PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review
AUTHORS	Yeowell, Gillian; Smith, Philip; Nazir, Jameel; Hakimi, Zalmai; Siddiqui, Emad; Fatoye, Francis

VERSION 1 – REVIEW

REVIEWER	Adrian Wagg University of Alberta, Edmonton, Canada
REVIEW RETURNED	15-Feb-2018

GENERAL COMMENTS	Reviewer's report: Adherence and persistence to oral medication in patients with overactive bladder (OAB) in a real-world setting – a systematic literature review The aim of this study was to examine evaluate persistence and adherence of oral pharmacotherapy used in the treatment of overactive bladder (OAB) using observational clinical data Abstract – presumably, the 30 papers met inclusion criteria, rather than were selected? The use of the term appears less robust The conclusion – "However, mirabegron was associated with greater persistence and adherence compared to antimuscarinics, supporting mirabegron as a first-line pharmacological treatment option for patients with OAB, may need qualifying as this finding is not consistent for all studies and is influenced by prior treatment exposure. Due to clinical practice guidelines, the majority of mirabegron exposed patients are not treatment naïve – which leads to an elevation in observed persistence. S&W: "Although determinants of persistence and adherence were evaluated in this study, other factors such as influence persistence with treatment in patients with overactive bladder including patient expectations, appropriate counselling and patient satisfaction with treatment could not be assessed" a couple of redundant words Introduction: The authors present no direct evidence that better adherence with OAB medication is associated with better outcomes – perhaps Ref 54, Neurourol Urodyn. 2016 Aug;35(6):738-42 would help here rather than later? Suggest instead of "Due to a distinct mechanism of action, the incidence of typical anticholinergic side effects with mirabegron is generally similar to placebo" due to its "mechanism of action" – its not an anticholinergic Method: For what number, if any studies was there disagreement in study selection requiring resolution through discussion and consultation with another member of the project team?

	Clear description of method and data extraction. The inclusion of the searches is of great value Results: clear and transparent – the proportion of treatment exposed and naïve patients in each group (AM /mira) in the more recent studies should be noted – the differences in adherence rates betwwwn compunds dependent on this should be highlighted Discussion Well thought out – the factors associated with lower adherence are well described. The limitations of this kind of study likewise The point about prior exposure and clinical guidelines should be made here The role of the authors as employees and commissioners of the paper is transparent

REVIEWER	Giannitsas Konstantinos Assistant Professor of Urology, Patras University, Greece
REVIEW RETURNED	26-Feb-2018

GENERAL COMMENTS	Comments with reference to "no" answers in the "review checklist" 1. As far as the clearness of definition of study objective is concerned, I feel a little uncertain: even though it is stated that the purpose of the study is to"…evaluate persistence and adherence of oral pharmacotherapy used in the treatment of overactive bladder (OAB) in a real-world setting" is seems that the paper evaluates adherence and persistence with mirabegron versus other oral OAB treatments. If oral treatments for OAB in general are the "target" then data on mirabegron should not be differentially reported. I suggest that authors change their title to reflect the content of the full paper. 2. Given that the clearness of the research question is not, at least to my opinion, perfect there are some concerns on the adequacy of study design and the description of methods. Authors report that: "Studies reporting persistence and adherence data solely from patient interviews or subjective questionnaires were excluded" and "Studies using data from hospital records, in addition to large-scale databases, were included provided that persistence and adherence data were directly recorded rather than extracted from supplemental patient interviews or subjective questionnaires": what are the ways of directly recording adherence? Are there any other than counting returned medication as done in RTCs? Please comment Authors should comment on why they included in their search terms the non- selective antimuscarinic Hyoscyamine which, despite being approved by the FDA for urinary indications, is mainly used for gastrointestinal indications. Furthermore why they included in their search terms imidafenacin if they wanted to report European and American data only: imidafenacin is approved and used in Japan. The inclusion of older studies and interventions such as imipramine, a tricyclic antidepressant with an unclear mechanism of action, should also be explained. 3. The discussion should elaborate more on the reasons for better adherence to and persistence with mirabegron versus antimuscarinics. For example the fact that is the newer with a different mechanism of action may be important factors influencing

