Title: Comparison of Risk of Neurovascular and Cardiovascular Side-Effects between Inhaled and Oral Anticholinergic Agents

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How this fits in with quality in primary care

What do we know?

Inhaled anticholinergics, namely tiotropium and ipratropium have been implicated in causing adverse neuro- and cardio-vascular events, although the evidence is not consistent. Further, the presence of COPD may also be a contributing factor to such events.

What does this paper add?

Based on adverse drug reactions reported to the Food and Drug Administration (FDA) in the US, anticholingeric agents appear to differ in their propensity to cause adverse neuro- and cardio-vascular adverse effects. Inhaled anticholinergics appear to pose a greater risk overall for vascular (neuro- and cardio-) adverse events compared to oral agents. However, for some vascular adverse effects, in particular stroke and hypertension, oral agents may pose a greater risk. These findings should be borne in mind when prescribing such agents to at risk patients.

Abstract

Purpose: The purpose of this study is to examine the risk of cardiovascular diseases among users of both inhaled (ipratropium bromide or tiotropium bromide) and oral (oxybutynin and propantheline, solifenacin, tolterodine) anticholinergics**. Method:** This retrospective study based on data were obtained from the Food and Drug Administration (FDA) regarding subjects who received either an inhaled or oral form of an anticholinergic drug and experienced some side-effect during the period 1988 to 2009. The recorded data included: patient's age, sex, list of drugs and side effects. Side-effect rates for the anticholinergic drugs were compared using univariate (Chi-square) and multivariate (Logistic regression) methods. **Results:** The files from the FDA held data for 36491 different subjects, of whom 2610 (7.15%) experienced a cardiovascular or neurovascular side-effect. Subjects were classified as taking the oral (45%) or inhaled (55%) class of the drug, with only 109 (0.3%) subjects taking drugs in both forms. Side-effect rates differed between anticholinergic drugs. Stroke and hypertension were significantly more common for subjects taking an oral drug, while the other vascular side-effects (cardiac ischaemia, arrhythmias, cardiac failure, cardiac arrest) were significantly more common for subjects taking an inhaled drug. These differences persisted after adjustment for age and gender. **Conclusion:** This observational study of recorded side-effects showed that, except for stroke and hypertension, patients who were treated with an inhaled anticholinergic drug appeared to be at higher risk of developing neurovascular or cardiovascular side-effects, than those treated with an oral drug. However, physicians should also be aware that oral anticholinergic drugs may have similar adverse impacts on health. Further studies on the association between anticholinergic drugs and cardiovascular and neurovascular side effects are recommended.

Introduction

Inhaled anticholinergic bronchodilators are widely used in chronic obstructive pulmonary disease (COPD). Ipratropium bromide is a short acting bronchodilator and its duration of action does not exceed 6 hours. In contrast, Tiotropium bromide is a long acting bronchodilator whose effect lasts for more than 24 hours. It exerts its effect by blocking the M3 muscarinic receptors. About eight million patients with COPD worldwide have been prescribed tiotropium to manage their symptoms since its approval in 2002.[1] It is an effective drug, producing improvement in lung function, dyspnoea, and exercise tolerance, as well as reducing both respiratory mortality and exacerbations. [2]

A 4-year UPLIFT trial of tiotropium in patients with COPD demonstrated a reduction in cardiovascular side effects such as (myocardial infarction and congestive heart failure) associated with tiotropium compared with placebo group. Similar results in the published pooled safety analysis of tiotropium were demonstrated that cardiovascular adverse events did not occur more frequently among patients who receiving Tiotropium.[3]

However, other studies demonstrated that patients who were on anticholinergic drugs at risk of having cardiovascular and or/ neurovascular side effects. Singh et al undertook a systematic review to determine whether inhaled anticholinergics increase the risk of major cardiovascular events.[4] Their review involved 17 randomised controlled trials (RCTs) in which patients had more than 30 days follow-up, involving 14,783 patients of average age 49-68 years. The majority of the patients in the trials were males (49-99%). Inhaled anticholinergics increased the risk of the composite end point, myocardial infarction (risk ratio 1.53, 95% CI 1.05-2.23) and cardiovascular death (risk ratio 1.80, 95% CI 1.17-2.77), but not stroke or all-cause death. This increased risk was seen in long-term use (follow-up 48

weeks to 5 years), but not short-term (6-26 weeks). Ipratropium had a risk ratio for major cardiovascular events of 1.70 (95% CI 1.19-2.42) compared to tiotropium risk ratio 1.43 (95% CI 0.95-2.16).

