Conceptmodules Urine-incontinentie (UI) 2e- en 3e-lijnszorg

INITIATIEF
Nederlandse Vereniging voor Urologie

IN SAMENWERKING MET
Nederlandse Vereniging voor Obstetrie en Gynaecologie
Nederlandse Vereniging voor Klinische Geriatrie
Bekkenbodem4All

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS)

Colofon

CONCEPTMODULES URINE-INCONTINENTIE (UI) 2E- EN 3E-LIJNSZORG

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Inhoudsopgave

Samenstelling van de werkgroep

Werkgroep

- Dhr. dr. M.R. (Michael) van Balken, uroloog, NVU (voorzitter)
- Dhr. dr. L.P.W. (Bart) Witte, uroloog, NVU
- Dhr. drs. M.A.C. (Martijn) Smits, uroloog, NVU
- Mevr. dr. M.K. (Marian) Engberts, urogynaecoloog, NVOG
- Mevr. dr. P. (Pieternel) Steures, urogynaecoloog, NVOG
- Mevr. drs. A.C. (Rianne) van der Meer, klinisch geriater, NVKG
- Mevr. C.W.L. (Tine) van den Bos, Bekkenbodem4All

Meelezers:

- Mevr. dr. T.A.M. (Doreth) Teunissen, huisarts, NHG
- Dhr. H.J. (Henk Jan) Mulder, urologie verpleegkundige, V&VN
- Mevr. drs. A. (Ana) Dos Santos, bekkenfysiotherapeut, NVFB
- Mevr. drs. C. (Corine) Adamse, bekkenfysiotherapeut, NVFB
- Dhr. dr. R.S. (Ramon) Dekker, internist, NIV

Met ondersteuning van:

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Startpagina – Richtlijn Urine-incontinentie in de 2e en 3e lijn

Waar gaat deze richtlijn over?

Deze richtlijn richt zich op wat volgens de huidige maatstaven de beste zorg voor patiënten met urine-incontinentie is in de tweede- en derdelijnszorg. In de richtlijn komen de volgende onderwerpen aan de orde:

- Diagnostiek
- Conservatieve behandeling
- Medicamenteuze behandeling
- Chirurgische behandeling
- Gemengde urine-incontinentie
- Urine-incontinentie bij kwetsbare ouderen

Voor wie is deze richtlijn bedoeld?

Deze richtlijn is bestemd voor alle zorgverleners in de tweede- en derdelijnszorg die betrokken zijn bij de zorg voor patiënten met urine-incontinentie.

Inleiding voor patiënten

Een patiënt met urine-incontinentie verliest urine op momenten dat zij (waar “zij” staat, kan ook “hij” gelezen worden en andersom) dat niet wil. Er zijn twee soorten urine-incontinentie: aandrang-incontinentie (ook wel urge-incontinentie) en inspannings-incontinentie (ook wel stress-incontinentie). Bij aandrang-incontinentie knijpt de blaas samen op momenten dat het niet goed uitkomt. De patiënt heeft al urineverlies als hij aandrang heeft, bijvoorbeeld op weg naar het toilet. Dit kan voorkomen bij ziektes van het zenuwstelsel of aandoeningen die de blaas prikkelen, zoals blaasstenen, tumoren of infecties. Aandrang-incontinentie kan ook voorkomen bij een vernauwing van de plasbuis. Vaak is er geen duidelijke oorzaak voor aandrang-incontinentie.
Bij inspannings-incontinentie verliest een patiënt urine bij drukverhogende momenten, zoals hoesten, niezen en persen. Vrouwen die kinderen hebben gekregen, hebben een grotere kans op inspannings-incontinentie. Mannen krijgen soms inspannings-incontinentie na een operatie aan de prostaat.
Sommige mensen krijgen beide vormen van urineverlies. Dit heet gemengde incontinentie. Ongewild urineverlies komt vaak voor. Ongeveer 25 tot 50 procent van de oudere vrouwen krijgt last van urineverlies en ongeveer 10 procent van de mannen. De kans op ongewild urineverlies neemt toe met de leeftijd.

Bij aanverwante informatie op deze website staat een link naar een patiëntensamenvatting van de richtlijn.

Meer informatie over urine-incontinentie is te vinden op Thuisarts:
https://thuisarts.nl/urineverlies-bij-vrouwen

Meer informatie over urine-incontinentie is ook te vinden op de website van de urologen/gynaecologen:
http://www.allesoverurologie.nl/welkom
www.bekkenbodemwijzer.nl

Meer informatie over urine-incontinentie is ook te vinden op de website van de patiëntenverenigingen:

- https://www.kanker.nl/bibliotheek/prostaatkanker/gevolgen/103-plasklachten-bij-prostaatkanker

- http://www.bekkenbodem.net/blaas-en-plasproblemen/

Hoe is de richtlijn tot stand gekomen?

Deze modules zijn in 2023 ontwikkeld op initiatief van de Nederlandse Vereniging voor Urologie (NVU). De richtlijn is opgesteld door een multidisciplinaire commissie met vertegenwoordigers vanuit de urologen, gynaecologen, klinisch geriaters en de patiëntenvereniging Bekkenbodem4All. Het Nederlands Huisartsen Genootschap, de Verpleegkundigen & Verzorgenden Nederland, de Nederlandse Vereniging voor Bekkenfysiotherapie en de Nederlandse Internisten Vereniging hebben met de richtlijn meegelezen.

Toepassen

- Indicatoren
- Samenvattingskaart
- Stroomschema algoritme chirurgische behandeling
- Stroomschema algoritme diagnostiek en conservatieve behandeling

Status van de richtlijn

Deze richtlijn wordt modulair herzien. In de laatste herziening (2023) zijn de volgende modules herzien/ontwikkeld:

- SUI en prolaps chirurgie
- Injectie bulkmateriaal vrouwen
- Male sling post-prostatectomie
- Botox bij volwassenen
- Beta 3 receptor agonist
- Medicamenteuze behandeling bij ouderen
- Organisatie van zorg:
    - Samen beslissen
    - Juiste zorg op de juiste plek
    - PROMS bij zorgevaluatie

Verantwoording

Leeswijzer

De verantwoording zal op de Richtlijnendatabase (Richtlijnendatabase.nl) bij elk van de herziene modules worden geplaatst.

[De verantwoording wordt op de Richtlijnendatabase bij elke module opgenomen. Aangezien deze richtlijn gedeeltelijk een herziening betreft, zal het gedeelte 'Autorisatie en geldigheid' per module verschillen. Voor de leesbaarheid is gekozen om dit onderdeel per module uit te schrijven. Het overige gedeelte van de verantwoording is gelijk voor alle herziende of nieuwe modules, en wordt slechts éénmaal bijgevoegd. De verantwoording van de herbevestigde module blijft, op het gedeelte 'Autorisatie en geldigheid' na, op de Richtlijnendatabase ongewijzigd.]

Autorisatie en geldigheid

Autorisatiedatum:	Volgt nog
Eerstvolgende beoordeling actualiteit	2024 [binnen cluster bekkenbodem en proctologie]
Geautoriseerd door:	Zal worden gevraagd aan: Nederlandse Vereniging voor Urologie (NVU), Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG), Nederlandse Vereniging voor Klinische Geriatrie (NVKG), Bekkenbodem4all
Belangrijkste wijzigingen t.o.v. vorige versie:	Er zijn vijf modules herzien: - Sympathicomimeticum bij UI in 2e-3e lijnszorg - Bulk materiaal bij vrouwen met SUI - Vrouwen met SUI en genitale prolaps - Slings voor mannen met SUI - Antimuscarinica, ouderen en cognitie bij UI Er is een nieuwe module ontwikkeld waarin intravesicale injecties met botulinetoxine A vergeleken worden met neuromodulatie, en er is één nieuwe module bestaande uit drie deelmodules ontwikkeld (Organisatie van zorg)
Herbevestiging:	01-11-2023
	De andere modules zijn niet herzien omdat de werkgroep van mening is dat de aanbevelingen nog steeds geldig zijn
Regiehouder(s):	NVU

Algemene gegevens

De ontwikkeling/herziening van deze richtlijnmodule werd ondersteund door het Kennisinstituut van de Federatie Medisch Specialisten (www.demedischspecialist.nl/kennisinstituut) en werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS). De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2021 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor patiënten met urine-incontinentie in de 2e- en 3e-lijnszorg.

Belangenverklaringen

De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.

Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Werkgroep				
Achternaam werkgroeplid	**Hoofdfunctie**	**Nevenwerkzaamheden**	**Gemelde belangen**	**Actie**
Van Balken (voorzitter)	Uroloog, Rijnstate Ziekenhuis, Arnhem	Bestuurslid NVU (vacatie) Opleider; voorzitter vakgroep (-) Lid Werkgroep Functionele en Reconstructieve urologie NVU (-) Lid Patient Information Group European Association of Urology (-) Co-promotor meerdere promovendi (-) Presentatie gehouden op de Post ICS IUGA congres in 2021 waarvoor vergoeding van Astellas	Transparantieregister 2018: - Dienstverlening spreker Dentsply 2018 700E = Hollister. Presentatie over laaggeletterdheid in de zorg. Hillister verzorgt continentiebenodigdheden - Diensteverlening honorarium Astellas 2018 840E = Astellas. Presentatie over incontinentie en prolapsproblemen. Astellas maakt tamsulosine en solifenacine Deelname als onderzoeker aan Renova-trial (OASIS). Bedrijf: Bluewind. Alleen tegemoetkoming onkosten te maken voor ziekenhuiskosten e.d.	geen dienstverlening bedrijven tijdens Richtlijn- ontwikkeling Extra kritisch commentaar gevraagd van onafhankelijke reviewers tijdens de commentaarfase
Engberts	Urogynaecoloog bij Isala	Trainer Altis Sling Coloplast -> tegen vergoeding Presentatie gehouden op de Post ICS IUGA congres in 2021 waarvoor vergoeding van Astellas	Trainer bij Coloplast SIMS Altis tegen SUI om die reden bij herziening richtlijn UI NVOG met name medicatie bij OAB in combinatie/PTNS beoordeeld Ik doe ook onderzoek naar Bulkamid & Altis sling maar hier is tot op heden nog geen vergoeding voor.	Extra kritisch commentaar gevraagd van onafhankelijke reviewers tijdens de commentaarfase

Witte	Uroloog, Isala Klinieken, Zwolle, Nederland	Secretaris Werkgroep Functionele en Reconstructieve Urologie van de Nederlandse Vereniging van Urologie, onbetaald. Lid Wetenschappelijke Commissie van de Nederlandse Vereniging van Urologie, onbetaald. Lid bouwcommissie Dutch Urological Research Organization van de Nederlandse Vereniging van Urologie, onbetaald.	In 2018 heb ik een vergoeding gekregen als spreker in opdracht van Pierre Fabre. Geen andere financiële belangen. In ons ziekenhuis lopen verschillende studies die extern gefinancierd worden. Van de OASIS studie is de inclusie net gesloten. Het gaat om een implanteerbaar device voor de behandeling van aandrangsincontinentie. Wij hebben 4 patiënten geïncludeerd. Follow up is 12 maanden.	Geen actie
Van den Bos	Bekkenfysiotherapeut zzp bij paramedisch centrum AdFysio te De Lier 0.5 fte	Voorzitter Bekkenbodem4All - vrijwilligers vergoeding Lid MAR LS en LP patiëntenverenigingen - onkostenvergoeding Namens NVFB zitting Registercie KNGF – onkostenvergoeding	Geen	Geen actie
Van der Meer	Klinische geriater, Groene Hart Ziekenhuis Gouda, 0,7 fte	Geen	Geen	Geen actie
Smits	Uroloog, Maastricht UMC+	Lid Werkgroep Functionele en Reconstructieve urologie NVU (-) Presentatie gehouden op de Post ICS IUGA congres in 2021 waarvoor vergoeding van Astellas	Diensteverlening honorarium Medtronic 2020 665euro = Deelname advisory board Medtronic Deelname als onderzoeker aan: - OASIS trial (PI), Bedrijf: Bluewind. - SANS-UUI trial, Bedrijf: Neuspera - CARE trial, Bedrijf: Saluda - ELITE trial (PI), Bedrijf: Medtronic Enkel support financiële support voor onkosten ziekenhuis	Extra kritisch commentaar gevraagd van onafhankelijke reviewers tijdens de commentaarfase

			geen dienstverlening bedrijven tijdens Richtlijn-ontwikkeling	
Steures	Lid	Geen	Geen	Geen actie
Klankbordgroep				
Achternaam klankbordgroeplid	**Hoofdfunctie**	**Nevenwerkzaamheden**	**Gemelde belangen**	**Actie**
Teunissen	Huisarts, zelfstandig 0,6 fte Docent, senior onderzoeker Radboudumc afdeling Eestelijnsgeneeskunde 0,4 fte	Geen	Geen	Geen
Adamse	Bekkenfysiotherapeut en Klinisch Epidemioloog, Antonius Ziekenhuis Sneek	Commissielid Wetenschapscommissie NVFB Commissielid Richtlijn chronische bekkenpijn FMS	Mogelijk positie bekkenfysiotherapie	Geen
Dekker	Internist ouderengeneeskunde bij Ziekenhuis Rivierenland Nevenwerkzaamheden: 2021 – heden Commissielid NIV kerngroep Ouderengeneeskunde – Kwaliteit & Richtlijnen 2021 – heden Lid project Medical audit FMS multidisciplinaire richtlijn Polyfarmacie bij ouderen	2021 – heden Commissielid NIV kerngroep Ouderengeneeskunde – Kwaliteit & Richtlijnen - onbetaald 2021 – heden Lid project Medical audit FMS multidisciplinaire richtlijn Polyfarmacie bij ouderen - onbetaald	Geen	Geen

Dos Santos	Geregistreerd bekkenfysiotherapeut MSc bij Pelvicentrum centrum voor bekkenfysiotherapie Leiden Eigenaaresse PelviCentrum centrum voor bekkenfysiotherapie Leiden	Lid van NVFB wetenschappelijke commissie vergoeding voor reiskosten en bijwonen vergaderingen In samenwerking met verloskundigenpraktijk en mamacafé Leiden geef ik workshops aan zwangeren en vrouw postpartum. Deze werkzaamheden zijn onbetaald.	Deelname aan het ontwikkelen kan ervoor zorgen dat collega gaan verwijzen naar mijn praktijk vanwege meer bekendheid.	Geen
Mulder	Verpleegkundig specialist Martini Ziekenhuis Groningen	Geen	Geen	Geen

Inbreng patiëntenperspectief

Er werd aandacht besteed aan het patiëntenperspectief door afvaardiging van Stichting Bekkenbodem4All in de werkgroep. De verkregen input is meegenomen bij het opstellen van de uitgangsvragen, de keuze voor de uitkomstmaten en bij het opstellen van de overwegingen (zie per module ook "Waarden en voorkeuren van patiënten"). De conceptrichtlijn is tevens voor commentaar voorgelegd aan Stichting Bekkenbodem4All en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijn is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling zijn richtlijnmodules op verschillende domeinen getoetst (zie het stroomschema op de Richtlijnendatabase).

Uit de kwalitatieve raming blijkt dat er waarschijnlijk geen substantiële financiële gevolgen zijn, zie onderstaande tabel.

Module	Uitkomst raming	Toelichting
Module SUI en prolaps chirurgie	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft. Er worden daarom geen financiële gevolgen verwacht.
Module injectie bulkmateriaal vrouwen	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft]. Er worden daarom geen financiële gevolgen verwacht.
Module male sling post-prostatectomie	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of

		andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft]. Er worden daarom geen financiële gevolgen verwacht.
Module botox A volwassenen	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft]. Er worden daarom geen financiële gevolgen verwacht.
Module beta 3 receptor agonist	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft]. Er worden daarom geen financiële gevolgen verwacht.
Module medicamenteuze behandeling ouderen	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat [het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet OF het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft]. Er worden daarom geen financiële gevolgen verwacht.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. Dit rapport is gebaseerd op het AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010).

Knelpuntenanalyse en uitgangsvragen

Tijdens de voorbereidende fase inventariseerde de werkgroep de knelpunten in de zorg voor patiënten met urine-incontinentie in de 2e en 3e lijnszorg. De werkgroep beoordeelde de aanbeveling(en) uit de eerdere richtlijnmodule (NVU, 2014) op noodzaak tot revisie. Tevens zijn er knelpunten aangedragen door de Nederlandse Vereniging voor Klinische Geriatrie (NVKG), Nederlandse Vereniging voor Obstetrie & Gynaecologie (NVOG), Nederlandse Vereniging voor Urologie (NVU), Bekkenbodem4All (B4A), Inspectie voor de Gezondheidszorg en Jeugd (IGJ), Nederlands Huisartsen Genootschap (NHG), Nederlandse Vereniging voor Fysiotherapie en Bekkenproblematiek en Pré- en Postpartum Gezondheidszorg (NVFB), Nederlandse Vereniging van Ziekenhuizen (NVZ), Patiëntenfederatie, Verpleegkundigen & Verzorgenden Nederland (V&VN), Zorginstituut Nederland (ZiNL), Zelfstandige Klinieken Nederland (ZKN) en Zorgverzekeraars Nederland (ZN) via een schriftelijke knelpunteninventarisatie.

Uitkomstmaten

Na het opstellen van de zoekvraag behorende bij de uitgangsvraag inventariseerde de werkgroep welke uitkomstmaten voor de patiënt relevant zijn, waarbij zowel naar gewenste als ongewenste effecten werd gekeken. Hierbij werd een maximum van acht uitkomstmaten gehanteerd. De werkgroep waardeerde deze uitkomstmaten volgens hun relatieve belang bij de besluitvorming rondom aanbevelingen, als cruciaal (kritiek voor de besluitvorming), belangrijk (maar niet cruciaal) en onbelangrijk. Tevens definieerde de werkgroep tenminste voor de cruciale uitkomstmaten welke verschillen zij klinisch (patiënt) relevant vonden.

Methode literatuursamenvatting

Een uitgebreide beschrijving van de strategie voor zoeken en selecteren van literatuur is te vinden onder ‘Zoeken en selecteren’ onder Onderbouwing. Indien mogelijk werd de data uit verschillende studies gepoold in een random-effects model. Review Manager 5.4 werd gebruikt voor de statistische analyses. De beoordeling van de kracht van het wetenschappelijke bewijs wordt hieronder toegelicht.

Beoordelen van de kracht van het wetenschappelijke bewijs

De kracht van het wetenschappelijke bewijs werd bepaald volgens de GRADE-methode. GRADE staat voor ‘Grading Recommendations Assessment, Development and Evaluation’ (zie http://www.gradeworkinggroup.org/). De basisprincipes van de GRADE-methodiek zijn: het benoemen en prioriteren van de klinisch (patiënt) relevante uitkomstmaten, een systematische review per uitkomstmaat, en een beoordeling van de bewijskracht per uitkomstmaat op basis van de acht GRADE-domeinen (domeinen voor downgraden: risk of bias, inconsistentie, indirectheid, imprecisie, en publicatiebias; domeinen voor upgraden: dosis-effect relatie, groot effect, en residuele plausibele confounding).
GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag. Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie, in het bijzonder de mate van zekerheid dat de

literatuurconclusie de aanbeveling adequaat ondersteunt (Schünemann, 2013; Hultcrantz, 2017).

GRADE	Definitie
Hoog	− er is hoge zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; − het is zeer onwaarschijnlijk dat de literatuurconclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Redelijk	− er is redelijke zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; − het is mogelijk dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Laag	− er is lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; − er is een reële kans dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Zeer laag	− er is zeer lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; − de literatuurconclusie is zeer onzeker.

Bij het beoordelen (graderen) van de kracht van het wetenschappelijk bewijs in richtlijnen volgens de GRADE-methodiek spelen grenzen voor klinische besluitvorming een belangrijke rol (Hultcrantz, 2017). Dit zijn de grenzen die bij overschrijding aanleiding zouden geven tot een aanpassing van de aanbeveling. Om de grenzen voor klinische besluitvorming te bepalen moeten alle relevante uitkomstmaten en overwegingen worden meegewogen. De grenzen voor klinische besluitvorming zijn daarmee niet één op één vergelijkbaar met het minimaal klinisch relevant verschil (Minimal Clinically Important Difference, MCID). Met name in situaties waarin een interventie geen belangrijke nadelen heeft en de kosten relatief laag zijn, kan de grens voor klinische besluitvorming met betrekking tot de effectiviteit van de interventie bij een lagere waarde (dichter bij het nuleffect) liggen dan de MCID (Hultcrantz, 2017).

Overwegingen (van bewijs naar aanbeveling)

Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en worden meegewogen, zoals aanvullende argumenten uit bijvoorbeeld de biomechanica of fysiologie, waarden en voorkeuren van patiënten, kosten (middelenbeslag), aanvaardbaarheid, haalbaarheid en implementatie. Deze aspecten zijn systematisch vermeld en beoordeeld (gewogen) onder het kopje 'Overwegingen' en kunnen (mede) gebaseerd zijn op expert opinion. Hierbij is gebruik gemaakt van een gestructureerd format gebaseerd op het evidence-to-decision framework van de internationale GRADE Working Group (Alonso-Coello, 2016a; Alonso-Coello 2016b). Dit evidence-to-decision framework is een integraal onderdeel van de GRADE methodiek.

Formuleren van aanbevelingen

De aanbevelingen geven antwoord op de uitgangsvraag en zijn gebaseerd op het beschikbare wetenschappelijke bewijs en de belangrijkste overwegingen, en een weging van de gunstige en ongunstige effecten van de relevante interventies. De kracht van het wetenschappelijk bewijs en het gewicht dat door de werkgroep wordt toegekend aan de

overwegingen, bepalen samen de sterkte van de aanbeveling. Conform de GRADE-methodiek sluit een lage bewijskracht van conclusies in de systematische literatuuranalyse een sterke aanbeveling niet a priori uit, en zijn bij een hoge bewijskracht ook zwakke aanbevelingen mogelijk (Agoritsas, 2017; Neumann, 2016). De sterkte van de aanbeveling wordt altijd bepaald door weging van alle relevante argumenten tezamen. De werkgroep heeft bij elke aanbeveling opgenomen hoe zij tot de richting en sterkte van de aanbeveling zijn gekomen.

In de GRADE-methodiek wordt onderscheid gemaakt tussen sterke en zwakke (of conditionele) aanbevelingen. De sterkte van een aanbeveling verwijst naar de mate van zekerheid dat de voordelen van de interventie opwegen tegen de nadelen (of vice versa), gezien over het hele spectrum van patiënten waarvoor de aanbeveling is bedoeld. De sterkte van een aanbeveling heeft duidelijke implicaties voor patiënten, behandelaars en beleidsmakers (zie onderstaande tabel). Een aanbeveling is geen dictaat, zelfs een sterke aanbeveling gebaseerd op bewijs van hoge kwaliteit (GRADE gradering HOOG) zal niet altijd van toepassing zijn, onder alle mogelijke omstandigheden en voor elke individuele patiënt.

Implicaties van sterke en zwakke aanbevelingen voor verschillende richtlijngebruikers		
	Sterke aanbeveling	*Zwakke (conditionele) aanbeveling*
Voor patiënten	De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet.	Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet.
Voor behandelaars	De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen.	Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund bij de keuze voor de interventie of aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.
Voor beleidsmakers	De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.	Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.

Organisatie van zorg

In de knelpuntenanalyse en bij de ontwikkeling van de richtlijnmodule is expliciet aandacht geweest voor de organisatie van zorg: alle aspecten die randvoorwaardelijk zijn voor het verlenen van zorg (zoals coördinatie, communicatie, (financiële) middelen, mankracht en infrastructuur). Randvoorwaarden die relevant zijn voor het beantwoorden van deze specifieke uitgangsvraag zijn genoemd bij de overwegingen. Meer algemene, overkoepelende, of bijkomende aspecten van de organisatie van zorg worden behandeld in de module Organisatie van zorg.

Commentaar- en autorisatiefase

De conceptrichtlijnmodule werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met de werkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijnmodule aangepast en definitief vastgesteld door de werkgroep. De definitieve richtlijnmodule werd aan de deelnemende (wetenschappelijke) verenigingen en

(patiënt) organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd.

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Module Stress urine-incontinentie en prolaps chirurgie

Uitgangsvraag

Wat is de waarde van een gecombineerde chirurgische ingreep (SUI en prolaps chirurgie) bij vrouwen met stress urine-incontinentie (SUI) en prolaps vergeleken met een enkele ingreep (SUI of prolaps chirurgie)?

Inleiding

Er is een duidelijk verband tussen genitale prolaps en SUI. Deze klachten komen samen voor en soms wordt SUI gemaskeerd door de aanwezigheid van een prolaps. Hoewel de behandeling van prolaps buiten het bestek van deze richtlijn valt, werd in 2014 voor het eerst in deze richtlijn besproken in hoeverre de aanwezigheid van een prolaps de behandeling van SUI kan beïnvloeden. In 2014 verscheen ook de richtlijn prolaps waarin bij vrouwen met een prolaps en SUI werd gekeken of prolaps chirurgie alleen of in combinatie met een anti-incontinentie operatie gedaan moest worden. Nu, tien jaar verder, willen wij de focus in deze richtlijn weer leggen bij de klacht SUI en de eventuele nieuwe inzichten met betrekking tot de chirurgische combinatiebehandeling van mid-urethrale sling met prolaps chirurgie tegenover alleen een mid-urethrale sling. Wat is de aangewezen behandeling bij vrouwen met SUI en prolaps, bij wie SUI de hoofdklacht is? Behandeling op de meest uitgesproken klacht of twee ingrepen in één keer verrichten voor beide klachten. Hierbij is het van belang om de effectiviteit, de kosten en de risico's mee te nemen.

Voor vrouwen met prolaps en occulte SUI wordt verwezen naar de richtlijn prolaps.

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of combined surgery (SUI and prolapse surgery) in women with SUI and prolapse compared to single surgery (SUI or prolapse surgery)?

P: Women with SUI and primary prolapse (main complain incontinence)
I: Combined surgery (SUI surgery and prolapse surgery (mesh for prolapse excluded))
C: Only SUI surgery (i.e., only slings); only prolapse surgery (mesh excluded)
O: Post-operative SUI (persistence of complaints), reoperation due to persistence of complaints, post-operative prolapse symptoms (persistence of prolapse symptoms), complications, serious complications, patient experience, quality of life

Relevant outcome measures

The guideline development group considered post-operative SUI, reoperation due to persistence of complaints, post-operative prolapse symptoms and serious complications as critical outcome measures for decision making; and complications, patient experience and quality of life as important outcome measures for decision making.

A priori, the working group defined complications as retention, urinary tract infection, bleeding, clean intermittent (self)catheterisation (CIC), dyspareunia and urgency. In addition, serious complications were defined as pain, exposure, bladder perforation and reoperation due to complications.

For other outcomes, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following minimal clinically (patient) important differences:

- Patient experience:
  - Urinary Distress Inventory (UDI-6, 0-100): ≥ 33.33 (Skorupska, 2021)
  - International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-SF, 0-21): ≥ 5 at 12 months, ≥ 4 at 24 months (Sirls, 2013)
- Sexuality:
  - Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12): >6 points (Mamik, 2014)
- Pain:
  - Visual Analogue Scale (VAS, 0-10): ≥1
  - Numerical Rating Scale (NRS, 0-10): ≥1

In all other cases, the working group defined the GRADE-standard limit of 25% difference for dichotomous outcomes (RR < 0.8 or > 1.25), and 0.5 SD for continuous outcomes as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until August 3rd, 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 415 hits. Studies were selected based on the following criteria:

- Systematic review (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available) or randomized controlled trial comparing combined surgery (SUI surgery and prolapse surgery) with only SUI surgery or only prolapse surgery
- Patients aged ≥ 18 years
- Full-text English language publication
- Studies including ≥ 20 patients (ten in each study arm); and
- Studies according to PICO.

Twenty-eight studies were initially selected based on title and abstract screening. After reading the full text, 26 studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included (Baessler 2018; Van der Ploeg 2018). The Cochrane review of Baessler 2018 and the systematic review with meta-analysis of Van der Ploeg 2018 defined a broader PICO than the PICO defined for this module. Therefore, two randomized controlled trials included in both reviews were selected for the literature analysis (Borstad, 2010; Van der Ploeg, 2015).

Results

The two randomized controlled trials included in the Cochrane review of Baessler 2018, and the systematic review with meta-analysis of Van der Ploeg 2018 were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables and table 1. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Baessler (2018) performed a Cochrane review to determine the outcome of surgery with or without concomitant or delayed (second stage) continence procedures in women with SUI and prolapse. Randomized controlled trials with a sample size of at least 20 in each group and a follow-up time of at least six months were included. The Cochrane Incontinence Group

Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE-In-Process, ClinicalTrials.gov, WHO ICTRP, handsearching journals and conference proceedings were searched on November 11th, 2017, and reference lists of relevant articles were checked. No language or other restrictions on the searches were imposed. In total, nineteen studies were included. However, the data from two randomized controlled trials (Borstad, 2010; Van der Ploeg, 2015) matching our defined PICO (included only patients with SUI and primary prolapse or reported on this subgroup) were extracted from this review. Outcomes included subjective postoperative SUI and prolapse and the need of a reoperation due to persistence of complaints. Since no complications were reported, the evidence from the Cochrane review will be extended with data from the systematic review and meta-analysis of Van der Ploeg 2018.

Van der Ploeg (2018) performed a systematic review and meta-analysis to compare the efficacy and safety of prolapse surgery with and without incontinence surgery. Randomized controlled trials published in English comparing prolapse surgery with or without a midurethral sling (MUS) or Burch colposuspension with at least three months of follow-up were included. A systematic search was performed in MEDLINE (via PubMed), EMBASE, the Cochrane Library and the Register of Current Controlled Trials from 1995 to 2017. Reference lists of relevant articles were checked. Studies including only obliterative procedures as prolapse surgery or other incontinence procedures such as Kelly plication or fascia slings were excluded by the authors. In total, ten studies were included. However, only the results about complications, as reported in the same two randomized controlled trials as included in the Cochrane review of Baessler 2018 (Borstad, 2010; Van der Ploeg, 2015), will be included in the literature analysis.

Table 1. Description of included studies.

Study	Intervention		Comparator		Follow-up	Outcomes
	Characteristics	**Intervention type/ dose**	**Characteristics**	**Type of control**		
Borstad, 2010	**Arm 1 (n= 95)** Mean age (range): 57.2 (31 to 89) yrs	TVT concomitantly with prolapse repair	**Arm 2 (n= 99)** Mean age (range): 59.9 (38 to 85) yrs	TVT 3 months after prolapse repair	12 months	Post-operative SUI (cure of SUI at 12 months follow up); Post-operative prolapse symptoms (reduction in POPQ score)
Van der Ploeg, 2015	**Arm 1 (n= 63)** Mean age: NR	Vaginal prolapse repair with MUS	**Arm 2 (n= 71)** Mean age: NR	Vaginal prolapse repair without MUS	12 months	Post-operative SUI; serious complication (reoperation)

Abbreviations: TVT, tension-free vaginal tape; MUS, mid-urethral sling; NR, not reported

Results

1. Post-operative SUI (critical outcome)
   Baessler (2018) included two studies (Borstad, 2010; van der Ploeg, 2015) who reported subjective postoperative SUI for vaginal prolapse repair with or without additional MUS (Figure 1). Borstad (2010) found that 4 out of 91 women (4%) had

postoperative SUI after undergoing vaginal prolapse repair with additional MUS as compared to 22 out of 94 women (23%) who underwent only vaginal prolapse repair (RR=0.19, 95%CI 0.07 to 0.52). Van der Ploeg (2015) demonstrated that 14 out of 63 women (22%) undergoing vaginal prolapse repair with additional MUS had postoperative SUI as compared to 43 out of 71 women (61%) undergoing only vaginal prolapse repair (RR=0.37, 95%CI 0.22 to 0.60). These differences were clinically relevant meaning that the outcome of combined surgery was more favourable.

