PUK28

Persistence and adherence with mirabegron, a beta-3 receptor agonist, versus antimuscarinics in overactive bladder: early experience in Canada

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INTRODUCTION

- Overactive bladder (OAB) is a common, distressing, chronic condition characterised by urinary urgency with or without urinary incontinence, usually with increased daytime frequency and nocturia[1]
- Antimuscarinic drugs have been the mainstay of medical therapy of OAB, but persistence with treatment is generally poor[2] and there is an unmet need for alternative medications
- Anticholinergic side-effects such as dry mouth and constipation commonly occur with antimuscarinics[3], which may contribute towards patients stopping treatment
- Mirabegron is the first in a novel class of β_3-adrenoceptor agonists, and has a different mechanism of action from that of antimuscarinics
- Mirabegron appears to be as effective as antimuscarinic drugs[4,5], whilst having a low incidence of treatment-emergent adverse events[6]
- However, it is not known if the favourable efficacy and tolerability of mirabegron are reflected in increased persistence levels

OBJECTIVE

- To report early experience with mirabegron in Canada, by comparing persistence and adherence versus commonly used antimuscarinic drugs
- To achieve this by analysing retrospective claims data from the largest Private Drug Plan database in Canada, using a prospectively defined method with robust statistical analyses

METHODS

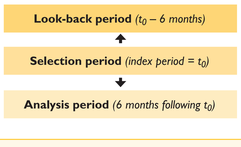
Data source

- Prescription claims from the Canadian Private Drug Plans (PDP) were provided by IMS Brogan (IMS Health Canada Inc., Kirkland, Quebec, Canada)
- This database captures 68% of all private claims and 86% of pay-direct private claims nationally, and is highly representative of the privately insured population
- Prescriptions for mirabegron and the following antimuscarinics were tracked: fesoterodine, oxybutynin extended and immediate release (ER/IR), solifenacin, and tolterodine ER

Study design

- Patients aged ≥18y who had a first prescription claim for a target medication during a four-month index period from April to July 2013 were identified (Fig 1)
- A six-month look-back period prior to the patient's first claim (the 'index date') was used to categorize patients as treatment-naïve (no claims for a target OAB medication or other drug in the antimuscarinic class) or treatment-experienced (≥1 prior OAB medication) during this time
- Prescription claims for a target drug were tracked for six months after the index claim date to calculate time to end of persistence (defined by a maximum gap in therapy of 30 days or switching to another medication); time to end of persistence was censored for patients who remained on initial therapy through to Month 6

Fig 1: Study design



- Adherence was calculated by medication possession ratio (MPR) through the 6-month period and was calculated using two methods:

  MPR-fixed: the number of days supply, divided by 183 days in the follow-up period

  MPR-variable: the number of days supply, divided by the number of days between the first and last claims, plus the number of days supply of the last claim; patients required at least two prescriptions to qualify for the MPR-variable method.
- Data for the following groups were captured:
  - treatment status (experienced/naïve)
  - gender
  - age category (<46 years, 46–64 years, ≥65 years)
  - index product
  - number of co-existing medications (0, 1–3, 4–5, 6–8, >8)
- Only anonymized patient-level data were analysed; no ethical committee review was required

Statistical analyses

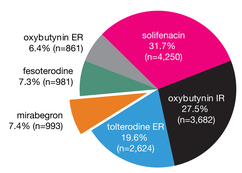
- Cox proportional hazards modeling was used to provide hazard ratios (HR), 95% confidence intervals (CI), and p-values versus predefined reference covariates (shown in the Results tables)
- Kaplan-Meier analysis was used to plot persistence rates over time
- In the MPR analysis, pairwise comparisons were calculated using Mood's median statistical test

RESULTS

Patient distribution

- The final cohort was 13,391 patients for the persistence and MPR-fixed analyses:
  - 74.7% female (n=9,999)
  - 89.6% treatment-naïve (n=12,004)
  - 58.2% aged 46-64 years (n=7,793)
  - 19.7% aged 65 years or older (n=2,644)
- 6,012 patients were eligible for the MPR-variable analysis
- The most frequently prescribed therapy was solifenacin (Fig 2)
- Mirabegron accounted for 7.4% (n=993) of claims

Fig 2. Patient distribution between individual target drugs



- The proportion of patients aged 65 years or older was higher for mirabegron (41.8%) than for any antimuscarinic (range 15.6–25.4%)
- The proportion of male-to-female patients was higher for mirabegron than for antimuscarinics (33.1% vs 21.4–28.7%)
- The proportion of treatment-experienced vs treatment-naïve patients was higher for mirabegron than for antimuscarinics (24.9% vs 5.2–10.1%), except for fesoterodine (26.9%)
- Approximately 46% of patients (n=6,120) were concurrently taking 1–3 non-OAB medications; only 8.9% of patients (n=1,198) were not taking any co-medications at the index date