	persistence given that medication use is not just a matter of efficacy and tolerability. It is advised by several official bodies that solifenacin and fesoterodine, which offer the advantage of dose titration and possibly higher efficacy, are used after other, usually less expensive antimuscarinics have been proven inadequate in terms of efficacy and or tolerability. Nevertheless, “lines” of pharmacological treatment are not strictly defined and suggesting in the discussion and conclusion that “mirabegron can be used as a first-line pharmacological treatment” is somewhat arbitrary, not directly supported by evidence presented (no efficacy or tolerability data) and possibly misleading. This conclusion should be toned-down or explained in more detail. General comment As a general comment the paper is well designed and written although it does not seem to offer breakthrough knowledge. The advantages of mirabegron compared to antimuscarinics in terms of drug use have been already shown in several studies, but reasons for this are multiple and not adequately explained. My main concern is that the aim to compare mirabegron to antimuscarinics is not clear in the title of the manuscript. Minor comments: 1. General definitions of the terms persistence and adherence and their measurements should be given even though they may be inferred form the paper. 2. Bullet 5 in “strengths and limitations” does not make sense: there is probably some typo that needs to be corrected

REVIEWER	Andrew Hinde University of Southampton
REVIEW RETURNED	13-Apr-2018

GENERAL COMMENTS	This paper is a systematic review of the literature which shows that, in observational studies, patients with overactive bladder who are treated with mirabegron show greater adherence and persistence with therapy than do patients treated with antimuscarinics. I am convinced by the analysis but have a general point to make and a few questions about the presentation. The general point is this. A vast amount of detail about the studies chosen for review is presented. I could not help feeling that a sledgehammer was being used to crack a nut. We already know from previous studies that mirabegron has a better tolerability profile than antimuscarinics, and the economic impact of using mirabegron against using antimuscarinics has been quantified. So I am a little unsure as to how necessary a review like this is. However, it has been done, and it is pretty conclusive, and so it is probably good that it be placed in the public domain. There are some inconsistencies in the presentation of data. For example, on p. 8, ll. 19-20 you write '[a]t 1 year, persistence rates for antimuscarinics, in 19 studies, ranged from around 5% up to 47%'. Yet later, on p. 11, ll. 3-4 you state that 'large proportions of patients discontinued treatment by 1 year (62 - 100%)'. If discontinuation is the complement of persistence (i.e. a patient must either be a discontinuer or a persister), then the percentage

	of discontinuers should be 100 minus the percentage of persisters, which it does not appear to be. Can you explain the difference? If you are going to quote a p-value, I should quote it on p. 9, l. 6 after 'was significantly greater with mirabegron vs antimuscarinics in two studies', and not on p. 11, l. 13. Also, on p. 11, l. 13, you cite three studies (15, 23 and 27) in support of the statement that 'persistence with mirabegron was statistically significantly greater', whereas on p. 9, ll. 4-6 you state that '[p]ersistence ... was significantly greater with mirabegron for two studies'. On p. 13, ll. 18-21 you write that there were two sets of two studies which reported data on 'the same patient group'. Does this mean that you have, effectively, only 28 independent studies? If so, do the figures you quote on pp. 8-10 reflect this? Or do the studies which deal with 'the same patient group' actually report on different patients? Can you clarify? Figure 1. In the note, l. 7, insert '(n = 1)' after 'English'. The total number of studies excluded should sum to 45. Then in the figure itself, the bottom box in the right-hand column should read 'Records excluded (n = 45)*'.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Abstract – presumably, the 30 papers met inclusion criteria, rather than were selected? The use of the term appears less robust

Thank you for your comments, the text in the abstract has been revised (page 3, paragraph 3) as follows:

'The search identified 3897 studies, of which 30 were ~~selected for extraction~~ included.'

2. The conclusion – "However, mirabegron was associated with greater persistence and adherence compared to antimuscarinics, supporting mirabegron as a first-line pharmacological treatment option for patients with OAB, may need qualifying as this finding is not consistent for all studies and is influenced by prior treatment exposure. Due to clinical practice guidelines, the majority of mirabegron exposed patients are not treatment naïve – which leads to an elevation in observed persistence.

