<0,01	2,90 (2,47-3,42) p<0,01
TACHYCARDIA					
PRR 1	4,45 (0,40-9,99) p=0,40	0,16 (0,0,5-0,48) p<0,01	0,33 (0,10-1,10) p=0,07	0,17 (0,02-1,27) p=0,08	0,63 (0,27-1,52) p=0,31
PRR 2	4,45 (0,40-9,99) p=0,40	0,27 (0,08-0,89) p=0,03	0,30 (0,09-0,98) p=0,04	0,10 (0,01-0,72) p=0,02	0,19 (0,10-0,40) p<0,01
PRR 3	3,22 (0,15-6,57) p=0,99	0,58 (0,33-1,02) p=0,07	0,91 (0,46-1,79) p=0,79	1,66 (0,73-3,79) p=0,22	3,27 (1,87-5,73) p<0,01
VISION BLURRED					
PRR 1	0,39 (0,04-0,71) p=0,02	0,13 (0,07-0,22) p<0,01	0,77 (0,37-1,59) p=0,48	0,57 (0,25-1,28) p=0,17	0,21 (0,09-0,48) p<0,01
PRR 2	0,23 (0,02-0,45) p<0,01	0,11 (0,07-0,20) p<0,01	0,43 (0,23-0,82) p=0,01	0,20 (0,10-0,40) p<0,01	0,23 (0,10-0,51) p<0,01
PRR 3	0,77 (0,35-1,24) p=0,20	1,08 (0,88-1,33) p=0,44	1,77 (1,01-3,10) p=0,05	2,85 (1,70-4,79) p<0,01	1,21 (0,83-1,76) p=0,30
CONSTIPATION					
PRR 1	0,21 (0,08-0,37) p<0,01	0,56 (0,40-0,79) p<0,01	1,17 (0,57-2,37) p=0,67	0,83 (0,44-1,58) p=0,57	0,25 (0,16-0,39) p<0,01
PRR 2	0,19 (0,09-0,40) p<0,01	0,24 (0,18-0,32) p<0,01	0,34 (0,20-0,58) p<0,01	0,21 (0,13-0,36) p<0,01	0,17 (0,11-0,25) p<0,01
PRR 3	0,75 (0,06-1,29) p=0,64	2,34 (1,89-2,90) p<0,01	3,41 (1,94-6,02) p<0,01	3,83 (2,43-6,04) p<0,01	1,51 (1,23-1,83) p<0,01
DRY MOUTH					
PRR 1	0,19 (0,07-0,32) p<0,01	0,13 (0,09-0,20) p<0,01	0,69 (0,42-1,12) p=0,13	0,51 (0,33-0,80) p<0,01	0,29 (0,18-0,47) p<0,01
PRR 2	0,22 (0,08-0,36) p<0,01	0,11 (0,07-0,15) p<0,01	0,31 (0,21-0,47) p<0,01	0,21 (0,14-0,32) p<0,01	0,18 (0,11-0,29) p<0,01
PRR 3	0,89 (0,71-1,10) p=0,29	1,28 (1,12-1,46) p<0,01	2,18 (1,55-3,05) p<0,01	2,42 (1,83-3,19) p<0,01	1,66 (1,30-2,13) p<0,01
COGNITIVE DISORDER					
PRR 1	0,28 (0,03-0,53) p=0,01	0,05 (0,01-0,38) p=0,01	0,20 (0,07-0,55) p<0,01	1,20 (0,42-3,42) p=0,73	0,29 (0,07-1,16) p=0,08
PRR 2	0,46 (0,05-0,83) p=0,03	0,05 (0,01-0,38) p=0,01	0,75 (0,20-2,79) p=0,67	0,60 (0,26-1,40) p=0,23	0,33 (0,08-1,39) p=0,13
PRR 3	0,81 (0,37-1,21) p=0,18	1,05 (0,67-1,69) p=0,81	9,00 (0,53-153,80) p=0,13	1,20 (0,51-2,84) p=0,69	0,86 (0,38-1,95) p=0,71
URINARY RETENTION					
PRR 1	0,29 (0,14-0,42) p<0,01	0,36 (0,28-0,45) p<0,01	0,47 (0,36-0,61) p<0,01	2,04 (1,64-2,53) p<0,01	1,26 (0,97-1,64) p=0,09
PRR 2	0,31 (0,17-0,54) p<0,01	0,33 (0,26-0,42) p<0,01	0,26 (0,20-0,33) p<0,01	0,32 (0,28-0,37) p<0,01	0,18 (0,15-0,22) p<0,01
	3,24 (1,86-5,69)	1,07 (0,93-1,24)	1,82 (1,54-2,16)	6,29 (5,20-7,60)	6,88 (5,63-8,42)

PRR1 confronted >85 vs <65, PRR2 confronted >85 vs 65-85, PRR3 confronted 65-85 vs <65

Table 6: Seriousness of AEs related to Oxybutinin

Reaction Groups	Non Serious	Serious	Total	Unknown	Resolving	Resolved with sequelae	Recovering	Not resolved	Fatal
Total	1059	4373	5441	1961	543	75	1720	811	331
Blood and Lymphatic system disorders	1/63 (1%)	62/63 (99%)	63	20/63 (31%)	9/63 (14%)	0/63 (0%)	22/63 (35%)	8/63 (12%)	4/63 (6%)
Cardiac disorers	10/168 (6%)	167/168 (94%)	168	55/168 (31%)	7/168 (4%)	3/168 (2%)	58/168 (35%)	16/168 (10%)	29/168 (17%)
Ear and Labyrinth disorders	0/28 (0%)	28/28 (100%)	28	10/28 (32%)	1/28 (4%)	1/28 (4%)	8/28 (30%)	11/28 (41%)	0/28 (0%)
Endocrine disorders	0/12 (0%)	12/12 (100%)	12	0/12 (0%)	4/12 (30%)	1/12 (10%)	1/12 (10%)	6/12 (50%)	0/12 (0%)
Eye Disorders	43/194 (22%)	151/194 (78%)	194	60/194 (31%)	21/194 (11%)	3/194 (2%)	59/194 (31%)	49/194 (25%)	2/194 (1%)
Gastrointestinal disorders	170/581 (29%)	411/581 (71%)	581	207/581 (35%)	59/581 (10%)	5/581 (1%)	210/581 (36%)	95/581 (16%)	5/581 (1%)
General disorders and administration site condition	184/750 (25%)	566/750 (75%)	750	299/750 (40%)	66/750 (9%)	5/750 (1%)	199/750 (27%)	97/750 (14%)	84/750 (11%)
Hepatobiliary disorders	1/34 (1%)	33/34 (99%)	34	7/34 (21%)	10/34 (29%)	1/34 (3%)	12/34 (35%)	0/34 (0%)	4/34 (12%)

