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Effectiveness of an intervention to optimise the use of mirabegron for overactive bladder:

a quasi-experimental study in primary care

Abstract

Background

Overactive bladder is a composite of lower urinary tract storage symptoms. Pharmacological treatment is widely employed despite markedly modest efficacy data, adverse effects, and costs for the health system.

Aim

To determine the 12-month efficacy of an intervention delivered by GPs on mirabegron revision and, if appropriate, discontinuation of treatment.

Design and setting

Multicentre, quasi-experimental study in Barcelona (Catalonia), Spain.

Method

Two groups composed of 17 intervention and 34 control practices were formed. The follow-up period was 12 months, from 1 January to 31 December 2017. A structured intervention was designed consisting of initiatives with GPs and urology/gynaecology specialists. The primary outcome was mirabegron use at 12 months.

Results

Of the 1932 patients, a significant discontinuation in treatment was observed at 12 months' follow-up in the intervention group (IG) ($n = 433$ out of 762, 56.8%), in contrast with the control one (CG) ($n = 484$ out of 1170, 41.4%) ($P < 0.001$). There was also a reduced incorporation of new treatments in the IG ($n = 214$ out of 762, 28.1%) compared with the CG ($n = 595$ out of 1170, 50.9%) ($P < 0.001$). In relation to patients with treatment at the beginning and end of the period, there was a decrease of 219 (28.7%) patients in the IG and an increase of 111 (9.5%) in the CG ($P < 0.001$).

Conclusion

The structured intervention showed optimisation in the use of mirabegron. When considering discontinuation it is necessary to provide clear data on the benefits and/or risks for patients and their caregivers, as such information is a precondition for shared decision making.

Keywords

costs; deprescribing; mirabegron; overactive bladder; patient-centred care; persistence (time to discontinuation).

INTRODUCTION

Overactive bladder (OAB) is a composite of lower urinary tract storage symptoms characterised by urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence.¹ The most effective, elective strategies are non-pharmacological, involving bladder training and lifestyle advice as first-line therapy.²⁻⁴

Current pharmacological treatment (antimuscarinics and β_3 adrenergic receptor agonists) plays a restricted role in urinary urgency and has shown modest efficacy, secondary effects, and elevated cost for the health system.²⁻⁴

Mirabegron, initially marketed in 2014, is a first-in-class selective β_3 receptor agonist of the detrusor muscle. It has been compared with placebo in short-term studies while several European regulatory agencies have positioned it as an alternative to antimuscarinics.^{3,5}

Mirabegron has been evaluated within the framework of the Pharmacotherapeutic Harmonization Program in Primary Care of the Catalan Health Service (CatSalut) and categorised as '*there exist more adequate therapeutic alternatives*'.^{6,7} This implies that mirabegron is included in the follow-up of the prescription quality indicators that are carried out by GPs and specialised care, and that prescription is limited.⁸ However,

mirabegron was the most prescribed medication in 2016 at primary healthcare service (PHCS) Muntanya of Barcelona at the Catalan Institute of Health (CIH), the main public healthcare provider in Catalonia.

Given that β_3 receptors are found in other tissues, such as the heart, serious adverse reactions have been described, including raised blood pressure, tachycardia, and cardiovascular events. It is, therefore, contraindicated in patients with severe uncontrolled hypertension,^{5,9,10} and its prescription in older people can result in increased morbidity, adverse drug events, and hospitalisations.^{11,12} An intervention was, therefore, proposed to review the use of mirabegron and, if appropriate,⁷ its deprescribing.¹³⁻¹⁷

Studies comparing the use of OAB medication are scarce and do not focus on reviewing treatment and deprescribing.¹⁸⁻²⁰ There is a need to carry out research regarding the real clinical conditions in which such drugs are used.²¹⁻²² This study aimed to determine the effectiveness of a training activity, followed by a reassessment of mirabegron prescription to achieve its short- and long-term deprescribing; also to establish the duration of medication in real clinical practice, and its prevalence of use before and after the intervention.

