REVIEW

Recent advances in pharmacological management of urinary incontinence [version 1; peer review: 2 approved]

Bronagh McDonnell¹, Lori Ann Birder ^{1,2}

¹Department of Medicine, University of Pittsburgh School of Medicine, A 1217 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA, 15261, USA

²Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, A 1217 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA, 15261, USA

V1 First published: 19 Dec 2017, 6(F1000 Faculty Rev):2148
<https://doi.org/10.12688/f1000research.12593.1>

Latest published: 19 Dec 2017, 6(F1000 Faculty Rev):2148
<https://doi.org/10.12688/f1000research.12593.1>

Abstract

Lower urinary tract symptoms—in particular, storage disorders (for example, urinary incontinence) as well as bladder underactivity—are major health-related problems that increase with age. Yet lower urinary tract symptoms remain under-diagnosed and poorly managed, and incontinence has been cited as the major reason for institutionalization in elderly populations and is one of the most common conditions in primary care practice. Although lifestyle and behavior therapy has been used as a useful treatment regimen for urge incontinence, medications (often used as adjunct) can provide additional benefit. This review will include current therapies used for treatment of urinary incontinence.

Keywords

urinary incontinence

Open Peer Review

Approval Status

	1	2
version 1 19 Dec 2017		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Stéphane Bolduc**, CHU de Québec-Université Laval, Québec, Canada

2. **Linda Cardozo**, King's College London, London, UK

Any comments on the article can be found at the end of the article.

Corresponding author: Lori Ann Birder (lbirder@pitt.edu)

Author roles: **McDonnell B:** Investigation, Writing – Original Draft Preparation; **Birder LA:** Conceptualization, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2017 McDonnell B and Birder LA. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: McDonnell B and Birder LA. **Recent advances in pharmacological management of urinary incontinence [version 1; peer review: 2 approved]** F1000Research 2017, **6**(F1000 Faculty Rev):2148 <https://doi.org/10.12688/f1000research.12593.1>

First published: 19 Dec 2017, **6**(F1000 Faculty Rev):2148 <https://doi.org/10.12688/f1000research.12593.1>

Introduction

Urinary incontinence (UI), alone or as an overactive bladder (OAB) symptom, is a growing global health-care problem that increases in prevalence with age¹⁻³. UI is 1.5 times more common in women than men, affecting approximately 45% and 77% of adult males and females, respectively, in the US, the UK, and Sweden⁴. Both severity and frequency of UI significantly increase mortality among men and women⁵. An industry report recently predicted a 2.9% global market growth rate of pharmacological treatments for OAB from 2017 to 2022 and projected a total cost of USD \$4.19 billion by the year 2020⁶. Despite its widespread prevalence and socioeconomic burden, incontinence therapy remains limited and often accompanied by significant adverse effects (AEs), low efficacy, and high discontinuation rates^{7,8}. In addition, there is surprisingly little information regarding biomarkers that can identify age-induced bladder dysfunction or patient response to treatment. There is a growing and pervasive need for pharmacologic therapies that are efficacious, safe, and tolerable. Efforts in the past three years have identified potential new targets in addition to combination therapies or adding a non-pharmacological intervention or both. This article will highlight advances within the last three years regarding current pharmacological treatments for both urge UI (UUI) and stress UI (SUI).

UI subtypes

Clinical and basic science has classified UI into subtypes based on pathophysiology and causal factors. The most bothersome subtype reported by women is UUI^{4,9} whereas the most prevalent subtype is SUI^{4,10}. The pathophysiology underlying UUI is complex and based on altered physiological mechanisms controlling bladder storage and emptying. Causal factors have been focused on myogenic, neurogenic, and (more recently) sensory dysfunction (see review [11](#)). SUI is urinary leakage due to increased abdominal pressure caused by sneezing, coughing, exercise, lifting, and position change. Its pathophysiology, compared with that of UUI, may be less complex and largely related to physical changes in structures forming or in relation to the lower urinary tract (for example, the pelvic floor muscles). A large proportion of women experience mixed urinary incontinence (MUI), which includes both UUI and SUI symptoms. Studies have reported MUI alone to affect 2–4 out of 10 women who are from 20 to more than 80 years old^{4,9}. Following clinical determination of urge or stress incontinence, a number of treatment regimens can be followed. Deciding on a treatment regimen is a multi-factorial decision process dictated in part by UI subtype and symptom severity.