Immune system disorders	**14/56 (25%)**	**42/56 (75%)**	**56**	**38/56 (67%)**	**6/56 (11%)**	**0/56 (0%)**	**9/56 (16%)**	**0/56 (0%)**	**3/56 (5%)**
Infections and infestations	**12/184 (7%)**	**172/184 (93%)**	**184**	**91/184 (49%)**	**22/184 (12%)**	**2/184 (1%)**	**39/184 (21%)**	**22/184 (12%)**	**8/184 (4%)**
Injury, poisoning and procedural complications	**66/409 (16%)**	**343/409 (84%)**	**409**	**203/409 (49%)**	**27/409 (7%)**	**7/409 (2%)**	**85/409 (21%)**	**35/409 (9%)**	**48/409 (12%)**
Investigations	**19/209 (9%)**	**190/209 (91%)**	**209**	**90/209 (43%)**	**25/209 (12%)**	**2/209 (1%)**	**58/209 (28%)**	**31/209 (15%)**	**3/209 (2%)**
Metabolism and nutrition disorders	**17/147 (12%)**	**130/147 (88%)**	**147**	**44/147 (30%)**	**12/147 (8%)**	**4/147 (3%)**	**65/147 (44%)**	**19/147 (13%)**	**3/147 (2%)**
Musculoskeletal and connective tissue disorders	**27/167 (16%)**	**140/167 (84%)**	**167**	**36/167 (24%)**	**22/167 (15%)**	**1/167 (1%)**	**41/167 (28%)**	**35/167 (24%)**	**2/167 (1%)**
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	**0/38 (0%)**	**38/38 (100%)**	**38**	**10/38 (26%)**	**1/38 (1%)**	**4/38 (10%)**	**0/38 (0%)**	**4/38 (10%)**	**20/38 (52%)**
Nervous system disorders	**129/672 (19%)**	**543/672 (81%)**	**672**	**228/672 (34%)**	**73/672 (11%)**	**8/672 (1%)**	**251/672 (37%)**	**97/672 (14%)**	**15/672 (2%)**
Product issues	**34/58 (59%)**	**24/58 (41%)**	**58**	**47/58 (81%)**	**0/58 (0%)**	**0/58 (0%)**	**6/58 (10%)**	**5/58 (9%)**	**0/58 (0%)**

Psychiatric disorders	**109/573 (19%)**	**464/573 (81%)**	**573**	**149/573 (26%)**	**64/573 (11%)**	**3/573 (<1%)**	**230/573 (40%)**	**68/573 (11%)**	**59/573 (10%)**
Renal and urinary disorders	**29/293 (10%)**	**264/293 (90%)**	**293**	**101/293 (34%)**	**37/293 (13%)**	**6/293 (2%)**	**93/293 (32%)**	**51/293 (17%)**	**5/293 (2%)**
Reproductive system and breasts disorders	**8/54 (15%)**	**46/54 (85%)**	**54**	**28/54 (52%)**	**4/54 (7%)**	**0/54 (0%)**	**11/54 (20%)**	**9/54 (17%)**	**2/54 (4%)**
Respiratory, thoracic and mediastinal disorders	**39/209 (19%)**	**170/209 (81%)**	**209**	**64/209 (30%)**	**14/209 (7%)**	**2/209 (1%)**	**75/209 (36%)**	**31/209 (15%)**	**23/209 (11%)**
Skin and subcutaneous tissue disorders	**125/333 (38%)**	**208/333 (62%)**	**333**	**98/333 (29%)**	**50/333 (15%)**	**15/333 (4%)**	**115/333 (35%)**	**53/333 (16%)**	**2/333 (1%)**
Social circumstances	**2/16 (12%)**	**14/16 (88%)**	**16**	**4/16 (25%)**	**1/16 (6%)**	**0/16 (0%)**	**5/16 (31%)**	**6/16 (38%)**	**0/16 (0%)**
Surgical and medical procedures	**0/34 (0%)**	**34/34 (100%)**	**34**	**28/34 (82%)**	**0/34 (0%)**	**0/34 (0%)**	**3/34 (9%)**	**2/34 (6%)**	**1/34 (3%)**
Vascular disorders	**20/150 (13%)**	**130/150 (87%)**	**150**	**53/150 (35%)**	**12/150 (9%)**	**2/150 (1%)**	**65/150 (43%)**	**9/150 (6%)**	**9/150 (6%)**