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How this fits in

Antimuscarinics and mirabegron play a restricted role in urinary urgency because of their modest efficacy, adverse effects, and elevated cost for the health system. With regard to mirabegron, it has been positioned as an alternative to antimuscarinics and has been used extensively. This study shows that a planned, structured intervention facilitates the revision and, if appropriate, discontinuation of mirabegron treatment.

METHOD

Study design

A multicentre, controlled, before-and-after trial was undertaken to estimate effectiveness related to the review of mirabegron and, if appropriate, its deprescribing. There was a 12-month follow-up, from 1 January 1 to 31 December 2017.

The study design, procedures, and reporting followed TREND guidelines for non-randomised evaluations of behavioural and public health interventions²³ (Trial Registration: NCT03536494).

Participants and recruitment

The intervention group (IG) comprised patients with mirabegron prescription from 1 January 2017 to 31 December 2017 assigned to any of the 225 GPs from the 17 urban primary healthcare centres (PHC) located in the northern area of Barcelona. These PHC belong to the PHCS Muntanya, which serves an assigned population of 351 737 inhabitants, 22.2% aged >64 years.

The control group (CG) comprised all patients with mirabegron prescription assigned to any of the other 34 PHC, located in Barcelona belonging to the CIH, which provides coverage to 860 391 inhabitants.

Inclusion criteria were patients ≥18 years with mirabegron prescription. The study population was composed of patients prescribed mirabegron in the PHC and financed by CatSalut. Exclusion criteria were patients <18 years.

Interventions

The structured intervention consisted of four major sections:

- Initiatives for healthcare professionals: information and training with written material (infographic format; Appendix 1) distributed to all GPs ($n=225$) and patient-centred deprescribing.²⁴ This written material concerned mirabegron

use based on clinical criteria,²⁻⁵ and a urinary incontinence management protocol⁷, and was supported by the CIH and CatSalut⁶⁻⁸ (Appendix 1).

- Initiatives for specialised hospital care: intervention information for urologists ($n=28$) and gynaecologists ($n=23$) at the reference hospital, Hospital Universitari Vall d'Hebron (HUVH).⁷
- Management support with the definition of a structured strategy for all the PHC and GPs.¹⁵
- Monthly intervention monitoring (feedback to all GPs).

A pharmacist and a clinical pharmacologist acted as consultants in case of doubts regarding specific patients.

Primary and secondary outcomes

The primary endpoint was mirabegron discontinuation. A baseline measurement (T0, day 0) was performed prior to the intervention. The percentage of change from baseline of the number of patients with treatment with respect to basal values at T1 (3 months after inclusion), T2 (6 months after inclusion), T3 (9 months after inclusion), and T4 (12 months after inclusion) was performed after T0.

Secondary outcomes were establishing medication duration in real clinical practice, and prevalence of use.

In order to establish the prevalence of use, the attended population >64 years from the CIH register, as of 31 December 2016, was used in the denominator.^{18,22}

The data collection procedure was performed by computerised reading of the individual health card and digitisation of the prescription data.²¹

Statistical analysis

Taking into account an expected overactive bladder syndrome prevalence of 12%,¹ it was necessary to have at least 442 patients for the sample size calculation.¹⁹ However, when considering the study objective, and the possible withdrawal of medication if appropriate, all those with an active mirabegron prescription were included.

A descriptive analysis of all the variables was performed. The comparison between groups was done using the χ^2 -test. A 5% statistical significance level was established ($P\leq 0.05$). SPSS version 19 was used for all analyses.