Thank you for this comment. We have amended our text accordingly (please see below). We also agree that not all studies (only 3 of the 4) concluded that mirabegron was associated with better persistence and adherence compared with antimuscarinics. Therefore, we have amended 'However' to 'In general' (please see below). We also agree that patients receiving mirabegron are less likely to be treatment native; however, in the four studies reporting data for mirabegron and

antimuscarinics, 40-81% of patients that received mirabegron were treatment-naïve. In addition, persistence and adherence were assessed in the treatment-naïve subgroups in 3 of the 4 studies. Also, treatment experience is only one determinant of persistence and adherence. Therefore, we have amended text in the abstract (page 3, paragraph 4) as follows:

> *~~'However~~In general, mirabegron was associated with greater persistence and adherence compared to antimuscarinics~~, supporting mirabegron as a first line pharmacological treatment option for patients with OAB~~. Combined with existing clinical trial evidence, this real-world review merits consideration of mirabegron for first-line pharmacological treatment among patients with OAB.'*

We have also added data on the number of naïve and treatment-experience patients to the Results section (please see comment 8) and have expanded the discussion (please see comment 9).

3. S&W:
"Although determinants of persistence and adherence were evaluated in this study, other factors such as influence persistence with treatment in patients with overactive bladder including patient expectations, appropriate counselling and patient satisfaction with treatment could not be assessed" a couple of redundant words

Thank you for your comment, this point within the 'strengths and weakness' bullet (page 5) points has been revised as follows:

> *'Although determinants of persistence and adherence were evaluated in this study, the influence of other factors such as ~~influence persistence with treatment in patients with overactive bladder including~~ patient expectations, appropriate counselling and patient satisfaction with treatment could not be assessed.'*

4. Introduction:
The authors present no direct evidence that better adherence with OAB medication is associated with better outcomes – perhaps Ref 54, Neurourol Urodyn. 2016 Aug;35(6):738-42 would help here rather than later?

Thank you for your comment. The introduction ~~this~~ has been revised accordingly (page 6 paragraph 3) and now refers to the association between better adherence with OAB medication and better outcomes as follows:

> *'Studies have reported that patients compliant and adherent to OAB medication experienced significantly improved urinary symptoms and HRQoL compared with patients who were non-persistent (Andy, 2016; Kim, 2016)'*

5. Suggest instead of "Due to a distinct mechanism of action, the incidence of typical anticholinergic

side effects with mirabegron is generally similar to placebo" due to its "mechanism of action" – it's not an anticholinergic.

Thank you for your comment. We have amended the text to clarify the statement as follows (page 7, paragraph 2):

> *'Due to ~~a distinct~~ mirabegron's mechanism of action, the incidence of side effects typically reported with antimuscarinic treatment are low ~~anticholinergic side effects~~ with mirabegron treatment and ~~is~~ generally similar to placebo, which may translate into better treatment persistence.'*

6. Method: For what number, if any studies was there disagreement in study selection requiring resolution through discussion and consultation with another member of the project team?

There was nil disagreement. Thank you for your comment, this has now been made explicit in the Results (page 10, paragraph 2) as follows:

> *'There was nil disagreement between the two independent researchers (PS, GY) during the screening process.'*

7. Clear description of method and data extraction. The inclusion of the searches is of great value

Thank you for this comment.

8. Results: clear and transparent – the proportion of treatment exposed and naïve patients in each group (AM /mira) in the more recent studies should be noted – the differences in adherence rates betwwwn compunds dependent on this should be highlighted

Thank you for your comment, the 'Antimuscarinic and mirabegron studies' section of the results (page 12, paragraph 2) has now been expanded to indicate the proportion of treatment naïve/experienced mirabegron patients across the four studies as follows:

> *'Across the four studies, 40–81% and 83–96% of the mirabegron and antimuscarinic patient cohorts were treatment naïve, having received no OAB drug for at least 6 months prior to their first index of OAB treatment (Wagg, 2015; Nitti, 2016; Chapple, 2017; Sussman, 2017)'. Studies typically found that treatment-naive patients prescribed mirabegron or antimuscarinics had lower persistence than treatment-experienced patients prescribed the same OAB treatments. In the three studies that assessed persistence in treatment-experienced and treatment-naïve populations, persistence was higher with mirabegron treatment (significantly in two studies) compared with antimuscarinics (Wagg, 2015; Chapple, 2017; Nitti 2016)'.*