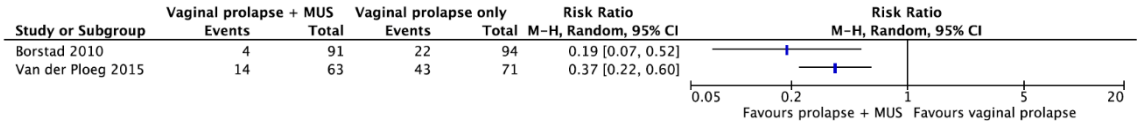

Figure 1: **Subjective postoperative SUI for vaginal prolapse repair with or without additional MUS**
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

2. <u>Reoperation due to persistence of complaints (critical outcome)</u>
Baessler (2018) included one study that reported reoperation (Van der Ploeg, 2015). For women receiving vaginal prolapse repair and MUS, none of the 63 women (0%) required further continence surgery, as compared to 12 out of 71 women who received only vaginal prolapse repair (RR=0.05, 95%CI 0.00 to 0.74). This difference was clinically relevant meaning that the outcome of the combined surgery was more favourable.

3. <u>Post-operative prolapse symptoms (critical outcome)</u>
Not reported.

4. <u>Complications (important outcome)</u>
Van der Ploeg (2018) included two studies that reported about adverse events (Borstad, 2010; van der Ploeg, 2015) (Figure 2).

Borstad (2010) found that 16 out of 87 women (18%) had complications after undergoing vaginal prolapse repair with additional MUS. Five women had hematomas, two women had deep infections, five women had voiding difficulties and four women experienced pulmonary and cardiac complications. For women who underwent only vaginal prolapse repair, 9 out of 94 women (10%) reported adverse events. Two women had hematomas, one woman had a deep infection, two women suffered from voiding difficulties, two women had pulmonary and cardiac complications and one other complication was reported. There was a clinically relevant higher risk of complications in women receiving prolapse and MUS meaning that the outcome of only vaginal prolapse repair was more favourable (RR=1.92, 95%CI 0.90 to 4.12).

Van der Ploeg (2015) reported that 33 out of 63 women (52%) undergoing vaginal prolapse repair with additional MUS experienced complications as compared to 24 out of 71 women (34%) undergoing only vaginal prolapse repair (RR=1.55, 95%CI 1.04 to 2.32). Van der Ploeg (2015) did not provide a specification of the reported complications. There was a clinically relevant higher risk of complications in women receiving prolapse and MUS meaning that the outcome of only vaginal prolapse repair was more favourable.

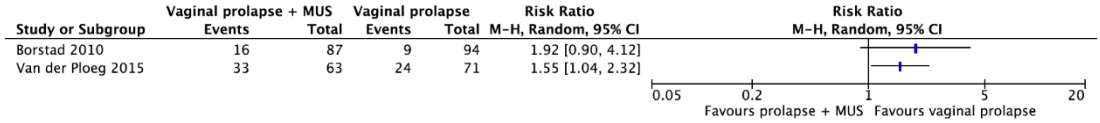

Figure 2: **Adverse events for vaginal prolapse repair with or without additional MUS**

Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval. **Figure 2..**

5. Serious complications (critical outcome)

5.1. Reoperation due to complications

Van der Ploeg (2018) included one study that specified the serious adverse events, but it was unclear whether a reoperation was required for these complications (Van der Ploeg, 2015).

5.2 Other serious complications

Van der Ploeg (2018) included one study that reported about serious adverse events (Van der Ploeg, 2015). Serious adverse events were found in 10 out of 63 women (16%) undergoing vaginal prolapse repair with MUS. Two women had vaginal tape exposures, one woman had bladder injury and later urethral tape exposure, one had ureterolysis for voiding dysfunction and two women experienced thigh pain with (partial) tape removal. These serious adverse events were related to the MUS. In addition, one women experienced bladder injury, one woman had rectal injury and one woman had pyometra related to pelvic organ prolapse (POP)-surgery. For women only receiving vaginal prolapse repair, 4 out of 71 women (6%) reported serious adverse events. One woman reported bladder injury, one woman had neuralgia and two women suffered from dyspareunia related to POP surgery. There was a clinically relevant higher risk of serious complications in women receiving combination surgery (prolapse and MUS) meaning that the outcome of only vaginal prolapse repair was more favourable (RR=2.82, 95% CI 0.93 to 8.54).

6. Patient experience (important outcome)

Not reported.

7. Quality of life (important outcome)

Not reported.

Level of evidence of the literature

1. Post-operative SUI (critical outcome)
   The level of evidence regarding the outcome measure post-operative SUI started as high because it was based on a systematic review of RCTs and was downgraded by two levels to low because of the clinical heterogeneity in the assessment of the effect (-1, risk of bias) and the optimal information size was not achieved (-1, imprecision).

2. Reoperation due to persistence of complaints (critical outcome)
   The level of evidence regarding the outcome measure reoperation started as high because it was based on a systematic review of RCTs and was downgraded by two levels to low because the optimal information size was not achieved and few events were reported (-2, imprecision).

3. Post-operative prolapse symptoms (critical outcome)
   The level of evidence regarding the outcome measure post-operative prolapse symptoms was not reported and therefore could not be assessed with GRADE.

4. Complications (important outcome)
   The level of evidence regarding the outcome measure complications started as high because it was based on a systematic review of RCTs and was downgraded by two levels to low because the 95% confidence intervals crossed the line of no (clinically relevant) effect and the optimal information size was not met (-2, imprecision).

5. Serious complications (critical outcome)
   5.1. *Reoperation due to complications*
   The level of evidence regarding the outcome measure reoperation due to complications was not reported and therefore could not be assessed with GRADE.

   5.2. *Serious complications*
   The level of evidence regarding the outcome measure serious complications started as high because it was based on a systematic review of RCTs and was downgraded by two levels to low because the 95% confidence interval crossed the line of no (clinically relevant) effect and the upper limit of the 95% CI was >3 times higher than the point estimate (-2, imprecision).

6. Patient experience (important outcome)
   The level of evidence regarding the outcome measure patient experience was not reported and therefore could not be assessed with GRADE.

7. Quality of life (important outcome)
   The level of evidence regarding the outcome measure quality of life was not reported and therefore could not be assessed with GRADE.

Conclusions

1. Post-operative SUI (critical outcome)

Low GRADE	The evidence suggests that vaginal prolapse repair with MUS results in less post-operative SUI when compared with vaginal prolapse repair alone in women with SUI and prolapse. *Source: Baessler, 2018*

2. Reoperation due to persistence of complaints (critical outcome)

Low GRADE	The evidence suggests that vaginal prolapse repair with additional MUS results in less second stage operation for SUI complaints when compared with only vaginal prolapse repair in women with SUI and prolapse. *Source: Baessler, 2018*

3. Post-operative prolapse symptoms (critical outcome)

No GRADE	No evidence was found regarding the effect of combined surgery (SUI and prolapse surgery) on post-operative prolapse symptoms when compared with single surgery (SUI or prolapse surgery) in women with SUI and prolapse.

4. Complications (important outcome)

Low GRADE	The evidence suggests that vaginal prolapse repair alone results in less complications when compared with vaginal prolapse repair with additional MUS in women with stress urinary incontinence and prolapse. *Source: Van der Ploeg, 2018*

5. Serious complications (critical outcome)

5.1. Reoperation due to complications

No GRADE	No evidence was found regarding the effect of combined surgery (SUI and prolapse surgery) on reoperation due to complications when compared with single surgery (SUI or prolapse surgery) in women with SUI and prolapse

5.2. Serious complications

Low GRADE	The evidence suggests that vaginal prolapse repair alone results in less serious complications when compared with vaginal prolapse repair with additional MUS in women with stress urinary incontinence and prolapse. *Source: Van der Ploeg, 2018*

6. Patient experience (important outcome)

No GRADE	No evidence was found regarding the effect of combined surgery (SUI and prolapse surgery) on patient experience when compared with single surgery (SUI or prolapse surgery) in women with SUI and prolapse.

7. Quality of life (important outcome)

No GRADE	No evidence was found regarding the effect of combined surgery (SUI and prolapse surgery) on quality of life when compared with single surgery (SUI or prolapse surgery) in women with SUI and prolapse.

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

In de literatuuranalyse werd onderzocht wat de waarde is van een gecombineerde chirurgische ingreep (SUI en prolaps chirurgie) bij vrouwen met stress urine-incontinentie en prolaps vergeleken met een enkele ingreep (SUI of prolaps chirurgie). Hoewel de uitgangsvraag vanuit de klacht stressincontinentie is gesteld, werden er geen aanvullende studies gevonden op de richtlijn prolaps uit 2014.

Bewijskracht voor de cruciale uitkomstmaten postoperatieve SUI-klachten was laag vanwege methodologische beperkingen. Voor de cruciale uitkomstmaten heroperatie vanwege aanhoudende SUI-klachten en ernstige complicaties werd een lage bewijskracht gevonden vanwege spreiding in de richting van het effect, en het feit dat de conclusies gebaseerd zijn op lage aantallen events in kleine studies. Voor de cruciale uitkomstmaat postoperatieve prolapsklachten werd geen literatuur gevonden. Dit leidt tot een zeer lage overall bewijskracht. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de literatuur geen sterke aanvullende aanbevelingen geformuleerd worden over de waarde van een gecombineerde chirurgische ingreep (prolaps en MUS) vergeleken met alleen mid urethrale sling.

Het verhelpen van SUI-klachten maar het behouden prolapsklachten of andersom kan een teleurstellend resultaat zijn voor vrouwen die vanwege beide klachten geopereerd worden. De onderzoeken zijn verricht door gynaecologen, daarom staat in de huidige literatuur de prolapsklacht op de voorgrond. Er kan daarom geen duidelijke aanbeveling gegeven worden voor patiënten waarbij de SUI-klacht op de voorgrond staat. De vergelijking mid-urethrale sling alleen ten opzichte van mid-urethrale sling met prolaps chirurgie werd dan ook niet teruggevonden.

Combinatie chirurgie (prolaps en anti-incontinentie chirurgie) bij vrouwen met SUI en een prolaps geeft klinische relevante verbetering op SUI, hoewel er wel meer perioperatieve complicaties worden gezien. Echter of dit aantal perioperatieve complicaties lager zou zijn als men enkel een mid-urethrale sling zou plaatsen bij vrouwen met een prolaps is niet onderzocht. Het is aannemelijk dat de aanwezigheid van een prolaps een verhoogd risico geeft op perioperatieve complicaties.

In de literatuur ontbreekt voor deze zoekvraag het antwoord of er een selectie gemaakt kan worden op basis van een slagingskans vooraf aan een behandeling, welke patiënte wel en welke beter geen behandeling kan ondergaan.

Pathofysiologisch kan overwogen worden dat de kritische complicaties van de chirurgische ingreep mogelijk vooral plaatsvinden bij vrouwen met een grotere mate van een prolaps, door de veranderde anatomie. Daarbij kan overwogen worden eerst de prolaps te verhelpen en in een tweede tempi de MUS te plaatsen om zo het complicatierisico te verminderen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Belangrijk in de afweging is duidelijk uit te vragen wat de hoofdklacht is. Samen met het uitvragen van het doel van de patiënte van de behandeling kan een patiënte beter gecounseld worden en de verwachtingen kunnen beter gemanaged worden.

Het gaat om klachten en geen ziektes, dus in de keuze voor een behandeling is het extra belangrijk om de doelen en overwegingen van de patiënt te kennen.
De gecombineerde behandeling is weliswaar effectiever, dus brengt met zich mee dat een patiënte sneller van haar klachten af is, en slechts één operatie hoeft te ondergaan. Uit de literatuur wordt echter steeds duidelijker dat patiënten vaker kiezen voor veiligheid dan voor effectiviteit (Schellart, 2023).

Hoewel op basis van de gevonden literatuur geen duidelijke uitspraak gedaan kan worden over de complicaties, zullen deze altijd benoemd moeten worden. Er is geen evidentie welke patiënt de grootste complicatierisico's heeft. Pathofysiologisch kan gedacht worden dat enkel een MUS of een gecombineerde ingreep (ploeg) bij een grotere mate van prolaps meer risico op een complicatie geeft. Bij een kleinere mate van prolaps is dit geheel onduidelijk.

<u>Kosten (middelenbeslag)</u>
Een operatie is kostbaar. Een midurethale sling wordt in dagbehandeling geplaatst. Prolaps chirurgie wordt sinds de schaarste (zichtbaar geworden tijdens de COVID-pandemie) steeds vaker in dagbehandeling gedaan. Op basis van de huidige literatuur is niet te zeggen of een gecombineerde operatie kosten-effectiever is. Er is namelijk niet bekend hoeveel patiënten alsnog een operatie zouden willen ondergaan nadat zij enkel een mid urethrale sling hebben gekregen. Andersom geldt dat 12 op de 71 patiënten na een prolaps operatie alsnog een midurethrale sling kregen. Indien er was gekozen voor een gecombineerde ingreep, had dit de kosten van 12 operaties gescheeld. Echter moet dit worden afgewogen tegen de kosten van de 59 extra mid urethrale slings die bij gecombineerde chirurgie geplaatst zouden zijn. De patiënten hadden met gecombineerde chirurgie wel een korter herstel gehad, met waarschijnlijk minder arbeidsuitval, maar dit moet dan afgezet worden tegen de kosten die de patiënten hebben gemaakt met ernstige complicaties.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
De haalbaarheid en implementatie zal geen probleem zijn, aangezien de behandeling al wordt toegepast in de huidige praktijk. Echter, in de huidige tijd is het gebruik van implantaten steeds meer onder vuur komen te liggen. Wanneer er dan weliswaar een effectievere benadering wordt gezien in de literatuur, maar de complicatie risico's niet op basis van evidentie gegeven kunnen worden, zal dit minder geaccepteerd en gekozen worden door de patiënten. Een enkele patiënte bij wie beide klachten (SUI en prolaps) prominent aanwezig zijn en voor wie het tweemaal ondergaan van de postoperatieve herstel-periode een grote belasting is, zal de onzekerheid van de waarschijnlijk verhoogde kansen op complicaties mogelijk niet zwaar wegen om te kiezen voor een gecombineerde ingreep.
Het plaatsen van een mid urethrale sling wordt door zowel een uroloog als een gynaecoloog gedaan, prolaps chirurgie alleen door een gynaecoloog. In de praktijk kan het voorkomen dat een patiënte door de uroloog wordt gezien in verband met SUI, maar eerst door een gynaecoloog geopereerd wil worden. Om de patiënte de juiste overwegingen te laten maken, zal volledig onderzoek en informatieverstrekking plaats moeten vinden en is samenwerking tussen uroloog en gynaecoloog van belang.

Aanbevelingen

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Uit bovenstaande kunnen we concluderen dat het combineren van de prolaps operatie met een anti-incontinentie operatie de kans op postoperatieve SUI vermindert maar dat de combinatie operatie het risico op complicaties vergroot.

Daarbij is er een risico van overbehandeling bij combinatie chirurgie waarschijnlijk aanwezig en kan er bij onvoldoende effect altijd nog een tweede operatie plaatsvinden, tegen een lager peroperatief risico. Deze aspecten zullen preoperatief goed met de vrouw doorgesproken moeten worden om op individueel niveau tot een juiste afweging te komen.

Aanbevelingen:

Vraag duidelijk uit wat de hoofdklacht is van de vrouw; SUI of prolapsklachten. Staan de prolapsklachten op de voorgrond: zie richtlijn prolaps.

Overweeg een combinatiechirurgie van incontinentie en prolaps wanneer SUI de hoofdklacht is en patiënte eveneens klachten van een prolaps aangeeft. Combinatiechirurgie kan mogelijk hogere kans op complicaties geven.

Wijs vrouwen op de mogelijkheid tot het ondergaan van de operaties in twee tempi waarbij gestart wordt met prolaps chirurgie. Indien de SUI nog overblijft gevolgd door een mid urethrale sling. Hierbij zijn de per-operatieve complicaties minder.

Literatuur

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Implementatieplan

Aanbeveling	Tijdspad voor implement	Verwacht effect	Randvoorwaarden voor implementatie (binnen	Mogelijke barrières voor	Te ondernemen acties voor	Verantwoordelijken voor acties[3]	Overige opmerkingen

	atie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	op kosten	aangegeven tijdspad)	implementatie[1]	implementatie[2]		
1-3	<1 jaar	Onbekend	Geen, sluit grotendeels aan bij klinische praktijk	n.v.t.	n.v.t.	n.v.t.	Geen

Table of excluded studies

Reference	Reason for exclusion
Bastani, 2014	Wrong population: women with only prolapse
Borstad, 2010	Included in SR of Baessler 2018
Christmann-Schmid, 2018	Wrong study design: prospective cohort study
Giugale, 2022	Wrong population: women with only prolapse
Law, 2015	Wrong study design: prospective cohort study
Lee, 2021	Wrong study design: prospective cohort study
Lo, 2019	Wrong study design: prospective cohort study
Naidu, 2014	Wrong study design: prospective cohort study
Schierlitz, 2014	Included in SR of Baessler 2018
Van der Ploeg, 2015	Included in SR of Baessler 2018
Van der Ploeg, 2016	Included in SR of Baessler 2018
Wei, 2012	Wrong population: only prolapse
Zargham, 2013	Wrong comparison: Anterior colporrhaphy and sling placement vs transvaginal mesh correction of AVWP and tension-free vaginal tape
Celik, 2014	Wrong study design: prospective cohort study
Futyma, 2014	Wrong study design: prospective longitudinal study Wrong comparison: only for women with SUI, additional sling was inserted Wrong outcome: de novo overactive bladder
Horosz, 2020	Wrong study design: cohort study. Wrong population: 56 of 84 women with SUI before POP surgery
Ovtcharenko, 2020	Wrong study design: retrospective cohort study
Stewart, 2021	Wrong study design: retrospective study
Ahmed, 2020	Wrong intervention: transobturator subvesical mesh
Baser, 2020	Wrong population: women without occult or obvious SUI
Boccasanta, 2010	Wrong study design: prospective cohort study
Lo, 2015	Wrong study design: no randomized trial
Montera, 2018	Wrong study design: no RCT, but prospective cohort study Macroplastique with POP surgery versus only POP surgery
Baessler, 2013	Older SR; updated in SR Baessler 2018
He, 2021	Better SR available; only few studies with suitable subgroups
Requena, 2018	Women with only prolapse; occult SUI

5

Module Injectie bulkmateriaal bij vrouwen met stress urine-incontinentie

Uitgangsvraag

Wat is de waarde van een injectie met bulkmateriaal bij vrouwen met stress urine-incontinentie?

Inleiding

De vorige richtlijn urine-incontinentie voor de 2e/3e lijnszorg dateert uit 2014. In deze richtlijn hadden bulkinjecties een bescheiden plek. Hierna zijn er echter drie ontwikkelingen geweest die het uitwerken van deze uitgangsvraag van belang maken. Ten eerste is er inmiddels wat langer ervaring met enkele van de bulkproducten. Ten tweede kwam het gebruik van mesh-materiaal bij operaties tegen urineverlies in het Verenigd Koninkrijk onder vuur te liggen, waardoor de optie van bulkinjecties als alternatieve behandeling van stress-incontinentie interessanter is geworden. Ten derde is met patiënten preferentie-onderzoek meer zicht verkregen over de keuzes van patiënten. Daardoor is toenemend duidelijk geworden dat patiënten effectiviteit niet altijd voorop willen zetten bij de behandeling van stress urine-incontinentie, als de ervoor te nemen operatieve risico's toenemen.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effectiveness of bulk injection in women with stress urinary incontinence compared to no treatment, physical therapy, or midurethal sling

P: Women with stress urinary incontinence (SUI)
I: Injection with bulking material as primary treatment
C: No treatment, physiotherapy, tape
O: Effect on/cure of complaints of SUI, quality of life, adverse events

<u>Relevant outcome measures</u>

The guideline development group considered effect on/cure of complaints of SUI as a critical outcome measure for decision making; and quality of life and adverse events as important outcome measures for decision making.

A priori, the working group defined adverse events as pain, retention, new overactive bladder complaints, sexual dysfunction, urinary tract infections, exposure, migration, and reoperation. For other outcomes, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following minimal clinically (patient) important differences:

- Quality of life:
    - Urinary Distress Inventory (UDI-6, 0-100): ≥ 33.33 (Skorupska, 2021)

In all other cases, the working group defined the GRADE-standard limit of 25% difference for dichotomous outcomes (RR < 0.8 or > 1.25), and 0.5 SD for continuous outcomes as a minimal clinically (patient) important difference.

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until 18 May 2022. The detailed search strategy is depicted

under the tab Methods. The systematic literature search resulted in 181 hits. Studies were selected based on the following criteria:

- Systematic review (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available) or randomized controlled trial comparing bulking material with no treatment, physiotherapy, or tape
- Patients aged ≥ 18 years
- Full-text English language publication
- Studies including ≥ 20 (ten in each study arm) patients; and
- Studies according to PICO.

Thirteen studies were initially selected based on title and abstract screening. After reading the full text, ten studies were excluded (see the table with reasons for exclusion under the tab Methods), and three studies were included (Kirchin, 2017; Itkonen Freitas, 2020; Itkonen Freitas, 2021). The systematic review of Kirchin 2017 defined a broader PICO than the PICO defined for this module. Therefore, three randomized controlled trials included in the systematic review of Kirchin that matched with our PICO were selected for the literature analysis (Maher, 2005; Corcos, 2005; Ter Meulen, 2009).

Results

The three randomized controlled trials included in the systematic review of Kirchin (2017) and the randomized controlled trials by Itkonen Freitas (2020 and 2021) were included in the analysis of the literature. Important study characteristics and results are summarized in table 1 and the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Kirchin (2017) performed a Cochrane systematic review to determine the effects of periurethral and transurethral bulking agents on cure or improvement of urinary incontinence in women. All randomised or quasi-randomised controlled trials in the treatment of urinary incontinence in women, in which at least one management arm involved urethral injection therapy were included. The Cochrane Incontinence Group Specialised Trials Register and the reference lists of relevant articles were searched on 8 November 2010. No language or other restrictions on the searches were imposed. In total, 14 trials were included. However, the data from three randomized controlled trials (Corcos, 2005; Maher, 2005; Ter Meulen, 2009) matching with the PICO were extracted from this review (table 1).

Itkonen Freitas (2020) performed a randomized, controlled, parallel group trial. The study aimed to assess whether polyacrylamide hydrogel (PAHG) is noninferior to tension-free vaginal tape (TVT) to treat women with primary SUI. Women were included when they had SUI not responsive to conservative treatment, were older than 18 years, had no previous incontinence procedure, a positive cough stress test without urge-type leakage, a post-void residual urine (PVR) volume less than 100 ml, and a bladder capacity greater than 300 ml. A body mass index more than 35 kg/m^2, neurogenic disease, use of anticholinergics or mirabegron, illness or another condition causing a risk of complications during the TVT operation, active malignancy, urinary tract infection, more than second degree urogenital prolapse, pregnancy or future plans for pregnancy, and inability to understand the purpose of the study were criteria for exclusion. In total, 108 women were randomized to PAHG and 104 women to TVT. However, due to lost to follow-up (n=4), 208 women were included in

the analysis. Length of follow up was 12 months. Patient satisfaction (measured with the Visual Analog Scale) was chosen as primary outcome. Secondary outcomes were treatment effectiveness in reducing urinary leakage (reported as objective cure defined as negative cough stress test and pad test, and subjective cure measured with the 5-point Likert-like scale) and complications, including pain during and after treatment (measured with the Numerical Rating Scale).

Another publication by Itkonen Freitas (2021) was based on the same study population but reported the quality of life (measured with the Urogenital Distress Inventory and Impact Questionnaire Short Form) after PAHG versus TVT.

Table 1. Description of included studies.

Study	Intervention		Comparator		Follow-up	Outcomes
	Characteristics	**Intervention type/ dose**	**Characteristics**	**Type of control**		
Corcos, 2005	**Arm 1 (n= 66)** Mean age (SD): NR BMI: NR	Bulking material (submucosal urethral injection with collagen; 1-4 injections in 6 months)	**Arm 2 (n= 67)** Mean age (SD): NR BMI: NR	Tape (bladder neck suspension (n=6), sling (n=24) or Burch (n=24))	12 months	Quality of life (IIQ questionnaire, Short Form 36 questionnaire, numbers not cured or improved, numbers not satisfied), adverse events (complications)
Maher, 2005	**Arm 1 (n= 23)** Median age: 65 yrs BMI: NR	Bulking material (Macroplastique)	**Arm 2 (n= 22)** Median age: 63 yrs BMI: NR	Tape (Pubovaginal sling)	6 months 12 months ± 62 months (range 43-71 months)	Effect on/cure of complaints of SUI (1-h pad test, objectively cured), quality of life (subjectively cured, patients satisfied, SUDI, SIIQ, success)
Ter Meulen, 2009	**Arm 1 (n= 24)** Mean age (SD): NR BMI: NR	Bulking material (Macroplastique)	**Arm 2 (n= 21)** Mean age (SD): NR BMI: NR	Physiotherapy (Pelvic floor muscle exercise and home-training programme)	3-months 12-months (only for bulking material)	Effect on/cure of complaints of SUI (pad test, number of pads used, frequency volume chart), quality of life (I-QoL, physician and patient cure self assessment), adverse effects (complications)
Itkonen Freitas, 2020 and Itkonen Freitas, 2021	**Arm 1 (n= 108)** Median age (IQR): 49 (42 to 60) yrs BMI: 25 (22 to 27)	Bulking material (Polyacrylamide Hydrogel)	**Arm 2 (n= 104)** Median age (IQR): 48 (42 to 57) yrs BMI: 24 (22 to 26)	Tape (Tension-free vaginal tape)	12 months	*Itkonen Freitas 2020:* Effect on/cure of complaints of SUI (objective cure), quality of life (subjective cure), adverse events (acute urinary retention, reoperation due to retention/erosion, UTI, pain) *Itkonen Freitas 2021:* Quality of life (UDI-6, IIQ-7)

Abbreviations: IIQ-7, Incontinence Impact Questionnaire Short Form; SUDI, Short Urinary Distress Inventory; SIIQ, Incontinence Impact Questionnaire; UDI-6, Urogenital Distress Inventory; UTI, urinary tract infection; NR, not reported

Results

1. Bulking material versus no treatment

Not reported.

2. Bulking material versus physiotherapy

2.1 Effects on/cure of complaints (critical)

Ter Meulen (2009) reported the mean number of pads used at three months for women undergoing treatment with the bulking material Macroplastique as compared with pelvic floor muscle exercises (PFME). For treatment with Macroplastique, the mean number of pads used at three months declined from 3.4 to 1.9 pads, while for women who performed PFME, the mean number declined from 2.7 to 2.5 pads. Since no standard deviations have been reported, no GRADE assessment can be performed.

2.2 Quality of life (important)

2.2.1. Incontinence quality of life score

Ter Meulen (2009) reported the mean Incontinence Quality-of-Life (I-QoL) score at baseline and at three months. For women receiving Macroplastique, the mean I-QoL score at baseline was 2.59 and 3.2 after three months (mean difference = 0.6, SD = 0.7) , as compared to a mean I-QoL score of 2.96 at baseline and 3.03 after three months for women who performed PFME (mean difference = 0.1, SD = 0.6). A mean difference of 0.54 (95% CI 0.16 to 0.92) was found between both groups for the change in I-QoL scores between baseline and after three months. This difference was clinically relevant favoring treatment with Macroplastique.

2.2.2. Patient satisfaction

In addition, Ter Meulen (2009) reported the number of women who were not cured (self reported as worse, unchanged or improved) and who did not improve (worse or unchanged) three months after treatment with either Macroplastique or performing PFME. In total, 16 of the 24 women (66.7%) who received Macroplastique were not cured as compared to 20 of the 21 women (95.2%) performing PFME (RR=0.7, 95% CI 0.52 to 0.94). This difference was clinically relevant favoring treatment with Macroplastique. One of the 24 women (4.2%) receiving Macroplastique did not improve as compared to four of the 21 women (19%) performing PFME (RR=0.22, 95% CI 0.03 to 1.81). This difference was also clinically relevant favoring treatment with Macroplastique.

2.3 Adverse events (important)

Ter Meulen (2009) reported peri-and postoperative complications for treatment with Macroplastique compared to PFME.

2.3.1 Pain

Mild pain occurred in 8% of the women receiving Macroplastique.

2.3.2 Retention

Retention occurred in 19 of the 24 women (79.2%) who underwent treatment with Macroplastique, but did not occur in women undergoing PFME. The corresponding risk ratio was 34.32 (95% CI 2.2 to 535.8). The corresponding absolute risk increase with Macroplastique was 0.79 (95% CI 0.62 to 0.97), translating in a number needed to treat (NNT) of 1.27 (95% CI 1.03 to 1.61). This difference was clinically relevant

favoring PFME.

2.3.3. Reoperation

In three of the 24 women (12.5%) receiving Macroplastique, an additional injection was performed after three months of follow-up. Other continence treatments were given to five women (21%) who underwent treatment with Macroplastique because of treatment failure.

3. Bulking material versus tape

3.1 Effects on/cure of complaints (critical)

Corcos (2005) compared the cure of complaints of SUI after a collagen injection versus an open Burch colposuspension, an open sling procedure, or open bladder neck suspension. Cure was assessed with a 24-hour pad test and defined as an increase in pad weight less than 2.5 grams and no additional interventions needed. In total, 34 of the 64 women (53%) who underwent a collagen injection were cured as compared to 39 of the 54 women (72%) receiving open surgery (according to per protocol with verbal update analysis). More women were cured after open surgery (RR 1.69, 95% CI 1.02 to 2.79). This difference was clinically relevant favoring open surgery.

Maher (2005) reported the objective cure for treatment with Macroplastique injection or a pubovaginal sling within one year post-operatively. Objective cure was defined as no urinary leakage due to SUI on repeat urodynamic studies. Cure was reported in 2 of the 22 women (9.1%) receiving Macroplastique and in 17 of the 21 women (81.0%) who got a pubovaginal sling (RR=0.11, 95% CI 0.03 to 0.43). This difference was clinically relevant in favour of a pubovaginal sling. In addition, the 1-hour pad test was reported. Women receiving Macroplastique had a median of 5 g (0 to 57 g) and women receiving a sling 2 g (0 to 20 g).