RESULTS

There were 1932 patients identified using mirabegron during January 2017 in the CIH

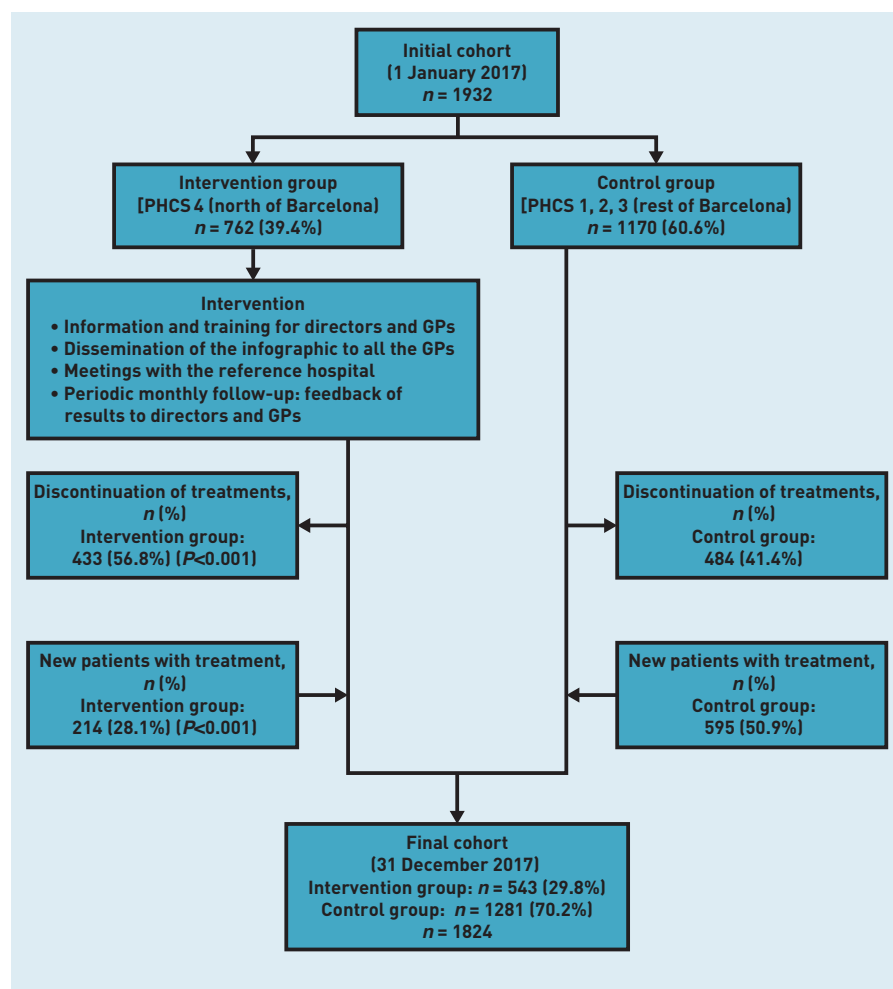


Figure 1. Flow of patients treated with mirabegron and intervention performed. PHCS = primary healthcare service.

Barcelona city area. Of the total, 1040 (53.8%) were female, and 762 (39.4%) belonged to the intervention group. All patients had a 12-month follow-up, and new ones ($n = 380$ at 3 months, $n = 552$ at 6 months, $n = 611$ at 9 months, $n = 809$ at 12 months) [Table 1, new patients with treatment] until 31 December 2017 (Figure 1).

Primary and secondary outcomes

Regarding the initial cohort, a greater reduction in treatment was observed at 12 months follow-up in the IG ($n = 433$, 56.8%) than in the CG ($n = 484$, 41.4%) ($P < 0.001$). There was also a lower incorporation of new treatments in the IG ($n = 214$, 28.1%) compared with the CG ($n = 595$, 50.9%) ($P < 0.001$) (Figure 1).

Table 1 shows the follow-up of patients at the commencement and end of the intervention, treatment persistence, and new patients compared with the initial cohort at 3, 6, 9, and 12 months. In relation to persistence, the differences between the IG and CG were statistically significant by 8.6, 12.7, 14.9, and 15.5 percentage points ($P < 0.001$) at 3, 6, 9,

and 12 months, respectively. Regarding the introduction of new treatments, statistically significant differences were observed between IG and CG at 6, 9, and 12 months by 8.0, 13.6, and 22.8 percentage points, respectively ($P < 0.001$).