Oral anticholinergic drugs such as tolterodine are commonly used in the treatment of overactive bladder (OAB) syndrome, which is characterised by urgency, with or without urge incontinence, usually with frequency and nocturia.[5,6] Antimuscarinic drugs prevent involuntary bladder contraction by blocking muscarinic receptors M2 and M3 which are found in human bladder.[7] The heart contains a high density of M2 muscarinic receptors as well, thus tachycardia can be a negative result of blocking these receptors due to an imbalance between the sympathetic and parasympathetic effects on the heart. [6]

Anticholinergic drugs are considered to be safe and well tolerated agents despite untoward side effects such as constipation, blurred vision and dry mouth, which result from the blockage of muscarinic receptors. [6,7] Tachycardia was not considered to be a serious side effect of anticholinergic drugs in OAB studies. However, even a small elevation in heart rate can be problematic, as the prevalence of OAB increases with advancing age, with about 17% of the general population who are 40 years or older having OAB syndrome. Thus, an increased heart rate in older patients elevates their risk of developing cardiovascular co-morbidities such as heart failure. [5,7,8]

This study was therefore undertaken to compare the neurovascular and cardiovascular side effects which have been reported in patients treated with either inhaled or oral anticholinergic drugs.

Method

A literature review was performed by searching Medline using terms such as “inhaled anticholinergics”, “oral anticholinergics” and “cardiovascular disease” without date limitations. Cardiovascular disease categorized in this report into: cardiac ischaemia, hypertension, arrhythmia, cardiac failure, cardiac arrest, ECG abnormality and unspecific cardiac events. While the neurovascular disease involves stroke in this study. A request was made to the FDA for all the case reports of side-effects associated with the use of anticholinergics, between 1988 and 2009. Analyses of this database are presented in this report.

All patients were treated with an oral or inhaled form of an anticholinergic drug. This file listed all side effects which were recorded from these patients between 1988 to 2009. There was no information in the FDA file concerning subjects who were taking these drugs and had no side-effects which might affects the results accuracy. Hence the present study is aimed at comparing the profile of side-effects (Cardiovascular / Neurovascular / Other) between the drugs, classified as oral or inhaled, and also treated separately.

The drug which each subject was taking at the time of the side-effect was recorded. If a subject was taking more than one anticholinergic drug, they were treated as a separate ‘mixed’ group. Tables were constructed showing the drug taken by the type of side-effect, and a Chi-square statistic was obtained to identify if there were any differences in side-effect profile for the different drugs. A similar table was constructed after classifying the drugs into the oral or inhaled categories. A logistic regression model was developed to identify if any differences between rates of vascular side-effects (cardiovascular or neurovascular taken

together) persisted after adjustment for age and gender. Finally, a similar logistic regression model was applied only to those subjects having a vascular side-effect, to identify any differences between the rates of cardiac and neurological side-effects between drugs. Results were presented as percentages of subjects experiencing the side-effect (univariate analyses) and Odds Ratios (OR) and their 95% confidence intervals (multivariate analyses). In all analyses, a p-value ≤ 0.05 was considered to indicate a significant association.

The FDA file listed side-effects in some detail. These were classified into categories as follows: *stroke*: (carotid arteriosclerosis, carotid artery disease, carotid artery occlusion, carotid artery stenosis, cerebral infarction, cerebral ischaemia, cerebrovascular accident, transient ischaemic attack), *cardiac ischaemia* (acute myocardial infarction, myocardial infarction**,** myocardial ischaemia**,** angina pectoris**,** acute coronary syndrome), *arrhythmia* (arrhythmia, bradycardia, cardiac pacemaker, palpitation, atrial fibrillation, atrial tachycardia, bradyarrhythmia, cardiac flutter, atrioventricular block, sinus arrhythmia, sinus bradycardia, ventricular arrhythmia, ventricular extrasystole, ventricular fibrillation, tachyarrhythmia, tachycardia, ventricular tachycardia, cardioversion), *cardiac failure* (cardiac failure, ventricular dysfunction, ventricular failure), *cardiac arrest* (cardio-respiratory arrest, cardiogenic shock), *ECG abnormalities* (electrocardiogram Q waves, electrocardiogram QRS, electrocardiogram QT, electrocardiogram T waves), *cardiac death* (sudden cardiac death, accidental death) *unspecific cardiac events* (cardiac disorder, ventricular hypertrophy). All side-effects listed above other than stroke ("neurovascular") were classified as "cardiovascular" side effects for the purpose of analyses.