Itkonen Freitas (2020) reported the objective cure with a negative cough stress test and a negative pad test for treatment with polyacrylamide hydrogel (PAHG) or tension-free vaginal tape (TVT). In total, 71 of the 107 women (66.4%) who received PAHG had a negative cough test as compared to 96 of the 101 women (95%) who got a TVT (RR=0.70, 95% CI 0.61 to 0.80). This difference was clinically relevant favoring TVT. A negative pad test was achieved in 68 of the 107 women (63.6%) receiving PAHG and in 96 of the 101 women (95%) who got TVT (RR=0.67, 95% CI 0.58 to 0.78). This difference was also clinically relevant favoring TVT.

3.2 Quality of life (important)

Corcos (2005) reported that 49 of the 64 women (76.6%) receiving a collagen injection were satisfied as compared to 40 of the 54 women (74.1%) of the women following open surgery (RR=1.03, 95% CI 0.84 to 1.27). This difference was not clinically relevant. The quality of life was also assessed with the Short Form 36 questionnaire and incontinence impact questionnaire (IIQ). No differences were found between collagen injection treatment and open surgery for seven of the eight domains of the Short Form 36 and the IIQ. The mean IIQ score was 45.2 (18.4) for treatment with collagen injection and 41.6 (17.6) after open surgery (mean difference is 3.6, 95% CI -2.91 to 10.11).

Maher (2005) reported that 13 of the 22 women (59.1%) receiving Macroplastique were satisfied (self-reported) as compared to 17 of the 21 women (81.0%) who got a pubovaginal sling (RR=0.73, 95% CI 0.49 to 1.09). This difference was clinically relevant, but not statistically significant, favoring a pubovaginal sling. In 17 of the 22 women (77.3%) receiving Macroplastique and in 19 of the 21 women (90.5%) who got a pubovaginal sling, subjective cure (defined as incontinence occurring once or more a week) was reported

(RR=0.85, 95% CI 0.65 to 1.11). This difference was not clinically relevant. In addition, Maher (2005) reported the quality of life with the Short Urinary Distress Inventory (SUDI) and the Incontinence Impact Questionnaire (IIQ) scores at six months post-operatively. No data were suitable for the analysis. However, no differences in median SUDI and IIQ scores were found.

Itkonen Freitas (2020) measured the subjective cure after treatment with PAHG or TVT using a 5-point Likert-like scale. In total, 25 of the 107 women (23.4%) who underwent PAGH and 84 of the 101 women (83.2%) who were treated with TVT reported cure (RR=0.28, 95% CI 0.20 to 0.40). This difference was clinically relevant favoring TVT. In addition, Itkonen Freitas (2020) defined quality of life as patient satisfaction using a Visual Analogue Scale (VAS) on a scale from 0 to 100. For women treated with PAHG, 64 of the 107 women (59.8%) had a score of 80 or higher, as compared to 96 of the 101 women (95%) who had a TVT (RR=0.63, 95% CI 0.54 to 0.74). This difference was also clinically relevant favoring TVT. The median satisfaction score was 85 (IQR 65 to 98) for women treated with PAHG and 99 (IQR 94 to 100) for women receiving TVT.

Itkonen Freitas (2021) reported the 1-year urinary incontinence-related quality of life with the Urogenital Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire Short Form (IIQ-7). For women treated with PAHG, the UDI-6 score (max. 100) after 1 year was 18.96 ± 13.20 while for women who got a TVT, the UDI-6 score was 7.89 ± 7.65 (MD=11.07, 95% CI 8.16 to 13.98). The IIQ-7 score (max. 100) was 19.34 ± 21.01 for women treated with PAHG and 3.49 ± 8.61 for women treated with TVT (MD=15.85, 95%CI 11.53 to 20.17). Less urinary symptom-related distress among TVT patients compared to PAHG were reported, but the differences were not clinically relevant.

3.3 Adverse events (important)

Corcos (2005) reported that 36 complications occurred in 64 women (56%) who received collagen injection as compared to 84 complications in 54 women (64%) who underwent open surgery.

Maher (2005) reported adverse effects for treatment with Macroplastique injections and pubovaginal sling.

- *Urinary tract infection (UTI)*
  Two women receiving Macroplastique and three women who got a pubovaginal sling reported an UTI.
- *Reoperation*
  Additional Macroplastique injections or surgery was required in seven of the 22 women (31.8%) who received initial Macroplastique injections. Further surgery was provided to one women who got a pubovaginal sling.

Itkonen Freitas (2020) reported perioperative and/or postoperative complications. In total, 21 of the 107 women (19.6%) who were treated with PAHG and 45 of the 101 women (44.6%) who underwent TVT mentioned complications (RR=0.44, 95%CI 0.28 to 0.68). This difference was clinically relevant favoring PAHG.

- *Pain*
  Twelve months postoperative, pelvic/implantation site/tape pain was reported in five of the 101 women (5.0%) who were treated with TVT.
- *Urinary tract infection (UTI)*
  Urinary tract infections were experienced by nine of the 107 women (8.4%) treated with PAHG and seven of the 101 women (6.9%) receiving TVT (RR 1.21, 95% CI 0.47 to 3.14). This difference was not clinically relevant.

- *Reoperation*
  Less than three months postoperative, reoperation due to retention was mentioned by three of the 101 women (3.0%) who underwent treatment with TVT.

Level of evidence of the literature

1. Bulking material versus no treatment

The level of evidence regarding the outcome measures effects on/cure of complaints, quality of life and adverse events could not be assessed with GRADE. The included studies did not compare bulking material versus no treatment.

2. Bulking material versus physiotherapy

2.1. Effects on/cure of complaints (critical)
The level of evidence regarding the outcome measure effects on/cure of complaints could not be assessed with GRADE. The included study did not report any measures of spread.

2.2 Quality of life (important)
The level of evidence regarding the outcome measure quality of life started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of blinding (-1, risk of bias) and a very small sample size (<50) combined with the 95% confidence interval crossed the line of no (clinically relevant) effect (-2 imprecision).

2.2 Adverse events (important)
The level of evidence regarding the outcome measure adverse events started as high because it was based on an RCT and was downgraded by two levels to low because of lack of blinding (-1, risk of bias) and small sample sizes resulting in insufficient statistical power (-1, imprecision).

3. Bulking material versus tape

3.1 Collagen injection versus open surgery

3.1.1. Effects on/cure of complaints (critical)
The level of evidence regarding the outcome measure effects on/cure of complaints started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of blinding (-1, risk of bias), the control group did not only receive tape (-1, indirectness) and the 95% confidence interval crossed the line of no (clinically relevant) effect (-1, imprecision).

3.1.2. Quality of life (important)
The level of evidence regarding the outcome measure quality of life started as high because it was based on an RCT and was downgraded by four levels to very low because of lack of blinding and the undesirable analysis of missing data that may have led to an overestimation of the effect (-2, risk of bias), the control group did not only receive tape (-1, indirectness) and the 95% confidence interval crossed the line of no (clinically relevant) effect (-1, imprecision).

3.1.3. Adverse events (important)
The level of evidence regarding the outcome measure adverse started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of blinding (-1, risk of bias), the control group did not only receive

tape (-1, indirectness) and small sample sizes resulting in insufficient statistical power (-1, imprecision).

3.2 Macroplastique versus pubovaginal sling

3.2.1. Effects on/cure of complaints (critical)

The level of evidence regarding the outcome measure effects on/cure of complaints started as high because it was based on an RCT and was downgraded by two levels to low because of lack of blinding (-1, risk of bias) and small sample sizes resulting in insufficient statistical power (-1, imprecision).

3.2.2. Quality of life (important)

The level of evidence regarding the outcome measure quality of life started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of blinding (-1, risk of bias), and the 95% confidence interval crossed the line of no (clinically relevant) effect (-2, imprecision).

3.2.3. Adverse events (important)

The level of evidence regarding the outcome measure adverse events started as high because it was based on an RCT and was downgraded by two levels to low because of lack of blinding (-1, risk of bias) and small sample sizes resulting in insufficient statistical power (-1, imprecision).

3.3 Polyacrylamide hydrogel (PAHG) versus tension-free vaginal tape (TVT)

3.3.1. Effects on/cure of complaints (critical)

The level of evidence regarding the outcome measure effects on/cure of complaints started as high because it was based on an RCT and was downgraded by two levels to low because of lack of blinding (-1, risk of bias) and and small sample sizes resulting in insufficient statistical power (-1, imprecision).

3.3.2. Quality of life (important)

The level of evidence regarding the outcome measure quality of life started as high because it was based on an RCT and was downgraded by two levels to low because of lack of blinding (-1, risk of bias) and and small sample sizes resulting in insufficient statistical power (-1, imprecision).

3.3.3. Adverse events (important)

The level of evidence regarding the outcome measure adverse started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of blinding (-1, risk of bias) and small sample sizes resulting in insufficient statistical power (-1, imprecision).

Conclusions

1. Bulking material versus no treatment

No GRADE	No evidence was found regarding the effect of bulking material on effects on/cure of complaints, quality of life and adverse events when compared with no treatment in women with stress urinary incontinence.

2. Bulking material versus physiotherapy

2.1 Effects on/cure of complaints (critical)

No GRADE	No evidence was found regarding the effects of Macroplastique on complaints when compared with pelvic floor muscle exercise in women with stress urinary incontinence. *Source: Ter Meulen (2009)*

2.2 Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of Macroplastique on quality of life when compared with pelvic floor muscle exercise in women with stress urinary incontinence. *Source: Ter Meulen (2009)*

2.3 Adverse events (important)

Low GRADE	The evidence suggests that pelvic floor muscle exercise reduces adverse events when compared with macroplastique in women with stress urinary incontinence. *Source: Ter Meulen (2009)*

3. Bulking material

3.1. Collagen injection versus open surgery

3.1.1 Effects on/cure of complaints (critical)

Very low GRADE	The evidence is very uncertain about the effect of collagen injection on the cure of complaints when compared with open surgery in women with stress urinary incontinence. *Source: Corcos (2005)*

3.1.2 Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of collagen injection on quality of life when compared with open surgery in women with stress urinary incontinence. *Source: Corcos (2005)*

3.1.3 Adverse events (important)

Very low GRADE	The evidence is very uncertain about the effect of collagen injection on adverse events when compared with open surgery in women with stress urinary incontinence. *Source: Corcos (2005)*

3. Bulking material versus tape

3.2. Macroplastique versus pubovaginal sling

3.2.1 Effects on/cure of complaints (critical)

Low GRADE	The evidence suggests pubovaginal slings increase cure of complaints when compared to macroplastique in women with stress urinary incontinence. *Source: Maher (2005)*

3.2.2 Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of Macroplastique on quality of life when compared with a pubovaginal sling in women with stress urinary incontinence. *Source: Maher (2005)*

3.2.3 Adverse events (important)

Low GRADE	The evidence suggests that Macroplastique results in little to no difference in adverse events when compared with a pubovaginal sling in women with stress urinary incontinence. *Source: Maher (2005)*

3. Bulking material versus tape

3.3. Polyacrylamide hydrogel (PAHG) versus tension-free vaginal tape (TVT)

3.3.1 Effects on/cure of complaints (critical)

Low GRADE	The evidence suggests tension-free vaginal tape in women increases cure of complaints when compared with polyacrylamide hydrogel in women with stress urinary incontinence. *Source: Itkonen Freitas (2020)*

3.3.2 Quality of life (important)

Low GRADE	The evidence suggests tension-free vaginal tape increases quality of life when compared with polyacrylamide hydrogel in women with stress urinary incontinence. *Source: Itkonen Freitas (2020); Itkonen Freitas (2021)*

3.3.3 Adverse events (important)

Low GRADE	The evidence suggests that polyacrylamide hydrogel reduces adverse events when compared with tension-free vaginal tape in women with stress urinary incontinence. *Source: Itkonen Freitas (2020)*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

In de literatuuranalyse werd onderzocht wat de waarde van een injectie met bulkmateriaal is bij vrouwen met stress urine-incontinentie (SUI). De effectiviteit van een injectie met

bulkmateriaal werd vergeleken met geen behandeling, fysiotherapie of tape. Voor de vergelijking tussen bulkmateriaal en geen behandeling werd geen studie gevonden. Er werd één RCT gevonden voor de vergelijking tussen bulkmateriaal en fysiotherapie (Ter Meulen, 2009). Voor de vergelijking tussen bulkmateriaal en tape werden vier RCT's gevonden (Corcos, 2005; Maher, 2005; Itkonen Freitas, 2020 and 2021). Bewijskracht voor de kritieke uitkomstmaat (effect op/genezing van klachten SUI) was laag tot zeer laag, mede wegens het feit dat enkel studie met kleine aantal aanwezig zijn. Dit betekent dat meerdere of groterestudies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van injectie met bulkmateriaal vergeleken met geen behandeling, fysiotherapie of tape voor vrouwen met SUI.

Ondanks de beperkte gevonden bewijslast voor de effectiviteit, past de werkgroep de aanbevelingen rondom bulkinjecties als behandeling van stress-incontinentie in lijn van die van de EAU en de huidige praktijk aan van een negatieve in 2014, naar een positievere nu. Hierbij overweegt de werkgroep de volgende punten. Allereerst is er in de jaren sinds de laatste richtlijn-update (2014) ook geen bewijs gevonden voor nadelen die in die tijd nog onbekend waren. Daarnaast is het gebruik van mesh bij de behandeling van incontinentie door bijwerkingen in een slecht daglicht komen te staan, onder meer leidend tot een verbod om het te gebruiken in diverse landen. Andere behandelingen, ook bulkinjecties, worden daarom gezocht als alternatief.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>

Patiënt preferentie wordt steeds duidelijker. Zo kiezen patiënten vaker voor een minder effectieve behandeling als de risico's dan ook minder aanwezig zijn. De patiënt zal dus duidelijk ingelicht moeten worden over de minimale invasiviteit, het lage risico's op complicaties, maar ook over de minder bewezen effectiviteit, de grote kans op herbehandeling en minder lange toepasbaarheid van deze therapie waardoor de veiligheid nog mogelijk niet geheel is gegarandeerd. Pas met al deze informatie kan de patiënte een goed overwogen keuze maken (Casteleijn, 2018; Casteleijn, 2020; Petrou, 2006).
Het feit dat bij afname van resultaten in de follow-up herhaling van de injecties meestal kan plaatsvinden, kan worden meegenomen in de besluitvorming kan worden dat bij afname van resultaat in de follow up, herhaling van de injecties meestal kan plaatsvinden.

Er zijn subgroepen waar bulking agents vaker gebruikt worden. De oudere patiënte al dan niet met aanwezigheid comorbiditeit, waarbij anders geen therapie zal worden gegeven, of de juist heel jonge patiënte die (nog) geen 'echte' operatie wil. Daarnaast zijn bulking agents worden ingezet als aanvulling op een (nog) niet geheel geslaagde tape omdat er sfincterinsufficientie is.

<u>Kosten (middelenbeslag)</u>

Er kan op twee manieren naar de kosten worden gekeken, namelijk hoe effectiever de behandeling hoe minder continentiemateriaal noodzakelijk is en dus hoe meer kosten worden bespaard. Daarin zouden injecties kost effectiever zijn dan niets doen. Over fysiotherapie kan geen uitspraak worden gedaan en tape is in deze redenatie kost effectiever dan injecties.
Wanneer men kijkt naar de kosten van de behandeling is nietsdoen het goedkoopst, gevolgd door respectievelijk fysiotherapie, injecties en tape. Waarbij injecties mogelijk leiden tot een kortere opname, minder complicaties, geen anesthesie en vlot herstel (wat hervatting van sociale en economische leven mogelijk maakt). Bij injecties is echter vaker een herhaling van de behadeling nodig. Tape wordt ook in dagopname gedaan en vindt ook op steeds meer

plekken plaats onder sedatie. Echter de complicaties kunnen mogelijk hoger zijn (Corcos, 2005). De studies tot op heden laten onvoldoende bewijs zien voor een fundeerde uitspraak.

Aanvaardbaarheid, haalbaarheid en implementatie

De mid-urethrale slings zijn onder urologen en gynaecologen steeds meer ingebed in de praktijk. Anders dan bijvoorbeeld in het geval van sacrale neuromodulatie, of bandjes voor mannen, speelt voor mid-urethrale slings gecentraliseerde of beperkte beschikbaarheid geen rol.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Aanbeveling-1

Conform de onder het kopje 'overwegingen' beschreven wens van vrouwen -zeker in het licht van de laatste jaren spelende mesh-discussies- om weinig risico te lopen en de bereidheid voor lief te nemen dat effectiviteit waarschijnlijk wat minder goed is, is de aanbeveling aangepast naar een 'biedt aan' ipv een 'biedt niet aan'. In het kader van samen beslissen dienen de kansen op minder effectiviteit, maar ook minder risico's in vergelijking met andere behandelingen nadrukkelijk te worden besproken.

Aanbeveling-2

In de overwegingen van vrouwen om eventueel urethrale bulkinjecties te ondergaan, dienen de als nadelen te ervaren eigenschappen van de behandeling eveneens nadrukkelijk besproken te worden.

Aanbevelingen:

Biedt urethrale bulkinjecties aan aan vrouwen die verbetering van hun stress-incontinentie zoeken en bespreek daarbij de kansen op minder effectiviteit, maar ook minder risico's in vergelijking met andere, niet-conservatieve behandelingen.

Biedt urethrale bulkinjecties aan aan vrouwen die verbetering van hun stress-incontinentie zoeken en bespreek daarbij expliciet dat naast een mindere effectiviteit ten opzichte van mid urethrale slings de kans op herhaalbehandeling groot is en de langetermijnseffecten (effectiviteit, veiligheid) onvoldoende duidelijk zijn.

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Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1 en 2	<1 jaar	Onbekend	Geen, sluit grotendeels aan bij klinische praktijk	n.v.t.	n.v.t.	n.v.t.	Geen

Table of excluded studies

Reference	Reason for exclusion
Pivazyan, 2022	Better systematic review available with higher quality of included studies

Leone Roberti Maggiore, 2015	More recent systematic review available which included the same studies
Matusuoka, 2016	Wrong population: not only SUI
Ismail, 2020	Wrong population: not only SUI
Davila, 2011	More recent systematic review available for better comparison
Chughtai, 2016	Wrong population: Medicare beneficiaries aged 65 or older Wrong intervention: unclear which bulking agent is used
Daneshpajooh, 2021	Wrong intervention: platelet-rich plasma
Balk, 2019	More recent systematic review available for better comparison
Cameron, 2011	Wrong comparison: no comparison between bulking agents and other interventions
Riemsma, 2017	No comparison of cure rates for slings and bulking agents

Module Male-sling postprostatectomie

Uitgangsvraag

Wat is de waarde van een male sling bij mannen met post-prostatectomie SUI?

Inleiding

Stress urine-incontinentie (SUI) is een gekende complicatie van radicale prostatectomie, als gevolg van de denervatie van het sfinctercomplex. Post prostatectomie SUI heeft een significante invloed op de kwaliteit van leven.
De artificiële sfincter wordt al tientallen jaren beschouwd als de gouden standaard in de behandeling van post-prostatectomie SUI, bij patiënten waarbij postoperatief natuurlijk herstel niet optreedt en waarbij bekkenfysiotherapie geen of onvoldoende resultaat heeft gehad. De artificiële sfincter bestaat uit een hydraulisch systeem welke compressie geeft rondom de urethra. In principe kan de sfincterprothese gebruikt worden voor alle vormen van post-prostatectomie SUI, ongeacht de ernst.

Tegenwoordig zijn er ook andere chirurgische behandelingen van SUI bij de man beschikbaar, die elk berusten op een ander chirurgisch principe. Het gaat dan om slings (al dan niet gefixeerd), bulkmateriaal en compressieballonnen. Al deze behandelingen hebben een meer minimaal invasief karakter wanneer vergeleken met de sfincter.
In deze module beperken we ons tot de waarde van de sling in vergelijk met de andere behandelingen van post-prostatectomie SUI.

De sling wordt gepositioneerd op het niveau van de bulbaire urethra, middels een retropubische of transobturatoire benadering. Er zijn slings op de markt die peroperatief worden gefixeerd en slings waar bij de spanning postoperatief nog aanpasbaar is.
Met de gefixeerde slings wordt de urethra gepositioneerd naar een meer proximale positie, zonder dat daarbij het sfinctermechanisme wordt beïnvloed.
De aanpasbare slings bieden de mogelijkheid om postoperatief de uiteinden van de sling aan te trekken of een kussen onder de urethra in meer of mindere mate op te blazen. De druk op de urethra is dus aanpasbaar.

In de praktijk wordt de artificiële sfincter toegepast voor matige tot ernstige SUI, daar waar de slings meestal worden gereserveerd voor milde tot matige SUI. Bulkmateriaal en ook plaatsing van compressieve ballonnen wordt met name verricht voor milde SUI. Echter de definities van milde en matige incontinentie lopen sterk uiteen.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effectiveness and safety of male sling in men with post-prostatectomy stress urine incontinence, compared with bulking material, artificial urinary sphincter (AUS) or PRO-ACT?

P: Men with stress urine incontinence after radical prostatectomy
I: male sling
C: bulking agents; PRO-ACT; artificial urinary sphincter (AUS)
O: Effect/recovery of SUI-complaints (objective, e.g. pads) subjective improvement, quality of life, adverse events, long term results (explantation/revision)

<u>Relevant outcome measures</u>

The guideline development group considered effect/recovery of SUI-complaints and subjective improvement as a critical outcome measure for decision making; and as an important outcome measure for decision making.

A priori, the working group defined adverse events as retention, complicated infections (material-related) and erosion. For other outcomes, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following minimal clinically (patient) important differences:

Subjective improvement:

- Urinary Distress Inventory (UDI-6, 0-100): ≥ 33.33 (Skorupska, 2021)
- International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF, 0-21): ≥ 5 at 12 months, ≥ 4 at 24 months (Sirls, 2013)
- The overactive bladder questionnaire (OAB-q, 0-100): ≥ 10 points (Coyne, 2006)
- The overactive bladder quality of life short-form questionnaire (OAB-q SF, 0-100): ≥ 11 points (Blanker, 2019)

In all other cases, the working group defined the GRADE-standard limit of 25% difference for dichotomous outcomes (RR < 0.8 or > 1.25), and 0.5 SD for continuous outcomes as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until June 6th 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 285 hits. Studies were selected based on the following criteria:

- Systematic review (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trial or observational study comparing male sling with bulking agents; PRO-ACT; artificial urinary sphincter (AUS);
- Patients aged ≥ 18 years;
- Full-text English language publication;
- Studies including ≥ 20 (ten in each study arm) patients; and
- Studies according to PICO.

A total of 27 studies were initially selected based on title and abstract screening. After reading the full text, 22 studies were excluded (see the table with reasons for exclusion under the tab Methods), and five studies were included (Abrams, 2021, Alwaal, 2016; Chughtai, 2016; Kretschmer, 2017 and Lin, 2022).

Results

Five studies were included in the analysis of the literature (Abrams, 2021; Alwaal, 2016; Chughtai, 2016; Kretschmer, 2017; Lin, 2022). Important study characteristics and results are summarized in table 1 and the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

1. *Male sling versus artificial urinary sphincter*

Abrams (2021) performed a multicenter noninferiority randomized trial at 27 sites in the United Kingdom. The study aimed to compare outcomes between male transobturator sling

(n= 190) and the artificial urinary sphincter (AUS) (n= 190) in men with bothersome post prostate surgery stress urine incontinence (SUI). Eligible patients had urodynamic confirmed SUI, failed conservative treatment and had prostate surgery at least 12 months prior to inclusion. At randomization, 190 participants (of which 180 post-prostatectomy) were randomized to receive a male transobturator sling, and 190 (of which 181 post-prostatectomy) participants were randomized to AUS. In the male sling group, 178 participants received the intended treatment. In the AUS group, 164 participants received intended treatment. After 12 months, 157 patients in the male sling group, and 161 patients in the AUS group responded. Due to the nature of the intervention, patients could not be blinded to the allocated intervention. Outcomes included intention to treat analyses on effect/recovery of SUI-complaints (pad-test), quality of life (EQ-5D), subjective improvement (ICIQ-UI SF) and revision within 12 months. Men reporting to be dry at 12 months did not need to complete the pad test. Complications rates for retention, complicated infections (material-related) and erosion were not reported.

In the observational study by Alwaal (2016), charts of 1205 patients receiving slings (n= 597) or AUS (n= 608) in the United States were reviewed. Type of incontinence was not stated, neither was the proportion of post-prostatectomy participants. Reported outcomes were 30-day procedure-specific complications.

In the observational study by Chughtai (2016), 1246 patients in the United States, ≥65 years receiving AUS (n= 436), slings (n= 453) or injection with bulking material (n= 357) were identified. Patients were mainly diagnosed with SUI (n= 1189) and 994 participants had a prostate cancer history. Complications after 90 days including infectious complications (including Kidney infection, UTI or cystitis, post-operative infections and wound infections) were reported.

In the observational study by Kretschmer (2017) of patients receiving slings (n= 113) and AUS (n= 120). Perioperative complications (retention, infection, erosion) and explantation rates were reported.

For the systematic review by Lin (2022), a search was performed in February 2021. Five observational studies comparing slings (n= 295) with AUS (n= 214) were included (Hoy, 2014; Lim, 2014; Kim, 2018; Khouri, 2020; and Sacco, 2020), and all outcomes were combined in meta-analysis. Participants were male patients with post prostatectomy SUI using five pads or less per day. Furthermore, surgical success rate had to be assessed using pad-tests, and patients were followed for at least 12 months. All included studies were retrospective chart reviews.

Table 1. Description of included studies

Studie	Male sling characteristics		AUS characteristics		Bulking material characteristics		Follow-up	Outcomes
	N	**Mean age**	**N**	**Mean age**	**N**	**Mean age**		
Abrams, 2021	190	68	190	69	-	-	12 months	Effect/recovery of SUI-complaints (24-hour pad test), Subjective improvement (ICIQ-UI SF), quality of life (EQ-5D) and complications (infection, erosion, and retention)
Alwaal, 2016	597	Aged 18-65: 160 Aged ≥65: 437	608	Aged 18-65: 165 Aged ≥65: 443	-	-	30 days	Surgical site infection (adverse events, complicated infection)
Chughtai, 2016	453	Aged 65-74: 298 Aged ≥75: 155	436	Aged 65-74: 298 Aged ≥75: 155	357	Aged 65-74: 211 Aged ≥75: 146	90 days	Adverse events (infection)
Kretschmer, 2017	113	70.0 (6.9)*	120	69.7 (9.4)*	-	-	-	Adverse events (postoperative infection, postoperative urinary retention)
Lin, 2022	-	-	-	-	-	-	-	-
Hoy, 2014	*76*	66.2	48	68.1	-	-	12 months	Effect/recovery of SUI-complaints (yes/no by pad-test) and complications (infection, erosion, and retention)
Lim, 2014	*20*	70.9	13	73.5				
Kim, 2018	*50*	70.8	53	69.1				
Khouri, 2020	*114*	66.5	65	70.8				
Sacco, 2020	*35*	69.64	35	70.64				

Abbreviations: AE, Adverse events; UTI, urinary tract infection

* mean age was reported per group for the total cohort, complications were reported for subgroup in high-volume centers (>20 implantations)

Results

1. Effect/recovery of SUI-complaints (critical)

Abrams (2021) reported on effect/recovery of SUI-complaints using the 24-hour pad-test, reporting on pad weight in grams. In the male sling-group (n= 50), mean pad weight after 24 hours was 30.0 gram (SD[1] 85.3). In the AUS group (n= 44), mean pad weight after 24 hours was 73.7 gram (SD 451.6). Analysis resulted in a mean difference of -43.70 gram (95% CI -179.22 to 91.82).

Lin (2022) reported on effect/recovery of SUI-complaints using the number of pads as indication for success (success, yes/no defined by ≤1 pad per day at follow-up). Five studies contributed to this outcome (Hoy, 2014; Lim, 2014; Kim, 2018; Khouri, 2020; and Sacco, 2020). In the groups receiving slings, 220 out of 295 patients were cured of their SUI-complaints. In the groups receiving AUS, 180 out of 214 participants were cured. Pooling the results using a random effect model led to an odds ratio of 0.61 (95% CI 0.34 to 1.11). Results are depicted in figure 1.

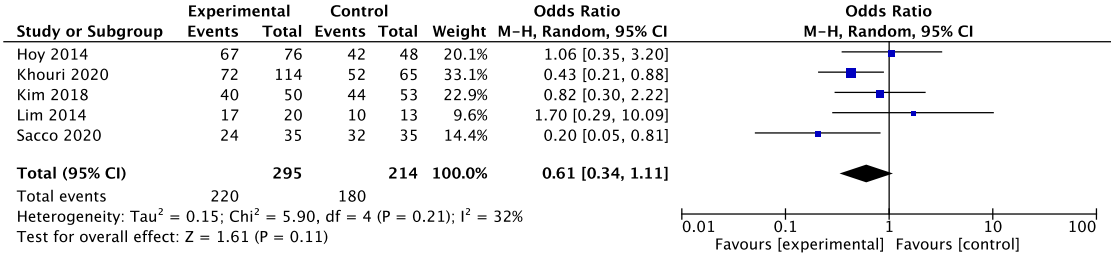

Figure 1: The effect of male-sling on number of pads.

Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

2. Subjective improvement (critical)

Abrams (2021) reported on subjective improvement using the International Consultation of Incontinence Questionnaire (ICIQ, range 0-21, higher scores indicate more severe UI). In the male sling-group (n= 151), the mean difference at 12 months was 8.7 (SD 0.6.1). In the AUS-group (n= 153), the mean difference was 7.5 (SD? 5.3). The adjusted mean difference was 1.4 (95% CI 0.2 to 2.6). This difference was not clinically relevant.

3. Quality of life (important)

Abrams (2021) reported on quality of life using the EQ-5D (range 0-100, higher scores indicate higher quality of life). In the male sling-group (n= 151), the mean difference at 12 months was 0.809 (SD 0.260). In the AUS-group (n= 158), the mean difference was 0.813 (SD 0.274). The adjusted mean difference was -0.019 (95% CI -0.062 to 0.024). This difference was not clinically relevant.

4. Adverse events (important)

4.1 Infection

In the study by Abrams (2021), one participant in the sling-group developed urosepsis, and three participants in the AUS group developed an infection.

In the study by Alwaal 2016), 30-day complications including separate amounts of surgical site infections were reported. In the patients receiving sling (n= 597), 6 (1%) developed a surgical site infection. In the patients receiving AUS (n= 608), 7 (1.2%)

[1] Tabular presentation of the results did not explicitly state mean (SD), based on presented mean differences however, this was assumed.

developed a surgical site infection. Comparing sling to AUS, this resulted in an odds ratio of 0.87 (95% CI 0.29 to 2.61).

In the study by Chughtai (2016), infection after 90 days including kidney infection, UTI or cystitis, post-operative infections and wound infections were reported. In the patients receiving sling (n= 453), 26 (5.7%) developed an infection. In the patients receiving AUS, n= 436), 40 (9.2%) developed an infection, and in the patients receiving injections with bulking material (n= 357), 19 (5.3%) developed an infection. Comparing slings to AUS, odds ratio for infection was 0.60 (95% CI 0.36 to 1.01). Comparing slings to bulking material, odds ratio for infection was 1.08 (95% CI 0.59 to 1.99).