Persistence

Total study population

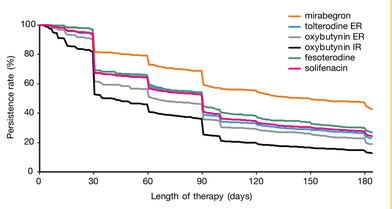
- Statistically significant differences were found within each covariate group compared with the reference variable (Table 1)
- The highest persistence rate was achieved with mirabegron (Fig 3)

Table 1: Persistence rates in the total study population (n=13,391) (Cox proportional hazards model)

	No. of patients	Hazard ratio	95% CI	p-value
Status				
Experienced*	1,387	1.000	*	*
Naïve	12,004	1.402	1.307–1.505	<0.001
Gender				
Male*	3,392	1.000	*	*
Female	9,999	0.947	0.906–0.990	0.016
Age category				
≥65 years*	2,644	1.000	*	*
46–64 years	7,793	1.136	1.077–1.197	<0.001
<46 years	2,954	1.374	1.293–1.459	<0.001
OAB drug				
mirabegron*	993	1.000	*	*
fesoterodine	981	1.515	1.356–1.692	<0.001
solifenacin	4,250	1.539	1.405–1.689	<0.001
tolterodine ER	2,624	1.785	1.441–1.742	<0.001
oxybutynin ER	861	1.785	1.596–1.996	<0.001
oxybutynin IR	3,682	2.316	2.114–2.538	<0.001
Polypharmacy				
0*	1,198	1.000	*	*
1–3	6,120	0.870	0.812–0.931	<0.001
4–5	3,149	0.772	0.716–0.831	<0.001
6–8	2,123	0.731	0.675–0.792	<0.001
>8	801	0.627	0.564–0.697	<0.001

* Reference variable, CI = Confidence Interval. Data from a single multivariate model

Fig 3: Kaplan-Meier estimated rates of persistence on each OAB drug over time for the total study population (n=13,391)



- Persistence at 6 months was 20.3% in treatment-naïve patients vs 36.5% in treatment-experienced patients. Mean [median] days on therapy were 86.8 [69.0] vs 114.5 [100.0], respectively
- Separate analyses were subsequently carried out on treatment-experienced and treatment-naïve cohorts

Treatment-experienced patients

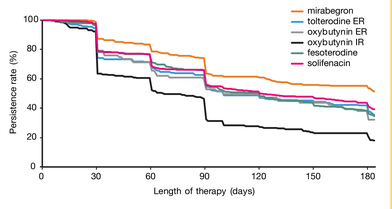
- Mirabegron demonstrated greater persistence than any antimuscarinic (Table 2 and Fig 4)
- Persistence at 6 months was 51.4% with mirabegron, compared with 17.7% for oxybutynin IR
- The risk of discontinuation with oxybutynin IR was 2.5 times that with mirabegron
- Patients taking solifenacin had the second highest level of persistence (39.3%)
- Other covariate groups were not included in the reduced model due to non-significance

Table 2: Persistence rates for all patients in the treatment-experienced cohort (n=1,387) (Cox proportional hazards model)

OAB drug	No. of patients	Hazard ratio	95% CI	p-value	Median (mean) days	6-month persistence
mirabegron*	247	1.000	*	*	132 (183)	51.4%
solifenacin	377	1.383	1.109–1.726	0.004	118 (120)	39.3%
fesoterodine	264	1.526	1.209–1.927	<0.001	115 (120)	34.5%
tolterodine ER	220	1.540	1.208–1.964	0.001	113 (100)	35.5%
oxybutynin ER	87	1.638	1.199–2.237	0.002	112 (100)	32.2%
oxybutynin IR	192	2.488	1.961–3.157	<0.001	86 (67)	17.7%

* Reference variable, CI = Confidence Interval

Fig 4: Kaplan-Meier estimated rates of persistence on each OAB drug over time for all patients in the treatment-experienced cohort (n=1,387)



Treatment-naïve patients

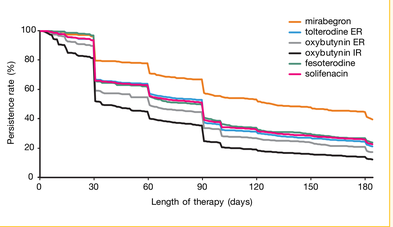
- There was significantly improved persistence with mirabegron vs antimuscarinics (Table 3 and Fig 5)