Results

The FDA provided data on a total 36,491 subjects, 11,296 males with a mean age of 69.8 ±14.5 years and 21,839 females with a mean age of 67.5 ±15.6 years, while the gender of 3,356 patients was unknown. In 61% of cases the age was missing from the record. However these cases were divided approximately equally between genders. Table 1 below shows the numbers of people taking each anticholinergic drug and experiencing each type of neurovascular and cardiovascular side-effect. The column headed 'Combined' shows subjects who were taking more than one anticholinergic drug. Of the 1199 subjects in this group, 1192 were taking two drugs, and seven subjects were taking three.

With the categorisation of cardiovascular and neurovascular side-effects as stated above in the method, records were classified as having either one of these side-effects alone, both together or neither. When tabulated against the type of drug taken, differences in the profile of side-effects emerge (Table 2).

The highly significant Chi-square statistic indicates that the side-effect profiles of the different drugs are significantly different. On inspection of the table, it appears that a very small number of subjects experience both neurological and cardiovascular side-effects, that very few records in the file are associated with propantheline, and that the majority of side-effects are of a non-cardiovascular or neurological type "other" (approximately 93% overall). However, there do appear to be differences in the proportions of subjects experiencing the two types of vascular side-effect. Table 3 suggests that cardiovascular side effects may be more common for subjects taking ipratropium (11.4%) than for other drugs (generally approximately 6%) and neurovascular side effects may be more common for oxybutynin (2.8%) than other drugs (approximately 1% or less).

Note that the ‘Combined’ row in Table 2 includes subjects who took any combination of drugs, whereas it includes only people who took drugs by different routes in Table 3, so that people who took two oral drugs appear in the ‘Oral’ row in this table, but in the ‘Combined’ row of Table 2. The highly significant Chi-square statistic for table 3 indicates a difference in side-effect profile between the oral and inhaled drugs.

In order to account for any differences in side-effect rate attributable to differences in the age or gender of the subjects, a logistic regression analysis was undertaken, with age, gender and type of drug as independent variables. The outcome variable for the regression analysis was the occurrence of a vascular side effect (cardio or neuro) versus other side-effect. The results of this analysis are shown in Table 4. Because the number of vascular side effects amongst people taking the drugs by both routes (oral and inhaled) is only 5/109, this small group was excluded from the regression modelling procedure. This means that the regression is based on 36,382 records rather than the full database of 36,491 records (Table 4).

The analysis shows that the oral drugs had a significantly lower association with a vascular side-effect than the inhaled drugs, after adjustment for age and gender. Females were less likely than males to experience a vascular side-effect. The younger age groups carried a similar risk of the vascular event as the older age-group (over 78 years), but the large group of records with missing ages corresponded to a much higher risk group. There are number of possible explanations for this, but the main point is that by including these subjects, their increased risk of vascular events can be taken into account when examining the odds ration associated with the route of administration. The alternative would be to exclude these subjects from analysis, but this would weaken the overall results as they form such a large group (n=22,213).

In order to investigate any differences between individual drugs, a second Logistic Regression model was applied to the data (Table 5). Subjects taking any combination of drugs were excluded from analysis, leaving a total of 35,267 records.

The data in Table 5 indicates that, after adjustment for age and gender, there remain some significant differences in the chance of a vascular side-effect between the various anticholinergic drugs. With the tiotropium group as reference, ipratropium and oxybutynin had significantly greater proportions of reported vascular side-effects, while solifenacin use appeared to be associated significantly lower risk of these side-effects. This analysis demonstrated a significant difference in the risk of a vascular side effect between the two inhaled drugs (tiotropium and ipratropium), with tiotropium appearing to have a much lower risk. The chance of a vascular side-effect with the tolterodine group appeared to be not significantly different from the Tiotropium group.