In the study by Kretschmer (2017), adverse events including postoperative infections within the first 6 months were reported. In the patients receiving sling (n=113), 4 (3.5%) developed postoperative infection. In the patients receiving AUS (n= 120), 8 (6.7%) developed postoperative infection. Comparing sling to AUS, this resulted in an odds ratio of 0.51 (95% CI 0.15 to 1.76).

Lin (2022) reported on infection pooling the results of four studies (Hoy, 2014; Lim, 2014; Kim, 2018; and Sacco, 2020). In the groups receiving slings, in 8 out of 181 patients infection was reported. In the groups receiving AUS, in 10 out of 149 patients infection was reported. Pooling the results using a random effect model led to an odds ratio of 0.65 (95% CI 0.16 to 2.67). Results are depicted in figure 2.

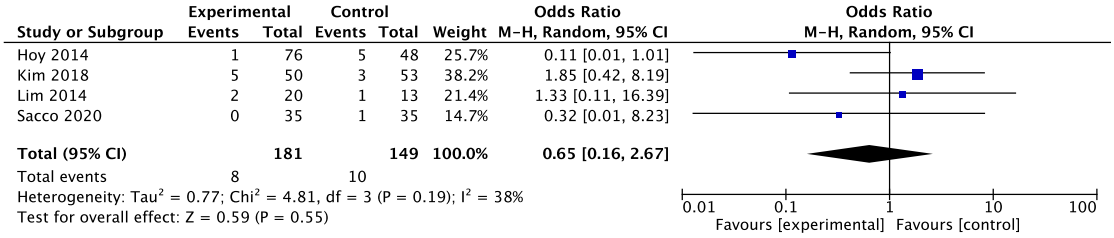

Figure 2: The odds ratio on infection for sling versus AUS

Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

4.2 Erosion

In the study by Abrams (2021), one participant in the sling-group developed mesh erosion, and in three participants in the AUS group erosion of the device was reported.

Lin (2022) reported on erosion pooling the results of four studies (Hoy, 2014; Lim, 2014; Kim, 2018; and Sacco, 2020). In the groups receiving slings, in 5 out of 181 patients infection was reported. In the groups receiving AUS, in 11 out of 149 patients infection was reported. Pooling the results using a random effect model led to an odds ratio of 0.48 (95% CI 0.17 to 1.37). Results are depicted in figure 3.

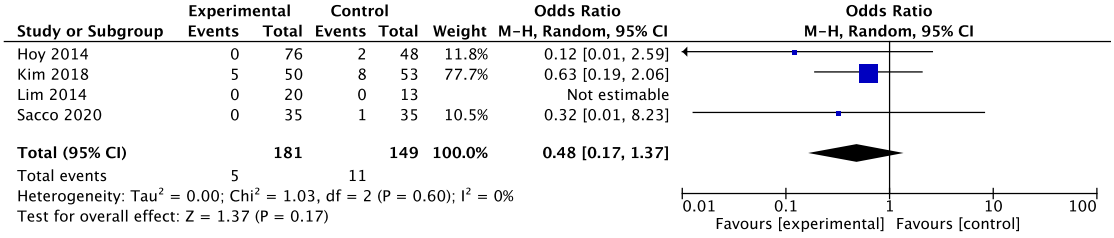

Figure 3: The odds ratio on erosion for slings versus AUS

Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

4.3 Retention

In the study by Abrams (2021), one participant in the AUS group reported urinary retention.

In the study by Kretschmer (2017), adverse events including postoperative urinary retention within the first 6 months was reported. In the group receiving sling (n= 113), 11 (9.7%) participants developed urinary retention post-surgery. In the group receiving AUS (n= 120), 13 (10.8%) developed urinary retention post-surgery. Comparing sling to AUS, this resulted in an odds ratio of 0.89 (95% CI 0.38 to 2.07).

Lin (2022) reported on retention pooling the results of four studies (Hoy, 2014; Lim, 2014; Kim, 2018; and Sacco, 2020). In the groups receiving slings, in 18 out of 181 patients infection was reported. In the groups receiving AUS, in 4 out of 149 patients infection was reported. Pooling the results using a random effect model led to an odds ratio of 2.46 (95% CI 0.31 to 19.45). Results are depicted in figure 4.

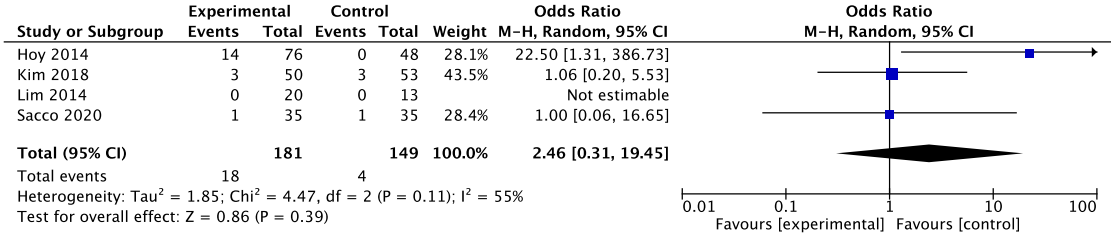

Figure 4: The odds ratio on retention for slings versus AUS

Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

Level of evidence of the literature

1. Effect/recovery of SUI-complaints (critical)

The level of evidence regarding the outcome measure effect/recovery of SUI-complaints started as low because it was partly based on observational studies and was downgraded by one level to very low because of the confidence interval crossing a border of clinical decision making (-1, imprecision).

2. Subjective improvement (critical)

The level of evidence regarding the outcome measure incontinence episodes started as high because it was based on an RCT and was downgraded by two levels to low because of lack of blinding and patient reported outcome (-2, risk of bias); and a small number of participants (-1, imprecision).

3. Quality of life (important)

The level of evidence regarding the outcome measure incontinence episodes started as high because it was based on an RCT and was downgraded by two levels to low because of and lack of blinding and patient reported outcome (-2, risk of bias); and a small number of participants (-1, imprecision).

4. Adverse events/complications (important)

4.1 Infection

The level of evidence regarding the outcome measure infection started as low because it was based on observational studies and was downgraded by one level to very low because of the confidence interval crossing borders of clinical decision making (-1, imprecision).

4.2 Erosion

The level of evidence regarding the outcome measure erosion started as low because it was based on observational studies and was downgraded by one level to very low because of the confidence interval crossing a border of clinical decision making (-1, imprecision).

4.3 Retention

The level of evidence regarding the outcome measure retention started as low because it was based on observational studies and was downgraded by one level to very low because of the confidence interval crossing a border of clinical decision making (-1, imprecision).

Conclusions

1. Effect/recovery of SUI-complaints (critical)

Very low GRADE	The evidence is very uncertain about the effect of male slings on effect/recovery of SUI-complaints when compared with AUS in patients with post-prostatectomy SUI. *Source: Abrams, 2021 and Lin, 2022*

2. Subjective improvement (critical)

Very low GRADE	The evidence is very uncertain about the effect of male slings on subjective improvement of SUI-complaints when compared with AUS in patients with post-prostatectomy SUI. *Source: Abrams (2021)*

3. Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of male slings on quality of life when compared with AUS in patients with post-prostatectomy SUI. *Source: Abrams (2021)*

4.1 Adverse events - infection

Very low GRADE	The evidence is very uncertain about the effect of male slings on infection rates when compared with AUS in patients with post-prostatectomy SUI. *Source: Abrams, 2021; Chughtai (2016) and Lin, 2022*

4.2 Adverse events - erosion

Very low GRADE	The evidence is very uncertain about the effect of male slings on erosion rates when compared with AUS in patients with post-prostatectomy SUI. *Source: Lin, 2022*

4.3 Adverse events - retention

Very low GRADE	The evidence is very uncertain about the effect of male slings on retention rates when compared with AUS in patients with post-prostatectomy SUI. *Source: Lin, 2022*

Male sling versus bulking agents; PRO-ACT
5.1 Adverse events - infection

Very low GRADE	The evidence is very uncertain about the effect of male slings on infection rates when compared with bulking agents in patients with post-prostatectomy SUI. *Source: Chughtai (2016)*

No GRADE	No evidence was found regarding the effect of male slings on any outcome when compared to bulking agents or PRO-ACT in patients with post-prostatectomy SUI. *Source: -*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

In de literatuuranalyse is onderzocht wat de waarde van het plaatsen van een male sling bij patiënten met post prostatectomie stress urine-incontinentie is, in vergelijking verschillende alternatieven (AUS, bulking agents, PRO-ACT). Er is één trial beschreven (Abrams, 2021) waarin de male sling vergeleken werd met AUS. Daarnaast is er één systematische review met vijf observationele studies gevonden (Lin, 2022) waarin male sling vergeleken werden met AUS. Ten slotte werd evidentie aangevuld met enkele individuele observationeel vergelijkende studies (Alwaal, 2016; Chughtai, 2016; Kretschmer, 2017). Naast methodologische beperkingen waren de studiepopulaties relatief klein en waren effectschattingen vaak onvoldoende nauwkeurig. Bewijskracht voor de kritieke uitkomstmaten (verbeteren/verhelpen SUI-klachten en subjectieve verbetering) was zeer laag. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van de male sling vergeleken met AUS, bulking agents of PRO-ACT voor patiënten met SUI post-prostatectomie.

Salvage radiotherapie wordt toegepast bij patiënten waarbij de postoperatief de prostatectomie niet radicaal bleek of bij hen met (kans op) recidief. Deze bestraling kan ook bijdragen aan de mate van incontinentie door schade aan de sfincter. Daarnaast zijn stenose van de urethra of blaashals gekende complicaties (Queissert, 2023)
Patiënten die een AUS ontvangen na prostatectomie en salvage radiotherapie, hebben een kleinere kans volledig continent te worden vergeleken met patiënten die geen salvage radiotherapie ondergaan. Daarnaast hebben patiënten na salvage radiotherapie een grotere kans op revisie en is de tijd van implantatie tot revisie vaak korter (Zhang, 2022; Queissert, 2023). Opvallend is er geen verschil in AUS gerelateerde kwaliteit van leven tussen patiënten met en zonder salvage bestraling (Joseph, 2019)
In de patiënten die salvage radiotherapie ondergaan na AUS plaatsing, is de kans op revisie evident groter dan de patiënten die salvage radiotherapie ontvingen alvorens de AUS plaatsing.

Alle genoemde interventies voor de behandeling van mannelijke stress-incontinentie bestaan uit het plaatsen van een lichaamsvreemd materiaal. Infectie van dit lichaamsvreemde materiaal is het belangrijkste risico van deze behandelingen, en veelal een indicatie voor explantatie. Daarnaast kan bij de ingreep ook iatrogene schade bestaan aan blaas

(retropubische sling) en urethra (sling en AUS). Indien een blaas- of urethradefect peroperatief wordt opgemerkt is dit een reden om de procedure af te breken en het implantaat niet te plaatsen. Het risico op secundaire infectie en nood voor explantatie is dan simpelweg te groot. Naast chirurgische componenten, dient er ook aandacht te zijn voor de co morbiditeit, zoals bij immuun gecompromitteerde patiënten of patiënten met diabetes mellitus en roken?.

Postoperatieve pijnklachten worden gerapporteerd bij zowel slings als de AUS. Indien pijn blijft bestaan op de langere termijn, kan explantatie worden overwogen. De behandelingen kennen beide een aanzienlijke kans op revisie. Revisie wordt verricht indien er afname van effect van de behandeling is. Bij de (gefixeerde) slings is de oorzaak veelal spanningsverlies. Bij de AUS staat mechanisch falen voorop. Ook atrofie van de bulbocavernosus ter plaatse van de manchet, is voor de AUS een revisie indicatie.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

De enige conservatieve behandeling voor post prostatectomie stress urine-incontinentie is bekkenfysiotherapie. Deze behandeling wordt vaak gestart al voor of kort na de prostatectomie. Patiënten wordt veelal geadviseerd zo'n 6 tot 12 maanden na prostatectomie de verbetering van de incontinentie af te wachten. Indien geen of subjectief onvoldoende verbetering, worden patiënten vaak verwezen voor invasieve behandeling.

Indien er geen andere afwijkingen worden gevonden op cystoscopie en eventueel urodynamisch onderzoek, zal patiënt een behandelvoorstel worden gedaan. De keuze voor de chirurgische incontinentiebehandeling wordt met name gebaseerd op de mate van de incontinentie en de conditie van de patiënt. Daar de AUS als gouden standaard wordt gezien voor de behandeling van post prostatectomie wordt deze veelal ingezet voor matig tot ernstige incontinentie. Incontinentie bij patiënten met eerdere behandeling met radiotherapie, hypo-contractiele blaas of veranderde anatomie (bijv. urethrastricturen) wordt bij voorkeur ook met AUS behandeld. Een voorwaarde voor de AUS is een goede handfunctie van de patiënt, aangezien het pompje bediend moet worden voor de mictie. De sling wordt veelal ingezet voor de behandeling van milde tot matige incontinentie, daar waar de behandeling met bulk en proACT in de praktijk voornamelijk gericht is op de milde incontinentie en is gecontra-indiceerd bij patiënten met status na radiotherapie.

Het doel van de behandeling is verbetering van de kwaliteit van leven. Volledige continentie wordt zeker niet altijd bereikt. Daarnaast resulteert significante afname van de incontinentie niet altijd in die verbetering van de kwaliteit van leven. Naast het advies voor een behandeling op basis van de patiënt-karakteristieken en de mogelijk specifieke voorkeur van de patiënt, is er dus ook een belangrijke rol voor verwachtingsmanagement.

Kosten (middelenbeslag)

De kosten van de verschillende behandelingen worden bepaald door nationale vergoedingssystemen voor zorg. Omdat in elk land de vergoedingssystemen anders zijn, zijn internationale studies hiernaar niet goed te vertalen naar de Nederlandse situatie.

Het Zorginstituut stelde in 2016 dat de behandelkosten van een sling operatie 35% bedragen van de kosten van een AUS (Zorginstituut Nederland, 2016).

Het vergelijken van de verschillende behandelingen wordt bemoeilijkt, door het feit doordat ze voor verschillende maten van incontinentie worden toegepast.

Naast de kosten van de behandeling dienen in een lange termijnevaluatie ook de kosten van chirurgische revisies, omwille van pijnklachten en mechanisch falen, te worden opgenomen. Patiënten die geen chirurgische behandeling ondergaan voor hun stress urine-incontinentie,

gebruiken veelal incontinentiemateriaal. De kosten van incontinentiemateriaal hebben een grote invloed op de zorgkosten. Een behandeling van de incontinentie zou volgens de werkgroep dus indirect ook tot een reductie van de kosten voor het opvangmateriaal leiden.

Aanvaardbaarheid, haalbaarheid en implementatie

De zorg voor PPSUI behoort tot de verzekerde zorg. Voor de behandeling van PPSUI worden patiënten door de hoofdbehandelaar van het prostaatcarcinoom of door de huisarts verwezen naar een centrum met functionele expertise. Het volledige pallet van behandeling wordt niet in elk centrum aangeboden. Dit wordt veroorzaakt door de hoge kosten, intensiviteit van de behandeling en follow up en ook de expertise en mogelijkheid om revisie chirurgie te verrichten.

Aanbevelingen

Aanbeveling-1

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Ondanks dat de verschillende maten van incontinentie niet eenduidig zijn gedefinieerd, blijkt er uit de literatuur wel een duidelijke correlatie tussen de mate van verlies en de voorgestelde behandeling. De rol voor de sling in de behandeling voor mannelijke stress-incontinentie wordt met name gelegd in de lichte tot matige incontinentie. De waarde van de AUS lijkt evident bij de zware incontinentie. En de minder invasieve opties als bulking en proACT wordt veelal toegepast in de lichte incontinentie. Conservatieve therapie middels bekkenfysiotherapie wordt erkend.

Gezien de behandeling de verbetering van de kwaliteit van leven na prostatectomie beoogt, is het bespreken van de verschillende opties met voor- en nadelen en verwachtingsmanagement de sleutel tot optimale behandeling van PPSUI.

Bied BFT aan direct postoperatief prostatectomie

Bied bij incontinentie primair conservatieve behandeling aan.

Indien na 6-12 maanden aanhoudende incontinentie en significante impact op QoL, kan chirurgische behandeling worden overwogen.

Shared decision making en verwachtingsmanagement lijken essentieel in de keuze voor de behandeling

Overweeg bij lichte en matige incontinentie een sling wanneer conservatieve behandeling heeft gefaald, monitor complicaties.

Overweeg bij behandeling van zware incontinentie AUS

Kies voor een AUS bij een patiënt die behandeld wil worden na bestraling.

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Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1-7	<1 jaar	Onbekend	Geen, sluit grotendeels aan bij klinische praktijk	n.v.t.	n.v.t.	n.v.t.	Geen

[1] Barrièhres kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Table of excluded studies

Deruyver 2021	compared characteristics for patients receiving sling/AUS, no postoperative outcomes compared (wrong outcome)
Chonière 2021	SR with MA but no comparative results presented (wrong study design)
Ginsburg 2020	patients were given AUS or sling, but no comparison between the two interventions (wrong study design)
Averbeck 2019	non-systematic review (wrong study design)
Shamout 2018	Cost effectiveness study without clinical outcomes (wrong outcome)
Barski 2017	SR but no comparative results presented (wrong study design)
Bach 2020	study in women (wrong population)
MacDonald 2017	no postoperative outcomes compared (wrong outcome)
Chen 2017	SR with MA but only pre-post outcomes presented, no comparison (wrong study design)
Liu 2016	no postoperative outcomes compared (wrong outcome)
Kretschmer 2016	narrative review (wrong study design)
Bauer 2011	nonsystematic review (wrong study design)
Trost 2012	nonsystematic review (wrong study design)
Bruwaene 2015	narrative review (wrong study design)
Angulo 2019	no comparative studies included (wrong study design)
Grabbert 2019	outcomes measured for unknown duration until max. follow up (wrong study design)
Grabbert 2020	outcomes measured for unknown duration until max. follow up (wrong study design)
Ajay 2015	patients were included for receiving sling, but were then either receiving secondary sling or AUS (wrong design)

Sacco 2012	Included in Lin (2022)
Khouri 2022	Included in Lin (2022)
Bretterbauer 2016	measurement of follow-up differed between 0.24 and 88 months (wrong outcome)
Tran 2014	large variation in follow-up time between two groups (wrong outcome)

Module Botox bij volwassenen

Uitgangsvraag

Wat is de plaats van behandeling met intravesicale botulinetoxine injecties ten opzichte van neuromodulatie bij volwassenen met een refractaire overactieve blaas (OAB)?

Inleiding

Patiënten met een refractaire OAB of urge-incontinentie kunnen behandeld worden met intravesicale injecties met onabotulinumtoxin-A (BoNT-A) of met neuromodulatie. Intravesicale injecties worden meestal poliklinisch toegediend middels een cystoscopie. De blaas wordt meestal voorbereid met een verdovende blaasspoeling. Bij percutane neuromodulatie (PTNS) en transcutane neurostimulatie (TENS) wordt elektrische stimulatie van de nervus tibialis aan de mediale zijde van de enkel gegeven. Bij sacrale neuromodulatie (SNM) wordt operatief een lead bij de sacrale zenuw, meestal S3, geplaatst. Alle behandelingen kennen specifieke voor- en nadelen. De uroloog kan samen met de patiënt beslissen welke behandeling het beste bij de situatie van de patiënt past, waarbij minder invasieve behandelingen voor meer invasieve behandelingen worden aangeboden.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effectiveness and safety of intravesical injection of botulinum toxin (type A or B) compared with neuromodulation for patients with refractory overactive bladder?

P: Adults with refractory overactive bladder
I: Intravesical injection of botulinum toxin (type A or B)
C: Neuromodulation (sacral nerve stimulation (SNM); percutaneous tibial nerve stimulation (PTNS); transcutaneous nerve stimulation (TENS)
O: Improvement/recovery of overactive bladder complaints, quality of life, adverse events/complications

<u>Relevant outcome measures</u>

The guideline development group considered improvement/recovery of overactive bladder as a critical outcome measure for decision making; and quality of life and adverse events/complications as an important outcome measure for decision making.

A priori, the working group defined adverse events as (recurrent) urinary tract infection, post void residual, urinary retention, and device related pain. For other outcomes, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following minimal clinically (patient) important differences:
Continuous outcomes:

- Improvement/recovery of overactive bladder complaints
    - Three-day diary: ≥ 50% reduction (Schmidt, 1990)
    - Urinary Distress Inventory (UDI-6, 0-100): ≥ 33.33 (Skorupska, 2021)
    - International Consultation on Incontinence Modular Questionnaire – Urinary incontinence (ICIQ-UI): ≥ 0.5 SD
    - International Consultation on Incontinence Questionnaire Overactive Bladder Module (ICIQ-OAB): ≥ 0.5 SD
- Quality of life:

- International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF, 0-21): ≥ 5 at 12 months, ≥ 4 at 24 months (Sirls, 2013)
- The overactive bladder questionnaire (OAB-q, 0-100): ≥ 10 points (Coyne, 2006)
- The overactive bladder quality of life short-form questionnaire (OAB-q SF, 0-100): ≥ 11 points (Blanker, 2019)

In all other cases, the working group defined the GRADE-standard limit of 25% difference for dichotomous outcomes (RR < 0.8 or > 1.25), and 0.5 SD for continuous outcomes as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until 3 January 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 92 hits. Studies were selected based on the following criteria:

- Systematic review (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trial or observational study comparing intravesical injection of botulinum toxin (type A or B) with neuromodulation (sacral nerve stimulation (SNM); percutaneous tibial nerve stimulation (PTNS); transcutaneous nerve stimulation (TENS);
- Patients aged ≥ 18 years;
- Full-text English language publication;
- Studies including ≥ 20 (ten in each study arm) patients; and
- Studies according to PICO.

A total of 15 studies were initially selected based on title and abstract screening. After reading the full text, 12 studies were excluded (see the table with reasons for exclusion under the tab Methods), and three studies were included (Amundsen, 2016; Amundsen, 2018 and Sherif, 2015). One systematic review matched the predefined PICO (He, 2021). This review reported on a randomized controlled trial (with outcomes described in two relevant publications; Amundsen, 2015 and Amundsen, 2018)), and three low quality cohort studies. Since the quality of these cohort studies was not sufficient, the review was not included.

Results

Three studies were included in the analysis of the literature (Amundsen, 2016; Amundsen, 2018 and Sherif, 2015). Important study characteristics and results are summarized in table 1 and the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

1. Onabotulinumtoxin A versus sacral neuromodulation (SNM)

Amundsen (2016) performed a multicenter randomized trial at nine sites. The study aimed to assess whether onabotulinumtoxin A 200IU (BoNT-A 200IU) was superior to sacral neuromodulation (SNM) in women with refractory urine incontinence symptoms. Women were included when they had at least six urgency incontinence episodes in three days at baseline (measured using a 3-day diary). Eligible patients had refractory urine incontinence defined as having symptoms despite at least one (physical/behavioral) intervention, and either failed previous interventions with at least two anticholinergics or were intolerant/contra- indicated for anticholinergics. Relevant neurologic disease, previous usage

of either BoNT-A 200IU or SNM, or a post void residual of more than 150ml were criteria for exclusion. At randomization, 192 participants were randomized to receive BoNT-A 200IU. Due to invalid diary-data, 190 participants of the BoNT-A 200IU -group were included in the primary analysis. Initially, 194 participants were randomized to receive SNM. However, due to lead removals (n= 3), implanted pulse generator in non-responder (n= 9) and invalid diary-data (n= 5), 174 participants of the SNM-group were included in the primary analysis. Length of follow up was 6 months. Outcomes included intention to treat analyses on number of daily episodes, quality of life and adverse events. Patients were not blinded to assignment of treatment.

Amundsen (2018) presented the two-year follow-up outcomes for the trial by Amundsen (2016). All efficacy endpoints after two years were analyzed only in responders, which did not match the population described in the PICO. Adverse events after two years were analyzed per protocol in the original randomized population. In the BoNT-A 200IU -group, 191 participants were followed for adverse events. In the neuromodulation group, 178 participants were followed for adverse events.

2. Onabotulinumtoxin A versus posterior tibial nerve stimulation (PTNS)

Sherif (2017) performed a randomized controlled trial at one study site. The investigators opted to study the efficacy and safety of 100 IU Onabotulinumtoxin A (BoNT-A 100IU) (n=30) versus 12 weekly treatments with percutane tibial nerve stimulation (PTNS) (n=30) in patients with refractory idiopathic OAB. Refractory urine incontinence was defined as not responding or being intolerant to 3 months of medical therapy with different antimuscarinic agents. Having a pacemaker or implantable defibrillator, a current UTI, uncorrectable coagulopathies, a bladder outlet obstruction, a neurogenic bladder, a post void residual volume of >150 mL, planning to become pregnant or being pregnant, and nerve damage that might affect function of the posterior tibial nerve/pelvic floor were criteria for exclusion. Length of follow up was 9 months. Outcomes included intention to treat analyses on frequency (3-day voiding diary), quality of life and adverse events. Patients were not blinded to assignment of treatment.

3. Botox versus transcutaneous electrical nerve stimulation (TENS)

No studies were found for Botox versus TENS.

Table 1. Description of included studies

Studie	Intervention		Comparator		Follow-up	Outcomes
	Characteristics	**Interventie type/ dose**	**Characteristics**	**Type of usual care**		
Amundsen , 2016 and Amundsen , 2018	**Arm 1 (n= 190)** Mean age (SD): 62.9 (11.5) Female (%): 190 (100) BMI: 32.6 (8.7)	OnabotulinumtoxinA injection (Allergan), 200 U into 10 mL of saline. Amundsen (2018): After 6 months additional injections for clinical responders.	**Arm 2 (n= 174)** Mean age (SD): 63.1 (11.8) Female (%): 174 (100) BMI: 31.7 (7.5)	SNM, lead placement (1st stage) followed by IPG implantation when ≥50% improvement.	6 months (Amundsen, 2016) 2 years (Amundsen, 2018)	Improvement/ recovery of overactive bladder complaints (number of daily episodes), quality of life (OBQ-SF) and AE (UTI)

Sherif, 2017	**Arm 1 (n= 30)** Mean age (SD): 45.6 (7.8) Female (%): 25 (83.3) BMI: 36.8 (4.9)	Onabotulinumtoxin A injection (Allergan), 100 U into 10 mL of saline, devided over 20 sites, using a 6 Fr injection needle.	**Arm 2 (n= 30)** Mean age (SD): 45.1 (10.1) Female (%): 26 (86.7) BMI: 36 (6.2)	PTNS, weekly 30-minute sessions (12 weeks), using a 0.22 mm needle electrode.	6 weeks 3 months 6 months 9 months	Frequency (3-day voiding diary), quality of life (OABSS), AE (post void volume)

Abbreviations: AE, Adverse events; IPG, implantable pulse generator; OBQ-SF, Overactive Bladder Questionnaire Short Form; OABSS, Overactive bladder symptom score; PTNS, posterior tibial nerve stimulation; SNM, sacral neuromodulation; UTI, urinary tract infection

Results

1. Onabotulinumtoxin A versus SNM

1.1 Improvement/recovery of overactive bladder complaints (critical)

Amundsen (2016) reported on improvement of overactive bladder complaints in mean number of daily episodes measured for 3 consecutive days every month, over 6 months measured with a 3-day bladder diary. In the BoNT-A 200IU group (n= 190), the adjusted mean number of daily urgency urinary incontinence episodes reduced with -3.89 (95% CI -4.26 to -3.52). In the SNM group (n= 174), adjusted mean number of daily urgency urinary incontinence episodes reduced with -3.25 (95% CI -3.64 to -2.87). The adjusted mean difference was 0.63 (95% CI: 0.13 to 1.14). This difference was not clinically relevant.

1.2 Quality of life (important)

Amundsen (2016) reported on quality of life using the Overactive Bladder Questionnaire Short Form (OABq-SF, range 0-100, higher scores indicate higher quality of life). Other quality of life questionnaires were completed (Urinary Distress Inventory short form (UDI-SF), Incontinence Impact Questionnaire short form (IIQ-SF) and Health Utility Index (HUI-3)), but defined as secondary endpoints. In the BoNT-A 200IU (n= 190), the mean score at 6 months was 41.6 (SD 25.9). In the SNM-group (n= 174), the mean score was 38.1 (SD 26.7). The mean difference was 3.5 (95% CI -1.91 to 8.91). This difference was not clinically relevant.

1.3 Adverse events (important)

Adverse events were measured up to six months after baseline and were defined as urinary tract infection. Amundsen (2016) reported on cumulative urinary tract infections after one month, three months and six months. Amundsen (2018) reported on urinary tract infections between 7 and 12 months and between 13 and 24 months. Results are presented in table 2. All differences were clinically relevant favoring the SNM-group.

No results were reported for device related pain.

Table 2. UTI's reported by Amundsen (2016)

	UTI BoNT-A 200IU	UTI in SNM	Risk ratio (95% CI)	absolute risk increase (95% CI)	NNT (95% CI)
Short term (Amundsen, 2016), cumulative					
After 1 month (cumulative)	22/191 (12%)	1/178 (1%)	20.50 (2.79 to 150.53)	0.11 (0.06 to 0.16),	-9.13 (-6.40 to -15.88).
After 3 months (cumulative)	47/191 (25%)	10/178 (6%)	4.38 (2.28 to 8.40	0.19 (0.12 to 0.26)	-5.27 (-3.85 to 8.33
After 6 months (cumulative)	66/191 (35%)	20/178 (11%)	3.08 (1.95 to 4.86	0.23 (0.15 to 0.32)	-4.29 (-3.17 to -6.61
Long term (Amundsen, 2018)					
After 7-12 months	42/191 (22%)	21/178 (12%)	1.86 (1.15 to 3.02).	0.10 (0.03 to 0.18	-9.81 (-5.64 to -37.81
After 13-24 months	35/191 (18%)	15/178 (8%)	2.17 (1.23 to 3.84).	0.10 (0.03 to 0.17)	-10.10 (-5.98 to -32.68

Abbreviations: ObA, Onabotulinumtoxin A; SNM, sacral neuromodulation; UTI, urinary tract infection

Amundsen (2016) used intermittend catheterization as a proxy for urinary retention (defined as a residual >300mL/ >200mL with symptoms of incomplete voiding). In the BoNT-A 200IU group, 38 out of 191 participants required intermittend self-catheterization. No results were reported for the SNM group, thus these results were not graded.

In the SNM group, in 6 out of 174 patients the device was removed or revised. Also, for this outcome, results were not graded since patients in the BoNT-A 200IU group were not at risk for device removal/revision.

Level of evidence of the literature

1.1 Improvement/recovery of overactive bladder complaints (critical)

The level of evidence regarding the outcome measure incontinence episodes started as high because it was based on an RCT and was downgraded by three levels to very low because of unbalanced dropout and lack of blinding (-2, risk of bias); and low number of included patients (-1, imprecision).