Pharmacological management for urge incontinence

Anti-muscarinic (anti-cholinergic) drugs remain the most widely used treatment option for UUI and often are used in primary care in combination with behavioral and lifestyle changes, which can include pelvic floor muscle training exercises or reduction of caffeine intake or both. An unfavorable balance between efficacy and tolerability of anti-muscarinic agents, despite their widespread use, exists and has raised questions regarding the overall benefits derived from use of these agents. Furthermore, caution regarding use of anti-muscarinics is recommended in frail elderly

patients because of an increased risk of cognitive impairment^{12,13}. Oxybutynin is the most widely prescribed anti-muscarinic for UUI¹⁴. Other drugs, such as β 3-agonists and phosphodiesterase 5 (PDE5) inhibitors, are available and may have fewer unwanted AEs but have not been shown to be any more effective in improving storage lower urinary tract symptoms. Several advances are being made to reduce anti-cholinergic side effects primarily by creating receptor-selective agents, altering formulation or administration (or both), thus minimizing AEs caused by systemic antagonism of cholinergic receptors.

Currently licensed anti-muscarinics indicated for incontinence include orally prescribed oxybutynin, tolterodine, and trospium available as immediate release (IR) and extended release (ER) formulations. In addition, US Food and Drug Administration (FDA)-approved anti-muscarinics include fesoterodine, darifenacin, and solifenacin as oral IR formulations. Propiverine is an oral anti-muscarinic approved in Asia and recently in Canada and is awaiting FDA approval for the US¹¹. Oxybutynin is the most widely available anti-muscarinic in the US, where it is also available in oral ER and transdermal formulations¹³.

Transdermal formulations of oxybutynin and tolterodine were introduced in 2007 to avoid/minimize systemic AEs associated with oral treatments. A comparison study in 2017 involving 1,530 patients (more than 20 years old) with OAB assessed efficacy and toxicity at 12 weeks between the oxybutynin patch and oral propiverine (20 mg). The authors reported non-inferiority in terms of reducing the number of incontinence episodes (urge or total incontinence). While a greater incidence of AEs was reported with oxybutynin patch versus propiverine group (74.8% versus 64.9%), the incidence of dry mouth or constipation was reduced more than 50% compared with propiverine. The predominant AE associated with the patch, which affected 40.2% of patients, was dermatitis and was reportedly mild in the majority of cases; 26.7% of the affected group (10.7% total) continued treatment with topical steroidal treatment¹⁵. A phase 3 study assessed the efficacy and safety of once-daily applied oxybutynin transdermal gel 3% (OTG3%) (84 or 56 mg) or placebo in 624 adult patients with OAB-UUI. At 12 weeks, OTG3% 84 mg reduced the weekly number of incontinence episodes (urge and mixed) compared with placebo (difference from baseline, -20.4 versus -18.1, respectively). The study concluded that OTG3% 84 mg/day was well tolerated and effective in this adult population¹⁶. Lastly, a large meta-analysis in women with OAB found that long-acting oxybutynin formulations (oral, patch, and gel), compared with IR, were more effective, had a lower incidence of AEs, and were better tolerated¹⁷.

Little evidence is available to support the long-term use of anti-muscarinics. Besides the typical systemic effects which can include dry mouth, constipation, and blurry vision, increasing new evidence indicates that cumulative anti-muscarinic use is associated with an increase in incident dementia¹⁸ as well as mood disorders, including depression¹⁹. These findings support earlier reports of associated depression with short-term anti-muscarinic treatment²⁰. The new knowledge of incident dementia and mood disorders warrants careful consideration by clinicians

and patients when considering treatment options for incontinence, particularly in elderly patients and those with neurobiological disease such as multiple sclerosis and Alzheimer's disease. In the past three years, clinicians have created FORTA (Fit FOR The Aged), a clinical tool to help aid decision making regarding appropriateness of pharmacotherapies in elderly patients often being treated for multiple conditions²¹.