Table 7: Seriousness of AEs related to Solifenacin

Reaction Groups	Non Serious	Serious	Total	Unknown	Resolving	Resolved with sequelae	Recovering	Not resolved	Fatal
Total	8274	2155	10429	4993	945	50	2919	1343	272
Blood and Lymphatic system disorders	46/51 (90%)	5/51 (10%)	51	22/51 (43%)	6/51 (12%)	0/51 (0%)	13/51 (25%)	9/51 (18%)	1/51 (2%)
Cardiac disorders	327/355 (92%)	28/355 (8%)	355	121/355 (34%)	47/355 (13%)	2/355 (<1%)	121/355 (34%)	33/355 (9%)	31/355 (9%)
Ear and Labyrinth disorders	49/68 (72%)	19/68 (18%)	68	24/68 (35%)	6/68 (9%)	0/68 (0%)	24/68 (35%)	14/68 (21%)	0/68 (0%)
Endocrine disorders	21/21 (100%)	0/21 (0%)	21	11/21 (53%)	4/21 (19%)	0/21 (0%)	3/21 (14%)	3/21 (14%)	0/21 (0%)
Eye Disorders	389/534 (73%)	145/534 (27%)	534	255/534 (48%)	5/534 (1%)	1/534 (<1%)	151/534 (28%)	122/534 (23%)	0/534 (0%)
Gastrointestinal disorders	925/1350 (69%)	425/1350 (31%)	1350	462/1350 (34%)	147/1350 (11%)	7/1350 (<1%)	488/1350 (36%)	233/1350 (17%)	13/1350 (1%)
General disorders and administration site condition	1037/1362 (76%)	325/1362 (24%)	1362	732/1362 (53%)	90/1362 (7%)	5/1362 (<1%)	273/1362 (20%)	139/1362 (10%)	123/1362 (10%)
Hepatobiliary disorders	93/97 (96%)	4/97 (4%)	97	18/97 (19%)	32/97 (33%)	0/97 (0%)	37/97 (38%)	8/97 (8%)	2/97 (2%)

Immune system disorders	**68/77 (88%)**	**9/77 (12%)**	**77**	**41/77 (53%)**	**6/77 (8%)**	**0/77 (0%)**	**22/77 (29%)**	**7/77 (9%)**	**1/77 (1%)**
Infections and infestations	**323/355 (91%)**	**32/355 (9%)**	**355**	**176/355 (50%)**	**22/355 (6%)**	**1/355 (<1%)**	**103/355 (29%)**	**41/355 (12%)**	**12/355 (3%)**
Injury, poisoning and procedural complications	**674/874 (77%)**	**200/874 (23%)**	**874**	**698/874 (80%)**	**23/874 (3%)**	**2/874 (1%)**	**108/874 (12%)**	**32/874 (4%)**	**11/874 (1%)**
Investigations	**429/475 (90%)**	**46/475 (10%)**	**475**	**244/475 (51%)**	**52/475 (11%)**	**0/475 (0%)**	**111/475 (23%)**	**61/475 (13%)**	**7/475 (1%)**
Metabolism and nutrition disorders	**198/222 (89%)**	**24/222 (11%)**	**222**	**103/222 (46%)**	**18/222 (8%)**	**0/222 (0%)**	**68/222 (31%)**	**27/222 (12%)**	**6/222 (3%)**
Musculoskeletal and connective tissue disorders	**230/283 (81%)**	**53/283 (19%)**	**283**	**175/283 (62%)**	**33/283 (12%)**	**1/283 (<1%)**	**86/283 (31%)**	**53/283 (19%)**	**1/283 (<1%)**
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	**112/112 (100%)**	**0/112 (0%)**	**112**	**77/112 (69%)**	**3/112 (3%)**	**1/112 (<1%)**	**15/112 (13%)**	**8/112 (7%)**	**8/112 (7%)**
Nervous system disorders	**872/1073 (81%)**	**201/1073 (19%)**	**1073**	**424/1073 (40%)**	**102/1073 (10%)**	**11/1073 (1%)**	**374/1073 (35%)**	**148/1073 (14%)**	**14/1073 (1%)**
Product issues	**16/40 (40%)**	**24/40 (60%)**	**40**	**16/40 (40%)**	**2/40 (5%)**	**0/40 (0%)**	**20/40 (50%)**	**2/40 (5%)**	**0/40 (0%)**

Psychiatric disorders	**409/509 (80%)**	**100/509 (20%)**	**509**	**180/509 (35%)**	**49/509 (10%)**	**2/509 (1%)**	**208/509 (41%)**	**64/509 (13%)**	**6/509 (1%)**
Renal and urinary disorders	**906/1106 (82%)**	**200/1106 (18%)**	**1106**	**534/1106 (48%)**	**106/1106 (10%)**	**8/1106 (<1%)**	**304/1106 (27%)**	**148/1106 (13%)**	**6/1106 (<1%)**
Reproductive system and breasts disorders	**71/109 (65%)**	**38/109 (35%)**	**109**	**47/109 (43%)**	**9/109 (9%)**	**2/109 (1%)**	**31/109 (28%)**	**19/109 (17%)**	**1/109 (1%)**
Respiratory, thoracic and mediastinal disorders	**313/410 (76%)**	**97/410 (24%)**	**410**	**149/410 (36%)**	**55/410 (13%)**	**2/410 (1%)**	**118/410 (29%)**	**64/410 (16%)**	**22/410 (5%)**
Skin and subcutaneous tissue disorders	**298/451 (66%)**	**153/451 (37%)**	**451/451**	**125/451 (28%)**	**89/451 (20%)**	**5/451 (1%)**	**154/451 (34%)**	**76/451 (17%)**	**2/451 (<1%)**
Social circumstances	**32/35 (91%)**	**3/35 (9%)**	**35**	**23/35 (66%)**	**2/35 (6%)**	**0/35 (0%)**	**5/35 (14%)**	**5/35 (14%)**	**0/35 (0%)**
Surgical and medical procedures	**256/257 (99%)**	**1/257 (1%)**	**257**	**221/257 (86%)**	**15/257 (6%)**	**0/257**	**14/257 (5%)**	**7/257 (3%)**	**0/257 (0%)**
Vascular disorders	**180/203 (87%)**	**23/203 (13%)**	**203**	**115/203 (57%)**	**22/203 (9%)**	**0/203 (0%)**	**68/203 (33%)**	**20/203 (9%)**	**5/203 (2%)**