1.2 Quality of life (important)

The level of evidence regarding the outcome measure quality of life started as high because it was based on an RCT and was downgraded by three levels to very low because of unbalanced dropout and lack of blinding (-2, risk of bias) and number of included patients (-1, imprecision).

1.3 Adverse events/complications (important)

1.3.1 Urinary tract infections (1-month post-intervention)

The level of evidence regarding the outcome measure AE after 1 month started as high because it was based on an RCT and was downgraded by two levels to low because of unbalanced drop-out (-1, risk of bias) and low number of included patients (-1 imprecision).

1.3.2 Cumulative urinary tract infections (up to 3 months post-intervention)

The level of evidence regarding the outcome measure AE after 3 months started as high because it was based on an RCT and was downgraded by two levels to low because of unbalanced drop-out (-1, risk of bias) and low number of included patients (-1 imprecision).

1.3.3 Cumulative urinary tract infection (up to 6 months post-intervention)
The level of evidence regarding the outcome measure AE after 6 months started as high because it was based on an RCT and was downgraded by two levels to low because of unbalanced drop-out (-1, risk of bias) and low number of included patients (-1 imprecision).

1.3.4 Urinary tract infections 7-12 months
The level of evidence regarding the outcome measure AE between 7 and 12 months started as high because it was based on an RCT and was downgraded by two levels to low because of unbalanced drop-out (-1, risk of bias) and low number of included patients (-1 imprecision).

1.3.5 Urinary tract infections 13-24 months
The level of evidence regarding the outcome measure AE between 13 and 24 months was downgraded by two levels to low because of unbalanced drop-out (-1, risk of bias) and low number of included patients (-1 imprecision).

Conclusions onabotulinumtoxin A versus SNM

1.1 Improvement/recovery of overactive bladder symptoms (critical)

Urgency incontinence episodes (BoNT-A 200IU versus SNM)

Very low GRADE	The evidence is very uncertain about the effect of BoNT-A 200IU on improvement/recovery of overactive bladder symptoms when compared to SNM in patients with refractory overactive bladder. *Source: Amundsen (2016)*

1.2 Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of BoNT-A 200IU on quality of life when compared with SNM in patients with refractory overactive bladder. *Source: Amundsen (2016)*

1.3 Adverse events (important)

1.3.1 Cumulative urinary tract infection after 1 month

Low GRADE	BoNT-A 200IU may result in an increase in urinary tract infections when compared with SNM in patients with refractory overactive bladder. *Source: Amundsen (2016)*

1.3.2 Cumulative urinary tract infection after 3 months

Low GRADE	BoNT-A 200IU may result in an increase in urinary tract infections when compared with SNM in patients with refractory overactive bladder. *Source: Amundsen (2016)*

1.3.3 Cumulative urinary tract infection after 6 months

Low GRADE	BoNT-A 200IU may result in an increase in urinary tract infections when compared with SNM in patients with refractory overactive bladder. *Source: Amundsen (2016)*

1.3.4 Cumulative urinary tract infection between 7 and 12 months

Low GRADE	BoNT-A 200IU may result in an increase in urinary tract infections when compared with SNM in patients with refractory overactive bladder. *Source: Amundsen (2018)*

1.3.5 Cumulative urinary tract infection after between 13 and 24 months

Low GRADE	BoNT-A 200IU may result in an increase in urinary tract infections when compared with SNM in patients with refractory overactive bladder. *Source: Amundsen (2018)*

2. Onabotulinumtoxin A 100 IU (BoNT-A 100IU) versus 12 weekly treatments with PTNS

2.1 Improvement/recovery of overactive bladder complaints (critical)

Sherif (2015) reported on leaking episodes using a 3-day voiding diary. In the BoNT-A 100IU -group (n= 29), the mean score at 9 months was 3.5 (SD 1.2). In the PTNS-group (n= 28), the mean score was 4.2 (SD 1.04). The mean difference was 0.30 (95% CI -0.28 to 0.88). This difference was not clinically relevant.

2.2 Quality of life (important)

Sherif (2017) reported on quality of life using the Overactive Bladder Symptom Score (OABSS), range 0-4, higher scores indicate lower quality of life) quality of life scale. In the BoNT-A 100IU group (n= 29), the mean score at 9 months was 2.6 (SD 0.6). In the PTNS-group (n= 28), the mean score was 2.9 (SD 0.6). The mean difference was -0.3 (95% CI -0.61 to 0.01). This difference was not clinically relevant.

2.3 Adverse events (important)

Sherif (2017) reported on post-void residual, using a 3-day voiding diary. In the BoNT-A 100IU -group (n= 29), the mean post-void residual at 9 months was 36.8 mL (SD 2.7). In the PTNS-group (n= 28), the mean post-void residual was 32.4 mL (SD 3.04). The mean difference was 4.40 mL (95% CI 2.91 to 5.89). This difference was not clinically relevant, favoring the PTNS-group.

Level of evidence of the literature

2.1 Improvement/recovery of overactive bladder complaints (critical)

The level of evidence regarding the outcome measure leaking episodes started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of blinding, poor description of analysis, lack of protocol-registration and other methodological shortcomings (-2, risk of bias); and low number of included patients (-1, imprecision).

2.2 Quality of life (important)

The level of evidence regarding the outcome measure quality of life started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of

blinding and methodological shortcomings (-2, risk of bias); and confidence interval overlap with threshold of clinical decision-making (-1 imprecision).

2.3 *Adverse events/complication (important)*
The level of evidence regarding the outcome measure adverse events started as high because it was based on an RCT and was downgraded by three levels to very low because of lack of blinding and methodological shortcomings (-2, risk of bias); and low number of included patients (-1, imprecision).

Conclusions onabotulinumtoxin A versus PTNS

2.1 Improvement/recovery of overactive bladder symptoms (critical)

Very low GRADE	The evidence is very uncertain about the effect of BoNT-A 100IU on improvement/recovery of overactive bladder symptoms when compared with PTNS in patients with refractory overactive bladder. *Source: Sherif (2015)*

2.2 Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of BoNT-A 100IU on quality of life when compared with PTNS in patients with refractory overactive bladder. *Source: Sherif (2015)*

2.3 Adverse events, post-void residual (important)

Very low GRADE	The evidence is very uncertain about the effect of BoNT-A 100IU on post-void residual when compared with PTNS in patients with refractory overactive bladder. *Source: Sherif (2015)*

Conclusions onabotulinumtoxin A versus TENS

No GRADE	No information was found regarding the effect of onabotulinumtoxin A on any outcome when compared with TENS in patients with refractory overactive bladder. *Source: -*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Het doel van deze uitgangsvraag was om te achterhalen wat de waarde van intravesicale botulinetoxine injecties bij patiënten met een refractair overactieve blaas is, in vergelijking verschillende vormen van neuromodulatie. Er is één trial beschreven in twee papers (Amundsen, 2016; Amundsen, 2018), waarin 200IE intravesicale onabotulinumtoxine A (BoNT-A) vergeleken werd met sacrale neuromodulatie (SNM). Er zijn geen studies gevonden met 100IE BoNT-A in vergelijking met SNM. De 100IE dosering is meer gebruikelijk dan de 200IE dosering voor patiënten met refractaire OAB. Daarnaast is er één RCT gevonden waarin 100IE intravesicale BoNT-A injecties vergeleken werden met 12 wekelijkse behandelingen percutaneous tibial nerve stimulation (PTNS) (Sherif, 2017). Voor transcutane elektrische neurostimulatie (TENS) werden geen gerandomiseerde gecontroleerde studies gevonden.

Voor BoNT-B werden tevens geen gerandomiseerde gecontroleerde studie gevonden. Naast methodologische beperkingen waren de studiepopulaties relatief klein. Bewijskracht voor de kritieke uitkomstmaten (verbeteren/verhelpen overactieve blaas-symptomen) was laag tot zeer laag. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van de literatuur alleen geen sterke aanbevelingen geformuleerd worden over de waarde van intravesicale botulinetoxine injecties vergeleken met neuromodulatie voor patiënten met refractair overactieve blaas.

Het voordeel van Intravesicale BoNT-A injecties is dat het poliklinisch gegeven kan worden in tegenstelling tot SNM. De injecties worden meestal goed verdragen. Nadelen zijn een verhoogde kans op urineweginfecties, een verhoogde kans op urineretentie en de noodzaak van herhaling van de behandeling. Voordeel van SNM ten opzichte van BoNT-A injecties is dat het effect langer aanhoudt. Door de recente beschikbaarheid van een oplaadbare batterij (levensduur van >15 jaar) en niet-oplaadbare batterijen met een langere levensduur (>10 jaar), is de kans op een heroperatie voor een batterijwissel kleiner. Nadelen van SNM zijn een kans op pijnklachten en technische defecten aan de lead of de batterij. Daarnaast is een nadeel van SNM dat twee operaties nodig zijn om de behandeling uit te voeren.

Subgroep kwetsbare ouderen

Op basis van de geïncludeerde studies is het niet mogelijk om een uitspraak te doen welke behandeling het meest geschikt is voor kwetsbare ouderen met OAB/urge-incontinentie. Als leidraad kan gelden dat therapiekeuze gebaseerd moet zijn op tolerantie van bijwerkingen, tolerantie van de complexiteit van een behandeling (inclusief algehele narcose in het geval van lead-plaatsing bij SNM), en kosteneffectiviteit van een behandeling bij kwetsbare ouderen met een beperkte levensverwachting.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

De voorkeur van een patiënt wordt bepaald door de bereidheid tot invasieve therapie en acceptatie van mogelijke bijwerkingen. Daarnaast speelt de duurzaamheid van de behandeling een rol, zoals hoe lang de therapie effectief is. In het geval van PTNS zal de bereidheid om telkens naar een behandelaar toe te gaan doorslaggevend zijn. Een groot voordeel aan PTNS is dat de bijwerkingen nihil zijn.

Vanuit patiëntenorganisaties en o.a. brancheorganisaties uit de medisch-specialistische zorg is een campagne gestart voor ‘samen beslissen’ (ZonMw, 2021). ‘Samen beslissen’ is het proces waarbij zorgverlener en patiënt samen een beslissing nemen over een behandeling of bepaalde zorg. Hierbij bespreken zij risico’s, voor- en nadelen van verschillende behandelopties en persoonlijke waarden en voorkeuren van de patiënt met elkaar. Het doel is dat samen beslissen bijvoorbeeld leidt tot meer tevredenheid over de genomen beslissing, meer therapietrouw en minder overbehandeling. Of het doel van ‘samen beslissen’ bereikt zal worden zal moeten blijken uit wetenschappelijke studies die dit evalueren. Een hulpmiddel bij het ‘samen beslissen’ is de keuzehulp voor de overactieve blaas, waarbij intravesicale BoNT-A injecties worden vergeleken met SNM (https://oab.keuzehulp.nl/inloggen).

Over het algemeen geldt dat minder invasieve behandelingen worden aangeboden voor meer invasieve behandelingen. Deze ‘stepped care’ benadering komt overeen met de adviezen uit de richtlijn ‘Non-neurogenic Female LUTS’ van de European Association of Urology (EAU, 2023).

Kosten (middelenbeslag)

De kosten van de verschillende behandelingen worden bepaald door nationale vergoedingssystemen voor zorg. Omdat in elk land de vergoedingssystemen anders zijn, zijn internationale studies hiernaar niet goed te vertalen naar de Nederlandse situatie. De kosten

van behandeling met intravesicale BoNT-A injecties worden bepaald door de methode van toediening: lokale anesthesie op de polikliniek of onder spinale of algehele anesthesie op de operatiekamer. Een andere kostendrijver is de herhaalfactor bij intravesicale injecties. De werkzaamheid van intravesicale BoNT-A injecties neemt af na verloop van tijd, waardoor de behandeling herhaald moet worden. Op langere termijn zullen de kosten hierdoor toenemen. De aanvangskosten voor SNM zijn hoger dan die van BoNT-A, omdat de kosten van de procedure en materialen hoog zijn. Een kosteneffectiviteitsanalyse van de Nederlandse situatie gaf aan dat SNM meer kosteneffectief is dan BoNT-A na 4 jaar (Leong, 2011). Met de komst van de oplaadbare batterijen en niet oplaadbare batterijen die een langere levensduur hebben (>10 jaar) zal de kosteneffectiviteit van SNM ten opzichte van BoNT-A naar verwachting toenemen. De kosten van SNM worden ook beïnvloed door het aantal operaties dat wordt verricht vanwege pijnklachten, technische defecten, zoals een draadbreuk van de lead, of afname van het therapeutische effect. De kosten voor behandeling met intravesicale BoNT-A injecties worden mede bepaald door de kosten van complicaties, zoals katheteriseren en urineweginfecties en de kosten van de extra behandelingen na uitwerken van BoNT-A.

Aanvaardbaarheid, haalbaarheid en implementatie

Intravesicale BoNT-A injecties worden in bijna elk Nederlands ziekenhuis aangeboden. In de meeste centra wordt de behandeling aangeboden als een poliklinische behandeling. SNM wordt in minder centra aangeboden. De indicaties voor SNM zijn refractaire OAB, niet obstructieve urineretentie en fecale incontinentie. Niet alle centra bieden SNM aan voor alle bovengenoemde indicaties. De beperktere beschikbaarheid van SNM wordt veroorzaakt door de kosten die de therapie met zich meebrengt, afspraken met zorgverzekeraars en de beschikbaarheid van klinische en poliklinische ondersteuning. Als er een indicatie is voor SNM, dan kan een patiënt verwezen worden naar een centrum waar deze zorg geboden wordt. Vervolgens kan samen met de patiënt besloten worden of SNM de meest geschikte behandeling is. Het is niet wenselijk dat patiënten geen SNM aangeboden krijgen, omdat de behandeling in bepaalde ziekenhuizen niet wordt aangeboden.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Bespreek samen met de patiënt de voor- en nadelen van intravesicale BoNT-A injecties en de verschillende vormen van neuromodulatie. Het gebruik van een keuzehulp wordt beperkt doordat deze niet vrij toegankelijk is. Voor meer informatie over het optimaal betrekken van de patiënt bij de therapiekeuze, kan de module 'Organisatie van Zorg' worden geraadpleegd.

De keuze voor een behandeling zal bepaald worden door de tolerantie van bijwerkingen, acceptatie van een invasieve procedure onder algehele anesthesie (SNM) en de duurzaamheid van het therapeutische effect. Als een patiënt in aanmerking komt voor een vorm van neuromodulatie en deze therapie wordt lokaal niet aangeboden, dan zou verwijzing naar een centrum waar neuromodulatie aangeboden wordt overwogen moeten worden.

Bespreek samen met de patiënt de voor- en nadelen van botox en neuromodulatie.

Pas 12 wekelijkse behandelingen met PTNS toe bij patiënten die weinig tot geen bijwerkingen prefereren ten koste van meer contactmomenten met zorgverleners.

Pas intravesicale BoNT-A injecties toe bij patiënten met een voorkeur voor poliklinische behandeling ten opzichte van een behandeling onder algehele anesthesie (SNM)

Pas SNM toe bij patiënten die de voorkeur hebben voor een langdurig effect.

Literatuur

Amundsen CL, Richter HE, Menefee SA, Komesu YM, Arya LA, Gregory WT, Myers DL, Zyczynski HM, Vasavada S, Nolen TL, Wallace D, Meikle SF. OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women: A Randomized Clinical Trial. JAMA. 2016 Oct 4;316(13):1366-1374. doi: 10.1001/jama.2016.14617. PMID: 27701661; PMCID: PMC5399419.

Amundsen CL, Komesu YM, Chermansky C, Gregory WT, Myers DL, Honeycutt EF, Vasavada SP, Nguyen JN, Wilson TS, Harvie HS, Wallace D; Pelvic Floor Disorders Network. Two-Year Outcomes of Sacral Neuromodulation Versus OnabotulinumtoxinA for Refractory Urgency Urinary Incontinence: A Randomized Trial. Eur Urol. 2018 Jul;74(1):66-73. doi: 10.1016/j.eururo.2018.02.011. Epub 2018 Feb 24. PMID: 29482936; PMCID: PMC6004242.

Blanker MH, Alma HJ, Devji TS, Roelofs M, Steffens MG, van der Worp H. Determining the minimal important differences in the International Prostate Symptom Score and Overactive Bladder Questionnaire: results from an observational cohort study in Dutch primary care. BMJ Open. 2019 Dec 23;9(12):e032795. doi: 10.1136/bmjopen-2019-032795. PMID: 31874883; PMCID: PMC7008409.

Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V. Determining the importance of change in the overactive bladder questionnaire. J Urol. 2006 Aug;176(2):627-32; discussion 632. doi: 10.1016/j.juro.2006.03.088. PMID: 16813906.

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Leong RK, de Wachter SG, Joore MA, van Kerrebroeck PE. Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. BJU Int. 2011 Aug;108(4):558-64. doi: 10.1111/j.1464-410X.2010.09905.x. Epub 2010 Dec 16. PMID: 21166750.

Schmidt RA, Senn E, Tanagho EA. Functional evaluation of sacral nerve root integrity. Report of a technique. Urology. 1990 May;35(5):388-92. doi: 10.1016/0090-4295(90)80078-2. PMID: 2336766.

Sirls LT, Tennstedt S, Brubaker L, Kim HY, Nygaard I, Rahn DD, Shepherd J, Richter HE. The minimum important difference for the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form in women with stress urinary incontinence. Neurourol Urodyn. 2015 Feb;34(2):183-7. doi: 10.1002/nau.22533. Epub 2013 Nov 23. PMID: 24273137; PMCID: PMC4032375.

ZonMw, 8 september 2021 via https://www.zonmw.nl/nl/actueel/nieuws/detail/item/nationale-campagne-samen-beslissen-van-start/. gedraadpleegd op 27 november 2022

Implementatieplan

Aanbeveling	Tijdspad voor implement	Verwacht effect op kosten	Randvoorwaarden voor	Mogelijke barrière	Te ondernemen acties voor	Verantwoordelijken	Overige opmerkingen

	atie: < 1 jaar, 1 tot 3 jaar of > 3 jaar		implementatie (binnen aangegeven tijdspad)	s voor implementatie[1]	implementatie[2]	voor acties[3]	
1 – 4	<1 jaar	Hoewel neuromodulatie in aanvangskosten hoger wordt ingeschat, is het op lange termijn naar verwachting kosteneffectief. Gezien de verhouding BTX of neuromodulatie met name wordt bepaald door patiëntvoorkeuren, ligt een groot effect op de kosten niet in de lijn der verwachtingen.	Bij indicatie SNM de patiënt kunnen doorverwijzen naar nabijgelegen centrum, indien SNM niet beschikbaar is.	Onbekendheid met behandelaanbod van neuromodulatie bij nabijgelegen centra.	Maken van samenwerkingsafspraken	NVU	Geen

Table of excluded studies

Reference	Reason for exclusion
Zhang Y, Ji F, Liu E, Wen JG. Mechanism and Priority of Botulinum Neurotoxin A versus Sacral Neuromodulation for Refractory Overactive Bladder: A Review. Urol Int. 2021;105(11-12):929-934. doi: 10.1159/000515991. Epub 2021 Jun 15. PMID: 34130295.	non-systematic review (wrong study design)
Andy UU, Amundsen CL, Honeycutt E, Markland AD, Dunivan G, Dyer KY, Korbly NB, Bradley M, Vasavada S, Mazloomdoost D, Thomas S; NICHD Pelvic Floor Disorders Network. Sacral neuromodulation versus onabotulinumtoxinA for refractory urgency urinary incontinence: impact on fecal incontinence symptoms and sexual function. Am J Obstet Gynecol. 2019 Nov;221(5):513.e1-513.e15. doi: 10.1016/j.ajog.2019.06.018. Epub 2019 Jun 15. Erratum in: Am J Obstet Gynecol. 2022 Apr 8;: PMID: 31211964; PMCID: PMC6911169.	post-hoc analysis on Amundsen2014, on sexual function and fecal incontinence (wrong outcome)
Amundsen CL, Richter HE, Menefee S, Vasavada S, Rahn DD, Kenton K, Harvie HS, Wallace D, Meikle S. The Refractory Overactive Bladder: Sacral NEuromodulation vs. BoTulinum Toxin Assessment: ROSETTA trial. Contemp Clin Trials. 2014 Mar;37(2):272-83. doi: 10.1016/j.cct.2014.01.009. Epub 2014 Jan 30. PMID: 24486637; PMCID: PMC3989885.	trial protocol (wrong publication type)
Reekmans M, Janssen JMW, Vrijens DMJ, Smits MAC, van Koeveringe GA, Van Kerrebroeck PEVA. Sacral neuromodulation in patients with refractory overactive bladder symptoms after failed Botulinum toxin therapy: Results in a large cohort of patients. Neurourol Urodyn. 2021 Jun;40(5):1120-1125. doi: 10.1002/nau.24670. Epub 2021 Apr 8. PMID: 33829519; PMCID: PMC8360188.	effect of sacral neuromodulation in botox naive patients versus in patients who received botox first (wrong intervention)
Komesu YM, Amundsen CL, Richter HE, Erickson SW, Ackenbom MF, Andy UU, Sung VW, Albo M, Gregory WT, Paraiso MF, Wallace D; Eunice Kennedy Shriver National Institute of Child Health and Human Development Pelvic Floor Disorders Network. Refractory urgency urinary incontinence treatment in women: impact of age on outcomes and complications. Am J Obstet Gynecol. 2018 Jan;218(1):111.e1-111.e9. doi:	age-related treatment efficacy and complications relative to these treatments based on Amundsen (2016) (wrong outcome)

10.1016/j.ajog.2017.10.006. Epub 2017 Oct 12. PMID: 29031894; PMCID: PMC5803754.	
Nobrega R, Greenwell T, Pickard R, Ockrim J, Harding C. Sacral nerve stimulation versus intravesical botulinum toxin injections for medically refractory overactive bladder: A contemporary review of UK treatment from both clinician and patients' perspectives. Journal of Clinical Urology. 2018;11(5):339-344. doi:10.1177/2051415817742565	practice and preference questionnaire in patients and consultant urologists (wrong study design)
Rachaneni S, Latthe P. Effectiveness of BTX-A and neuromodulation in treating OAB with or without detrusor overactivity: a systematic review. Int Urogynecol J. 2017 Jun;28(6):805-816. doi: 10.1007/s00192-016-3225-z. Epub 2017 Jan 12. PMID: 28083714.	effect of botox in patients with versus without detrusor overactivity (wrong comparison)
Tubaro A, Puccini F, De Nunzio C. The management of overactive bladder: percutaneous tibial nerve stimulation, sacral nerve stimulation, or botulinum toxin? Curr Opin Urol. 2015 Jul;25(4):305-10. doi: 10.1097/MOU.0000000000000180. PMID: 26049873.	non-systematic review (wrong study design)
He Q, Li B, Zhang C, Zhang J, Luo D, Wang K. Treatment for refractory overactive bladder: a systematic review and meta-analysis of sacral neuromodulation and onabotulinumtoxinA. Int Urogynecol J. 2021 Mar;32(3):477-484. doi: 10.1007/s00192-020-04427-w. Epub 2020 Jul 13. PMID: 32661556.	Review containing two studies included in the literature analysis, and lower quality cohort studies
Niu HL, Ma YH, Zhang CJ. Comparison of OnabotulinumtoxinA versus sacral neuromodulation for refractory urinary urge incontinence: A systematic review and meta-analysis of randomized controlled trials. Int J Surg. 2018 Dec;60:141-148. doi: 10.1016/j.ijsu.2018.10.041. Epub 2018 Nov 9. PMID: 30415088.	Systematic review with mixed designs and dubble counted participants (wrong study design)
Al-Azzawi IS, Al-Hindawi HT. A comparative study between sacral neuromodulation and intravesical botulinum toxin injection for patients with refractory overactive bladder. Arab J Urol. 2020 Mar 23;18(2):88-93. doi: 10.1080/2090598X.2020.1740391. PMID: 33029412; PMCID: PMC7473272.	Cohort study with insufficient quality
Singh R, El Nashar SA, Trabuco EC, Klingele CJ, Gebhart JB, Occhino JA. Comparison of Short Term Outcomes of Sacral Nerve Stimulation and Intradetrusor Injection of OnabotulinumtoxinA (Botox) in Women With Refractory Overactive Bladder. Female Pelvic Med Reconstr Surg. 2015 Nov-Dec;21(6):369-73. doi: 10.1097/SPV.0000000000000200. PMID: 26506168.	Cohort study with insufficient quality

Module Bèta-3 receptor agonist

Uitgangsvraag

Wat is de waarde van een bèta-3-receptor agonist (sympathicomimeticum) bij UI in de tweede- en derdelijnszorg in vergelijking met geen behandeling of antimuscarinicum dan wel een combinatie?

Inleiding

Antimuscarinica (ook vaak anticholinergica genoemd) vormen de hoeksteen van de behandeling van urge urine-incontinentie (UUI). De werkzaamheid berust op blokkade van de muscarine-receptoren in de blaaswand. Dit vermindert de detrusorcontractiliteit en verandert het blaasgevoel. Ieder antimuscarinicum heeft een eigen farmacologisch profiel (bijvoorbeeld met betrekking tot affiniteit voor muscarine-receptoren of interacties), farmacokinetiek (bijvoorbeeld vetoplosbaarheid en halfwaardetijd) en toedieningsvorm (orale directe/vertraagde afgiftepreparaten, transdermaal, intravesicaal).

De meest voorkomende bijwerking van antimuscarinica is droge mond, maar ook obstipatie, wazig zien, moeheid en cognitieve disfunctie kunnen vóórkomen. Mensen met een droge mond zullen geneigd zijn meer te gaan drinken; het is niet duidelijk of deze toegenomen vochtinname ook leidt tot het tenietdoen van het behandeleffect.

Mirabegron is een nieuw bèta-3 sympathicomimeticum dat sinds 1 april 2014 in Nederland beschikbaar is. In de setting van de verrichte trials (en dus de specifieke patiëntengroepen die daarin zijn onderzocht) lijken de adrenerg gemedieerde bijwerkingen van mirabegron mild en klinisch amper relevant te zijn. Ten tijde van het schrijven van deze update, is nog onbekend wanneer Vibegron beschikbaar zal zijn op de Nederlandse markt.

Deze module gaat in op de waarde van medicatie. Raadpleeg voor conservatieve behandelingen zoals blaastraining de betreffende modules in deze richtlijn.

Search and select

A systematic review of the literature was performed to answer the following question: What is the efficacy of a beta-3 receptor agonist (sympathomimetic) in adults with UI compared to placebo/no treatment, antimuscarinic or a combination?

P: Adults with urine incontinence (UI)
I: Beta-3 receptor agonist (sympathomimetic: mirabegron [50 mg] or vibegron [75 mg])
C1: Placebo/no treatment
C2: Antimuscarinic (e.g., oxybutynin, solifenacin, tolterodine, darifenacin, fesoterodine)
C3: Combination of an antimuscarinic and beta-3 receptor agonist
O: Volume voided per micturition, number of micturitions per 24h, number of urinary incontinence episodes per 24h, number of urgency episodes per 24h, adverse events, blood pressure, hypertension, pulse rate, tachycardia, palpitations

<u>Relevant outcome measures</u>

The guideline development group considered number of urinary incontinence episodes per 24h and number of urgency episodes per 24h as critical outcome measures for decision making; and volume voided per micturition, number of micturitions per 24h, adverse events, blood pressure, hypertension, pulse rate, tachycardia and palpitations as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following minimal clinically (patient) important differences:

- Improvement of overactive bladder complaints:
    - Urinary Distress Inventory (UDI-6): ≥ 8 points (Barber, 2009)

In all other cases, the working group defined a 25% difference for dichotomous outcomes (0.8 ≤ RR ≤ 1.25), and 0.5 SD or -0.5 > SMD > 0.5 for continuous outcomes as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until 18 September 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 479 hits. Studies were selected based on the following criteria:

- Systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available) or randomized controlled trials;
- Patients aged ≥ 18 years
- Studies including ≥20 (ten in each study arm) patients;
- Full-text English language publication; and
- Studies according to the PICO.

Initially, 89 studies were selected based on title and abstract screening. After reading the full text, 86 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 3 studies were included. One of these studies (Mostafaei, 2022) is a systematic review and network meta-analysis, also investigating other treatment options for adults with UI that were not conform our PICO. Studies that were conform our PICO were extracted from the systematic review (Abrams, 2015; Herschorn, 2017; Khullar, 2013; Kuo, 2015; Nitti, 2013; Shin, 2018; Yamaguchi, 2014; Yamaguchi, 2015). These studies were all found in our own search as well. Two additional RCTs (Staskin, 2021; Suzuki, 2021) published after the search date of the systematic review, were also included.

Results

Ten studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Because the PICO consisted of three comparators, this module is divided into three submodules:

1. *Beta-3 receptor agonist versus placebo/no treatment*
2. *Beta-3 receptor agonist versus antimuscarinic*
3. *Beta-3 receptor agonist versus combination (antimuscarinic + beta-3 receptor agonist)*

All submodules include a summary of the literature including a description of the included studies, results, grading of the level of evidence and conclusions.

1. *Beta-3 receptor agonist versus placebo/no treatment*

Summary of literature

Description of studies

For the first comparison, a total of eight RCTs were found *(Abrams, 2015; Herschorn, 2017; Khullar, 2013; Kuo, 2015; Nitti, 2013; Shin, 2018; Yamaguchi, 2014; Yamaguchi, 2015)*. Study characteristics, including the outcome measures reported, are shown in *Table 1*. Results for studies in the elderly population are described in the 'chapter drug treatment for elderly' in this guideline.