Children

Anti-muscarinics are the main pharmacological treatment for children (<12 years) when non-pharmacological or neuro-modulation or both are not effective, usually in severe cases²². Oxybutynin IR and ER (dosing 0.3–0.6 mg/kg per day daily dose, not exceeding 15 mg/day total) are the only currently FDA-approved anti-muscarinics for treatment of OAB symptoms in children. Newer anti-muscarinics have not yet been approved but are prescribed off-label in treatment-resistant children. In these cases, tolterodine and solifenacin have shown comparable efficacy with fewer side effects²². Propiverine (oral) (0.4–0.8mg/kg per day in two doses) is approved for children in other countries, including Japan²³. Trials in children have reported efficacy in reducing incontinence with an acceptable tolerability using propiverine open-label^{24,25} and trospium²⁶. Oxybutynin transdermal patches may offer a viable alternative to oral oxybutynin, reducing AEs and difficulty of dosing, in children with OAB symptoms, including incontinence²⁷. Solifenacin seems a promising drug option for children and adolescents with incontinence as part of OAB and non-neurogenic detrusor overactivity and those refractory to other anti-muscarinics (oxybutynin and tolterodine treatment). Nadeau *et al.* have reported efficacy using solifenacin in children as part of a dual anti-muscarinic therapy approach²⁸. In addition, a phase 3 placebo-controlled trial concluded a clinically relevant improvement in mean voided volume in children at 12 weeks following once-daily treatment with solifenacin oral suspension²⁹. This study was one of the first to report long-term use of solifenacin in 119 children/adolescents compared with placebo, reporting improvement in incontinence by 3 weeks (change from baseline) which was maintained for the study period (52 weeks)³⁰. Further studies are needed to establish efficacy, safety, and tolerability compared with placebo and other anti-muscarinics.

Beta-adrenergic receptor agonists

Mirabegron, a β_3 -adrenoceptor (AR) agonist, is a first-in-its-class drug approved for the treatment of OAB with symptoms of UUI, urgency, and urinary frequency^{31,32}. This drug is associated with improved bladder compliance, increased bladder capacity, reduced urinary frequency, and reduced incontinence³². Recent evidence has suggested that mirabegron may relax the smooth muscle via a dual mechanism of action which includes activation of β_3 -AR in addition to blockade α_1 -AR^{33,34}. It is acknowledged that long-term toxicity and efficacy, compared with those of standard treatment, remain to be established.

In phase II and III clinical trials, mirabegron was found to be efficacious in reducing OAB symptoms as well as reducing the number of incontinence episodes. Improvement was found to be maintained throughout treatment (up to 12 months) and

appeared to be well tolerated in patients, including those at least 65 years old^{35,36}. A recent *post hoc* analysis of three phase III randomized control trials (RCTs) in women with OAB-incontinence concluded a significant improvement in the number of incontinence episodes with mirabegron versus placebo and established a greater treatment effect with increasing severity of incontinence³⁷. These results raise the possibility that mirabegron is more effective in severe forms of OAB-incontinence and thus may provide a preferred treatment option for these patients. Available evidence would suggest that it offers an effective alternative to anti-muscarinic therapy³⁸.

A large meta-analysis of 44 RCTs of 27,309 patients concluded that mirabegron (50 mg) has similar efficacy to most anti-muscarinic drugs but with fewer incidences of AEs, particularly dry mouth, which is the most frequently reported anti-muscarinic AE and reason for discontinuation among patients³⁹. Further head-to-head comparisons between mirabegron and anti-muscarinic drugs are necessary to compare efficacy and safety. Notably, mirabegron appears effective in adult patients who are refractory to or unsuitable for anti-muscarinic therapy³⁵. This finding is further supported by a recent phase III, multicenter, open-label RCT in Japan, where the authors reported long-term (52 weeks) efficacy and safety of mirabegron in patients with OAB. The majority of patients remained on 50 mg treatment with concomitant improvement in all domains of quality of life (QOL) scores⁴⁰.