Table 3: Persistence rates for all patients in the treatment-naïve cohort (n=12,004) (Cox proportional hazards model)

OAB drug	No. of patients	Hazard ratio	95% CI	p-value	Median (mean) days	6-month persistence
mirabegron*	746	1.000	*	*	120 (129)	39.8%
fesoterodine	717	1.512	1.333–1.716	<0.001	94 (89)	24.1%
solifenacin	3,873	1.555	1.406–1.721	<0.001	93 (90)	22.9%
tolterodine ER	2,404	1.592	1.433–1.767	<0.001	92 (90)	21.4%
oxybutynin ER	774	1.802	1.595–2.035	<0.001	83 (60)	17.4%
oxybutynin IR	3,490	2.315	2.093–2.561	<0.001	69 (34)	12.5%

* Reference variable, CI = Confidence Interval

Fig 5: Kaplan-Meier estimated rates of persistence on each OAB drug over time for all patients in the treatment-naïve cohort (n=12,004)



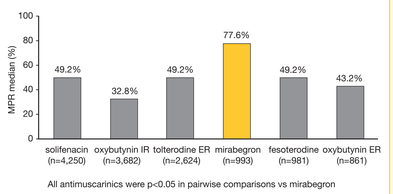
- Men (n=3,092) were slightly more likely to discontinue than women (n=8,912) (HR 0.952, CI: 0.909–0.997; p=0.039); mean [median] days to discontinuation was 87 [65] in men vs 87 [70] in women
- Patients under 46 years old were on average 38% more likely to discontinue than those ≥65 years (HR 1.381, CI: 1.297–1.469; p<0.001); mean [median] days to discontinuation was 73 [5] vs 96 [90], respectively
- Patients aged 46–64 years were on average 14% more likely to discontinue than those ≥65 years (HR 1.136, CI: 1.076–1.200; p<0.001); mean [median] days to discontinuation was 89 [81]
- Patients taking 1–3 co-medications were on average 13% less likely to discontinue an OAB drug compared with those not taking any co-medications (HR 0.867, CI: 0.808–0.931; p<0.001; 17.9% vs 13.8% persistence at 6 months). This difference increased progressively as the number of co-medications increased

Adherence

Fixed method for calculating MPR

- Patients taking mirabegron demonstrated significantly better adherence than those taking antimuscarinics (p<0.05 in pairwise comparisons) (Fig 6)

Fig 6: Adherence with mirabegron and antimuscarinics, when measured using the fixed method for Medical Possession Ratio (MPR median values)



All antimuscarinics were p<0.05 in pairwise comparisons vs mirabegron

- Treatment-experienced patients demonstrated significantly better adherence over 6 months than treatment-naïve patients (median MPR: 62.5% vs 48.2%, respectively; p<0.001)
- Patients under the age of 46 years were the least adherent (median MPR: 32.8% [age <46 years], 49.2% [age 46–64 years], 49.2% [age ≥65 years]; p<0.05 for the <46 and 46–64 years age categories vs ≥65 years)
- There was no significant difference between men and women in the median MPR (49.2% vs 49.2%, respectively; p=0.896)

Variable method for calculating MPR

- Mirabegron gave the highest mean and median MPR, but was only statistically significantly different from oxybutynin IR in pairwise comparisons of median MPR (97.8% vs 95.5%; p<0.05)

STUDY LIMITATIONS

- This was an early analysis of private prescription claims, and it was not possible to relate persistence to symptom severity
- Patients classified as treatment-naïve should be regarded as 'relatively' naïve, as they might have received medication before the 6-month look-back period

CONCLUSIONS

- Mirabegron was associated with higher levels of persistence and adherence than antimuscarinics
- The optimum place for mirabegron in the treatment algorithm relative to antimuscarinics has not yet been established

ACKNOWLEDGEMENTS

Editorial assistance was provided by S Sharpe PhD of SharpeCom Ltd (Midhurst, West Sussex, UK), and was funded by Astellas Pharma Canada Inc. Retrospective prescription claims data and statistical analyses were provided by IMS Brogan (IMS Health Canada Inc., Kirkland, Quebec, Canada). Team members: Kristen Reidel (Statistician), Brad Millson (Engagement Manager). The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Brogan information service(s): OAB LOT Study. Data Period 2007-2014. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Brogan or any of its affiliated or subsidiary entities.

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Presented at ISPOR 17th Annual European Congress, 8-12 November 2014, Amsterdam, The Netherlands