Table 8: Seriousness of AEs for Tolterodine

Reaction Groups	Non Serious	Serious	Total	Unknown	Resolving	Resolved with sequelae	Recovering	Not resolved	Fatal
Total	913	5038	5605	2998	413	97	1329	918	230
Blood and Lymphatic system disorders	0/41 (0%)	41/41 (100%)	41	8/41 (20%)	0/41 (0%)	0/41 (0%)	13/41 (32%)	4/41 (10%)	4 (10%)
Cardiac disorders	180/194 (93%)	14/194 (7%)	194	85/194 (43%)	10/194 (5%)	1/194 (<1%)	68/194 (35%)	23/194 (12%)	13/194 (7%)
Ear and Labyrinth disorders	5/73 (7%)	68/73 (93%)	73	43/73 (59%)	3/73 (4%)	0/73 (0%)	9 /73 (12%)	17/73 (23%)	0/73 (0%)
Endocrine disorders	0/17 (0%)	17/17 (100%)	17	10/17 (59%)	0/17 (0%)	0/17 (0%)	4/17 (24%)	3/17 (18%)	0/17 (0%)
Eye Disorders	20/196 (10%)	184/196 (94%)	196	94 /196 (48%)	17/196 (9%)	2/196 (1%)	54/196 (28%)	53/196 (27%)	1/196 (<1%)
Gastrointestinal disorders	488/924 (53%)	436/924 (47%)	924	241/924 (26%)	61/924 (7%)	3/924 (<1%)	159/924 (17%)	110/924 (12%)	6/924 (<1%)
General disorders and administration site condition	51/743 (7%)	687/743 (92%)	743	409/743 (55%)	47 /743 (6%)	3/743 (<1%)	142/743 (19%)	116/743 (16%)	89/743 (12%)

Hepatobiliary disorders	**1/32 (3%)**	**31/32 (97%)**	**32**	**12/32 (38%)**	**4/32 (13%)**	**0/32 (0%)**	**11/32 (34%)**	**5 /32 (16%)**	**1/32 (3%)**
Immune system disorders	**4/60 (7%)**	**56/60 (93%)**	**60**	**29/60 (48%)**	**6 /60 (10%)**	**21/60 (35%)**	**0/60 (0%)**	**4/60 (7%)**	**1/60 (2%)**
Infections and infestations	**5/232 (2%)**	**227/232 (98%)**	**232**	**146/232 (63%)**	**21/232 (9%)**	**0/232 (0%)**	**43/232 (19%)**	**23/232 (10%)**	**10/232 (4%)**
Injury, poisoning and procedural complications	**10/364 (3%)**	**354/364 (97%)**	**364**	**276/364 (76%)**	**24/364 (7%)**	**2/364 (<1%)**	**47/364 (13%)**	**36/364 (10%)**	**10/364 (3%)**
Investigations	**9/297 (3%)**	**288/297 (97%)**	**297**	**170/297 (57%)**	**21/297 (7%)**	**0 /297 (0%)**	**72/297 (24%)**	**49/297 (16%)**	**5/297 (2%)**
Metabolism and nutrition disorders	**8/145 (6%)**	**137/145 (94%)**	**145**	**83/145 (57%)**	**7/145 (5%)**	**0/145 (0%)**	**30/145 (21%)**	**18/145 (12%)**	**8/145 (6%)**
Musculoskeletal and connective tissue disorders	**7/263 (3%)**	**254/263 (97%)**	**263**	**161/263 (61%)**	**17/263 (6%)**	**0/263 (0%)**	**41/263 (16%)**	**66/263 (25%)**	**1/263 (<1%)**
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	**0/112 (0%)**	**112/112 (100%)**	**112**	**75/112 (67%)**	**3/112 (3%)**	**0/112 (0%)**	**14/112 (12%)**	**7/112 (6%)**	**16/112 (14%)**
Nervous system disorders	**60/663 (9%)**	**601/663 (91%)**	**663**	**353/663 (53%)**	**58/663 (9%)**	**9/663 (1%)**	**159/663 (24%)**	**125/663 (19%)**	**9/663 (1%)**
Product issues	**4/16 (25%)**	**12/16 (75%)**	**16**	**10/16 (63%)**	**0/16 (0%)**	**0/16 (0%)**	**4/16 (25%)**	**2/16 (13%)**	**0/16 (0%)**

Psychiatric disorders	**28/354 (8%)**	**320/354 (91%)**	**354**	**161/354 (45%)**	**22/354 (6%)**	**4/354 (1%)**	**114/354 (32%)**	**57/354 (16%)**	**22/354 (6%)**
Renal and urinary disorders	**26/582 (4%)**	**554/582 (95%)**	**582**	**279/582 (48%)**	**53/582 (9%)**	**3/582 (<1%)**	**170/582 (29%)**	**115/582 (20%)**	**10/582 (2%)**
Reproductive system and breasts disorders	**4/71 (6%)**	**65/71 (92%)**	**71**	**47/71 (66%)**	**3/71 (4%)**	**0/71 (0%)**	**16/71 (23%)**	**6/71 (8%)**	**0/71 (0%)**
Respiratory, thoracic and mediastinal disorders	**11/198 (6%)**	**187/198 (94%)**	**198**	**96/198 (48%)**	**21/198 (11%)**	**0/198 (0%)**	**61/198 (31%)**	**23/198 (12%)**	**13/198 (7%)**
Skin and subcutaneous tissue disorders	**29/172 (17%)**	**143/172 (83%)**	**172/172**	**61/172 (35%)**	**20/172 (12%)**	**0/172 (0%)**	**62/172 (36%)**	**31/172 (18%)**	**3/172 (2%)**
Social circumstances	**1/22 (5%)**	**21/22 (95%)**	**22**	**15/22 (68%)**	**0/22 (0%)**	**3/22 (14%)**	**0/22 (0%)**	**4/22 (18%)**	**0/22 (0%)**
Surgical and medical procedures	**0/93 (0%)**	**93/93 (100%)**	**93**	**68/93 (73%)**	**6/93 (6%)**	**2/93 (2%)**	**14/93 (15%)**	**6/93 (6%)**	**0/93 (0%)**
Vascular disorders	**2/138 (1%)**	**136/138 (99%)**	**138**	**66/138 (48%)**	**9/138 (7%)**	**44/138 (32%)**	**22/138 (16%)**	**15/138 (11%)**	**8/138 (6%)**