Mirabegron is not currently licensed for use in children; however, it is prescribed open-label for various types of incontinence, including nocturnal enuresis and daytime incontinence. Safety and efficacy in children remain to be confirmed. Two open-label trials in Canada have shown mirabegron to be effective and safe in children (ages 5 to 17 years) with OAB-incontinence/enuresis^{41,42}. Blais *et al.* (2016) reported improvement in continence and QOL in children/adolescents with refractory OAB and unsatisfactory management of symptoms with anti-muscarinic therapy⁴¹. The second trial reported mirabegron to be beneficial as an add-on therapy along with anti-muscarinic therapy, again in children with refractory OAB. The addition of mirabegron to the treatment schedule was well tolerated and appeared to be safe⁴².

Combination therapy

Combination therapy using an anti-cholinergic agent coupled with mirabegron has also been used. Several phase III trials in the past three years have assessed its efficacy and safety as add-on to anti-muscarinic treatment (dual therapy). The phase II randomized control SYMPHONY trial (2015) assessed combination mirabegron 25 or 50 mg and solifenacin 5 or 10 mg in women with OAB⁴³. In a follow-up study, SYMPHONY II, Abrams *et al.* reported improvement in objective and subjective efficacy outcomes with combination mirabegron 25/50 mg and solifenacin 5/10 mg compared with placebo or solifenacin 5 mg alone⁴⁴. Herschorn *et al.* evaluated solifenacin 5 mg combined with mirabegron 25 or 50 mg and found superior efficacy in patients with OAB-UI⁴⁵. The effect size (from baseline) in both treatment groups compared with placebo was superior to either therapy alone⁴⁵. Only one phase IV trial, performed in Japan,

confirmed that mirabegron was effective as an add-on therapy to anti-muscarinic treatment⁴⁶. This study (MILAI) assessed mirabegron (25 or 50 mg) with solifenacin (2.5 or 5 mg) over 16 weeks in 223 patients (at least 20 years old) with OAB. The authors reported significant improvements in mean number of UI or UUI episodes per 24 hours, OAB symptom score, and QOL-related scores in all treatment groups.

Endocannabinoids

Early studies demonstrated that cannabis had therapeutic benefit on urgency incontinence in patients with multiple sclerosis. Constitutively active fatty acid amide hydrolase (FAAH) is the enzyme that breaks down endogenous cannabinoids which are released 'on demand' and can target cannabinoid and vanilloid receptors all of which play a role in bladder dysfunction. Thus, targeting FAAH (inhibitors/inactivators) may have a number of therapeutic applications, including treatment of bladder dysfunction and incontinence. A number of animal studies have shown that inhibition of FAAH has benefit in normalizing a number of urodynamic parameters in experiment bladder disorders (see review⁴⁷). Although pre-clinical studies have shown a potential benefit of FAAH inhibitors, recent evidence involving a phase I study in healthy human volunteers had revealed a number of off-target AEs showing that the drug was not safe to use in human studies⁴⁸. This also indicates a cautionary note whereby more extensive pre-clinical screening (including in human cells) for off-target effects may help to identify potential risks.

Pharmacological management for stress incontinence

SUI is the involuntary leakage of urine on exertion, sneezing, or coughing⁴⁹. In clinical practice, the most efficacious approach to reduce the number of incontinence episodes is to increase musculature tone in the pelvic region (pelvic floor muscles) with exercise^{12,50}. Although data supporting long-term use are limited, α 1-AR antagonists have been used to increase urethral tone to ensure continued closure during episodes of increased pressure. Alternative drugs such as β 2-AR agonists have been used in Japan for SUI treatment²³.

Studies report an increased risk of pelvic floor disorders after menopause and this may be linked to estrogen deficiency; thus, estrogen therapy may be beneficial in improving SUI in post-menopausal women. A meta-analysis of clinical trial data rated the evidence for efficacy of estrogen in reducing incontinence as low but well tolerated, much more so than alternative drugs for OAB/incontinence^{51,52}. The route of administration appears to be very important as recently concluded by a Cochrane review. The authors reported worsening of UI with systemic estrogen

versus an improvement in UI when estrogen was applied locally⁵³. Conversely, the addition of vaginal estrogen to IR or ER tolterodine did not improve urinary symptoms more than tolterodine alone⁵¹. In addition, vaginal estrogen has been shown to normalize the microbiota and bladder function, making the case for preventive treatment^{54,55}. Current guidelines suggest the use of estrogen as an adjunct therapy⁵¹.