The analyses above treat all vascular side-effects as a single group. In order to identify if the drugs vary in their association with particular side-effects, a third series of Logistic Regression models was applied to the records relating to a vascular side-effect only. In this way, the differences already noted above were removed, and the analyses could focus on any differences in proportions of cases in each drug group associated with the specific endpoints. Odds ratios for age and gender are not presented as they are not the primary focus for this research, but the odds ratios for the drugs presented in Table 6 have been adjusted for these variables.

Discussion

Inhaled anticholinergics

The results show that the use of inhaled anticholinergics significantly increases the risk of developing cardiovascular side effects when compared to the use of oral anticholinergic agents as a group, when adjustment was made for age and gender (Adjusted OR 0.79; 95% CI 0.73-0.86, $p < 0.0001$). These findings were similar to a systemic review of 17 clinical trials involving 14,783 patients which suggested that inhaled anticholinergics increase the risk of mortality and/ or cardiovascular events. [4, 9] In comparison to tiotropium, ipratropium appeared more likely to be associated with vascular events [the composite of neuro- and cardio-] (AOR 1.78; 95% CI 1.58-2.00). However, when looking at individual adverse effects ipratropium was less likely to be associated with stroke (AOR 0.62; 95% CI 0.40-0.96, $p \leq 0.05$), but more likely to be associated with cardiac arrhythmias (AOR 1.31, 95% CI 1.04-1.64, $p \leq 0.05$), cardiac arrest (AOR 3.70; 95% CI 2.38-5.75, $p < 0.0001$), ECG abnormalities (AOR 3.37; 95% CI 1.65-7.72) and other unspecified cardiac events (AOR 1.80; 95% CI 1.21-2.68, $p = 0.004$).

These results are similar to the findings of Singh et al which suggest that ipratropium was overall more likely to cause major cardiovascular events. A large clinical trial did demonstrate a significant increase in cardiovascular mortality and morbidity in patients with ipratropium compared with placebo.[10] It also showed a higher incidence of supraventricular tachycardia amongst ipratropium users, which was attributed to the drug's vagolytic effects. [10]

There is a suggestion that the risk/benefit ratio of inhaled anticholinergic treatment should be assessed for patients according to their cardiovascular tendency. Patients who are at a higher risk of developing cardiovascular diseases and who have mild to moderate symptoms of COPD should not use anticholinergics while, those without any cardiac risks but with severe COPD symptoms are strongly recommended to use these agents. [11]

Oral anticholinergics

Oral anticholinergic drugs are widely used to manage OAB in elderly patients who are prone to urge incontinence. Such drugs act in OAB by blocking cholinergic M2 and M3 receptors in bladder smooth muscle. M2 receptors are present in the heart as well and are responsible for slowing heart rate, thus, blocking these receptors may lead to tachycardia. OAB patients tend to be elderly and any impact on their heart rate will risk them to cardiovascular comorbidities.[5] Because of this, it was decided to undertake a comparison of risk of cardiovascular and neurovascular side effects with inhaled anticholinergic (tiotropium) and oral anticholinergics.

Solifenacin succinate

Solifenacin succinate is a more recently developed antimuscarinic drug. [8,13] Solifenacin has a higher selectivity to M3 over M2 receptors compared with other antimuscarinic drugs such as tolterodine. [8] Solifenacin has shown efficacy in improving symptoms of OAB, and is reported to be well tolerated without any serious cardiovascular side effects. [13]

The analysis comparing solifenacin to tiotropium demonstrated that solifenacin was less likely to be associated with vascular events [the composite of neuro- and cardio-] (AOR 0.65; 95% CI 0.54-0.77). However, in the case of each specific side effect, solifenacin was associated with significantly greater risk of hypertension (AOR 2.59; 95% CI 1.53-4.36, p = 0.0004) and ECG abnormality (AOR 6.26; 95% CI 2.39-16.36, p = 0.0002), when compared to tiotropium.

There is a case report of an 81 year-old-female who was using solifenacin 5 mg once daily for about 3 weeks who developed QT prolongation and torsades de point (TDP). [14] Whilst, ECG abnormalities were reported with solifenacin, the FDA files lacked critical information

such as past medical history, genetic factors, and electrolyte status. Without such information one cannot be sure whether solifenacin was indeed the sole cause of these side effects or if there are other factors involved.