9. Discussion
Well thought out – the factors associated with lower adherence are well described. The limitations of this kind of study likewise
The point about prior exposure and clinical guidelines should be made here. The role of the authors as employees and commissioners of the paper is transparent

Thank you for your comment. We have added to following text to the Discussion (page 14, paragraph 3):

> *'In studies that assessed both mirabegron and antimuscarinics, persistence in the mirabegron cohorts, including the treatment-naïve populations, was statistically significantly greater (p<0.001).[18 26 31] Due to the recommended treatment sequence for OAB [10 58], the majority of patients that receive mirabegron are treatment-experienced; however, these studies suggest a benefit of mirabegron treatment regardless of treatment status.*

Reviewer: 2

1. As far as the clearness of definition of study objective is concerned, I feel a little uncertain: even though it is stated that the purpose of the study is to"…evaluate persistence and adherence of oral pharmacotherapy used in the treatment of overactive bladder (OAB) in a real-world setting" is seems that the paper evaluates adherence and persistence with mirabegron versus other oral OAB treatments. If oral treatments for OAB in general are the "target" then data on mirabegron should not be differentially reported.

I suggest that authors change their title to reflect the content of the full paper.

Thank you for your comment. We have amended the title to:

> ***'Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review'***

2. Given that the clearness of the research question is not, at least to my opinion, perfect there are some concerns on the adequacy of study design and the description of methods.
Authors report that: "Studies reporting persistence and adherence data solely from patient interviews or subjective questionnaires were excluded" and "Studies using data from hospital records, in addition to large-scale databases, were included provided that persistence and adherence data were directly recorded, rather than extracted from supplemental patient interviews, or subjective questionnaires": what are the ways of directly recording adherence? Are there any other than counting returned medication as done in RTCs? Please comment.

Thank you, for your comment. We have amended the text in these sections to clarify the Methods as follows:

> *Abstract (page 3, paragraph 2):* *'Studies ~~reporting~~ obtaining persistence and adherence data from sources other than electronic prescription claims were excluded. ~~solely from patient interviews or subjective questionnaires were excluded.~~'*

> *Methods (page 9, paragraph 3):* *'Studies using data from hospital records, in addition to large-scale databases, were included provided that persistence and adherence data were determined from prescription claims data ~~directly recorded~~ rather than extracted from supplemental patient interviews, patient-supplied pill counts or subjective questionnaires.'*

3. Authors should comment on why they included in their search terms the non- selective antimuscarinic Hyoscyamine which, despite being approved by the FDA for urinary indications, is mainly used for gastrointestinal indications. Comment can be made Furthermore why they included in their search terms imidafenacin if they wanted to report European and American data only: imidafenacin is approved and used in Japan.

Thank you for your comments. Although the anticholinergic hyoscyamine is uncommon as an OAB treatment, it is indicated for such use and has been shown to be prescribed among patients with OAB.

We imposed no geographical limitations within this review's search strategy, therefore it seemed pertinent to include imidafenacin in the initial search terms. The 'inclusion and exclusion criteria' section has now been amended (page 8, paragraph 4) as follows:

> *'Inclusion criteria were: prospective and retrospective observational database studies investigating persistence and adherence to oral medication for the treatment of OAB in adults, conducted in any geographical location and ~~which were~~ published on any date, in a peer-reviewed source.'*

4. The inclusion of older studies and interventions such as imipramine, a tricyclic antidepressant with an unclear mechanism of action, should also be explained.

Thank you for your comment. Imipramine was not included as a drug within our initial search terms, however, one retrieved study (Kleinmann et al, 2014) demonstrated it as being prescribed at the time, or shortly after, OAB diagnosis. The drug was therefore added into the data table and manuscript for information. Reference to this medication's uncommon use (n=1) within the included articles for this SR has now been made in the manuscript (Results, page 10, paragraph 3) as follows:

'Uncommon oral interventions were imipramine, a tricyclic anti-depressant with an unknown mechanism of action in the context of OAB, and bethanechol, a muscarinic receptor agonist.'

5. The discussion should elaborate more on the reasons for better adherence to and persistence with mirabegron versus antimuscarinics. For example the fact that is the newer with a different mechanism of action may be important factors influencing persistence given that medication use is not just a matter of efficacy and tolerability.