Duloxetine is a dual serotonin and noradrenaline reuptake inhibitor currently approved in Canada, the US, and Europe for depression. In 2004, duloxetine, under the trade name Yentreve, was approved and licensed in Europe as an add-on therapy for SUI⁵⁶. Despite reported efficacy in US and Canadian phase III trials^{57,58}, licensing in the US and Canada failed because of concerns over incident suicidality. The FDA reported a doubling in suicide attempts in women receiving the drug for SUI compared with that in the general population (see product information at: <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm328101.pdf>). An independent analysis of the dataset used by the European Medicines Agency to license duloxetine was performed by a Canadian research group specifically assessing psychological disturbances. The authors concluded that the risks outweighed the benefits, thus raising concerns regarding the rationale for duloxetine use for treatment of SUI^{59,60}. As of 2013, National Institute for Health and Care Excellence guidelines recommend duloxetine (Yentreve) as a second-line therapy in place of surgery for women with SUI, and counseling on expected AEs is advised⁶¹.

Conclusions

In terms of pharmacologic treatment for UI, many drugs exhibit poor efficacy and increased incidence of AEs. Alternative approaches such as the herbal medicine drug AOBO-001 have been introduced for OAB-incontinence and frequency in adults, and a phase II clinical trial is under way to study efficacy in adults with urge incontinence. There is a need for development of new therapeutic approaches, especially in terms of SUI, which have limited options. However, given the recent examples of off-target effects, one should carefully consider increased patient vulnerability to toxicity and AEs due to change in organ function which presents more opportunity for drug-disease interactions.

Competing interests

The authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

- Zhang L, Zhu L, Xu T, *et al.*: **A Population-based Survey of the Prevalence, Potential Risk Factors, and Symptom-specific Bother of Lower Urinary Tract Symptoms in Adult Chinese Women.** *Eur Urol.* 2015; **68**(1): 97–112.
[PubMed Abstract](#) | [Publisher Full Text](#)
- de Ridder D, Roumeguère T, Kaufman L: **Overactive bladder symptoms, stress urinary incontinence and associated bother in women aged 40 and above; a Belgian epidemiological survey.** *Int J Clin Pract.* 2013; **67**(3): 198–204.
[PubMed Abstract](#) | [Publisher Full Text](#)