The FDA data failed to reveal any significant association between the use of solifenacin and stroke, cardiac ischaemia, arrhythmias, cardiac failure, cardiac arrest or unspecific cardiac events. No heart rate elevation was reported of an open-label, post-marketing surveillance study in which the cardiac safety of solifenacin in 4450 patients with OAB was examined during a 12 week treatment course. [8] One of the possible explanations for this result is that receptors which are exposed to long-term muscarinic receptor antagonists can be modified, similar to tissue denervation, which cases upregulation of the receptors. Therefore, the heart became less responsive to the heart rate-elevating effects of solifenacin. [8] Also, this study demonstrated that solifenacin has no effect on blood pressure during this course, but no explanation of such result was provided. In contrast, hypertension was associated significantly with solifenacin according to the FDA results (p= 0.0004).

Toltrodine

Tolterodine is a competitive non-selective M2/M3 receptor blocker. [5,15] Due to its bladder selectivity, tolterodine has been a well tolerated agent compared with other antimuscarinic drugs. [16] Further, age does not appear to be a factor in determining the safety profile of tolterodine based on randomized, double-blind studies, as no laboratory (clinical chemistry and haematological parameters) or electrocardiographic changes were reported among older patients who were on tolterodine.[15,17,18]

In comparison to tiotropium, tolterodine appears to have the similar propensity to be associated with both cardiovascular and neurovascular events (AOR 0.94; 95% CI 0.85-1.04, p = 0.2428). However, the analysis of individual side effects demonstrated that tolterodine

was more likely to be associated with neurovascular side effects (stroke) (AOR 2.13; 95% CI 1.58-2.87, $p < 0.001$) and hypertension (AOR 4.40; 95% CI 3.21-6.03, $p < 0.0001$), but less likely to be associated with cardiac ischaemia (AOR 0.54; 95% CI 0.40-0.72, $p < 0.0001$), arrhythmia (AOR 0.68; 95% CI 0.55-0.84, $p = 0.0002$) and cardiac failure (AOR 0.51; 95% CI 0.37-0.70, $p < 0.0001$).

Ventricular arrhythmia, atrial fibrillation, cardiac failure, palpitations, bradycardia, collapse, transient ischaemic attack and hypertension are included in postmarketing reports of neurovascular and cardiovascular side effects of tolterodine. These are reported infrequently and discussed in the manufacturer's product information but supporting evidence of causality is lacking.[15]

The results of a study in the UK, using a technique of prescription-event monitoring showed that tolterodine is a well tolerated agent in general practice at the recommended daily dose and is associated with infrequent cardiac side effects. [17] It showed that only 0.3 % of patients using tolterodine had cardiovascular side effects such as tachycardia or palpitations, atrial fibrillation and chest pain. [17] In contrast, in another study involving 162 healthy participants who were aged 50 or more, tolterodine users experienced a significant increase in heart rate compared with darfinacin (a highly selective M3 receptor blocker) and placebo. [5]

Tachycardia is a serious event as it may increase the risk of patients developing congestive heart failure and arrhythmias. [5]

Smoking, hypertension, hyperlipidaemia, low physical activity and obesity are all risk factors which have an important role in causing stroke. FDA data provided did not have sufficient information for patients on tolterodine to determine whether it was solely the drug which was responsible for patient's cerebrovascular events (stroke) or whether they were due to other risk factors. [19] Furthermore, tolterodine is metabolised completely by the liver and excreted

renally. Thus, patients with hepatic and or/ renal impairment will have a higher serum concentration and a longer elimination half-life. [17, 20] The FDA data did not contain information on patients' renal or liver function. Renal and/or hepatic dysfunction could influence patients' risk of tolterodine-related side effects.