Figure 2 depicts the monthly monitoring of mirabegron use between IG and CG. In general, there was an increase in those treated with mirabegron in the CG, but not in the IG, in which a continuous decrease was observed up to December, with the exception of October and November.

In relation to patients with treatment at the beginning and end of the period, there was a decrease of 219 (28.7%) in the IG, and an increase of 111 (9.5%) in the CG ($P < 0.001$) (Figure 3).

Figure 4 shows the number of treated patients from all the PHCS, adjusted by the attended population >64 years per 1000 inhabitants. It can be seen that the results follow the same trend.

In the analysis of the pharmaceutical expenditure of urinary antispasmodics (G04BD — the Anatomical Therapeutic Chemical [ATC] classification system group) in 2017 with respect to 2016, a decrease of 6.9% in IG and 4.7% in CG was observed. Regarding mirabegron, in the CG there was an increase of 6.1% (€27 298), whereas in the IG the opposite effect, a reduction of 16.1%, occurred. This signifies a difference of 22.2 percentage points between the IG and CG, and an estimated potential saving of approximately €65 000. (This information is from the official CatSalut data. Information about pharmaceutical expenditure of ATC group G04BD on patients, cost per defined daily dose, and the savings produced are available from the authors on request.)

DISCUSSION

Summary

The study shows the effectiveness of a structured intervention to achieve the objectives of a mirabegron review and, if considered appropriate by the GP and agreed on by the patient, discontinuation of the medication.⁷ The results regarding mirabegron follow a pattern similar to other deprescribing studies that have demonstrated efficacy.^{25–28} Regarding the initial cohort, 12 months after the intervention, there was an approximately 57% treatment discontinuation in the IG, which was considerably higher than the 41% observed in the CG. Likewise, a lower introduction of new treatments was observed.

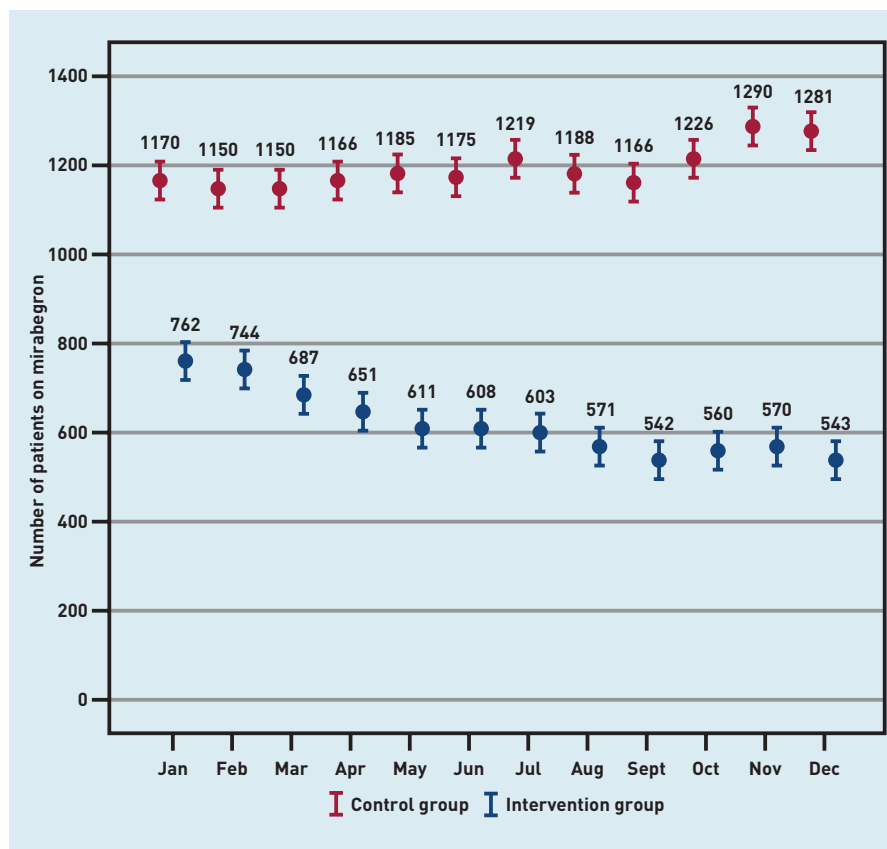
The intervention focused on patient care and the possible benefits/risks of