'Although these studies did not directly assess the reason(s) for the observed benefits of mirabegron, proposed reasons include lower rates of bothersome anticholinergic adverse events, particularly dry-mouth, compared with antimuscarinics and unmet expectations of antimuscarinic treatment… add in mechanism of action.'

Thank you for your comment, we have amended the Discussion (page 15, paragraph 1) as follows:

'*Although these studies did not directly assess the reasons for the observed benefits of mirabegron, proposed reasons include a distinct mechanism of action, lower rates of bothersome or adverse events…….*'

6. It is advised by several official bodies that solifenacin and fesoterodine, which offer the advantage of dose titration and possibly higher efficacy, are used after other, usually less expensive antimuscarinics have been proven inadequate in terms of efficacy and or tolerability. Nevertheless, "lines" of pharmacological treatment are not strictly defined and suggesting in the discussion and conclusion that "mirabegron can be used as a first-line pharmacological treatment" is somewhat arbitrary, not directly supported by evidence presented (no efficacy or tolerability data) and possibly misleading. This conclusion should be toned-down or explained in more detail.

Thank you for your comment. We have amended sentences relating to the first-line use of mirabegron to tone down the conclusions in the abstract and main body of the manuscript. The results and discussion sections now contain greater reference to mirabegron patients who were previously treatment-naïve to oral OAB medication, with presented data suggesting improved tolerability with mirabegron over antimuscarinic via better adherence/persistence values. We have also mentioned previous clinical studies in the conclusions.

7. General comment
As a general comment the paper is well designed and written although it does not seem to offer breakthrough knowledge. The advantages of mirabegron compared to antimuscarinics in terms of drug use have been already shown in several studies, but reasons for this are multiple and not adequately explained. My main concern is that the aim to compare mirabegron to antimuscarinics is not clear in the title of the manuscript.

Thank you for your comment, the title has now been amended to better reflect the aim of the study:

> *'Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review'*

Minor comments:
1. General definitions of the terms persistence and adherence and their measurements should be given even though they may be inferred form the paper.

Thank you, this has been amended and definitions of persistence and adherence have been described in the Introduction (page 6, paragraph 3) as follows:

> *'Lack of persistence (time from treatment initiation to discontinuation) [Cramer, 2008] and adherence (extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen) [Cramer, 2008] to medication are considered the leading causes of preventable morbidity in patients with chronic conditions;[12 13] they are also associated with greater indirect costs.[13]'*

2. Bullet 5 in "strengths and limitations" does not make sense: there is probably some typo that needs to be corrected.

Thank you, this bullet point has now been corrected.

Reviewer: 3

1. The general point is this. A vast amount of detail about the studies chosen for review is presented. I could not help feeling that a sledgehammer was being used to crack a nut. We already know from previous studies that mirabegron has a better tolerability profile than antimuscarinics, and the economic impact of using mirabegron against using antimuscarinics has been quantified. So I am a little unsure as to how necessary a review like this is. However, it has been done, and it is pretty conclusive, and so it is probably good that it be placed in the public domain.

Thank you for your comment.

2. There are some inconsistencies in the presentation of data. For example, on p. 8, ll. 19-20 you write '[a]t 1 year, persistence rates for antimuscarinics, in 19 studies, ranged from around 5% up to 47%'. Yet later, on p. 11, ll. 3-4 you state that 'large proportions of patients discontinued treatment by 1 year (62 - 100%)'. If discontinuation is the complement of persistence (i.e. a patient must either be a discontinuer or a persister), then the percentage of discontinuers should be 100 minus the percentage of persisters, which it does not appear to be. Can you explain the difference?

Thank you for your comment. This is due to the nature of the information reported in the various studies; some reported persistence while others reported discontinuation. In addition, discontinuation is not truly the complement of persistence. For example, in Ivanova et al. 2014, persisters were defined as patients who did not switch *or* discontinue the index antimuscarinic during the first 6 months after the treatment initiation date, and discontinuation was defined by a gap of at least 60 days between refills within the first 6 months after the treatment initiation date.

If you are going to quote a p-value, I should quote it on p. 9, l. 6 after 'was significantly greater with mirabegron vs antimuscarinics in two studies', and not on p. 11, l. 13. Also, on p. 11, l. 13, you cite three studies (15, 23 and 27) in support of the statement that 'persistence with mirabegron was statistically significantly greater', whereas on p. 9, ll. 4-6 you state that '[p]ersistence ... was significantly greater with mirabegron for two studies'.