Oxybutynin

Oxybutynin is an anticholinergic drug with some selectivity for M1 and M3 over M2 receptors. A study of 21 patients taking oxybutynin to treat their OAB symptoms suggested that oxybutynin does not cause QTc prolongation or tachycardia at recommended doses even if the patients are at high risk of developing cardiovascular diseases. This may relate to the selectivity of oxybutynin for M3 compared to M2 receptors. However, higher doses of oxybutynin may cause QT prolongation. [12] A 34 year old female who ingested an overdose of nearly 100 mg of oxybutynin experienced hypertension and sinus tachycardia with frequent ventricular ectopics and bigeminy. [21]

Based on the FDA data oxybutynin more likely to be associated with cardiovascular and neurovascular events compared with tiotropium (AOR 1.38; 95% CI 1.16-1.64). This was true in the case of stroke (AOR 3.52; 95% CI 2.34-5.28, $p < 0.001$), hypertension (AOR 2.99; 95% CI 1.85-4.82, $p < 0.0001$), cardiac ischaemia (AOR 0.23; 95% CI 0.11-0.46, $p < 0.0001$) and arrhythmia (AOR 0.52; 95% CI 0.36-0.73, $p = 0.0002$).

About half of the hypertensive patients were on antihypertensive medications to control their blood pressure which indicates that they suffered from hypertension prior to the commencement of oxybutynin as some patients drug lists were provided by the FDA file.

Propantheline bromide

Propantheline bromide is an antimuscarinic agent which has been used in the past in duodenal ulcer treatment to inhibit acid secretion. It acts by blocking both M1 and M2 receptors. M1 receptors are located on the postganglionic neurons in the stomach wall and M2 receptors are located on the parietal cell membranes. It is also used in the treatment of OAB, but it use has been reduced with the introduction of newer agents such as oxybutynin. Analysis of the FDA data failed to demonstrate any significant increase in the risk of adverse cardiovascular or neurovascular events possibly because of the small number of patients in each side effects group.

In a placebo-controlled, double-blind study of 10 duodenal ulcer patients, a significant increase in heart rate was seen ($p< 0.05$) in those who were treated with propantheline. [22] This was the only evidence found of the association between oral propantheline and risk of cardiovascular events.

Limitations

This is an observational study of subjects taking an anticholinergic drug and experiencing side-effects which were voluntarily reported to the FDA. The analyses aim to compare the side-effects profile between drugs. However, the analyses cannot compare the absolute rate of side-effects as there were no data on the number of subjects who were taking these drugs but did not experience any side-effects. Because the data assembled by the FDA are reported on a voluntary basis, its completeness is somewhat uncertain. If under reporting of side effects is different for the different drugs, this could lead to a bias.

Some important information was not available from this database, including: past medical history, patients details (weight, smoking status, cholesterol levels, blood pressure) which all have a negative influence on the heart and brain. There were no data on the patients' liver and renal function which may influence the drug safety profile. The gender of 11,296 patients was missing from the FDA data. This group of patients were treated as a separate group in the analysis so that some adjustment for their unknown age could be made. Accurate ages for these patients would have made the comparisons between drugs more precise, as both advancing age and male gender influence the risk of developing cardiovascular and cerebrovascular disease.

Conclusion

It is clear that inhaled anticholinergic drugs are associated with neurovascular and cardiovascular side effects. In comparing tiotropium with oral anticholinergics, these adverse effects appear to be less common with tolterodine and solifenacin but were reported more frequently with oxybutynin. Patients who are using the oral anticholinergics should be aware that they may suffer such side-effects.

A large randomised controlled trial would be required in order to confirm the trends found in this observational study to determine the true nature of the risk of neuro- and cardio-vascular adverse events amongst users of anticholinergic agents both inhaled and oral.

Conflict of Interest

None of the authors have any conflict of interest.

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Table 1: Numbers of people taking each drug and experiencing each type of adverse reaction. Rows highlighted in bold print are total number of subjects experiencing any side effect within the group (neuro, cardiovascular, or both). Totals for each specific side effect within each group include subjects identified as having that side effect, regardless of any other side effect they may have experienced. Therefore, the addition of the numbers in each cardiovascular side effect for each drug, for example, may exceed the total of cardiovascular side effects (bold).