Table 1: study characteristics of included studies for comparison 1

Study	Patients	Intervention		Comparison		Outcomes of interest reported	N	Follow-up
		Characteristics	Type/dose	Characteristics	Type			
Abrams, 2015	Adults with OAB ≥ 3 months	n = 78 Mean age (SD): 53.4 (14) Female (%): 66.7 Mean BMI (SD): 26.6 (3.6)	Mirabegron (50 mg) tablet, and two placebo tablets once daily orally	n = 81 Mean age (SD): 54.6 (13.4) Female (%): 66.7 Mean BMI (SD): 27.1 (13.6)	Three placebo tablets once daily orally	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Urgency episodes/24h Adverse events Blood pressure Hypertension Pulse rate Tachycardia	159	14 weeks
Herschorn, 2017	Adults with wet OAB ≥ 3 months	n = 422 Mean age (SD): 56.7 (13.3) Female (%): 76.5 Mean BMI (SD): 28.3 (6.0)	Mirabegron (50 mg) tablet once daily orally	n = 429 Mean age (SD): 57.9 (13) Female (%): 76.2 Mean BMI (SD): 28.7 (6.1)	Placebo tablet once daily orally	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Adverse events	851	14 weeks
Khullar, 2013	Adults with OAB ≥ 3 months	n = 493 Mean age (SD): 59.1 (12.4) Female (%): 72.4 Mean BMI (SD): 27.5 (4.9)	Mirabegron (50 mg) orally once daily	n = 494 Mean age (SD): 59.2 (12.3) Female (%): 72.1 Mean BMI (SD): 27.8 (5.0)	Placebo orally once daily	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Urgency episodes/24h Adverse events Hypertension	987	12 weeks + 30 days
Kuo, 2015	Adults with OAB ≥ 3 months	n = 338 Mean age (SD): 54.3 (14.2) Female (%): 67.5	Mirabegron (50 mg) orally once daily	n = 323 Mean age (SD): 55.3 (13.6) Female (%): 69.7	Placebo orally once daily	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Urgency episodes/24h	661	14 weeks

		Mean BMI (SD): N.R.		Mean BMI (SD): N.R.		Adverse events Blood pressure Hypertension		
Nitti, 2013	Adults with OAB ≥ 3 months	n = 442 Mean age (SD): 59.2 (13.5) Female (%): 72.9 Mean BMI (SD): 30.0 (6.6)	Mirabegron (50 mg)	n = 453 Mean age (SD): 60.1 (13.8) Female (%): 76.2 Mean BMI (SD): 30.4 (7.4)	Placebo	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Hypertension Tachycardia	895	12 weeks + 30 days
Shin, 2018	Adult males with OAB ≥ 12 weeks	n = 310 Mean age (SD): 66.4 (9.5) Mean BMI (SD): 24.2 (2.8)	Mirabegron (50 mg) orally once daily	n = 154 Mean age (SD): 65.2 (10) Mean BMI (SD): 23.9 (3.7)	Placebo orally once daily	Micturitions/24h Adverse events Blood pressure Pulse rate	464	12 weeks + 14 weeks extended treatment period
Yamaguchi, 2014	Adults with OAB ≥ 24 weeks	n = 369 Mean age (SD): 58.3 (13.9) Female (%): 84.3 Mean BMI (SD): N.R.	Mirabegron (50 mg) orally once daily	n = 368 Mean age (SD): 58.2 (14.2) Female (%): 84.2 Mean BMI (SD): N.R.	Placebo orally once daily	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Urgency episodes/24h Adverse events Blood pressure Hypertension Pulse rate Tachycardia	737	14 weeks
Yamaguchi, 2015	Adults with OAB ≥ 24 weeks	n = 208 Mean age (SD): 56.2 (13.6) Female (%): 85.1 Mean BMI (SD): N.R.	Mirabegron (50 mg) orally once daily	n = 211 Mean age (SD): 55.7 (12.9) Female (%): 80.1 Mean BMI (SD): N.R.	Placebo orally once daily	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Urgency episodes/24h Adverse events Hypertension Pulse rate Tachycardia Palpitations	419	12 weeks

Abbreviations: OAB = overactive bladder; BMI = body mass index; SD = standard deviation.

Results

1. *Urinary incontinence episodes/24h*

Seven studies reported on the number of urinary incontinence episodes per 24h (Table 1). *Abrams (2015), Herschorn (2017), Khullar (2013)* and *Kuo (2015)* reported on the number of urinary incontinence episodes per 24h, defined as the adjusted mean change from baseline to end of treatment. *Nitti (2013)* reported the adjusted mean change from baseline to final visit. *Yamaguchi (2014)* reported the mean change from baseline to final assessment, and *Yamaguchi (2015)* the mean change from baseline to end of study.

Data of *Abrams (2015), Herschorn (2017)* and *Kuo (2015)* could not be pooled because no absolute change or SE/SD values were reported. *Abrams (2015)* reported that a reduction in the number of urinary incontinence episodes/24h was observed at end of treatment in the mirabegron group (n = 78) as well as the placebo group (n = 81). *Herschorn (2017)* reported a mean change in urinary incontinence episodes/24h of -1.76 in the mirabegron group (n = 406), and -1.34 in the placebo group (n = 412). *Kuo (2015)* reported a baseline number of incontinence episodes of 2.4 (SD 2.5) in the mirabegron group (n = 338), and 2.4 (SD 2.7) in the placebo group (n = 323). It was mentioned that mirabegron was associated with improvement in urinary incontinence episodes/24h over time.

The pooled data show a standardized mean difference of -0.26 (95%CI -0.39 to -0.14), favoring beta-3 receptor agonists (Figure 3). This difference was not considered clinically relevant.

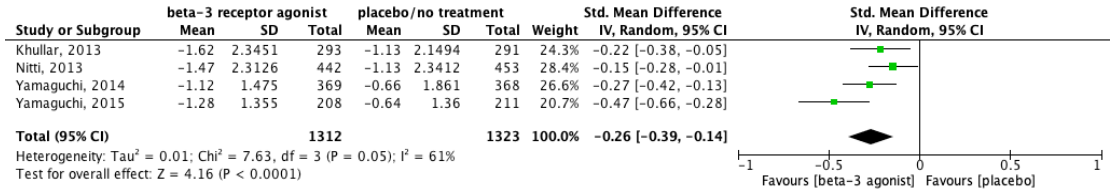

Figure 3: The effect of a beta-3 agonist on urinary incontinence episodes/24h.
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

2. *Urgency episodes/24h*

Five studies reported on the number of urgency episodes per 24h (Table 1). *Abrams (2015), Khullar (2013)* and *Kuo (2015)* reported on the number of urinary incontinence episodes per 24h, defined as the adjusted mean change from baseline to end of treatment. *Yamaguchi (2014)* reported the mean change from baseline to final assessment, and *Yamaguchi (2015)* the mean change from baseline to end of study.

Data of *Abrams (2015)* and *Kuo (2015)* could not be pooled because no absolute (SE/SD) values were reported. *Abrams (2015)* reported no absolute values, but a graph shows that there is a larger (non-significant) increase in the mean number of urgency episodes/24h from baseline to end of treatment in the mirabegron group (n = 78) compared to the placebo group (n = 81). *Kuo (2015)* reported a baseline number of urgency episodes/24h of 5.2 (SD 4.6) in the mirabegron group (n = 338), and 5.6 (SD 5.3) in the placebo group (n = 323).

The pooled data show a standardized mean difference of -0.03 (95%CI -0.27 to 0.21), favoring beta-3 receptor agonists (Figure 4). This difference was not considered clinically relevant.

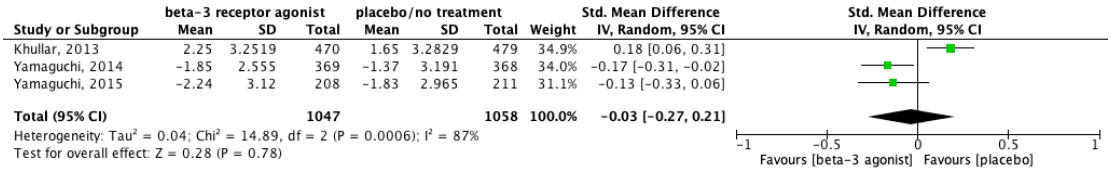

Figure 4: The effect of a beta-3 agonist on urgency episodes/24h.
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

3. Volume voided/micturition

Seven studies reported on the volume voided per micturition (Table 1). *Abrams (2015), Herschorn (2017), Khullar (2013)* and *Kuo (2015)* reported on volume voided per micturition, defined as the adjusted mean change from baseline to end of treatment. *Nitti (2013)* reported the adjusted mean change from baseline to final visit. *Yamaguchi (2014)* reported the mean change from baseline to final assessment, and *Yamaguchi (2015)* the mean change from baseline to end of study.

Data of *Herschorn (2017)* and *Kuo (2015)* could not be pooled because no absolute change or SE/SD values were reported. *Herschorn (2017)* reported a mean change in volume voided/micturition of 21.99 in the mirabegron group (n = 408), and 8.44 in the placebo group (n = 413). *Kuo (2015)* reported a baseline volume voided/micturition of 147.8 (SD 52.7) for the mirabegron group (n = 338), and 152.6 (SD 55.0) for the placebo group (n = 323). This study mentioned that the magnitude of the increase in mean volume voided/micturition was numerally larger in the mirabegron group compared to the placebo group at all timepoints.

The pooled data show a standardized mean difference of 0.33 (95%CI 0.24 to 0.43) ml, favoring beta-3 receptor agonists (Figure 1). This difference was not considered clinically relevant.

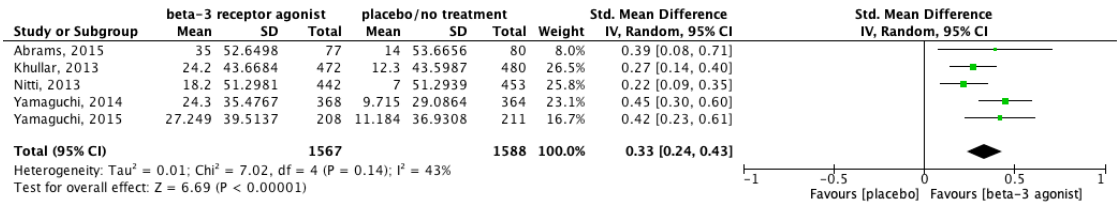

Figure 1: The effect of a beta-3 agonist on volume voided/micturition.
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

4. Micturitions/24h

Eight studies reported on the number of micturitions per 24 hour (Table 1). *Abrams (2015), Herschorn (2017), Khullar (2013)* and *Kuo (2015)* reported on micturitions per 24h, defined as the adjusted mean change from baseline to end of treatment. *Nitti (2013)* reported the adjusted mean change from baseline to final visit. *Yamaguchi (2014)* reported the mean change from baseline to final assessment, and *Shin (2018)* and *Yamaguchi (2015)* the mean change from baseline to end of study.

Data of *Abrams (2015), Herschorn (2017)* and *Kuo (2015)* could not be pooled because no absolute change or SE/SD values were reported. *Abrams (2015)* reported no absolute values, but a graph shows that there is a larger (non-significant) decrease from baseline to end of treatment in the mean number of micturitions/24h in the mirabegron group compared (n = 78) to the placebo group (n = 81). *Herschorn (2017)* reported a mean change in micturitions/24h of -2.03 in the mirabegron group (n = 406), and -1.64 in the placebo group (n = 412). *Kuo (2015)* reported a baseline number of micturitions/24h of 12.1 (SD 4.1) in the

mirabegron group (n = 338), and 12.6 (SD 4.9) in the placebo group (n = 323). They reported that the mean number of micturitions/24h decreased over time in both groups.

The pooled data show a standardized mean difference of -0.23 (95%CI -0.37 to -0.09), favoring beta-3 receptor agonists (Figure 2). This difference was not considered clinically relevant.

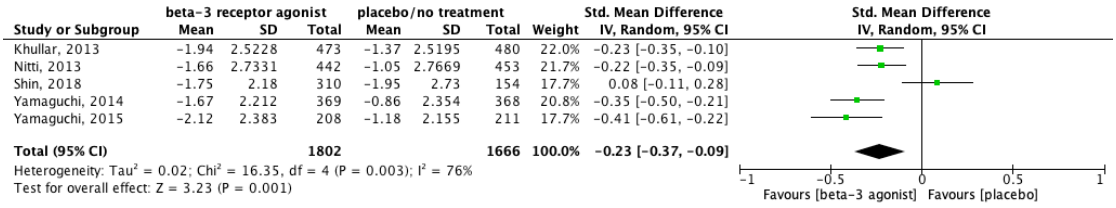

Figure 2: The effect of a beta-3 agonist on micturitions/24h.
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

5. Adverse events

Seven studies reported on adverse events (Table 1). *Abrams (2015), Herschorn (2017), Kuo (2015)* and *Yamaguchi (2015)* reported on the frequency of treatment-emergent adverse events (TEAEs), whereas *Khullar (2013), Shin (2018)* and *Yamaguchi (2014)* reported on the total of adverse events (AEs).

Data of these studies was pooled with two subgroups because of the diversity in definitions of adverse events (Figure 5). For subgroup 1, the relative risk was 1.04 (95%CI 0.90 to 1.20), favoring placebo. This difference was not considered clinically relevant. For subgroup 2, the relative risk was 1.01 (95%CI 0.90 to 1.14), favoring placebo. This difference was not considered clinically relevant.

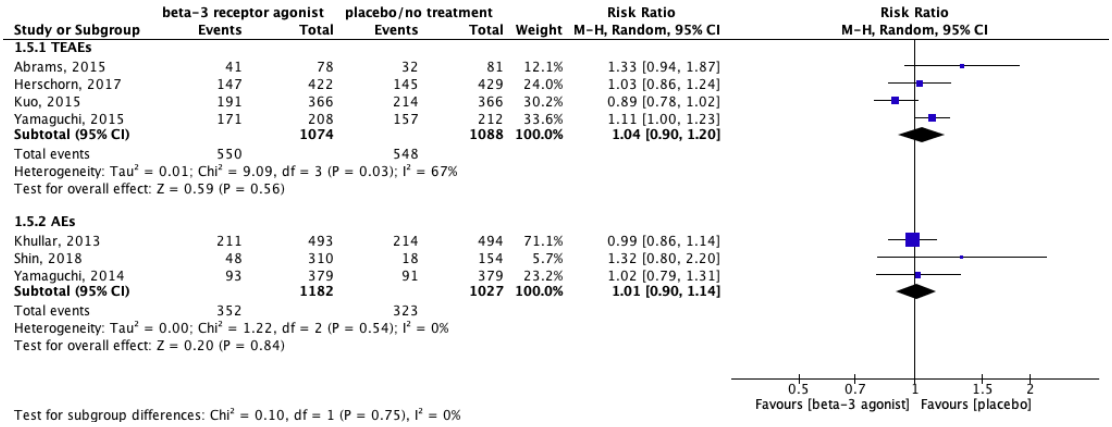

Figure 5: The effect of a beta-3 agonist on adverse events.
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

a. Blood pressure (continuous outcome): mean difference between groups

Two studies reported on blood pressure (Table 1) as a continuous outcome. Data could not be pooled due to the diversity in reporting of the outcome measure blood pressure.

Abrams (2015) reported on blood pressure, defined as the adjusted mean change from baseline to end of treatment. The mean change in systolic blood pressure was 0.7 (SD 9.8) for the mirabegron group (n = 78) and -2.6 (SD 9.81) for the placebo group (n = 81). The standardized mean difference was 0.33 (95%CI 0.02 to 0.65) in favor of placebo treatment, which was not considered clinically different. For diastolic blood pressure, the mean change

was 0.3 (SD 6.7) for the mirabegron group, and -1.2 (SD 6.7) for the placebo group. The standardized mean difference was 0.22 (95%CI -0.09 to 0.53), favoring placebo treatment, which was not considered clinically different.

Shin (2018) reported on blood pressure, defined as the mean change from baseline to final visit. The mean change in systolic blood pressure was -0.21 (SD 12.0) for the mirabegron group (n = 310), and 0.76 (SD 12.5) for the placebo group (n = 154). Standardized mean difference was -0.08 (95%CI -0.27 to 0.11) in favor of mirabegron treatment, which was not considered clinically different. For diastolic blood pressure, the mean change was 0.13 (SD 9.1) for the mirabegron group, and 0.7 (SD 8.4) for the placebo group. The standardized mean difference was -0.06 (95%CI -0.26 to 0.13), favoring mirabegron treatment, which was not considered clinically different.

b. Blood pressure (dichotomous outcome): Hypertension/increased blood pressure

Eight studies reported on hypertension (Table 1). All studies reported on the incidence of hypertension. Data of *Yamaguchi (2015)* could not be pooled because nothing was reported about the incidence of hypertension in the placebo group. *Yamaguchi (2015)* reported hypertension in 1 out of 208 (0.5%) patients in the mirabegron group.

Kuo (2015) reported on the proportion of patients with an increased blood pressure. Blood pressure was increased in 1 out of 366 (0.3%) patients in the placebo group, and in 0 out of 366 patients in the mirabegron group. The risk ratio was 0.33 (95%CI 0.01 to 8.16) in favor of mirabegron treatment, which was considered clinically relevant.

Yamaguchi (2014) reported on the proportion of patients with an increased blood pressure. Blood pressure was increased in 1 out of 379 (0.3%) patients in the placebo group, and in 0 out of 379 patients in the mirabegron group. The risk ratio was 0.33 (95%CI 0.01 to 8.16) in favor of mirabegron treatment, which was considered clinically relevant.

The pooled data for hypertension show a risk ratio of 0.94 (95%CI 0.68 to 1.28), favoring beta-3 receptor agonists (Figure 6). This difference was not considered clinically relevant.

Figure 6: The effect of a beta-3 agonist on hypertension.

Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

c. Pulse rate

Four studies reported on pulse rate (Table 1). *Abrams (2015)* reported on pulse rate, defined as the adjusted mean change from baseline to end of treatment. *Shin (2018)* reported on pulse rate, defined as the mean change from baseline to final visit. *Yamaguchi (2015)* reported on pulse rate, defined as the change from baseline to end of study.

The pooled data show a standardized mean difference of 0.14 (95%CI -0.14 to 0.43), favoring placebo treatment (Figure 7). This difference was not considered clinically relevant.

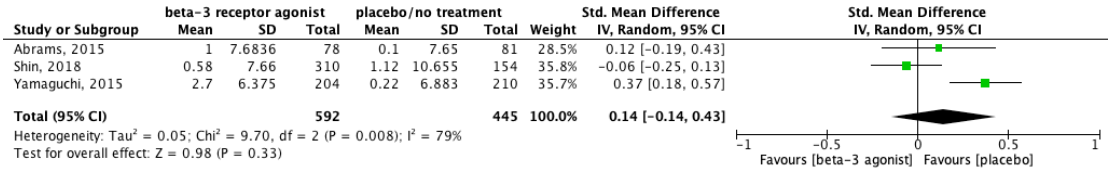

Figure 7: The effect of a beta-3 agonist on pulse rate.
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

d. Tachycardia/increased heart rate

Four studies reported on tachycardia (Table 1). All studies reported on the incidence of tachycardia. Data of *Yamaguchi (2015)* could not be pooled because nothing was reported about the incidence of tachycardia in the placebo group. *Yamaguchi (2015)* reported tachycardia in 1 out of 208 (0.5%) patients in the mirabegron group.

Data of *Yamaguchi (2014)* could not be pooled because of the diversity in reporting of the outcome measure pulse rate. *Yamaguchi (2014)* reported the proportion of patients who had an increased heart rate. Heart rate was increased in 0 out of 379 patients in the placebo group, and in 1 out of 379 (0.3%) patients in the mirabegron group.

The pooled data show a risk ratio of 2.76 (95%CI 0.81 to 9.39), favoring placebo treatment (Figure 8). This difference was considered clinically relevant.

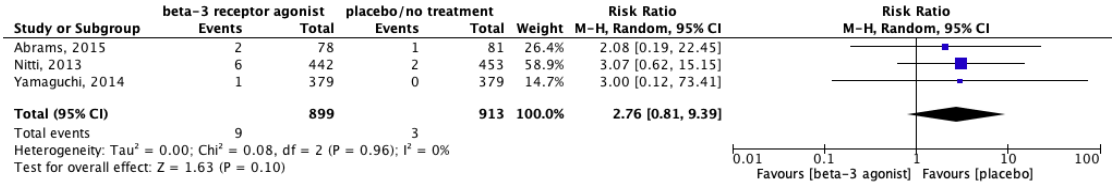

Figure 8: The effect of a beta-3 agonist on tachycardia.
Z: p-value of the pooled effect; df: degrees of freedom; I2: statistic heterogeneity; CI: confidence interval.

e. Palpitations

One study reported on palpitations (Table 1). *Yamaguchi (2015)* reported treatment-related palpitations in 1 out of 212 (0.5%) patients in the placebo group and 4 out of 208 (1.9%) patients in the mirabegron group. The risk ratio was 4.08 (95%CI 0.46 to 36.17) in favor of placebo treatment, which was considered clinically relevant.

6. Total urine volume

None of the studies reported on the outcome measure total urine volume.

<u>Level of evidence of the literature</u>

The level of evidence of the literature was assessed per outcome measure, using the GRADE-methodology.

1. Urinary incontinence episodes/24h

The level of evidence regarding urinary incontinence episodes/24h started as high because it was based on RCTs and was downgraded by one level to moderate because the sponsors of most studies had a role in the design and conduct of the study (Abrams, 2015; Khullar, 2013; Kuo, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1).

2. Urgency episodes/24h

The level of evidence regarding urgency episodes/24h started as high because it was based on RCTs and was downgraded by two levels to low because the sponsors of all studies had a role in the design and conduct of the study (Abrams, 2015; Khullar, 2013; Kuo, 2015;

Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1) and because of conflicting results (inconsistency: -1).

3. Volume voided/micturition

The level of evidence regarding volume voided/micturition started as high because it was based on RCTs and was downgraded by one level to moderate because the sponsors of most studies had a role in the design and conduct of the study (Abrams, 2015; Khullar, 2013; Kuo, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1).

4. Micturitions/24h

The level of evidence regarding micturitions/24h started as high because it was based on RCTs and was downgraded by two levels to low because the sponsors of most studies had a role in the design and conduct of the study (Abrams, 2015; Khullar, 2013; Kuo, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1) and because of conflicting results (inconsistency: -1).

5. Adverse events

The level of evidence regarding adverse events started as high because it was based on RCTs and was downgraded by two levels to low because the sponsors of most studies had a role in the design and conduct of the study (Abrams, 2015; Khullar, 2013; Kuo, 2015; Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1), and because of the diversity in definitions of adverse events (indirectness: -1).

6. Blood pressure

The level of evidence regarding blood pressure started as high because it was based on RCTs and was downgraded by three levels to very low because the sponsors of most studies had a role in the design and conduct of the study (Abrams, 2015; Kuo, 2015; Yamaguchi, 2014) (risk of bias: -1), because of conflicting results (inconsistency: -1), because the confidence interval crosses the border of clinical relevance (imprecision: -1).

7. Hypertension

The level of evidence regarding hypertension started as high because it was based on RCTs and was downgraded by two levels to low because the sponsors of all studies had a role in the design and conduct of the study (Abrams, 2015; Khullar, 2013; Kuo, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1), and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

8. Pulse rate

The level of evidence regarding pulse rate started as high because it was based on RCTs and was downgraded by two levels to low because the sponsors of most studies had a role in the design and conduct of the study (Abrams 2015; Shin, 2018; Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1), and because of conflicting results (inconsistency: -1).

9. Tachycardia

The level of evidence regarding tachycardia started as high because it was based on RCTs and was downgraded by three levels to very low because the sponsors of all studies had a role in the design and conduct of the study (Abrams 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015) (risk of bias: -1), and because the confidence interval crosses the border of clinical relevance and the low number of events (imprecision: -2).

10. Palpitations

The level of evidence regarding palpitations started as high because it was based on RCTs and was downgraded by three levels to very low because the sponsor of the study had a role in the design and conduct of the study (risk of bias: -1), and because the confidence interval crosses the borders of clinical relevance and the low number of events (imprecision: -2).

11. Total urine volume

None of the studies reported on this outcome measure and could therefore not be graded.

Conclusions

1. Urinary incontinence episodes/24h

Moderate GRADE	Beta-3 receptor agonist treatment likely results in little to no difference in urinary incontinence episodes/24h when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Herschorn, 2017; Khullar, 2013; Kuo, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015.*

2. Urgency episodes/24h

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in urgency episodes/24h when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Khullar, 2013; Kuo, 2015; Yamaguchi, 2014; Yamaguchi, 2015.*

3. Volume voided/micturition

Moderate GRADE	Beta-3 receptor agonist treatment likely results in little to no difference in volume voided/micturition when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Herschorn, 2017; Khullar, 2013; Kuo, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015.*

4. Micturitions/24h

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in micturitions/24h when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Herschorn, 2017; Khullar, 2013; Kuo, 2015; Nitti, 2013; Shin, 2018; Yamaguchi, 2014; Yamaguchi, 2015.*

5. Adverse events

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in adverse events when compared with placebo treatment in adults with UI.

	Source: Abrams, 2015; Herschorn, 2017; Khullar, 2013; Kuo, 2015; Shin, 2018; Yamaguchi, 2014; Yamaguchi, 2015.

6. Blood pressure

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on blood pressure when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Kuo, 2015; Shin, 2018; Yamaguchi, 2014.*

7. Hypertension

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in hypertension when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Khullar, 2013; Kuo, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015.*

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8. Pulse rate

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in pulse rate when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Shin, 2018; Yamaguchi, 2014; Yamaguchi, 2015.*

9. Tachycardia

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on tachycardia when compared with placebo treatment in adults with UI. *Source: Abrams, 2015; Nitti, 2013; Yamaguchi, 2014; Yamaguchi, 2015.*

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10. Palpitations

Very Low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on palpitations when compared with placebo treatment in adults with UI. *Source: Yamaguchi, 2015.*

11. Total urine volume

no GRADE	No evidence was found regarding the effect of beta-3 receptor agonist treatment on total urine volume compared with placebo treatment in adults with UI. *Source: -*

2. *Beta-3 receptor agonist versus antimuscarinic*

Summary of literature

Description of studies

For the second comparison, a total of four RCTs were found *(Abrams, 2015; Herschorn, 2017; Staskin, 2021; Suzuki, 2021)*. Study characteristics, including the outcome measures reported, are shown in Table 2.

Table 2: study characteristics of included studies for comparison 2

Study	Patients	Intervention		Comparison		Outcomes of interest reported	N	Follow-up
		Characteristics	Type/dose	Characteristics	Type			
Abrams, 2015 (SYMPHONY)	Adults with OAB ≥ 3 months	n = 78 Mean age (SD): 53.4 (14) Female (%): 66.7 Mean BMI (SD): 26.6 (3.6)	Mirabegron (50 mg) tablet, and two placebo tablets once daily orally	n = 79 Mean age (SD): 56.1 (11.7) Female (%): 64.6 Mean BMI (SD): 27.3 (4.8)	Solifenacin (2.5 mg) tablet, and two placebo tablets once daily orally	Volume voided/micturition Adverse events Blood pressure Hypertension Pulse rate Tachycardia	391	14 weeks
				n = 156 Mean age (SD): 54.2 (15.5) Female (%): 66 Mean BMI (SD): 26.3 (3.9)	Solifenacin (5 mg) tablet, and two placebo tablets once daily orally			
				n = 78 Mean age (SD): 55 (12.8) Female (%): 67.9 Mean BMI (SD): 27.2 (3.7)	Solifenacin (10 mg) tablet, and two placebo tablets once daily orally			
Herschorn, 2017 (SYNERGY)	Adults with wet OAB ≥ 3 months	n = 422 Mean age (SD): 56.7 (13.3) Female (%): 76.5 Mean BMI (SD): 28.3 (6.0)	Mirabegron (50 mg) tablet once daily orally	n = 423 Mean age (SD): 58.2 (12.8) Female (%): 78.3 Mean BMI (SD): 28.5 (5.9)	Solifenacin (5 mg) tablet once daily orally	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Adverse events	845	14 weeks
Staskin, 2021 (EMPOWUR)	Adults with OAB	n = 92	Vibegron (75 mg) orally once daily	n = 91	Tolterodine extended release	Micturitions/24h	183	40 weeks of extension

		Mean age (SD): 58.8 (13.7) Female (%): 79.3 Mean BMI (SD): N.R.		Mean age (SD): 62.1 (12.1) Female (%): 76.9 Mean BMI (SD): N.R.	(4 mg) orally once daily	Incontinence episodes/24h Urgency episodes/24h Adverse events Hypertension		(52 weeks of total treatment)
Suzuki, 2021	Adult females with OAB $\geq$ 8 weeks	n = 49 Mean age (SD): 72.7 (11.3) Mean BMI (SD): 23.3 (3.4)	Mirabegron (50 mg) orally once daily	n = 51 Mean age (SD): 68.2 (11.3) Mean BMI (SD): 24.1 (3.9)	Oxybutynin patch (73.5 mg) placed on the lower abdomen or thighs once daily	Volume voided/micturition Incontinence episodes/24h Urgency episodes/24h Total urine volume Adverse events	100	8 weeks

Results

1. *Urinary incontinence episodes/24h*

Three studies reported on the number of urinary incontinence episodes per 24 hour (Table 2). *Herschorn (2017)* reported on urinary incontinence episodes/24h, defined as the adjusted mean change from baseline to end of treatment. *Staskin (2021)* reported on the LS mean change from baseline to end of treatment. *Suzuki (2021)* reported on urgency incontinence episodes/24h, defined as the mean change from baseline to end of treatment. Data could not be pooled because no absolute SE/SD values were reported in *Herschorn (2017)* resulting in limited data.

Herschorn (2017) reported a mean change in urinary incontinence episodes/24h of -1.76 in the mirabegron group (n = 406), and -1.79 in the antimuscarinic group (n = 413).

Staskin (2021) reported a mean change in urinary incontinence episodes/24h of -2.5 (SD 2.0) in the vibegron group (n = 176), and -1.9 (SD 2.4) in the antimuscarinic group (n = 136). The standardized mean difference was -0.28 (95%CI -0.50 to -0.05) in favor of vibegron treatment, which was not considered clinically different.

Suzuki (2021) reported a mean change in urgency incontinence episodes/24h of -0.6 (SD 1.0) in the mirabegron group (n = 49), and -1.1 (SD 2.0) in the antimuscarinic group (n = 51). The standardized mean difference was 0.31 (95%CI -0.08 to 0.71) in favor of antimuscarinic treatment (oxybutynin), which was not considered clinically different.

2. *Urgency episodes/24h*

Two studies reported on the number of urgency episodes per 24 hour (Table 2). *Staskin (2021)* reported on the LS mean change from baseline to end of treatment. *Suzuki (2021)* reported on urinary urgency/24h, defined as the mean change from baseline to end of treatment. Data could not be pooled because of the limited availability of data.

Staskin (2021) reported a mean change SD in urgency episodes/24h of -3.4 (SD 4.7) in the vibegron group (n = 176), and -3.2 (SD 4.1) in the antimuscarinic group (n = 136). The standardized mean difference was -0.04 (95%CI -0.27 to 0.18) in favor of vibegron treatment, which was not considered clinically different.

Suzuki (2021) reported a mean change in urinary urgency/24h of -1.3 (SD 1.6) in the mirabegron group (n = 49), and -1.7 (SD 2.7) in the antimuscarinic group (n = 51). The standardized mean difference was 0.18 (95%CI -0.21 to 0.57) in favor of antimuscarinic treatment (oxybutynin), which was not considered clinically different.

3. *Volume voided/micturition (5 mg)*

Three studies reported on the volume voided per micturition (Table 2). *Abrams (2015)* and *Herschorn (2017)* reported on volume voided per micturition, defined as the adjusted mean change from baseline to end of treatment. *Suzuki (2021)* reported on the mean change from baseline to end of treatment. Data could not be pooled because no absolute SE/SD values were reported in *Herschorn (2017)*.

Abrams (2015) reported a mean change in volume voided per micturition of 35 (SD 53) in the mirabegron group (n = 78), and 36 (SD 53) in the antimuscarinic group (n = 150). The standardized mean difference was -0.02 (95%CI -0.29 to 0.26) in favor of antimuscarinic treatment, which was not considered clinically different.

Herschorn (2017) reported a mean change in volume voided per micturition of 22 in the mirabegron group (n = 408), and 31 in the antimuscarinic group (n = 411).