Table 9: Seriousness of AEs for Fesoterodine

Reaction Groups	Non Serious	Serious	Total	Unknown	Resolving	Resolved with sequelae	Recovering	Not resolved	Fatal
Total	550	5959	6731	3634	498	22	1850	812	96
Blood and Lymphatic system disorders	0/14 (0%)	14/14 (100%)	14	6/14 (43%)	0/14 (0%)	0/14 (0%)	0/14 (0%)	4/14 (29%)	4/14 (29%)
Cardiac disorders	12/182 (7%)	170/182 (93%)	182	85/182 (47%)	15/182 (8%)	1/182 (<1%)	58/182 (32%)	14/182 (8%)	16/182 (9%)
Ear and Labyrinth disorders	9/71 (13%)	61/71 (87%)	71	38/71 (54%)	1/71 (1%)	0/71 (0%)	10/71 (14%)	22/71 (31%)	0/71 (0%)
Endocrine disorders	0/8 (0%)	8/8 (100%)	8	5/8 (64%)	1/8 (12%)	0/8 (0%)	1/8 (12%)	0/8 (0%)	1/8 (12%)
Eye Disorders	32/220 (15%)	188/220 (85%)	220	131 /220 (60%)	9 /220 (4%)	1 /220 (<1%)	50/220 (23%)	41/220 (19%)	0 /220 (0%)
Gastrointestinal disorders	152/659 (23%)	507/659 (77%)	659	343/659 (52%)	55/659 (8%)	1/659 (<1%)	197/659 (30%)	113/659 (17%)	2/659 (<1%)
General disorders and administration site condition	79/795 (10%)	716/795 (90%)	795	502/795 (63%)	49/795 (6%)	1/795 (<1%)	162/795 (20%)	114/795 (14%)	40/795 (5%)
Hepatobiliary disorders	5/35 (14%)	30/35 (86%)	35	19/35 (54%)	5/35 (14%)	0/35 (0%)	10 /35 (29%)	3/35 (9%)	0/35 (0%)
Immune system disorders	2/39 (5%)	37/39 (95%)	39	19/39 (49%)	0/39 (0%)	0/39 (0%)	17/39 (44%)	3/39 (8%)	0/39 (0%)

Infections and infestations	11/222 (5%)	211/222 (95%)	222	116/222 (52%)	15/222 (7%)	1/222 (<1%)	70/222 (32%)	26/222 (12%)	2 /222 (<1%)
Injury, poisoning and procedural complications	23/399 (6%)	349/399 (87%)	399	276/399 (69%)	15/399 (4%)	2/399 (<1%)	69/399 (17%)	31/399 (7%)	6/399 (2%)
Investigations	13/260 (5%)	233/260 (90%)	260	163/260 (63%)	17/260 (7%)	0/260 (0%)	51/260 (20%)	28/260 (11%)	1/260 (<1%)
Metabolism and nutrition disorders	6/108 (5%)	100/108 (93%)	108	55/108 (51%)	6/108 (6%)	0/108 (0%)	34/108 (31%)	13/108 (12%)	0/108 (0%)
Musculoskeletal and connective tissue disorders	11/205 (5%)	184/205 (89%)	205	121/205 (59%)	14/205 (7%)	1/205 (<1%)	39/205 (19%)	31/205 (15%)	0/205 (0%)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	1/80 (1%)	78/80 (99%)	80	55/80 (69%)	3/80 (4%)	1/80 (1%)	7/80 (9%)	9/80 (11%)	5/80 (6%)
Nervous system disorders	44/620 (7%)	531/620 (86%)	620	339/620 (55%)	49/620 (8%)	5/620 (<1%)	135/620 (22%)	85/620 (14%)	7/620 (1%)
Product issues	3/12 (25%)	9/12 (75%)	12	8/12 (66%)	0/12 (0%)	0/12 (0%)	2/12 (17%)	2/12 (17%)	0/12 (0%)
Psychiatric disorders	33/280 (12%)	229/280 (81%)	280	154/280 (55%)	11/280 (4%)	1/280 (<1%)	70/280 (25%)	43/280 (15%)	1/280 (<1%)
Renal and urinary disorders	44/1878 (2%)	1766/1878 (94%)	1878	886/1878 (47%)	172/1878 (9%)	7/1878 (<1%)	698/1878 (37%)	114/1878 (6%)	1/1878 (<1%)

Reproductive system and breasts disorders	**13/89 (15%)**	**76/89 (85%)**	**89**	**63/89 (71%)**	**5/89 (6%)**	**0/89 (0%)**	**11/89 (12%)**	**10/89 (11%)**	**0/89 (0%)**
Respiratory, thoracic and mediastinal disorders	**23/230 (10%)**	**187/230 (81%)**	**230**	**104/230 (45%)**	**28/230 (12%)**	**0/230 (0%)**	**65/230 (28%)**	**31/230 (13%)**	**2/230 (1%)**
Skin and subcutaneous tissue disorders	**27/149 (18%)**	**119/149 (81%)**	**149**	**55/149 (37%)**	**13/149 (9%)**	**0/149 (0%)**	**55/149 (37%)**	**26/149 (17%)**	**0/149**
Social circumstances	**0/21 (0%)**	**21/21 (100%)**	**21**	**15/21 (70%)**	**0/21 (0%)**	**0/21 (0%)**	**2/21 (10%)**	**4/21 (20%)**	**0/21 (0%)**
Surgical and medical procedures	**0/17 (0%)**	**17/17 (100%)**	**17**	**13/17 (76%)**	**0/17 (0%)**	**0/17 (0%)**	**0 /17 (0%)**	**4/17 (24%)**	**0/17 (0%)**
Vascular disorders	**7/138 (4%)**	**120/138 (89%)**	**138**	**63/138 (46%)**	**15/138 (11%)**	**0/138 (0%)**	**37/138 (27%)**	**15/138 (11%)**	**8/138 (6%)**