Adverse Effect	*Number of Patients						
	Ipratropium	Tiotropium	Oxybutynin	Tolterodine	Solifenacin	Propantheline	Combined
Total neurovascular SE	24	95	44	113	16	0	15
Stroke	29	102	48	124	16	0	15
Total cardiovascular SE	434	887	131	568	141	4	111
Cardiac Ischaemia	79	204	9	76	25	0	12
Hypertension	32	68	30	171	23	3	5
Arrhythmias	246	423	59	261	83	1	41
Cardiac Failure	92	174	27	61	19	0	35
Cardiac Arrest	66	36	10	17	11	0	8
Abnormal ECG	20	11	5	17	9	0	0
Cardiac Death	2	3	0	0	0	0	1
Cardiac – Unspecified	50	66	4	52	3	0	17
Both Cardiovascular & neurovascular SE	5	7	4	11	0	0	0
Non-vascular side-effect	3357	14396	1386	10978	2670	21	1073
Total Subjects	3820	15385	1565	11670	2827	25	1199

* Note that some patients suffered more than one adverse effect

Table 2: Relationship between side effect and drug. In each cell of the table are the number of subjects, and the percentage of those in each row who experienced each type of side-effect. Subjects with both cardiovascular and neurovascular side-effects, and subjects taking propantheline were excluded from the calculation of the Chi-square statistic in the following table because of the small numbers in these groups. The Chi-square statistic was highly significant ($p<0.0001$).

Drug	Side-Effect				
	Cardiovascular only	Neurovascular only	Both cardio- and neuro-vascular	Other Side Effects	Total
Ipratropium	434 (11.4%)	24 (0.6%)	5 (0.1%)	3357 (87.9%)	3820
Tiotropium	887 (5.8%)	95 (0.6%)	7 (0.1%)	14396 (93.6%)	15385
Oxybutynin	131 (5.8%)	44 (2.8%)	4 (0.3%)	1386 (88.6%)	1565
Tolterodine	568 (4.9%)	113 (1.0%)	11 (0.1%)	10978 (94.1%)	11670
Solifenacin	141 (5.0%)	16 (0.6%)	0	2670 (94.5%)	2827
Propantheline	4 (16.0%)	0	0	21 (84%)	25
Combined	111 (9.3%)	15 (1.3%)	0	1073 (89.5%)	1199
Total	2276	307	27	33881	36491

Table 3: Relationship between side effect and drug.
In each cell of the table are the number of subjects, and the percentage of those in each row who experienced each type of side-effect. The 'Combined' group contains records where anticholinergic drugs were taken by both routes. Subjects with both cardiovascular and neurovascular side-effects, and subjects taking propantheline were excluded from the calculation of the Chi-square statistic in the following table because of the small numbers in these groups. The Chi-square statistic was highly significant ($p<0.0001$), indicating that the prevalence of side effects differed for oral and inhaled drugs.

Drug	Side-Effect				
	Cardio only	Neuro only	Both cardio and neuro	Other SE	Total
Oral	857 (5.3%)	183 (1.1%)	15 (0.1%)	15247 (93.5%)	16302
Inhaled	1414 (7.0%)	124 (0.6%)	12 (0.1%)	18530 (92.3%)	20080
Combined	5 (4.6%)	0	0	104 (95.4%)	109
Total	2276	307	27	33881	36491

Table 4: Influence of Gender and Agent. This Logistic regression analysis is based on 36,382 records, containing 2,605 vascular events). Subjects taking both oral and inhaled drugs were excluded from this analysis because they were small number (n=109). The term 'Endpoint' refers to the subjects who experienced a vascular side-effect.

Variable	Events	Odds Ratio	95% confidence interval	p-value
Gender				
Male	1055	1 (reference)		
Female	1407	0.72	0.66 to 0.79	<0.0001
Unknown	143	0.60	0.49 to 0.72	<0.0001
Age				
> 78	346	1 (reference)		
63-78	775	0.92	0.81 to 1.06	0.25
<63	352	1.07	0.91 to 1.25	0.43
Unknown	1132	2.06	1.81 to 2.34	<0.0001
Route:				
Inhaled	1550	1 (reference)		
Oral	1055	0.79	0.73 to 0.86	<0.0001

Table 5: Comparative Effects of Different Anticholinergic Agents. Tiotropium was named as the reference drug for the drug variable in the model. This means that the Odds Ratios for the other drugs are expressed relative to the side-effect rate for tiotropium. The outcome variable for the regression analysis was the occurrence of a vascular side effect (cardio or neuro).