Suzuki (2021) reported a mean change in volume voided per micturition of 27.8 (SD 36.1) in the mirabegron group (n = 49), and 36.8 (SD 48.4) in the antimuscarinic group (n = 51). The

standardized mean difference was -0.21 (95%CI -0.60 to 0.18) in favor of antimuscarinic treatment, which was not considered clinically different.

4. Micturitions/24h

Two studies reported on the number of micturitions per 24 hour (Table 2). *Herschorn (2017)* reported on micturitions/24h, defined as the adjusted mean change from baseline to end of treatment. *Staskin (2021)* reported on the LS mean change from baseline to end of treatment. Data could not be pooled because no absolute SE/SD values were reported in *Herschorn (2017)* resulting in limited data.

Herschorn (2017) reported a mean change in micturitions/24h of -2.03 in the mirabegron group (n = 406), and -2.20 in the antimuscarinic group (n = 413).

Staskin (2021) reported a mean change in micturitions/24h of -2.4 (SD 2.7) in the vibegron group (n = 176), and -2.0 (SD 2.9) in the antimuscarinic group (n = 136). The mean difference was -0.40 (95%CI -1.04 to 0.24) in favor of vibegron treatment, which was not considered clinically different.

5. Adverse events

Four studies reported on adverse events (Table 2). *Abrams (2015) and Herschorn (2017)* reported on the frequency of treatment-emergent adverse events (TEAEs). *Staskin (2021)* reported on the proportion of patients with at least one TEAE. *Suzuki (2021)* reported on the frequency of any adverse event. Data could not be pooled because of the diversity in reporting of the outcome measure adverse events.

Abrams (2015) reported TEAEs in 41 out of 78 (52.6%) patients in the mirabegron group, and in 70 out of 156 (44.9%) patients in the antimuscarinic group. The risk ratio was 1.17 (95%CI 0.89 to 1.54) in favor of antimuscarinic treatment (solifenacin), which was not considered clinically different.

Herschorn (2017) reported TEAEs in 147 out of 422 (34.8%) patients in the mirabegron group, and 149 out of 423 (35.2%) patients in the antimuscarinic group. The risk ratio was 0.99 (95%CI 0.82 to 1.19) in favor of mirabegron treatment, which was not considered clinically different.

Staskin (2021) reported at least one TEAE in 171 out of 273 (62.6%) patients in the vibegron group, and 126 out of 232 (54.3%) patients in the antimuscarinic group. The risk ratio was 1.15 (95%CI 0.99 to 1.34) in favor of vibegron treatment, which was not considered clinically different.

Suzuki (2021) reported adverse events in 1 out of 49 (2%) patients in the mirabegron group, and in 26 out of 51 (51%) patients in de antimuscarinic group. The risk ratio was 0.04 (95%CI 0.01 to 0.28) in favor of mirabegron treatment, which was clinically different. Among these adverse events, in the Oxybutynin patch group application site dermatitis was seen 20 times, dry mouth 9 times, and other adverse events once. In the Mirabegron group, the adverse event was labeled as constipation.

6. Blood pressure

One study reported on blood pressure (Table 2). *Abrams (2015)* reported on blood pressure, defined as the adjusted mean change from baseline to end of treatment. The mean change in systolic blood pressure was 0.7 (SD 9.8) for the mirabegron group (n = 78) and -1.7 (SD 9.9) for the antimuscarinic group (n = 156). The mean difference was 2.4 (95%CI -0.27 to 5.07) in favor of antimuscarinic treatment (solifenacin), which was not considered clinically different. For diastolic blood pressure, the mean change was 0.3 (SD 6.7) for the mirabegron group, and -0.6 (SD 6.7) for the antimuscarinic group. The mean difference was 0.90 (95%CI -0.93 to 2.73), favoring antimuscarinic treatment, which was not considered clinically different.

7. Hypertension

Two studies reported on hypertension (Table 2), defined as the incidence of hypertension. *Abrams (2015)* reported hypertension in 11 out of 78 (14.1%) patients in the mirabegron group, and in 18 out of 156 (11.5%) patients in the antimuscarinic group. The risk ratio was 1.22 (95%CI 0.61 to 2.46) in favor of antimuscarinic treatment (solifenacin), which was not considered clinically different.
Staskin (2021) reported hypertension in 24 out of 273 (8.8%) patients in the vibegron group, and 20 out of 232 (9.6%) patients in the antimuscarinic group. The risk ratio was 1.02 (95%CI 0.58 to 1.80) in favor of antimuscarinic treatment (tolterodine), which was not considered clinically different.

8. Pulse rate

One study reported on pulse rate (Table 2), defined as the adjusted mean change from baseline to end of treatment. *Abrams (2015)* reported a mean change in pulse rate of 1.0 (SD 7.7) in the mirabegron group (n = 78), and 0.1 (SD 7.7) in the antimuscarinic group (n = 156). The mean difference was 0.90 (95%CI -1.19 to 2.99) in favor of antimuscarinic treatment (solifenacin), which was not considered clinically different.

9. Tachycardia

One study reported on tachycardia (Table 2), defined as the incidence of tachycardia. *Abrams (2015)* reported tachycardia in 2 out of 78 (2.6%) patients in the mirabegron group, and 6 out of 156 (3.8%) patients in the antimuscarinic group. The risk ratio was 0.67 (95%CI 0.14 to 3.23) in favor of mirabegron treatment, which was clinically different.

10. Palpitations

None of the studies reported on the outcome measure palpitations.

Level of evidence of the literature

The level of evidence of the literature was assessed per outcome measure, using the GRADE-methodology.

1. Urinary incontinence episodes/24h

The level of evidence regarding urinary incontinence episodes/24h started as high because it was based on RCTs and was downgraded by three levels to very low because of conflicting results (inconsistency: -1), diversity in the definitions of urinary incontinence episodes/24h (indirectness: -1) and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

2. Urgency episodes/24h

The level of evidence regarding urgency episodes/24h started as high because it was based on RCTs and was downgraded by three levels to very low because of conflicting results (inconsistency: -1), diversity in the definitions of urinary incontinence episodes/24h (indirectness: -1) and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

3. Volume voided/micturition

The level of evidence regarding volume voided/micturition started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of one study had a role in the design and conduct of the study (Abrams, 2015) (risk of bias: -1), and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

4. Micturitions/24h

The level of evidence regarding micturitions/24h started as high because it was based on RCTs and was downgraded by two levels to low because of conflicting results (inconsistency: -1), and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

5. Total urine volume

The level of evidence regarding total urine volume started as high because it was based on RCTs and was downgraded by three levels to very low because of the low number of included patients and the width of the confidence interval (imprecision: -3).

6. Adverse events

The level of evidence regarding adverse events started as high because it was based on RCTs and was downgraded by three levels to very low because the sponsor of one study had a role in the design and conduct of the study (Abrams, 2015) (risk of bias: -1), the diversity in definitions of adverse events (indirectness: -1), and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

7. Blood pressure

The level of evidence regarding blood pressure started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of this study had a role in the design and conduct of the study (risk of bias: -1), and because of the low number of patients (imprecision: -1).

8. Hypertension

The level of evidence regarding hypertension started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of one study had a role in the design and conduct of the study (Abrams, 2015) (risk of bias: -1), and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

9. Pulse rate

The level of evidence regarding pulse rate started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of this study had a role in the design and conduct of the study (risk of bias: -1), and because of the low number of patients (imprecision: -1).

10. Tachycardia

The level of evidence regarding tachycardia started as high because it was based on RCTs and was downgraded by three levels to very low because the sponsor of this study had a role in the design and conduct of the study (risk of bias: -1), and because the confidence interval crosses the border of clinical relevance and the low number of events (imprecision: -2).

11. Palpitations

None of the studies reported on this outcome measure and could therefore not be graded.

Conclusions

1. Urinary incontinence episodes/24h

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on urinary incontinence episodes/24h when compared with antimuscarinic treatment in adults with UI. *Source: Herschorn, 2017; Staskin, 2021; Suzuki, 2021.*

2. Urgency episodes/24h

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on urgency episodes/24h when compared with antimuscarinic treatment in adults with UI. *Source: Staskin, 2021; Suzuki, 2021.*

3. Volume voided/micturition

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in volume voided/micturition when compared with antimuscarinic treatment in adults with UI. *Source: Abrams, 2015; Herschorn, 2017; Suzuki, 2021.*

4. Micturitions/24h

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in micturitions/24h when compared with antimuscarinic treatment in adults with UI. *Source: Herschorn, 2017; Staskin, 2021.*

5. Total urine volume

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on total urine volume when compared with antimuscarinic treatment in adults with UI. *Source: Suzuki, 2021.*

6. Adverse events

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on adverse events when compared with antimuscarinic treatment in adults with UI. *Source: Abrams, 2015; Herschorn, 2017; Staskin, 2021; Suzuki, 2021.*

7. Blood pressure

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in blood pressure when compared with antimuscarinic treatment in adults with UI.

	Source: Abrams, 2015.

8. Hypertension

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in hypertension when compared with antimuscarinic treatment in adults with UI. *Source: Abrams, 2015; Staskin, 2021.*

9. Pulse rate

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in pulse rate when compared with antimuscarinic treatment in adults with UI. *Source: Abrams, 2015.*

5

10. Tachycardia

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on tachycardia when compared with antimuscarinic treatment in adults with UI. *Source: Abrams, 2015.*

11. Palpitations

no GRADE	No evidence was found regarding the effect of beta-3 receptor agonist treatment on palpitations compared with antimuscarinic treatment in adults with UI. *Source: -*

3. Beta-3 receptor agonist versus combination (beta-3 receptor agonist + antimuscarinic)

Summary of literature

Description of studies

For the third comparison, a total of two RCTs were found *(Abrams, 2015; Herschorn, 2017)*. Study characteristics, including the outcome measures reported, are shown in Table 3.

Table 3: study characteristics of included studies for comparison 3

Study	Patients	Intervention		Comparison		Outcomes of interest reported	N	Follow-up
		Characteristics	Type/dose	Characteristics	Type			
Abrams, 2015 (SYMPHONY)	Adults with OAB ≥ 3 months	n = 78 Mean age (SD): 53.4 (14) Female (%): 66.7 Mean BMI (SD): 26.6 (3.6)	Mirabegron (50 mg) tablet, and two placebo tablets once daily orally	n = 149 Mean age (SD): 53.7 (14.6) Female (%): 67.1 Mean BMI (SD): 26.5 (4.0)	Mirabegron 50 mg + solifenacin 2.5 mg tablet, and two placebo tablets once daily orally	Volume voided/micturition Adverse events Blood pressure Hypertension Pulse rate Tachycardia	461	14 weeks
				n = 153 Mean age (SD): 54.1 (14.1) Female (%): 66.0 Mean BMI (SD): 26.5 (3.6)	Mirabegron 50 mg + solifenacin 5 mg tablet, and two placebo tablets once daily orally			
				n = 81 Mean age (SD): 55.5 (13.8) Female (%): 66.7 Mean BMI (SD): 26.3 (3.3)	Mirabegron 50 mg + solifenacin 10 mg tablet, and two placebo tablets once daily orally			
Herschorn, 2017 (SYNERGY)	Adults with wet OAB ≥ 3 months	n = 422 Mean age (SD): 56.7 (13.3) Female (%): 76.5 Mean BMI (SD): 28.3 (6.0)	Mirabegron (50 mg) tablet once daily orally	n = 848 Mean age (SD): 57.6 (13.4) Female (%): 76.8 Mean BMI (SD): 28.6 (5.9)	Mirabegron 50 mg + solifenacin 5 mg tablet once daily orally	Volume voided/micturition Micturitions/24h Incontinence episodes/24h Adverse events	1270	14 weeks

Results

1. Urinary incontinence episodes/24h

One study reported on the number of urinary incontinence episodes per 24 hour (Table 3), defined as the adjusted mean change from baseline to end of treatment. *Herschorn (2017)* reported a mean change in urinary incontinence episodes/24h of -1.76 in the mirabegron group (n = 406), and -1.98 in the combination treatment group (n = 816). Since no measures of dispersion were reported, this result was not evaluated using grade.

2. Adverse events

Two studies reported on adverse events (Table 3). Both studies reported on the frequency of treatment-emergent adverse events (TEAEs).

Abrams (2015) reported TEAEs in 41 out of 78 (52.6%) patients in the mirabegron group, and in 67 out of 153 (43.8%) patients in the combination treatment group. The risk ratio was 1.20 (95%CI 0.91 to 1.58) in favor of combination treatment (mirabegron + solifenacin), which was not considered clinically different. *Herschorn (2017)* reported TEAEs in 147 out of 422 (34.8%) patients in the mirabegron group, and in 314 out of 848 (37%) patients in the combination treatment group. The risk ratio was 0.94 (95%CI 0.80 to 1.10) in favor of mirabegron treatment, which was not considered clinically different.

3. Volume voided/micturition

Two studies reported on volume voided per micturition (Table 3). *Abrams (2015)* and *Herschorn (2017)* reported on volume voided per micturition, defined as the adjusted mean change from baseline to end of treatment.

Abrams (2015) reported a mean change in volume voided per micturition of 35 (SD 53) in the mirabegron group (n = 78), and 54 (SD 53) in the combination treatment group (n = 150). The mean difference was -19.2 (95%CI -33.67 to -4.73) in favor of combination treatment, which was not considered clinically different.

Herschorn (2017) reported a mean change in volume voided per micturition of 22 in the mirabegron group (n = 408), and 40 in the combination treatment group (n = 821).

4. Micturitions/24h

One study reported on the number of micturitions per 24 hour (Table 3), defined as the adjusted mean change from baseline to end of treatment. *Herschorn (2017)* reported a mean change in micturitions/24h of -2.03 in the mirabegron group (n = 406), and -2.59 in the combination treatment group (n = 816). Since no measures of dispersion were reported, this result was not evaluated using grade.

5. Volume voided/micturition

Two studies reported on volume voided per micturition (Table 3). *Abrams (2015)* and *Herschorn (2017)* reported on volume voided per micturition, defined as the adjusted mean change from baseline to end of treatment.

Abrams (2015) reported a mean change in volume voided per micturition of 35 (SD 53) in the mirabegron group (n = 78), and 54 (SD 53) in the combination treatment group (n = 150). The mean difference was -19.2 (95%CI -33.67 to -4.73) in favor of combination treatment, which was not considered clinically different.

Herschorn (2017) reported a mean change in volume voided per micturition of 22 in the mirabegron group (n = 408), and 40 in the combination treatment group (n = 821).

6. Micturitions/24h

One study reported on the number of micturitions per 24 hour (Table 3), defined as the adjusted mean change from baseline to end of treatment. *Herschorn (2017)* reported a mean change in micturitions/24h of -2.03 in the mirabegron group (n = 406), and -2.59 in the combination treatment group (n = 816). Since no measures of dispersion were reported, this result was not evaluated using grade.

7. Blood pressure

One study reported on blood pressure (Table 3). *Abrams (2015)* reported on blood pressure, defined as the adjusted mean change from baseline to end of treatment. The mean change in systolic blood pressure was 0.7 (SD 9.8) for the mirabegron group (n = 78) and -2.1 (SD 9.9) for the combination treatment group (n = 153). The mean difference was 2.8 (95%CI 0.12 to 5.48) in favor of combination treatment (mirabegron + solifenacin), which was not considered clinically different. For diastolic blood pressure, the mean change was 0.3 (SD 6.7) for the mirabegron group, and -0.8 (SD 6.8) for the combination treatment group. The mean difference was 1.1 (95%CI -0.74 to 2.94), favoring combination treatment, which was not considered clinically different.

8. Hypertension

One study reported on hypertension (Table 3), defined as the incidence of hypertension. *Abrams (2015)* reported hypertension in 11 out of 78 (14.1%) patients in the mirabegron group, and in 9 out of 153 (5.9%) patients in the combination treatment group. **The risk ratio was 2.40 (95%CI 1.04 to 5.54) in favor of combination treatment (mirabegron + solifenacin), which was considered clinically different.**

9. Pulse rate

One study reported on pulse rate (Table 3), defined as the adjusted mean change from baseline to end of treatment. *Abrams (2015)* reported a mean change in pulse rate of 1.0 (SD 7.7) in the mirabegron group (n = 78), and 0.6 (SD 7.7) in the combination treatment group (n = 153). The mean difference was 0.40 (95%CI -1.69 to 2.49) in favor of combination treatment (mirabegron + solifenacin), which was not considered clinically different.

10. Tachycardia

One study reported on tachycardia (Table 3), defined as the incidence of tachycardia. *Abrams (2015)* reported tachycardia in 2 out of 78 (2.6%) patients in the mirabegron group, and 3 out of 153 (2.0%) patients in the combination treatment group. **The risk ratio was 1.31 (95%CI 0.22 to 7.66) in favor of combination treatment (mirabegron + solifenacin), which was considered clinically different.**

11. Urgency episodes/24h, 10. Palpitations, 11. Total urine volume

None of the studies reported on the outcome measures urgency episodes/24h, palpitations and total urine volume.

<u>Level of evidence of the literature</u>

The level of evidence of the literature was assessed per outcome measure, using the GRADE-methodology.

1. Urinary incontinence episodes/24h

The outcome measure urinary incontinence episodes/24h could not be graded, because no standard deviation or standard error values were reported.

2. Adverse events

The level of evidence regarding adverse events started as high because it was based on RCTs and was downgraded by three levels to very low because the sponsors of one study had a role in the design and conduct of the study (Abrams, 2015) (risk of bias: -1), because of conflicting results (inconsistency: -1), and because the confidence interval is crossing the border of clinical relevance (imprecision: -1).

3. Volume voided/micturition

The level of evidence regarding volume voided/micturition started as high because it was based on RCTs and was downgraded by two levels to low because the sponsors of one study had a role in the design and conduct of the study (Abrams, 2015) (risk of bias: -1), and because the confidence interval crosses the border of clinical relevance (imprecision: -1).

4. Micturitions/24h

The outcome measure micturitions/24h could not be graded, because no standard deviation or standard error values were reported.

5. Blood pressure

The level of evidence regarding blood pressure started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of this study had a role in the design and conduct of the study (risk of bias: -1), and because the confidence interval is crossing the border of clinical relevance (imprecision: -1).

6. Hypertension

The level of evidence regarding hypertension started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of this study had a role in the design and conduct of the study (risk of bias: -1), and because the confidence interval is crossing the border of clinical relevance (imprecision: -1).

7. Pulse rate

The level of evidence regarding pulse rate started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of this study had a role in the design and conduct of the study (risk of bias: -1), and because of the low number of included patients (imprecision: -1).

8. Tachycardia

The level of evidence regarding tachycardia started as high because it was based on RCTs and was downgraded by two levels to low because the sponsor of this study had a role in the design and conduct of the study (risk of bias: -1), and because the confidence interval is crossing the border of clinical relevance (imprecision: -1).

9. Urgency episodes/24h, 10. Palpitations, 11. Total urine volume

None of the studies reported on the outcome measures urgency episodes/24h, palpitations and total urine volume and could therefore not be graded.

Conclusions

1. Urinary incontinence episodes/24h

no GRADE	No GRADE-assessment could be performed. *Source: Herschorn, 2017.*

2. Adverse events

Very low GRADE	The evidence is very uncertain about the effect of beta-3 receptor agonist treatment on adverse events when compared with combination treatment in adults with UI. *Source: Abrams, 2015; Herschorn.*

3. Volume voided/micturition

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in volume voided/micturition when compared with combination treatment in adults with UI. *Source: Abrams, 2015; Herschorn, 2017.*

4. Micturitions/24h

no GRADE	No GRADE-assessment could be performed. *Source: Herschorn, 2017.*

5. Blood pressure

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in blood pressure when compared with combination treatment in adults with UI. *Source: Abrams, 2015.*

6. Hypertension

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in hypertension when compared with combination treatment in adults with UI. *Source: Abrams, 2015.*

7. Pulse rate

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in pulse rate when compared with combination treatment in adults with UI. *Source: Abrams, 2015.*

8. Tachycardia

Low GRADE	Beta-3 receptor agonist treatment may result in little to no difference in tachycardia when compared with combination treatment in adults with UI. *Source: Abrams, 2015.*

9. Urgency episodes/24h, 10. Palpitations, 11. Total urine volume

no GRADE	No evidence was found regarding the effect of beta-3 receptor agonist treatment on urgency episodes/24h, palpitations and total urine volume compared with combination treatment in adults with UI. *Source: -*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is een literatuuronderzoek verricht naar de effectiviteit en veiligheid van beta-3 receptor agonisten in de behandeling van urine-incontinentie (UI). In totaal zijn er 10 RCT's gevonden die beta-3 receptor agonisten vergeleken met placebo, een antimuscarinicum of een combinatie van een beta-3 receptor agonist en een antimuscarinicum.

1. Beta-3 receptor agonist versus placebo

Voor de vergelijking tussen mirabegron(/vibegron) en placebo werd de bewijskracht voor de uitkomstmaten *volume voided/micturition* en *urinary incontinence episodes/24h* beoordeeld als gemiddeld vanwege risico op bias door de rol van de studie sponsors bij de opzet en uitvoering van de studie. Het gebruik van mirabegron bij volwassenen met UI leidt mogelijk niet tot een klinisch relevant (er zijn minder urine-incontinentie episodes/24u in de Beta-3 agonist groep vergeleken met placebo -0.26 (95%CI -0.39 to -0.14), verschil in uitgescheiden volume per mictie of tot minder urine-incontinentie episodes per 24 uur. Voor de overige uitkomstmaten komt de bewijskracht uit op laag of zeer laag. De overall bewijskracht is hierdoor laag, wat betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van mirabegron bij volwassenen met UI in de tweede- en derdelijnszorg.

2. Beta-3 receptor agonist versus antimuscarinica

Voor de vergelijking tussen mirabegron/vibegron en antimuscarinica werd de bewijskracht voor alle uitkomstmaten beoordeeld als laag of zeer laag. Redenen hiervoor zijn onder andere risico op bias, brede betrouwbaarheidsintervallen, verscheidenheid in de definities van uitkomstmaten, conflicterende resultaten en kleine onderzoekspopulaties. Dit leidt tot een zeer lage overall bewijskracht. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de huidige literatuur geen eenduidige aanbevelingen geformuleerd worden over de waarde van mirabegron/vibegron vergeleken met antimuscarinica bij volwassenen met UI in de tweede- en derdelijnszorg.

3. Beta-3 receptor agonist versus combinatie (beta-3 receptor agonist + antimuscarinica)

Voor de vergelijking tussen mirabegron en een combinatie van mirabegron met solifenacin werd de bewijskracht voor alle uitkomstmaten beoordeeld als laag of zeer laag. Redenen hiervoor zijn risico op bias, brede betrouwbaarheidsintervallen, conflicterende resultaten en kleine onderzoekspopulaties. Dit leidt tot een zeer lage overall bewijskracht, wat betekent dat andere studies kunnen leiden tot nieuwe inzichten. Herschorn (2017) vermeldt bijvoorbeeld een afname van incontinentie episodes per 24u van -1.76 in de mirabegron groep (n = 406), en -1.98 in de combinatie therapie groep (n = 816), maar omdat er geen spreiding wordt gerapporteerd is de grade systematiek niet toe te passen. Er kunnen dus op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van mirabegron vergeleken met een combinatie van mirabegron met solifenacin bij volwassenen met UI in de tweede- en derdelijnszorg.

Naast de hierboven genoemde literatuur analyse is ook gekeken naar aanbevelingen vanuit andere (Europese en landelijke) richtlijnen aangaande de behandeling van aandrang urine-incontinentie met beta-3 agonisten:

In de richtlijn van de European Association of Urology (EAU, 2020) over non-neurogenic female LUTS wordt het volgende beschreven over het gebruik van beta-3 agonisten bij vrouwen:

Mirabegron en vibegron zijn beter dan placebo voor de verbetering van OAB/UUI symptomen. Beta-3 agonists zijn net zo effectief als antimuscarinica in de behandeling van OAB, maar met minder klachten van droge mond. De meest genoemde bijwerkingen in de beta-3 agonisten groep waren hypertensie (7.3%), nasopharyngitis (3.4%) en urineweginfecties (3%), maar deze waren vergelijkbaar met de placebo groep. Het is onduidelijk of dit bijwerkingen betreffen of toevalsbevindingen zijn. Aanbeveling vanuit de EAU richtlijn is dan ook om beta-3 agonisten te gebruiken als alternatief voor antimuscarinica als conservatieve behandeling faalt. De tweede aanbeveling luidt dat patiënten die inadequaat behandeld zijn met solifenacin 5 mg meer baat kunnen hebben bij de toevoeging van mirabegron, dan bij het ophogen van de dosis solifenacine.
Tevens wordt in dezelfde EAU-richtlijn gesteld dat Mirabegron effectief en veilig is bij ouderen. In deze richtlijn wordt ook aandacht besteed aan medicatie gebruik bij kwetsbare ouderen. Literatuur uit de EAU-richtlijn komt op veel vlakken niet overeen met de gevonden literatuur in de samenvatting van deze module. Omdat een overzicht van selectiecriteria en redenen voor excluderen van studies niet gepresenteerd is binnen deze EAU richtlijn, kunnen oorzaken voor verschillen met onze uitkomstem niet worden achterhaald.
Raadpleeg voor medicatie bij ouderen de betreffende module.

In de NVOG richtlijn urine incontinentie bij vrouwen (verwacht 2023) wordt het volgende geschreven over beta 3 sympaticomimetica:
Er zijn geen studies geïncludeerd die beta3-agonisten (bijv., mirabregon) bestuderen in een populatie van uitsluitend vrouwen, dit is genoteerd als kennislacune. Er wordt in deze richtlijn wel melding gemaakt van studies die beta-3 sympaticomimetica bij gemengde populaties hebben onderzocht, op basis waarvan
De EMPOWUR-trial bestudeert het nog niet in Nederland beschikbare vibegron (Staskin, 2020). In deze internationale dubbel geblindeerde RCT werden 1518 patiënten (85% vrouw) geïncludeerd die 12 weken vibegron 75mg, tolterodine 4mg of placebo kregen. In de vibegron groep had 52.4% een ≥75% reductie van urge incontinentie episodes vs. 47.6% van de patiënten die tolterodine kregen en 36.38% in de placebogroep (p<0.05). De resultaten van deze studie zijn terug te vinden in de literatuursamenvatting van deze module.
Een ander artikel beschrijft de veiligheid en effectiviteit van alle door de producent gesponsorde fase 2-4 studies met mirabegron met antimuscarinica (solifenacine en tolterodine) en placebo in mannen en vrouwen (65-76% is vrouw in deze studies) met OAB wereldwijd (Chapple, 2020). Medicatie gerelateerde bijwerkingen komen meer voor bij antimuscarinica, dan bij mirabegron en de placebogroep. Het vóórkomen van hypertensie was gelijk in de antimuscarinica, mirabegron en in de placebogroep. Mirabegron zou een gunstiger bijwerkingenprofiel hebben bij ouderen en patiënten met bekende obstipatie. Hierbij moet opgemerkt worden dat dit onderzoek gefinancierd is door de producent. Deze studie is echter niet opgenomen in de huidige literatuursamenvatting omdat dit een gepoolde analyse van meerdere studies betreft, zonder systematische selectiecriteria.
In de SYNERGY II dubbel geblindeerde multicenter RCT werden 1829 patiënten (80% vrouw) geïncludeerd met urge urine-incontinentie. Zij kregen solifenacine 5mg, mirabegron 50mg of een combinatie van beiden gedurende 1 jaar (Mueller, 2019). Combinatietherapie gaf minder incontinentie episodes vergeleken met mirabegron of solifenacine monotherapie (versus mirabegron: adjusted mean difference (AMD) −0.5, 95%CI −0.7 tot −0.2, $p < 0.001$; versus solifenacine: AMD −0.1, 95% CI −0.4 tot 0.1, $p = 0.002$) en mictiefrequentie (versus mirabegron: AMD −0.5, 95% CI −0.8 tot −0.2, $p < 0.001$; versus solifenacine: AMD −0.4, 95% CI −0.7 tot −0.1, $p = 0.004$). De publicatie van Mueller (2019) is echter niet meegenomen in de literatuursamenvatting van dit hoofdstuk, gezien dit een subgroep analyse betreft van de SYNERGY-trial door Gratzke (2018), en dus een analyse op observationele data is. Een andere publicatie van de SYNERGY-trial laat de PROs (patient reported outcomes) zien waarbij de

combinatietherapie verbetering geeft op HRQOL-parameters zoals de OAB-q symptom bother score (Robinson, 2018). Deze publicatie is echter niet meegenomen in de literatuursamenvatting, omdat de gerapporteerde uitkomsten niet overeenkwamen met de vooraf gedefinieerde PICO.

Op basis hiervan wordt geconcludeerd dat mirabegron mogelijk effectiever is dan placebo en even effectief als antimuscarinica voor de verbetering van OAB/urge incontinentie symptomen. Hierbij wordt genoteerd dat dit niet naar voren is gekomen uit de samenvatting van de literatuur van die richtlijn (omdat de PICO-vraag zich heeft gelimiteerd tot literatuur met uitsluitend vrouwen), maar dus wel wordt beschreven in de EAU richtlijn urine-incontinentie. Het uiteindelijke advies van de NVOG richtlijn urine-incontinentie bij vrouwen is dan ook om mirabegron aan te bieden als alternatief voor antimuscarinica bij gebrek aan effect of hinderlijke bijwerkingen.

De RCT van Kosilov (2015) staat beschreven in de module 'Medicamenteuze behandeling ouderen' van deze richtlijn. Hierin werd ten opzichte van placebo een gemiddelde afname van 2,1 episodes gezien voor mirabegron. Echter, kon gezien het ontbreken van spreidingsmaten deze uitkomst in de betreffende module niet met de Grade systematiek beoordeeld worden op kwaliteit. Op basis van de huidige PICO en literatuurselectie, met analyse en toepassing van de Grade systematiek, is er in de huidige richtlijn echter onvoldoende bewijs dat beta3 receptor sympaticomimetica effectief zijn in de behandeling van OAB/urge incontinentie, vergeleken met placebo, of met antimuscarinica. Combinatietherapie (antimuscarinica met een beta3 sympaticomimeticum) geeft op basis van alleen de literatuur ook geen sterke verbetering bij volwassenen met UI in de tweede- en derdelijnszorg.

Deze bevindingen conflicteren echter met de aanbevelingen van de recent herziene EAU richtlijn non-neurogenic female LUTS en de NVOG richtlijn urine-incontinentie bij vrouwen zoals hierboven beschreven. Om dit verschil in uitkomst te onderzoeken is nogmaals naar de manier van literatuurselectie en beoordeling gekeken en is daarnaast ook nogmaals gecheckt of er:

a. Geen relevante literatuur ontbreekt in de huidige selectie
b. Correcte analyses zijn verricht
c. Op de juiste manier duiding is gegeven aan de analyses (zijn de klinisch relevante verschillen bijvoorbeeld wel correct genoteerd)

Hieruit kwam naar voren dat aan alle bovenstaande voorwaarden is voldaan. Door de strenge literatuurselectie ontbreken observationele cohort studies in deze analyse, wat het verschil in uitkomst met de EAU mogelijk voor een deel zou kunnen verklaren. Dit is echter niet te achterhalen. Probleem is verder dat er ten eerste geen duidelijk antwoord gegeven kan worden op de vraag wat het minimal clinically important difference is waarop de literatuur succes of falen van therapie beoordeelt. Een klein verschil in klinische relevantie wordt nu beschouwd als niet relevant, terwijl de huidige analyse juist allemaal hele kleine verschillen ten faveure van beta3 sympaticomimetica toont. Ten tweede zijn de studieresultaten bijna allemaal gebaseerd op een 'mean', terwijl de uitkomsten van deze studies vaak niet normaal verdeeld zijn, waardoor het beter zou zijn om een 'median' te bepalen. Verder is er geen verschil in effectiviteit tussen gebruik van beta3 sympaticomimetica en antimuscarinica aangetoond. Daarnaast laten alle studies een groot placebo effect zien. Er zijn ook geen studies gedaan naar patiënttevredenheid.