Table 1. Demographic characteristics of patients at the beginning and at the end, persistence of treatment, and new patients with treatment, by control and intervention groups

	Total, <i>n</i>	Control group	Intervention group	<i>P</i> -value	Difference, % (95% CI)
Patient characteristics at baseline					
Patients, <i>n</i> (%)	1932	1170 (60.6)	762 (39.4)		
Age, years					
Mean, <i>n</i> (SD)	71.6 (12.3)	72.4 (12.3)	70.47 (12.3)		
Median	74	75	73		
Sex, female (%)	53.8	49.8	60.0		
Persistence (time to discontinuation)					
3 months, <i>n</i> (%)	1457	922 (78.8)	535 (70.2)	<0.001	-8.6 [-12.6 to -4.6]
6 months, <i>n</i> (%)	1231	804 (68.7)	427 (56.0)	<0.001	-12.7 [-17.1 to -8.3]
9 months, <i>n</i> (%)	1097	733 (62.6)	364 (47.8)	<0.001	-14.9 [-19.4 to -10.4]
12 months, <i>n</i> (%)	1015	686 (58.6)	329 (43.2)	<0.001	-15.5 [-20.0 to -10.9]
New patients with treatment					
3 months, <i>n</i> (%)	380	228 (19.5)	152 (19.9)	0.782	0.5 [-3.2 to 4.1]
6 months, <i>n</i> (%)	552	371 (31.7)	181 (23.8)	<0.001	-8.0 [-12.0 to -3.9]
9 months, <i>n</i> (%)	611	433 (37.0)	178 (23.4)	<0.001	-13.6 [-17.7 to -9.6]
12 months, <i>n</i> (%)	809	595 (50.9)	214 (28.1)	<0.001	-22.8 [27.1 to 18.5]
Patient characteristics at the end, 12 months,^a (%)					
Patients, <i>n</i>	1824	1281 (70.2)	543 (29.8%)		
Sex, female (%)	51.0	48.0	58.1		

^aInitial patients with persistence to treatment plus new treatments. CI = confidence interval. SD = standard deviation.

Figure 2. Follow-up of patients under treatment with mirabegron from January to December 2017, by control and intervention groups. New treatments are also included.



treatment. Infographics were developed in order to facilitate information to the patient. One of the most important aspects

in obtaining these results was the explicit support of the primary care teams and reference hospital. Especially noteworthy was the follow-up by the GPs. All GPs in the IG (*n* = 225) were provided monthly with information regarding their patients' treatment and the intervention follow-up, accompanied by infographics. In this regard, the results concur with other authors where educational strategies and individualised follow-ups are some of the most effective ways to modify prescription habits.²⁵⁻²⁸

Comparison with existing literature

Although there are publications regarding the use of mirabegron and antimuscarinics in OAB treatment, to the best of the authors' knowledge, this is the first study that focuses on a review accompanied by the deprescribing of drugs that act on β_3 receptors. This is possibly due to the fact that, as other authors suggest,¹⁹ it is a relatively recently commercialised drug. This study included a large sample of patients with demographic characteristics similar to those participating in other studies¹⁸ aiming to establish the persistence of mirabegron under usual clinical practice conditions. In this regard, the current results are consistent with those obtained by other authors, although there is considerable variation in results.