Variable	Endpoints/Total	Odds Ratio	95% confidence interval	p-value
Gender				
Male	998/10778	1 (reference)		
Female	1340/21165	0.72	0.66 to 0.78	<0.0001
Unknown	142/3324	0.61	0.51 to 0.74	<0.0001
Age				
> 78	328/3348	1 (reference)		
63-78	752/6608	0.91	0.79 to 1.04	0.18
<63	339/3664	1.16	0.98 to 1.36	0.08
Unknown	1061/21647	2.08	1.82 to 2.39	<0.0001
Drug:				
Tiotropium	989/15385	1 (reference)		
Ipratropium	463/3820	1.78	1.58 to 2.00	<0.0001
Oxybutynin	179/1565	1.38	1.16 to 1.64	0.0003
Tolterodine	692/11670	0.94	0.85 to 1.04	0.2428
Solifenacin	157/2827	0.65	0.54 to 0.77	<0.0001

Table 6: **Logistic regression analyses, adjusting for age and gender, applied to subjects who experienced a vascular side-effect.** In these analyses, the subjects who took more than one anticholinergic drug were excluded. As before, tiotropium was taken as the reference level for the Odds Ratios presented. These analyses are based on 2,480 records.

Endpoint	Drug	Endpoints / Total	Odds Ratio	95% confidence interval	p-value
Stroke (n=319)	Tiotropium	102/989	1 (reference)		
	Ipratropium	29/463	0.62	0.40 to 0.96	0.0311
	Oxybutynin	48/179	3.52	2.34 to 5.28	<0.001
	Tolterodine	124/692	2.13	1.58 to 2.87	<0.001
	Solifenacin	16/157	1.01	0.57 to 1.78	0.9815
Cardiac Ischaemia (n=393)	Tiotropium	204/989	1 (reference)		
	Ipratropium	79/463	0.82	0.61 to 1.10	0.1811
	Oxybutynin	9/179	0.23	0.11 to 0.46	<0.0001
	Tolterodine	76/692	0.54	0.40 to 0.72	<0.0001
	Solifenacin	25/157	0.85	0.53 to 1.36	0.4926
Hypertension (n=324)	Tiotropium	68/989	1 (reference)		
	Ipratropium	32/463	1.01	0.65 to 1.56	0.9755
	Oxybutynin	30/179	2.99	1.85 to 4.82	<0.0001
	Tolterodine	171/692	4.40	3.21 to 6.03	<0.0001
	Solifenacin	23/157	2.59	1.53 to 4.36	0.0004
Arrhythmia (n=1072)	Tiotropium	423/989	1 (reference)		
	Ipratropium	246/463	1.31	1.04 to 1.64	0.0213
	Oxybutynin	59/179	0.52	0.36 to 0.73	0.0002
	TolterodineSolifenacin	261/692 83/157	0.68 1.27	0.55 to 0.84 0.89 to 1.80	0.0002 0.1893
Cardiac failure (n=373)	Tiotropium	174/989	1 (reference)		
	Ipratropium	92/463	1.32	0.99 to 1.76	0.0615
	Oxybutynin	27/179	0.91	0.57 to 1.43	0.6732
	Tolterodine	61/692	0.51	0.37 to 0.70	<0.0001
	Solifenacin	19/157	0.63	0.37 to 1.06	0.0788
Cardiac Arrest (n=140)	Tiotropium	36/989	1 (reference)		
	Ipratropium	66/463	3.70	2.38 to 5.75	<0.0001
	Oxybutynin	10/179	1.32	0.63 to 2.78	0.4608
	Tolterodine	17/692	0.71	0.38 to 1.30	0.2640
	Solifenacin	11/157	2.02	0.98 to 4.17	0.0586
ECG abnormality (n=62)	Tiotropium	11/989	1 (reference)		
	Ipratropium	20/463	3.57	1.65 to 7.72	0.0012
	Oxybutynin	5/179	2.24	0.73 to 6.84	0.1563
	Tolterodine	17/692	2.22	0.99 to 5.00	0.0536
	Solifenacin	9/157	6.26	2.39 to 16.36	0.0002
Cardiac unspecified (n=175)	Tiotropium	66/989	1 (reference)		
	Ipratropium	50/463	1.80	1.21 to 2.68	0.0036
	Oxybutynin	4/179	0.37	0.13 to 1.03	0.0577
	Tolterodine	52/692	1.15	0.77 to 1.71	0.5000
	Solifenacin	3//157	0.33	0.10 to 1.09	0.0687