3. **F** Schreiber Pedersen L, Lose G, Høybye MT, *et al.*: **Prevalence of urinary incontinence among women and analysis of potential risk factors in Germany and Denmark.** *Acta Obstet Gynecol Scand.* 2017; 96(8): 939–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
4. Coyne KS, Kvasz M, Ireland AM, *et al.*: **Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States.** *Eur Urol.* 2012; 61(1): 88–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. **F** John G, Bardini C, Combescure C, *et al.*: **Urinary Incontinence as a Predictor of Death: A Systematic Review and Meta-Analysis.** *PLoS One.* 2016; 11(7): e0158992.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
6. MarketsandMarkets: **Overactive Bladder Treatment Market by Pharmacotherapy (Anticholinergic- Solifenacin, Oxybutynin, Fesoterodine, Darifenacin; Mirabegron; BOTOX; Neurostimulation), Disease Type (Idiopathic and Neurogenic Bladder Overactivity) - Global Forecast to 2022.** Report No. PH 5449, 244 (US). 2017.
[Reference Source](#)
7. **F** Vouri SM, Kebodeaux CD, Stranges PM, *et al.*: **Adverse events and treatment discontinuations of antimuscarinics for the treatment of overactive bladder in older adults: A systematic review and meta-analysis.** *Arch Gerontol Geriatr.* 2017; 69: 77–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
8. Kim TH, Lee KS: **Persistence and compliance with medication management in the treatment of overactive bladder.** *Investig Clin Urol.* 2016; 57(2): 84–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Ebbesen MH, Hunskaar S, Rortveit G, *et al.*: **Prevalence, incidence and remission of urinary incontinence in women: longitudinal data from the Norwegian HUNT study (EPINCONT).** *BMC Urol.* 2013; 13: 27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. **F** McKenzie S, Watson T, Thompson J, *et al.*: **Stress urinary incontinence is highly prevalent in recreationally active women attending gyms or exercise classes.** *Int Urogynecol J.* 2016; 27(8): 1175–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
11. Aoki Y, Brown HW, Brubaker L, *et al.*: **Urinary incontinence in women.** *Nat Rev Dis Primers.* 2017; 3: 17042.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. National Collaborating Centre for Women's and Children's Health: **Urinary Incontinence in Women: The Management of Urinary Incontinence in Women.** Royal College of Obstetricians and Gynaecologists 2013 National Collaborating Centre for Women's and Children's Health. 2013.
[PubMed Abstract](#)
13. **F** Gormley EA, Lightner DJ, Burgio KL, *et al.*: **Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline.** *J Urol.* 2012; 188(6 Suppl): 2455–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
14. Sussman DO: **Overactive bladder: treatment options in primary care medicine.** *J Am Osteopath Assoc.* 2007; 107(9): 379–85.
[PubMed Abstract](#)
15. Yamaguchi O, Uchida E, Higo N, *et al.*: **Efficacy and safety of once-daily oxybutynin patch versus placebo and propiverine in Japanese patients with overactive bladder: A randomized double-blind trial.** *Int J Urol.* 2014; 21(6): 586–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. **F** Goldfischer ER, Sand PK, Thomas H, *et al.*: **Efficacy and safety of oxybutynin topical gel 3% in patients with urgency and/or mixed urinary incontinence: a randomized, double-blind, placebo-controlled study.** *Neurourol Urodyn.* 2015; 34(1): 37–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
17. **F** Reynolds WS, McPheeters M, Blume J, *et al.*: **Comparative Effectiveness of Anticholinergic Therapy for Overactive Bladder in Women: A Systematic Review and Meta-analysis.** *Obstet Gynecol.* 2015; 125(6): 1423–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
18. **F** Gray SL, Anderson ML, Dublin S, *et al.*: **Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study.** *JAMA Intern Med.* 2015; 175(3): 401–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
19. **F** Chung SD, Weng SS, Huang CY, *et al.*: **Antimuscarinic Use in Females With Overactive Bladder Syndrome Increases the Risk of Depressive Disorder: A 3-Year Follow-up Study.** *J Clin Pharmacol.* 2017; 57(8): 1064–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
20. Chu FM, Dmochowski RR, Lama DJ, *et al.*: **Extended-release formulations of oxybutynin and tolterodine exhibit similar central nervous system tolerability profiles: a subanalysis of data from the OPERA trial.** *Am J Obstet Gynecol.* 2005; 192(6): 1849–54; discussion 1854–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. **F** Wehling M, Burkhardt H, Kuhn-Thiel A, *et al.*: **VALFORTA: a randomised trial to validate the FORTA (Fit For The Aged) classification.** *Age Ageing.* 2016; 45(2): 262–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