Regarding persistence, in a retrospective study conducted in Catalonia and Asturias,¹⁸

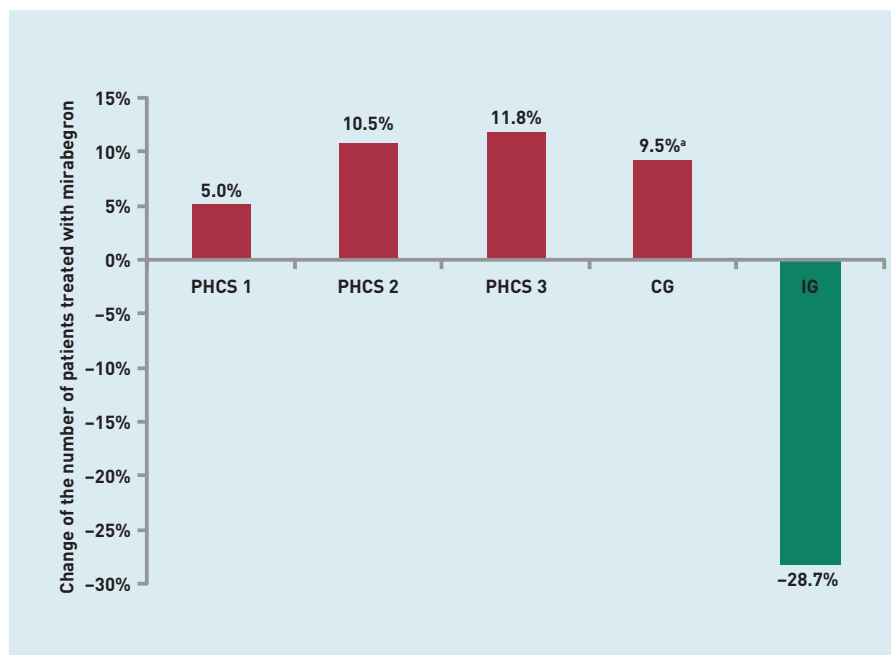
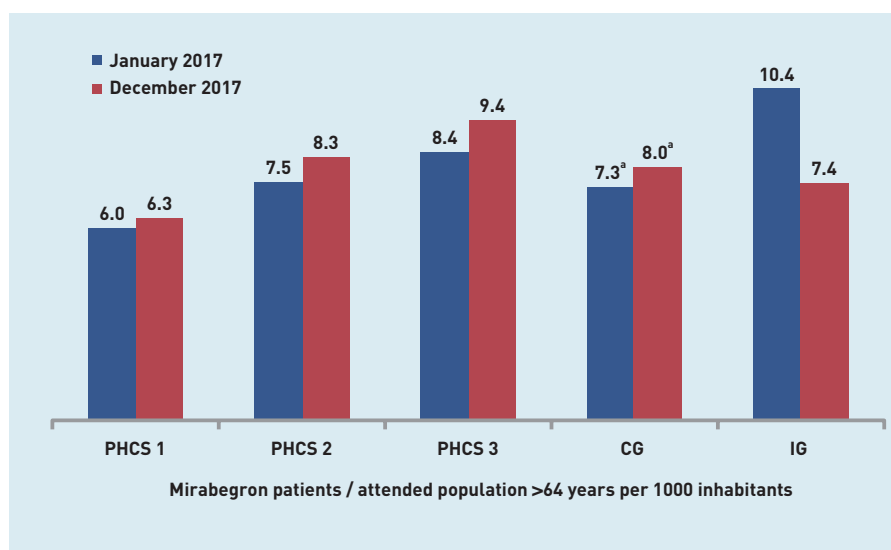


Figure 3. Change over the baseline period (December versus January 2017) of the number of patients treated with mirabegron, by the primary care service, control group, and intervention group. Patients without discontinuation of treatment and new patients are included. CG = control group. IG = intervention group. PHCS = primary healthcare service. *Differences between CG and IG ($P < 0.001$).