Table 10: Seriousness of AEs related to Mirabegron

Reaction Groups	Non Serious	Serious	Total	Unknown	Resolving	Resolved with sequelae	Recovering	Not resolved	Fatal
Total	11741	2452	14193	7889	1207	69	4084	1525	111
Blood and Lymphatic system disorders	55/57 (96%)	2/57 (4%)	57	19/57 (33%)	8/57 (14%)	0/57 (0%)	25/57 (44%)	4/57 (7%)	1/57 (2%)
Cardiac disorders	845/980 (86%)	135/980 (14%)	980	400/980 (41%)	96/980 (10%)	7/980 (<1%)	373/980 (38%)	84/980 (9%)	20/980 (2%)
Ear and Labyrinth disorders	60/81 (74%)	21/81 (26%)	81	32/81 (39%)	7/81 (9%)	0/81 (0%)	27/81 (33%)	15/81 (19%)	0/81 (0%)
Endocrine disorders	13/13 (100%)	0/13 (0%)	13	8/13 (55%)	0/13 (0%)	0/13 (0%)	2/13 (18%)	3/13 (27%)	0/13 (0%)
Eye Disorders	281/368 (76%)	87/368 (24%)	368	172/368 (47%)	17/368 (5%)	5/368 (1%)	114/368 (31%)	60/368 (16%)	0/368 (0%)
Gastrointestinal disorders	838/1177 (71%)	339/1177 (29%)	1177	483/1177 (41%)	108/1177 (9%)	3/1177 (<1%)	401/1177 (34%)	177/1177 (15%)	5/1177 (1%)
General disorders and administration site condition	1446/1841 (79%)	395/1841 (21%)	1841	1163/1841 (63%)	116/1841 (6%)	3/1841 (<1%)	339/1841 (18%)	170/1841 (9%)	50/1841 (3%)
Hepatobiliary disorders	84/86 (98%)	2/86 (2%)	86	29/86 (34%)	10/86 (12%)	0/86 (0%)	35/86 (41%)	11/86 (13%)	1/86 (1%)
Immune system disorders	105/113 (93%)	8/113 (7%)	113	54/113 (48%)	7/113 (6%)	2/113 (2%)	41/113 (36%)	8/113 (7%)	1/113 (<1%)

Infections and infestations	521/584 (89%)	63/584 (11%)	584	270/584 (46%)	46/584 (8%)	1/584 (<1%)	168/584 (29%)	51/584 (9%)	4/584 (1%)
Injury, poisoning and procedural complications	1056/1232 (86%)	176/1232 (14%)	1232	1094/1232 (89%)	35/1232 (3%)	1/1232 (<1%)	67/1232 (5%)	30/1232 (2%)	5/1232 (1%)
Investigations	1342/1501 (89%)	159/1501 (11%)	1501	787/1501 (52%)	142/1501 (9%)	1/1501 (<1%)	445/1501 (30%)	124/1501 (8%)	2/1501 (<1%)
Metabolism and nutrition disorders	184/199 (92%)	15/199 (8%)	199	89/199 (45%)	25/199 (13%)	0/199 (0%)	64/199 (32%)	19/199 (10%)	2/199 (1%)
Musculoskeletal and connective tissue disorders	383/482 (80%)	99/482 (20%)	482	264/482 (55%)	47/482 (10%)	4/482 (1%)	124/482 (26%)	89/482 (19%)	0/482 (0%)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	129/130 (99%)	1/130 (1%)	130	97/130 (75%)	5/130 (4%)	0/130 (0%)	12/130 (9%)	17/130 (13%)	5/130 (4%)
Nervous system disorders	1157/1398 (82%)	241/1398 (18%)	1398	644/1398 (46%)	112/1398 (8%)	16/1398 (1%)	447/1398 (32%)	167/1398 (12%)	12/1398 (<1%)
Product issues	19/33 (58%)	14/33 (42%)	33	33/33 (100%)	0/33 (0%)	0/33 (0%)	0/33 (0%)	0/33 (0%)	0/33 (0%)
Psychiatric disorders	420/640 (66%)	120/640 (34%)	640	365/640 (57%)	50/640 (8%)	1/640 (<1%)	157/640 (25%)	67/640 (10%)	0/640 (0%)
Renal and urinary disorders	1427/1595 (89%)	168/1595 (11%)	1595	782/1595 (49%)	143/1595 (9%)	5/1595 (<1%)	490/1595 (31%)	171/1595 (11%)	4/1595 (<1%)

Reproductive system and breasts disorders	**119/168 (71%)**	**49/168 (29%)**	**168**	**89/168 (53%)**	**9/168 (5%)**	**0/168 (0%)**	**47/168 (28%)**	**23/168 (14%)**	**0/168 (0%)**
Respiratory, thoracic and mediastinal disorders	**389/438 (89%)**	**49/438 (11%)**	**438**	**184/438 (42%)**	**46/438 (11%)**	**4/438 (1%)**	**146/438 (33%)**	**51/438 (12%)**	**7/438 (2%)**
Skin and subcutaneous tissue disorders	**479/683 (70%)**	**204/683 (30%)**	**683**	**254/683 (37%)**	**88/683 (13%)**	**8/683 (1%)**	**228/683 (33%)**	**105/683 (15%)**	**0/683 (0%)**
Social circumstances	**38/47 (81%)**	**9/47 (19%)**	**47**	**35/47 (82%)**	**2/47 (4%)**	**0/47 (0%)**	**7/47 (9%)**	**3/47 (5%)**	**0/47 (0%)**
Surgical and medical procedures	**214/215 (99%)**	**1/215 (1%)**	**215**	**190/215 (89%)**	**5/215 (2%)**	**0/215 (0%)**	**11/215 (5%)**	**9/215 (4%)**	**0/215 (0%)**
Vascular disorders	**738/835 (88%)**	**95/835 (12%)**	**835**	**352/835 (42%)**	**83/835 (10%)**	**8/835 (1%)**	**314/835 (38%)**	**77/835 (9%)**	**1/835 (<1%)**