22. **F** Chang SJ, Van Laecke E, Bauer SB, *et al.*: **Treatment of daytime urinary incontinence: A standardization document from the International Children's Continence Society.** *Neurourol Urodyn.* 2017; 36(1): 43–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
23. Takahashi S, Takei M, Nishizawa O, *et al.*: **Clinical Guideline for Female Lower Urinary Tract Symptoms.** *Low Urin Tract Symptoms.* 2016; 8(1): 5–29.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Alloussi S, Mürtz G, Braun R, *et al.*: **Efficacy, tolerability and safety of propiverine hydrochloride in comparison to oxybutynin in children with urge incontinence due to overactive bladder: Results of a multicentre observational cohort study.** *BJU Int.* 2010; 106(4): 550–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. **F** Marschall-Kehrel D, Feustel C, Persson de Geeter C, *et al.*: **Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial.** *Eur Urol.* 2009; 55(3): 729–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
26. Lopez Pereira P, Miguez C, Caffarati J, *et al.*: **Trospium chloride for the treatment of detrusor instability in children.** *J Urol.* 2003; 170(5): 1978–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Gleason JM, Daniels C, Williams K, *et al.*: **Single center experience with oxybutynin transdermal system (patch) for management of symptoms related to non-neuropathic overactive bladder in children: an attractive, well tolerated alternative form of administration.** *J Pediatr Urol.* 2014; 10(4): 753–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Nadeau G, Schröder A, Moore K, *et al.*: **Double anticholinergic therapy for refractory neurogenic and nonneurogenic detrusor overactivity in children: Long-term results of a prospective open-label study.** *Can Urol Assoc J.* 2014; 8(5–6): 175–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. **F** Newgreen D, Bosman B, Hollestein-Havelaar A, *et al.*: **Solifenacin in Children and Adolescents with Overactive Bladder: Results of a Phase 3 Randomised Clinical Trial.** *Eur Urol.* 2017; 71(3): 483–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
30. **F** Newgreen D, Bosman B, Hollestein-Havelaar A, *et al.*: **Long-Term Safety and Efficacy of Solifenacin in Children and Adolescents with Overactive Bladder.** *J Urol.* 2017; 198(4): 928–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
31. Gras J: **Mirabegron for the treatment of overactive bladder.** *Drugs Today (Barc).* 2012; 48(1): 25–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Sacco E, Bientinesi R, Tienforti D, *et al.*: **Discovery history and clinical development of mirabegron for the treatment of overactive bladder and urinary incontinence.** *Expert Opin Drug Discov.* 2014; 9(4): 433–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. **F** Alexandre EC, Kiguti LR, Calmasini FB, *et al.*: **Mirabegron relaxes urethral smooth muscle by a dual mechanism involving β_3 -adrenoceptor activation and α_1 -adrenoceptor blockade.** *Br J Pharmacol.* 2016; 173(3): 415–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
34. Andersson KE: **Pharmacology: On the mode of action of mirabegron.** *Nat Rev Urol.* 2016; 13(3): 131–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. **F** Rossanese M, Novara G, Challacombe B, *et al.*: **Critical analysis of phase II and III randomised control trials (RCTs) evaluating efficacy and tolerability of a β_3 -adrenoceptor agonist (Mirabegron) for overactive bladder (OAB).** *BJU Int.* 2015; 115(1): 32–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
36. Chapple CR, Kaplan SA, Mitcheson D, *et al.*: **Mirabegron 50 mg once-daily for the treatment of symptoms of overactive bladder: an overview of efficacy and tolerability over 12 weeks and 1 year.** *Int J Urol.* 2014; 21(10): 960–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. **F** Chapple C, Khullar V, Nitti VW, *et al.*: **Efficacy of the β_3 -adrenoceptor agonist mirabegron for the treatment of overactive bladder by severity of incontinence at baseline: a post hoc analysis of pooled data from three randomised phase 3 trials.** *Eur Urol.* 2015; 67(1): 11–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
38. Robinson D, Thiagamoorthy G, Cardozo L: **A drug safety evaluation of mirabegron in the management of overactive bladder.** *Expert Opin Drug Saf.* 2016; 15(5): 689–96.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Maman K, Aballea S, Nazir J, *et al.*: **Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison.** *Eur Urol.* 2014; 65(4): 755–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. **F** Yamaguchi O, Ikeda Y, Ohkawa S: **Phase III Study to Assess Long-Term (52-Week) Safety and Efficacy of Mirabegron, a β_3 -Adrenoceptor Agonist, in Japanese Patients with Overactive Bladder.** *Low Urin Tract Symptoms.* 2017; 9(1): 38–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
41. **F** Blais AS, Nadeau G, Moore K, *et al.*: **Prospective Pilot Study of Mirabegron**