Figure 4. Change in the baseline of patients treated with mirabegron adjusted by the population served, by intervention and control groups. CG = control group. IG = intervention group. PHCS = primary health care service. *Differences between the intervention and control groups ($P < 0.001$).



to lack of efficacy, and 4% the appearance of undesirable effects.¹⁹ However, in a study conducted in Japanese urology units, at 12 months low levels of persistence of 12.2% were obtained. Nevertheless, their sample was not comparable to this current study, because 76% were female²⁹ and there are considerable social and cultural differences, in addition to variations in healthcare services.

Two studies conducted with a UK registry reported at 12 months a persistence of 38% and 23.7%. However, the methodology does not allow the comparison of results because these were retrospective design studies based on the registration of prescriptions and not on patients.^{30,31} A retrospective analysis from records of private insurers conducted in Canada also found at 12 months a persistence of 39% and 30% depending on whether the patients had been previously treated or not.²²

In general, results are not comparable. It seems that a greater persistence is obtained in those of retrospective design compared with the prospective ones (with patient follow-up), with the exception of a prospective case series of 354 patients, which showed a persistence of 25% at 12 months.³²

This current study's treatment review, based on safety and efficacy criteria, achieved a reduction in the IG leading to potential saving, as calculated from the official expenditure data provided by the public insurer (CatSalut). In the literature there are studies that evaluate the economic cost of OAB, although methodological differences do not allow comparisons, and the authors believe that caution should be employed in the generalisation of results. Nevertheless, the authors concur with those who consider the relevance of cost reduction from the point of view of efficiency in clinical management given the high prevalence of OAB and the limited treatment efficacy.^{33,34}

Strengths and limitations

Strengths include the large sample of GPs and patients. This study was not created to answer questions about efficacy, but was developed as a pragmatic trial to ascertain whether a structured deprescribing strategy was cost-effective when implemented in general practice.

The various analyses carried out in the number of patients treated, adjusted by population, provide parallel results that add robustness to the study.

However, there are a number of limitations in this study. One is the possible variability of

Funding

Not applicable.

Ethical approval

The study protocol was approved by the University Institute for Primary Care Research (IDIAP) Jordi Gol ethics committee (Barcelona) (reference number: P18/002) and conducted in accordance with the Declaration of Helsinki. The confidentiality of the records was respected according to the Organic Law of Data Protection/Law 15/1999, 13 December. Confidentiality of data was guaranteed in all the processes of the study, and data available for research purpose were anonymous. Because the data obtained underwent a double process of anonymisation and the research team had no access to the patient information, the ethics committee did not consider patient informed consent necessary.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

Contributors

The investigators from the Urinary Incontinence Improvement Investigators Group who contributed to this study were: Eladio Fernández-Liz, Pere Vivó Tristante, Antonio Aranzana Martínez, Maria Estrella Barceló Colomer, Josep Ossó Rebull, Maria Josep López Dolcet, Rosa Abellana Sangrà, Francesc Anguera Cugat, Xavier Bayona Huguet, Raquel Burón Leandro, Angel Cano Romera, Joan Juvanteny Gorgals, Francisco Luque Mellado, María Martínez Roger, Manuel Milian Marquez, Xavier Navarro Molas, Joan Antoni Pérez Pérez, Rosa Romero Suau, Nuria Sabaté Auge (HUVH), and Carmen Troyano Cussó.

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the healthcare professionals, and patients (of medium to low socioeconomic level), as it is a prospective intervention study and not randomised, although with the advantage of being pragmatic.³⁵ In addition, it is important to consider that all the patients, healthcare professionals, and PHC of the IG territory were selected and any possible selection bias minimised. The authors understand that the main limitation of the study can refer to the external validity and the generalisation of the results due to the type of design used. A possible bias from contamination of the IG with the CG cannot be ruled out, although it would imply underestimating the results obtained.