Table 11: Seriousness of AEs related to Trospium

Reaction Groups	Non Serious	Serious	Total	Unknown	Resolving	Resolved with sequelae	Recovering	Not resolved	Fatal
Total	526/1557 (34%)	925/1557 (59%)	1557	537/1557 (34%)	592/1557 (38%)	10/1557 (<1%)	200/1557 (13%)	234/1557 (15%)	21/1557 (1%)
Blood and Lymphatic system disorders	1/13 (8%)	12/13 (92%)	13	8/13 (61%)	1/13 (7%)	0/13 (0%)	1/13 (7%)	2/13 (15%)	0/13 (0%)
Cardiac disorders	19/63 (30%)	41/63 (65%)	63	22/63 (35%)	32/63 (51%)	0/63 (0%)	7/63 (11%)	8/63 (13%)	1/63 (2%)
Ear and Labyrinth disorders	4/8 (50%)	4/8 (50%)	8	3/8 (38%)	2/8 (25%)	0/8 (0%)	0/8 (0%)	3/8 (38%)	0/8 (0%)
Endocrine disorders	0 (0%)	0 (0%)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Eye Disorders	42/77 (54%)	34/77 (44%)	77	23/77 (30%)	8/77 (10%)	1/77 (2%)	28/77 (36%)	17/77 (22%)	0/77 (0%)
Gastrointestinal disorders	144/268 (54%)	121/268 (45%)	268	82/268 (31%)	112/268 (46%)	2/268 (1%)	34/268 (13%)	47/268 (18%)	3/268 (1%)
General disorders and administration site condition	72/170 (42%)	98/170 (58%)	170	76/170 (45%)	59/170 (35%)	0/170 (0%)	16/170 (9%)	26/170 (15%)	4/170 (2%)
Hepatobiliary disorders	2/18 (11%)	15/18 (84%)	18	7/18 (41%)	2/18 (12%)	0/18 (0%)	6/18 (36%)	1/18 (6%)	2/18 (12%)
Immune system disorders	6/24 (25%)	17/24 (71%)	24	6/24 (24%)	10/24 (42%)	0/24 (0%)	4/24 (16%)	3/24 (12%)	0/24 (0%)

Infections and infestations	**0/22 (0%)**	**17/22 (77%)**	**22**	**8/22 (41%)**	**9/22 (46%)**	**1/22 (5%)**	**2/22 (8%)**	**2/22 (8%)**	**0/22 (0%)**
Injury, poisoning and procedural complications	**14/76 (20%)**	**56/76 (75%)**	**76**	**39/76 (55%)**	**25/76 (35%)**	**1/76 (2%)**	**7/76 (10%)**	**5/76 (7%)**	**0/76 (0%)**
Investigations	**26/79 (33%)**	**47/79 (62%)**	**79**	**34/79 (43%)**	**24/79 (31%)**	**0/79 (0%)**	**8/79 (10%)**	**13/79 (16%)**	**0/79 (0%)**
Metabolism and nutrition disorders	**5/33 (15%)**	**27/33 (83%)**	**33**	**10/33 (30%)**	**13/33 (40%)**	**0/33 (0%)**	**3/33 (10%)**	**5/33 (16%)**	**2/33 (7%)**
Musculoskeletal and connective tissue disorders	**18/46 (40%)**	**22/46 (50%)**	**46**	**19/46 (41%)**	**16/46 (35%)**	**0/46 (0%)**	**3/46 (6%)**	**8/46 (15%)**	**0/46 (0%)**
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	**0/8 (0%)**	**6/8 (75%)**	**8**	**3/8 (38%)**	**0/8 (0%)**	**0/8 (0%)**	**0/8 (0%)**	**4/8 (50%)**	**1/8 (14%)**
Nervous system disorders	**60/156 (38%)**	**93/156 (60%)**	**156**	**40/156 (26%)**	**70/156 (45%)**	**1/156 (<1%)**	**19/156 (12%)**	**24/156 (15%)**	**1/156 (<1%)**
Product issues	**4/6 (67%)**	**2/6 (33%)**	**6**	**4/6 (67%)**	**2/6 (33%)**	**0/6 (0%)**	**0/6 (0%)**	**0/6 (0%)**	**0/6 (0%)**
Psychiatric disorders	**22/102 (22%)**	**80/102 (78%)**	**102**	**37/102 (37%)**	**56/102 (56%)**	**1/102 (1%)**	**16/102 (16%)**	**4/102 (4%)**	**0/102 (0%)**
Renal and urinary disorders	**29/108 (27%)**	**77/108 (71%)**	**108**	**36/108 (35%)**	**50/108 (50%)**	**1/108 (1%)**	**9/108 (9%)**	**15/108 (15%)**	**3/108 (3%)**

Reproductive system and breasts disorders	**6/16 (43%)**	**7/16 (52%)**	**16**	**5/16 (33%)**	**6/16 (43%)**	**0/16 (0%)**	**0/16 (0%)**	**3/16 (20%)**	**0/16 (0%)**
Respiratory, thoracic and mediastinal disorders	**22/74 (31%)**	**49/74 (66%)**	**74**	**20/74 (27%)**	**31/74 (42%)**	**1/74 (1%)**	**9/74 (12%)**	**12/74 (16%)**	**1/74 (1%)**
Skin and subcutaneous tissue disorders	**61/148 (43%)**	**71/148 (50%)**	**148**	**32/148 (22%)**	**52/148 (35%)**	**0/148 (0%)**	**31/148 (21%)**	**31/148 (21%)**	**2/148 (1%)**
Social circumstances	**2/5 (40%)**	**3/5 (60%)**	**5**	**3/5 (60%)**	**2/5 (40%)**	**0/5 (0%)**	**0/5 (0%)**	**0/5 (0%)**	**0/5 (0%)**
Surgical and medical procedures	**1/5 (20%)**	**4/5 (80%)**	**5**	**4/5 (80%)**	**0/5 (0%)**	**0/5 (0%)**	**1/5 (20%)**	**0/5 (0%)**	**0/5 (0%)**
Vascular disorders	**8/32 (25%)**	**22/32 (62%)**	**32**	**16/32 (50%)**	**10/32 (30%)**	**1/32 (3%)**	**5/32 (15%)**	**1/32 (3%)**	**1/32 (3%)**