- in Pediatric Patients with Overactive Bladder. *Eur Urol*. 2016; **70**(1): 9–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
42. **F** Morin F, Blais AS, Nadeau G, *et al.*: **Dual Therapy for Refractory Overactive Bladder in Children: A Prospective Open-Label Study.** *J Urol*. 2017; **197**(4): 1158–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  43. **F** Abrams P, Kelleher C, Staskin D, *et al.*: **Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony).** *Eur Urol*. 2015; **67**(3): 577–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  44. **F** Abrams P, Kelleher C, Staskin D, *et al.*: **Combination treatment with mirabegron and solifenacin in patients with overactive bladder: exploratory responder analyses of efficacy and evaluation of patient-reported outcomes from a randomized, double-blind, factorial, dose-ranging, Phase II study (SYMPHONY).** *World J Urol*. 2017; **35**(5): 827–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  45. **F** Herschorn S, Chapple CR, Abrams P, *et al.*: **Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study).** *BJU Int*. 2017; **120**(4): 562–575.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  46. **F** Yamaguchi O, Kakizaki H, Homma Y, *et al.*: **Safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin: a post-marketing, open-label study in Japan (MILAI study).** *BJU Int*. 2015; **116**(4): 612–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  47. Hedlund P, Gratzke C: **The endocannabinoid system - a target for the treatment of LUTS?** *Nat Rev Urol*. 2016; **13**(8): 463–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
  48. Mallet C, Dubray C, Dualé C: **FAAH inhibitors in the limelight, but regrettably.** *Int J Clin Pharmacol Ther*. 2016; **54**(7): 498–501.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  49. Bettez M, Le Tu M, Carlson K, *et al.*: **2012 update: guidelines for adult urinary incontinence collaborative consensus document for the canadian urological association.** *Can Urol Assoc J*. 2012; **6**(5): 354–63.
[PubMed Abstract](#) | [Free Full Text](#)
  50. Gormley EA, Lightner DJ, Faraday M, *et al.*: **Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment.** *J Urol*. 2015; **193**(5): 1572–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
  51. **F** Rahn DD, Ward RM, Sanses TV, *et al.*: **Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines.** *Int Urogynecol J*. 2015; **26**(1): 3–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  52. **F** Weber MA, Kleijn MH, Langendam M, *et al.*: **Local Oestrogen for Pelvic Floor Disorders: A Systematic Review.** *PLoS One*. 2015; **10**(9): e0136265.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  53. **F** Cody JD, Jacobs ML, Richardson K, *et al.*: **Oestrogen therapy for urinary incontinence in post-menopausal women.** *Cochrane Database Syst Rev*. 2012; **10**: CD001405.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  54. Drake MJ, Morris N, Apostolidis A, *et al.*: **The urinary microbiome and its contribution to lower urinary tract symptoms; ICI-RS 2015.** *Neurourol Urodyn*. 2017; **36**(4): 850–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
  55. Brubaker L, Nager CW, Richter HE, *et al.*: **Urinary bacteria in adult women with urgency urinary incontinence.** *Int Urogynecol J*. 2014; **25**(9): 1179–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  56. National Collaborating Centre for Women's and Children's Health (UK): **Urinary Incontinence: The Management of Urinary Incontinence in Women.** (RCOG Press National Collaborating Centre for Women's and Children's Health). 2006.
[PubMed Abstract](#)
  57. Norton PA, Zinner NR, Yalcin I, *et al.*: **Duloxetine versus placebo in the treatment of stress urinary incontinence.** *Am J Obstet Gynecol*. 2002; **187**(1): 40–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
  58. Dmochowski RR, Miklos JR, Norton PA, *et al.*: **Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence.** *J Urol*. 2003; **170**(4 pt 1): 1259–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
  59. **F** Maund E, Guski LS, Gotzsche PC: **Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports.** *CMAJ*. 2017; **189**(5): E194–E203.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  60. Wieseler B, McGauran N: **Secrecy or transparency? The future of regulatory trial data.** *CMAJ*. 2017; **189**(5): E185–E186.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  61. Smith A, Bevan D, Douglas HR, *et al.*: **Management of urinary incontinence in women: summary of updated NICE guidance.** *BMJ*. 2013; **347**: f5170.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Linda Cardozo**
Urogynaecology Department, King's College London, London, SE5 9RS, UK
Competing Interests: No competing interests were disclosed.
2. **Stéphane Bolduc**
Division of Urology, CHU de Québec-Université Laval, Québec, Canada
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research