Likewise, there was a greater percentage of females in the IG than in the CG throughout the follow-up period. Another consideration to be highlighted that may have influenced prescription is the existence of a post-regulation study on the quality of life of patients taking mirabegron in which HUVH gynaecologists participated. This may have led to higher awareness of the topic and facilitated greater prescription in females. Nevertheless, the participation of a larger number of females in the IG was not considered as influencing results or treatment discontinuation.

Moreover, although in the clinical interview where the GP took the decision to continue, suspend, or reintroduce the treatment, no formal record was taken on aspects of the patients' quality of life. Consequently, there is a lack of data regarding possible benefits or not in health outcomes, which have been suggested by other authors.³⁶

Implications for research and practice

The present results suggest that a more detailed treatment plan for overactive bladder, and in particular the use of

mirabegron, discussed by both GP and patient, plus an explanation about its advantages and disadvantages, may prevent unnecessary long-term use.

It was considered crucial to inform the patients of the benefits and/or risks of the treatment, and to modulate their expectations. In this regard, it was proposed that the specialist/healthcare provider initiating the treatment (especially the hospital doctor; note in Catalonia, within the Catalan Institute of Health, if the hospital doctor begins the prescription, within 2 months the GP has to decide whether to assume the treatment or not, and consequently the GP writes the prescriptions) explain to the patient that it was recommended as a test/short-term solution and, consequently, in a few weeks its safety and effectiveness would be evaluated. In the case of it not being effective, or leading to adverse effects, it would be withdrawn.

In conclusion, a structured intervention has been shown to optimise the use of pharmacological treatments for urinary incontinence, and facilitate their deprescribing, particularly in the case of mirabegron (57% discontinuation). These results confirm previous findings concerning the need to provide clear data on the benefits and/or risks of treatment options for patients and their caregivers, which is also a precondition for shared decision making.³⁷


Given the modest efficacy of treatment, future recommendations for a more precise long-term analysis are required to advance studies that evaluate the capacity of interventions reducing the frequency of urgency urinary incontinence episodes, and their impact on the cost of managing urinary incontinence.^{38,39}

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Mirabegron

Promotion or solution?



October 2016


- In case of symptoms of overactive bladder, hygienic-dietetic measures are the first treatment option
- In urgency urinary incontinence, drugs are indicated despite their limited efficacy. Reevaluate periodically
- If pharmacological treatment is necessary, follow the recommendations of the CatSalut urinary incontinence protocol

EFFECTIVENESS

Baseline symptoms of patients	Results from clinical trials
2/3 episodes of incontinence/day	Reduction in 0.40 episodes/day
11/12 micturitions/day	Reduction in 0.59 micturitions/day

The efficacy is modest and clinically irrelevant

PRECAUTIONS



Hypertension

SBP ≥ 160 or DBP ≥ 110 mm Hg

Contraindicated in patients with severe uncontrolled arterial hypertension

Blood pressure

Should be controlled at the start of treatment and suspended if it increases

Renal and hepatic impairment

Do not use in kidney or liver failure since the dosage cannot be adjusted

ADVERSE EFFECTS

Mirabegron has been associated with:




<ul style="list-style-type: none"> Tachycardia Cardiovascular events Arrhythmia due to atrial fibrillation Stroke 	<ul style="list-style-type: none"> Urinary tract infections Vulvar and vaginal infections
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PLACE IN THERAPY

Mirabegron can be an alternative when:

- Two anticholinergics have been tried and are not effective
- Serious or intense adverse effects appear and difficult control with anticholinergics
- Anticholinergics are formally contraindicated

"We advise the review of the medication for the modest efficacy and the severe adverse effects"

 Institut Català de la Salut
 Gerència Territorial de Barcelona
  PrimàriaBCN
 Do you want to know more about  mirabegron?