Table 12: Seriousness of AEs related to Propiverine

Reaction Groups	Non Serious	Serious	Total	Unknown	Resolving	Resolved with sequelae	Recovering	Not resolved	Fatal
Total	387/1237 (31%)	838/1237 (68%)	1237	412/1237 (33%)	520/1237 (42%)	4/1237 (<1%)	137/1237 (11%)	115/1237 (9%)	14/1237 (1%)
Blood and Lymphatic system disorders	0/19 (0%)	19/19 (100%)	19	3/19 (16%)	7/19 (40%)	0/19 (0%)	1/19 (5%)	2/19 (10%)	1/19 (5%)
Cardiac disorders	3/31 (10%)	27/31 (88%)	31	9/31 (27%)	12/31 (36%)	0/31 (0%)	5/31 (15%)	1/31 (3%)	2/31 (6%)
Ear and Labyrinth disorders	3/7 (34%)	4/7 (56%)	7	2/7 (28%)	3/7 (34%)	0/7 (0%)	0/7 (0%)	2/7 (28%)	0/7 (0%)
Endocrine disorders	0/2 (0%)	2/7 (100%)	2	1/2 (50%)	0/2 (0%)	0/2 (0%)	1/2 (50%)	0/2 (0%)	0/2 (0%)
Eye Disorders	46/91 (47%)	42/91 (43%)	91	29/91 (30%)	36/91 (37%)	3/91 (4%)	8/91 (9%)	18/91 (19%)	0/91 (0%)
Gastrointestinal disorders	77/167 (47%)	88/167 (53%)	167	59/167 (33%)	70/167 (50%)	0/167 (0%)	15/167 (9%)	23/167 (14%)	1/167 (<1%)
General disorders and administration site condition	53/138 (39%)	84/138 (61%)	138	59/138 (44%)	52/138 (37%)	0/138 (0%)	14/138 (9%)	8/138 (5%)	3/138 (2%)
Hepatobiliary disorders	0/26 (0%)	26/26 (100%)	26	4/26 (16%)	11/26 (44%)	0/26 (0%)	7/26 (28%)	2/26 (8%)	0/26 (0%)

Immune system disorders	**0/4 (0%)**	**4/4 (100%)**	**4**	**2/4 (50%)**	**1/4 (25%)**	**0/4 (0%)**	**1/4 (25%)**	**0/4 (0%)**	**0/4 (0%)**
Infections and infestations	**2/20 (10%)**	**18/20 (90%)**	**20**	**4/20 (20%)**	**9/20 (45%)**	**0/20 (0%)**	**3/20 (15%)**	**3/20 (15%)**	**0/20 (0%)**
Injury, poisoning and procedural complications	**19/66 (29%)**	**47/66 (71%)**	**66**	**53/66 (78%)**	**12/66 (16%)**	**0/66 (0%)**	**3/66 (6%)**	**0/66 (0%)**	**0/66 (0%)**
Investigations	**13/60 (22%)**	**45/60 (75%)**	**60**	**17/60 (26%)**	**26/60 (39%)**	**0/60 (0%)**	**7/60 (11%)**	**5/60 (8%)**	**1/60 (<1%)**
Metabolism and nutrition disorders	**3/32 (10%)**	**29/32 (90%)**	**32**	**9/32 (20%)**	**12/32 (40%)**	**0/32 (0%)**	**0/32 (0%)**	**4/32 (11%)**	**0/32 (0%)**
Musculoskeletal and connective tissue disorders	**4/39 (10%)**	**35/39 (90%)**	**39**	**7/39 (16%)**	**22/39 (33%)**	**1/39 (3%)**	**6 / 39 (11%)**	**2/39 (6%)**	**1/39 (3%)**
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	**0/1 (0%)**	**1/1 (100%)**	**1**	**1/1 (100%)**	**0/1 (0%)**	**0/1 (0%)**	**0/1 (0%)**	**0/1 (0%)**	**0/1 (0%)**
Nervous system disorders	**58/157 (37%)**	**96/157 (61%)**	**157**	**44/157 (28%)**	**74/157 (47%)**	**0/157 (0%)**	**17 /157 (9%)**	**16/157 (8%)**	**2/157 (1%)**
Product issues	**7/7 (100%)**	**0/7 (0%)**	**7**	**6/7 (90%)**	**1 (10%)**	**0/7 (0%)**	**0/7 (0%)**	**0/7 (0%)**	**0/7 (0%)**
Psychiatric disorders	**36/163 (24%)**	**123/163 (75%)**	**163**	**45/163 (27%)**	**80/163 (49%)**	**0/163 (0%)**	**20/163 (12%)**	**12/163 (7%)**	**0/163 (0%)**

Renal and urinary disorders	**12/83 (14%)**	**71/83 (86%)**	**83**	**24 /83 (34%)**	**30 /83 (45%)**	**0/83 (0%)**	**8 /83 (14%)**	**6 /83 (10%)**	**1/83 (1%)**
Reproductive system and breasts disorders	**5/7 (71%)**	**2/7 (29%)**	**7**	**3/7 (43%)**	**1/7 (14%)**	**0/7 (0%)**	**0/7 (0%)**	**2/7 (29%)**	**0/7 (0%)**
Respiratory, thoracic and mediastinal disorders	**7/35 (21%)**	**27/35 (77%)**	**35**	**6/35 (18%)**	**12/35 (36%)**	**0/35 (0%)**	**10/35 (30%)**	**3/35 (9%)**	**2/35 (6%)**
Skin and subcutaneous tissue disorders	**30/53 (59%)**	**23/53 (41%)**	**53**	**14/53 (28%)**	**23/53 (46%)**	**0/53 (0%)**	**10/53 (20%)**	**3 /53 (2%)**	**0/53 (0%)**
Social circumstances	**0/1 (0%)**	**1/1 (100%)**	**1**	**0/1 (0%)**	**1/1 (100%)**	**0/1 (0%)**	**0/1 (0%)**	**0/1 (0%)**	**0/1 (0%)**
Surgical and medical procedures	**1/5 (20%)**	**4/5 (80%)**	**5**	**2/5 (40%)**	**2/5 (40%)**	**0/5 (0%)**	**0/5 (0%)**	**0/5 (0%)**	**0/5 (0%)**
Vascular disorders	**8/28 (29%)**	**20/28 (71%)**	**28**	**9/28 (36%)**	**14/28 (48%)**	**0/28 (0%)**	**2/28 (8%)**	**1/28 (4%)**	**0/28 (0%)**

Supplementary Digital Material

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