Thank you for your comment. The described sentence, previously on p.9, ll. 4-6, has been removed and replaced with the following sentence (on page 11, paragraph 5) for improved clarity:

> *'Where tested inferentially, persistence was statistically significantly greater with mirabegron compared to antimuscarinics ($p < 0.0001$), with the exception of oxybutynin ($p = 0.002$)* [15] *The risk of discontinuing within 1 year was also greater with antimuscarinics compared to mirabegron ($p < 0.001$)* [15 23]'

3. On p. 13, ll. 18-21 you write that there were two sets of two studies which reported data on 'the same patient group'. Does this mean that you have, effectively, only 28 independent studies? If so, do the figures you quote on pp. 8-10 reflect this? Or do the studies which deal with 'the same patient group' actually report on different patients? Can you clarify?

Thank you. The sentence previously on p.13 l.20 has been adjusted to alter '*same patient group'* to '*same patients'*. Clearer reference to there being 30 articles, but 28 independent studies, has also been made in the 'brief overview of studies' (page 10, paragraph 2) as follows:

> *'The articles described the findings of 28 independent studies.'*

4. Figure 1. In the note, l. 7, insert '(n = 1)' after 'English'. The total number of studies excluded should sum to 45. Then in the figure itself, the bottom box in the right-hand column should read 'Records excluded (n = 45)*'.

Thank you, both of these points have been amended. Please note that the n number has been amended to 48 (instead of 45)

VERSION 2 – REVIEW

REVIEWER	Adrian Wagg University of Alberta, Edmonton, Alberta, Canada
REVIEW RETURNED	02-Jul-2018

GENERAL COMMENTS	Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review – revision 1 Abstract: Female sex, rather than gender, to the best of my knowledge prescription databases do not capture gender. Discussion: In the sentence “Although these studies did not directly assess the reason(s) for the observed benefits of mirabegron, proposed reasons include a distinct mechanism of action, lower rates of bothersome anticholinergic adverse events, particularly dry mouth, compared with antimuscarinics and unmet expectations of antimuscarinic treatment” The list is chiefly composed of patient observable factors, a distinct mechanism of action would not fit the list and would not be noticed by patients, although perhaps attributed by researchers Secondly, benefits is a generic word, a more appropriate term here might be “persistence and adherence” We do not know if the increased persistence in these studies led to benefits, although it might be reasonable to suggest that this was so- there are no data to support that here

REVIEWER	Andrew Hinde University of Southampton, United Kingdom
REVIEW RETURNED	02-Jul-2018

GENERAL COMMENTS	Thank you for addressing the comments I made on the previous version. I am happy to recommend acceptance of this version.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Adrian Wagg

Abstract:

Female sex, rather than gender, to the best of my knowledge prescription databases do not capture gender.

This has been amended in the abstract as follows:

… included female (sex),

Reviewer: 1

Discussion:

“Although these studies did not directly assess the reason(s) for the observed benefits of mirabegron, proposed reasons include a distinct mechanism of action, lower rates of bothersome anticholinergic adverse events, particularly dry mouth, compared with antimuscarinics and unmet expectations of antimuscarinic treatment”

The list is chiefly composed of patient observable factors, a distinct mechanism of action would not fit the list and would not be noticed by patients, although perhaps attributed by researchers Secondly, benefits is a generic word, a more appropriate term here might be “persistence and adherence”

We do not know if the increased persistence in these studies led to benefits, although it might be reasonable to suggest that this was so- there are no data to support that here

This has been amended as follows (p12):

Although these studies did not directly assess the reason(s) for an observed difference in persistence and adherence with mirabegron vs antimuscarinics, …

Authors’ response

Reviewer: 3

Reviewer Name: Andrew Hinde

Thank you for addressing the comments I made on the previous version. I am happy to recommend acceptance of this version. Thank you.

Reviewer: 1

Reviewer Name: Adrian Wagg

Abstract:

Female sex, rather than gender, to the best of my knowledge prescription databases do not capture gender.

This has been amended in the abstract as follows:

… included female (sex),