Dit maakt het lastig om de huidige resultaten te interpreteren en om een concreet behandeladvies te geven. Na ampel beraad wordt geadviseerd dat gebruik van beta3 sympaticomimetica niet de behandeling van voorkeur is, maar wel overwogen kan worden als antimuscarinica falen of de bijwerkingen intolerabel zijn. Na 6 weken moet geëvalueerd worden of de behandeling aanslaat. Indien er geen verbetering optreedt, dient het beta3 sympaticomimeticum te worden gestaakt.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

De tolerantie (balans tussen effectiviteit en bijwerkingen) van antimuscarinica en mirabegron is onderzocht in o.a. de PREFER-studie (Staskin, 2018), waarbij patiënten (73% vrouw) met OAB mirabegron met tolterodine in een cross-over design als monotherapie gedurende 3 maanden gebruikten. De 'medication tolerability score' en klinische verbetering was meer uitgesproken in de mirabegron groep dan bij tolterodine groep, en meer uitgesproken bij vrouwen, patiënten ouder ≥65 jaar en patiënten zonder incontinentie bij start van de studie. Een alternatief voor de behandeling van aandrang urine-incontinentie in plaats van conservatieve therapie (middels bekkenfysiotherapie/blaastraining en medicatie) is PTNS, danwel botox of neuromodulatie. Deze behandelingen zijn echter veel tijdrovender (PTNS) en invasiever (PTNS, botox, neuromodulatie) voor de patiënt.

Kosten (middelenbeslag)

Ten aanzien van de kosten varieert de prijs van antimuscarinica per dag tussen de € 0.24 (solifenacine 10mg/oxybutinine 5mg) en de € 0.90 (fesoterodine 4mg/mirabegron 50mg) (Farmacotherapeutisch Kompas, solfenacine, oxybutinine, fesoterodine, mirabegron 2023). Op jaarbasis kan dit een behoorlijke impact geven op het eigen risico (zie onderstaande tabel). Voor deze geneesmiddelen hoeft naast het eigen risico niet te worden bijbetaald.

Aanvaardbaarheid, haalbaarheid en implementatie

Bij mirabegron is de tijd tot maximaal effect langer dan bij antimuscarinica, namelijk rond de 6 weken. Raadzaam is het recept voor maximaal 6 weken uit te schrijven met het oog op duurzaamheid en na 6 weken telefonisch de behandeling te evalueren t.a.v. effect en bijwerkingen. Patiënten kunnen geïnstrueerd worden bij hinderlijke bijwerkingen de medicatie te staken en eerder met de behandelaar contact op te nemen. Frequent gerapporteerde bijwerkingen van mirabegron zijn tachycardie (1-10%) en palpitaties (0,1-1%). Daarnaast adviseert de FDA (U.S. Food and Drug Administration 2015) periodieke bloeddrukcontrole bij patiënten die mirabegron gebruiken, maar additionele studies zijn vereist om een volledige beoordeling van cardiale effecten ten tijde van gebruik van mirabegron te kunnen verrichten.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De werkgroep concludeert na ampel beraad dat gebruik van beta3 sympaticomimetica niet de behandeling van voorkeur is bij aandrang urine-incontinentie, maar wel overwogen kan worden als antimuscarinica falen of de bijwerkingen intolerabel zijn. Na 6 weken moet geëvalueerd worden of de behandeling aanslaat. Indien er geen verbetering optreedt, dient het beta3 sympaticomimeticum te worden gestaakt

Daarnaast kan mirabegron de bloeddruk verhogen. De FDA adviseert dan ook om een bloeddrukcontrole bij patiënten die mirabegron gebruiken, maar additionele studies zijn vereist om een volledige beoordeling van cardiale effecten ten tijde van gebruik van mirabegron te kunnen verrichten.

Gebruik van beta3 sympathicomimetica kan overwogen worden als alternatief voor antimuscarinica, indien antimuscarinica onvoldoende effect genereren of de bijwerkingen intolerabel zijn. Staak de behandeling indien er na 6 weken geen verbetering van klachten optreedt.

Het toepassen van combinatietherapie met een beta3 sympathicomimeticum, in plaats van ophogen van antimuscarinica kan overwogen worden. Let hierbij op tolereerbaarheid bijwerkingen en staak de behandeling indien er na 6 weken geen verbetering van klachten optreedt.

Overweeg de bloeddruk te evalueren bij gelijktijdig gebruik van beta3 sympathicomimetica en antihypertensiva.

Literatuur

Abrams P, Kelleher C, Staskin D, Rechberger T, Kay R, Martina R, Newgreen D, Paireddy A, van Maanen R, Ridder A. 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 Mar;67(3):577-88. doi: 10.1016/j.eururo.2014.02.012. Epub 2014 Feb 19. PMID: 24612659.

Herschorn S, Chapple CR, Abrams P, Arlandis S, Mitcheson D, Lee KS, Ridder A, Stoelzel M, Paireddy A, van Maanen R, Robinson D. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU Int. 2017 Oct;120(4):562-575. doi: 10.1111/bju.13882. Epub 2017 Jun 8. PMID: 28418102.

Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I, Radziszewski P, Rechberger T, Boerrigter P, Drogendijk T, Wooning M, Chapple C. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol. 2013 Feb;63(2):283-95. doi: 10.1016/j.eururo.2012.10.016. Epub 2012 Nov 6. PMID: 23182126.

Kuo HC, Lee KS, Na Y, Sood R, Nakaji S, Kubota Y, Kuroishi K. Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a β3-adrenoceptor agonist, in patients with overactive bladder in Asia. Neurourol Urodyn. 2015 Sep;34(7):685-92. doi: 10.1002/nau.22645. Epub 2014 Aug 17. PMID: 25130281.

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Mostafaei H, Salehi-Pourmehr H, Jilch S, Carlin GL, Mori K, Quhal F, Pradere B, Grossmann NC, Laukhtina E, Schuettfort VM, Aydh A, Sari Motlagh R, König F, Roehrborn CG, Katayama S, Rajwa P, Hajebrahimi S, Shariat SF. Choosing the Most Efficacious and Safe Oral Treatment for Idiopathic Overactive Bladder: A Systematic Review and Network Meta-analysis. Eur Urol Focus. 2022 Jul;8(4):1072-1089. doi: 10.1016/j.euf.2021.08.011. Epub 2021 Sep 22. PMID: 34563481.

Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol. 2013 Apr;189(4):1388-95. doi: 10.1016/j.juro.2012.10.017. Epub 2012 Oct 16. PMID: 23079373.

Shin DG, Kim HW, Yoon SJ, Song SH, Kim YH, Lee YG, Joo KJ, Bae JH, Kang TW, Jeong SJ, Woo SH, Yoo ES, Son H, Koo KC, Kim SW. Mirabegron as a treatment for overactive bladder symptoms in men (MIRACLE study): Efficacy and safety results from a multicenter, randomized, double-blind, placebo-controlled, parallel comparison phase IV study. Neurourol Urodyn. 2019 Jan;38(1):295-304. doi: 10.1002/nau.23852. Epub 2018 Oct 12. PMID: 30311691.

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Yamaguchi O, Marui E, Igawa Y, Takeda M, Nishizawa O, Ikeda Y, Ohkawa S. Efficacy and Safety of the Selective β3 -Adrenoceptor Agonist Mirabegron in Japanese Patients with Overactive Bladder: A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study. Low Urin Tract Symptoms. 2015 May;7(2):84-92. doi: 10.1111/luts.12053. Epub 2014 Mar 11. PMID: 26663687.

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1 tot 3 jaar	Zie module	Zie module	Geen	Vragen toevoegen in kennisquiz NVOG	NVU/NVOG	geen

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling,

onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Table of excluded studies

Reference	Reason for exclusion
Abrams P, Kelleher C, Staskin D, Kay R, Martan A, Mincik I, Newgreen D, Ridder A, Paireddy A, van Maanen R. 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 May;35(5):827-838. doi: 10.1007/s00345-016-1908-1. Epub 2016 Aug 11. PMID: 27514371.	Wrong publication type (exploratory responder analyses)
Alcántara Montero A. Long-term safety and efficacy of mirabegron and solifenacin in combination compared with monotherapy in patients with overactive bladder: SYNERGY II study. Actas Urol Esp (Engl Ed). 2019 Jan-Feb;43(1):51-52. English, Spanish. doi: 10.1016/j.acuro.2018.06.002. Epub 2018 Jul 17. PMID: 30025617.	Foreign language
Alcántara-Montero A. Combined treatment of solifenacin and mirabegron, an alternative in patients with overactive bladder (BESIDE study). Actas Urol Esp. 2016 Nov;40(9):593-594. English, Spanish. doi: 10.1016/j.acuro.2016.03.005. Epub 2016 Apr 25. PMID: 27126125.	Foreign language
Batista JE, Kölbl H, Herschorn S, Rechberger T, Cambronero J, Halaska M, Coppell A, Kaper M, Huang M, Siddiqui E; BEYOND study group. The efficacy and safety of mirabegron compared with solifenacin in overactive bladder patients dissatisfied with previous antimuscarinic treatment due to lack of efficacy: results of a noninferiority, randomized, phase IIIb trial. Ther Adv Urol. 2015 Aug;7(4):167-79. doi: 10.1177/1756287215589250. PMID: 26445596; PMCID: PMC4580095.	Less recent and complete compared to Mostafaei (2022)
Chapple CR, Amarenco G, López Aramburu MA, Everaert K, Liehne J, Lucas M, Vik V, Ridder A, Snijder R, Yamaguchi O; BLOSSOM Investigator Group. A proof-of-concept study: mirabegron, a new therapy for overactive bladder. Neurourol Urodyn. 2013 Nov;32(8):1116-22. doi: 10.1002/nau.22373. Epub 2013 Feb 19. PMID: 23424164.	Published prior to February 2021 (search period Mostafaei, 2022)
Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC. Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. Neurourol Urodyn. 2014 Jan;33(1):17-30. doi: 10.1002/nau.22505. Epub 2013 Oct 11. PMID: 24127366.	Wrong publication type (review)
Chapple CR, Dvorak V, Radziszewski P, Van Kerrebroeck P, Wyndaele JJ, Bosman B, Boerrigter P, Drogendijk T, Ridder A, Van Der Putten-Slob I, Yamaguchi O; Dragon Investigator Group. A phase II dose-ranging study of mirabegron in patients with overactive bladder. Int Urogynecol J. 2013 Sep;24(9):1447-58. doi: 10.1007/s00192-013-2042-x. Epub 2013 Mar 8. PMID: 23471546; PMCID: PMC3745617.	Published prior to February 2021 (search period Mostafaei, 2022)
Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, Dorrepaal C, Martin N. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. Eur Urol. 2013 Feb;63(2):296-305. doi: 10.1016/j.eururo.2012.10.048. Epub 2012 Nov 6. PMID: 23195283.	Published prior to February 2021 (search period Mostafaei, 2022)
Frankel J, Staskin D, Varano S, Kennelly M, Newman DK, Rosenberg MT, Jankowich RA, Shortino D, Mudd PN Jr, Girman CJ. Interpretation of the Meaningfulness of Symptom Reduction with Vibegron in Patients with Overactive Bladder: Analyses from EMPOWUR. Adv Ther. 2022 Feb;39(2):959-970. doi: 10.1007/s12325-021-01972-8. Epub 2021 Dec 18. PMID: 34921665; PMCID: PMC8866263.	Wrong outcome (patient perception of improvement)
Frankel J, Varano S, Staskin D, Shortino D, Jankowich R, Mudd PN Jr. Vibegron improves quality-of-life measures in patients with overactive bladder: Patient-reported outcomes from the EMPOWUR study. Int J Clin Pract. 2021 May;75(5):e13937. doi: 10.1111/ijcp.13937. Epub 2021 Jan 22. PMID: 33332699; PMCID: PMC8244055.	Wrong outcome (patient-reported QoL outcomes)

Gratzke C, van Maanen R, Chapple C, Abrams P, Herschorn S, Robinson D, Ridder A, Stoelzel M, Paireddy A, Yoon SJ, Al-Shukri S, Rechberger T, Mueller ER. Long-term Safety and Efficacy of Mirabegron and Solifenacin in Combination Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II). Eur Urol. 2018 Oct;74(4):501-509. doi: 10.1016/j.eururo.2018.05.005. Epub 2018 Jun 1. PMID: 29866467.	Published prior to February 2021 (search period Mostafaei, 2022)
Griebling TL, Campbell NL, Mangel J, Staskin D, Herschorn S, Elsouda D, Schermer CR. Effect of mirabegron on cognitive function in elderly patients with overactive bladder: MoCA results from a phase 4 randomized, placebo-controlled study (PILLAR). BMC Geriatr. 2020 Mar 18;20(1):109. doi: 10.1186/s12877-020-1474-7. PMID: 32183741; PMCID: PMC7079371.	Wrong outcome (cognitive function)
Herschorn S, Barkin J, Castro-Diaz D, Frankel JM, Espuna-Pons M, Gousse AE, Stölzel M, Martin N, Gunther A, Van Kerrebroeck P. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology. 2013 Aug;82(2):313-20. doi: 10.1016/j.urology.2013.02.077. Epub 2013 Jun 13. Erratum in: Urology. 2013 Dec;82(6):1457. PMID: 23769122.	Published prior to February 2021 (search period Mostafaei, 2022)
Herschorn S, Staskin D, Schermer CR, Kristy RM, Wagg A. Safety and Tolerability Results from the PILLAR Study: A Phase IV, Double-Blind, Randomized, Placebo-Controlled Study of Mirabegron in Patients ≥ 65 years with Overactive Bladder-Wet. Drugs Aging. 2020 Sep;37(9):665-676. doi: 10.1007/s40266-020-00783-w. PMID: 32725584; PMCID: PMC7473960.	Wrong population (elderly)
Herschorn S, Staskin D, Tu LM, Fialkov J, Walsh T, Gooch K, Schermer CR. Patient-reported outcomes in patients with overactive bladder treated with mirabegron and tolterodine in a prospective, double-blind, randomized, two-period crossover, multicenter study (PREFER). Health Qual Life Outcomes. 2018 Apr 19;16(1):69. doi: 10.1186/s12955-018-0892-0. PMID: 29673355; PMCID: PMC5909214.	Wrong outcome (patient-reported outcomes)
Hsiao SM, Chang TC, Chen CH, Wu WY, Lin HH. Comparisons of the Clinical Outcomes and Urodynamic Effects of Mirabegron versus Tolterodine Treatment for Female Overactive Bladder Syndrome: A Subgroup Analysis of a Controlled, Randomised, Prospective Study. Low Urin Tract Symptoms. 2018 Sep;10(3):215-220. doi: 10.1111/luts.12167. Epub 2017 Apr 23. PMID: 28436145.	Published prior to February 2021 (search period Mostafaei, 2022)
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Khullar V, Amarenco G, Angulo JC, Blauwet MB, Nazir J, Odeyemi IA, Hakimi Z. Patient-reported outcomes with the β3 -adrenoceptor agonist mirabegron in a phase III trial in patients with overactive bladder. Neurourol Urodyn. 2016 Nov;35(8):987-994. doi: 10.1002/nau.22844. Epub 2015 Aug 19. PMID: 26288118.	Wrong outcome (patient-reported outcomes)
Khullar V, Cambronero J, Angulo JC, Wooning M, Blauwet MB, Dorrepaal C, Martin NE. Efficacy of mirabegron in patients with and without prior antimuscarinic therapy for overactive bladder: a post hoc analysis of a randomized European-Australian Phase 3 trial. BMC Urol. 2013 Sep 18;13:45. doi: 10.1186/1471-2490-13-45. PMID: 24047126; PMCID: PMC3849064.	Wrong publication type (post-hoc analysis irrelevant subgroups)
Kinjo M, Sekiguchi Y, Yoshimura Y, Nutahara K. Long-term Persistence with Mirabegron versus Solifenacin in Women with Overactive Bladder: Prospective, Randomized Trial. Low Urin Tract Symptoms. 2018 May;10(2):148-152. doi: 10.1111/luts.12151. Epub 2016 Dec 2. PMID: 27911988.	Wrong population (elderly)
Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. A randomized, controlled trial of effectiveness and safety of management of OAB	Wrong population (elderly)

symptoms in elderly men and women with standard-dosed combination of solifenacin and mirabegron. Arch Gerontol Geriatr. 2015 Sep-Oct;61(2):212-6. doi: 10.1016/j.archger.2015.06.006. Epub 2015 Jun 25. PMID: 26169181.	
Andersson KE, Martin N, Nitti V. Selective β_3-adrenoceptor agonists for the treatment of overactive bladder. J Urol. 2013 Oct;190(4):1173-80. doi: 10.1016/j.juro.2013.02.104. Epub 2013 Feb 28. PMID: 23458471.	Wrong publication type (overview of available literature)
Mirabegron Extended-Release Tablets (Myrbetriq): Treatment of Overactive Bladder (OAB) with Symptoms of Urgency, Urgency Incontinence and Urinary Frequency [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Jul. PMID: 26962607.	Less recent and complete compared to Mostafaei (2022)
Athanasiou S, Pitsouni E, Grigoriadis T, Zacharakis D, Salvatore S, Serati M. Mirabegron in female patients with overactive bladder syndrome: What's new? A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020 Aug;251:73-82. doi: 10.1016/j.ejogrb.2020.05.018. Epub 2020 May 15. PMID: 32480182.	Less recent and complete compared to Mostafaei (2022)
Bhide AA, Digesu GA, Fernando R, Khullar V. Use of mirabegron in treating overactive bladder. Int Urogynecol J. 2012 Oct;23(10):1345-8. doi: 10.1007/s00192-012-1724-0. Epub 2012 Mar 13. PMID: 22411211.	Wrong publication type (review)
Bragg R, Hebel D, Vouri SM, Pitlick JM. Mirabegron: a Beta-3 agonist for overactive bladder. Consult Pharm. 2014 Dec;29(12):823-37. doi: 10.4140/TCP.n.2014.823. PMID: 25521658; PMCID: PMC4605389.	Wrong publication type (review)
Bridgeman MB, Friia NJ, Taft C, Shah M. Mirabegron: β3-adrenergic receptor agonist for the treatment of overactive bladder. Ann Pharmacother. 2013 Jul-Aug;47(7-8):1029-38. doi: 10.1345/aph.1S054. Epub 2013 Jun 11. PMID: 23757386.	Wrong publication type (review)
Caremel R, Loutochin O, Corcos J. What do we know and not know about mirabegron, a novel β3 agonist, in the treatment of overactive bladder? Int Urogynecol J. 2014 Feb;25(2):165-70. doi: 10.1007/s00192-013-2161-4. Epub 2013 Aug 7. PMID: 23922008.	Wrong publication type (review)
Chen HL, Chen TC, Chang HM, Juan YS, Huang WH, Pan HF, Chang YC, Wu CM, Wang YL, Lee HY. Mirabegron is alternative to antimuscarinic agents for overactive bladder without higher risk in hypertension: a systematic review and meta-analysis. World J Urol. 2018 Aug;36(8):1285-1297. doi: 10.1007/s00345-018-2268-9. Epub 2018 Mar 19. PMID: 29556972.	Less recent and complete compared to Mostafaei (2022)
Cui Y, Zong H, Yang C, Yan H, Zhang Y. The efficacy and safety of mirabegron in treating OAB: a systematic review and meta-analysis of phase III trials. Int Urol Nephrol. 2014 Jan;46(1):275-84. doi: 10.1007/s11255-013-0509-9. Epub 2013 Jul 30. PMID: 23896942.	Less recent and complete compared to Mostafaei (2022)
De Nunzio C, Brucker B, Bschleipfer T, Cornu JN, Drake MJ, Fusco F, Gravas S, Oelke M, Peyronnet B, Tutolo M, van Koeveringe G, Madersbacher S. Beyond Antimuscarinics: A Review of Pharmacological and Interventional Options for Overactive Bladder Management in Men. Eur Urol. 2021 Apr;79(4):492-504. doi: 10.1016/j.eururo.2020.12.032. Epub 2021 Jan 2. PMID: 33402296.	Less recent and complete compared to Mostafaei (2022)
De Nunzio C, Presicce F, Pirozzi L, Castellan P, Schips L, Cindolo L, Lombardo R, Tubaro A. The Current Indications and the Benefits of Combining a β3-Agonist with an Anticholinergic for the Treatment of OAB. Curr Drug Targets. 2015;16(11):1198-206. doi: 10.2174/1389450116666150806124345. PMID: 26245475.	Wrong publication type (review)
Duong V, Iwamoto A, Pennycuff J, Kudish B, Iglesia C. A systematic review of neurocognitive dysfunction with overactive bladder medications. Int Urogynecol J. 2021 Oct;32(10):2693-2702. doi: 10.1007/s00192-021-04909-5. Epub 2021 Jul 2. PMID: 34213600.	Wrong outcome (cognitive dysfunction)
Fest J, Pfalzgraf D, Weiss C, Hetjens S. Evaluating the efficacy and tolerability of mirabegron, a β3-adrenoceptor agonist, for the treatment of overactive bladder: Systematic review and network	Less recent and complete compared to Mostafaei (2022)

meta-analysis. Journal of Clinical Urology. 2017;10(6):557-567. doi:10.1177/2051415817706045	
Gratzke C, Chapple C, Mueller ER, Robinson D, Rolland C, Staskin D, Stoelzel M, Maanen RV, Siddiqui E. Efficacy and Safety of Combination Pharmacotherapy for Patients with Overactive Bladder: A Rapid Evidence Assessment. Eur Urol. 2019 Dec;76(6):767-779. doi: 10.1016/j.eururo.2019.07.010. Epub 2019 Aug 13. PMID: 31416636.	Wrong publication type (rapid evidence assessment)
Kuo, H. C., Lin, H. H., Yu, H. J., Cheng, C. L., Hung, M. J. and Lin, A. T. L. Results of a randomized, double-blind, placebo-controlled study of mirabegron in a Taiwanese population with overactive bladder and comparison with other clinical trials. Urol. Sc. 2015, 26(1):41-48. doi: 10.1016/j.urols.2014.12.010	Corrigendum of this study is already included (Kuo, 2015)
Hou J, Xu F, Du H, Li N. Adverse events associated with mirabegron 50mg versus placebo: A systematic review and meta-analysis. Prog Urol. 2021 Sep;31(11):627-633. doi: 10.1016/j.purol.2021.05.005. Epub 2021 Jul 24. PMID: 34312078.	Less recent and complete compared to Mostafaei (2022)
Hsu FC, Weeks CE, Selph SS, Blazina I, Holmes RS, McDonagh MS. Updating the evidence on drugs to treat overactive bladder: a systematic review. Int Urogynecol J. 2019 Oct;30(10):1603-1617. doi: 10.1007/s00192-019-04022-8. Epub 2019 Jul 25. PMID: 31346670; PMCID: PMC6795617.	Less recent and complete compared to Mostafaei (2022)
Iino S, Kaneko M, Narukawa M. Factors influencing efficacy endpoints in clinical trials for new oral medicinal treatments for overactive bladder: a systematic literature review and meta-analysis. Int Urol Nephrol. 2018 Jun;50(6):1021-1030. doi: 10.1007/s11255-018-1869-y. Epub 2018 Apr 12. PMID: 29651695.	Wrong outcome (factors influencing endpoints)
Jayarajan J, Radomski SB. Pharmacotherapy of overactive bladder in adults: a review of efficacy, tolerability, and quality of life. Res Rep Urol. 2013 Dec 6;6:1-16. doi: 10.2147/RRU.S40034. PMID: 24400248; PMCID: PMC3862648.	Wrong publication type (review)
Jian Z, Yuan C, Li H, Zhang W, Wang K. Vibegron 50 mg is the optimal algorithm in the pharmacologic management of overactive bladder: outcomes from a systematic review and meta-analysis. Int Urol Nephrol. 2020 Dec;52(12):2215-2221. doi: 10.1007/s11255-020-02536-5. Epub 2020 Jun 9. PMID: 32519241.	Wrong intervention (vibegron 50 mg)
Kelleher C, Hakimi Z, Zur R, Siddiqui E, Maman K, Aballéa S, Nazir J, Chapple C. Efficacy and Tolerability of Mirabegron Compared with Antimuscarinic Monotherapy or Combination Therapies for Overactive Bladder: A Systematic Review and Network Meta-analysis. Eur Urol. 2018 Sep;74(3):324-333. doi: 10.1016/j.eururo.2018.03.020. Epub 2018 Apr 23. PMID: 29699858.	Included studies not reported
Kennelly MJ, Rhodes T, Girman CJ, Thomas E, Shortino D, Mudd PN Jr. Efficacy of Vibegron and Mirabegron for Overactive Bladder: A Systematic Literature Review and Indirect Treatment Comparison. Adv Ther. 2021 Nov;38(11):5452-5464. doi: 10.1007/s12325-021-01902-8. Epub 2021 Sep 18. PMID: 34537953; PMCID: PMC8520873.	Less recent and complete compared to Mostafaei (2022)
Kistler KD, Xu Y, Zou KH, Ntanios F, Chapman DS, Luo X. Systematic literature review of clinical trials evaluating pharmacotherapy for overactive bladder in elderly patients: An assessment of trial quality. Neurourol Urodyn. 2018 Jan;37(1):54-66. doi: 10.1002/nau.23309. Epub 2017 Aug 1. PMID: 28763112.	Wrong population (elderly)
Lozano-Ortega G, Walker DR, Johnston K, Mickle A, Harrigan S, Rogula B, Kristy RM, Hairston JC, Schermer CR. Comparative Safety and Efficacy of Treatments for Overactive Bladder Among Older Adults: A Network Meta-analysis. Drugs Aging. 2020 Nov;37(11):801-816. doi: 10.1007/s40266-020-00792-9. PMID: 32960422; PMCID: PMC7595992.	Wrong population (elderly)
Maman K, Aballea S, Nazir J, Desroziers K, Neine ME, Siddiqui E, Odeyemi I, Hakimi Z. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. Eur Urol. 2014	Less recent and complete compared to Mostafaei (2022)

Apr;65(4):755-65. doi: 10.1016/j.eururo.2013.11.010. Epub 2013 Nov 18. PMID: 24275310.	
Obloza A, Kirby J, Yates D, Toozs-Hobson P. Indirect treatment comparison (ITC) of medical therapies for an overactive bladder. Neurourol Urodyn. 2017 Sep;36(7):1824-1831. doi: 10.1002/nau.23189. Epub 2017 Feb 21. PMID: 28220521.	Wrong publication type (comparative study)
Olivera CK, Meriwether K, El-Nashar S, Grimes CL, Chen CC, Orejuela F, Antosh D, Gleason J, Kim-Fine S, Wheeler T, McFadden B, Balk EM, Murphy M; Systematic Review Group for the Society of Gynecological Surgeons. Nonantimuscarinic treatment for overactive bladder: a systematic review. Am J Obstet Gynecol. 2016 Jul;215(1):34-57. doi: 10.1016/j.ajog.2016.01.156. Epub 2016 Feb 4. PMID: 26851599.	Included only 3 relevant RCTs (mirabegron)
Mitcheson HD, Samanta S, Muldowney K, Pinto CA, Rocha BA, Green S, Bennett N, Mudd PN Jr, Frenkl TL. Vibegron (RVT-901/MK-4618/KRP-114V) Administered Once Daily as Monotherapy or Concomitantly with Tolterodine in Patients with an Overactive Bladder: A Multicenter, Phase IIb, Randomized, Double-blind, Controlled Trial. Eur Urol. 2019 Feb;75(2):274-282. doi: 10.1016/j.eururo.2018.10.006. Epub 2018 Oct 25. PMID: 30661513.	Wrong intervention (vibegron 3, 15, 50 and 100 mg)
Mueller ER, van Maanen R, Chapple C, Abrams P, Herschorn S, Robinson D, Stoelzel M, Yoon SJ, Al-Shukri S, Rechberger T, Gratzke C. Long-term treatment of older patients with overactive bladder using a combination of mirabegron and solifenacin: a prespecified analysis from the randomized, phase III SYNERGY II study. Neurourol Urodyn. 2019 Feb;38(2):779-792. doi: 10.1002/nau.23919. Epub 2019 Jan 15. PMID: 30644570; PMCID: PMC6850571.	Wrong population (elderly)
Ohlstein EH, von Keitz A, Michel MC. A multicenter, double-blind, randomized, placebo-controlled trial of the β3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol. 2012 Nov;62(5):834-40. doi: 10.1016/j.eururo.2012.05.053. Epub 2012 Jun 5. PMID: 22695239.	Wrong intervention (solabegron)
Otsuka A, Kageyama S, Suzuki T, Matsumoto R, Nagae H, Kitagawa M, Furuse H, Ozono S. Comparison of mirabegron and imidafenacin for efficacy and safety in Japanese female patients with overactive bladder: A randomized controlled trial (COMFORT study). Int J Urol. 2016 Dec;23(12):1016-1023. doi: 10.1111/iju.13231. Epub 2016 Sep 29. PMID: 27686226.	Published prior to February 2021 (search period Mostafaei, 2022)
Özkidik M, Coşkun A, Asutay MK, Bahçeci T, Hamidi N. Efficacy and tolerability of mirabegron in female patients with overactive bladder symptoms after surgical treatment for stress urinary incontinence. Int Braz J Urol. 2019 Jul-Aug;45(4):782-789. doi: 10.1590/S1677-5538.IBJU.2018.0518. PMID: 31136113; PMCID: PMC6837616.	Published prior to February 2021 (search period Mostafaei, 2022)
Robinson D, Kelleher C, Staskin D, Mueller ER, Falconer C, Wang J, Ridder A, Stoelzel M, Paireddy A, van Maanen R, Hakimi Z, Herschorn S. Patient-reported outcomes from SYNERGY, a randomized, double-blind, multicenter study evaluating combinations of mirabegron and solifenacin compared with monotherapy and placebo in OAB patients. Neurourol Urodyn. 2018 Jan;37(1):394-406. doi: 10.1002/nau.23315. Epub 2017 Jul 13. PMID: 28704584.	Wrong outcome (patient-reported outcomes)
Bragg R, Hebel D, Vouri SM, Pitlick JM. Mirabegron: a Beta-3 agonist for overactive bladder. Consult Pharm. 2014 Dec;29(12):823-37. doi: 10.4140/TCP.n.2014.823. PMID: 25521658; PMCID: PMC4605389.	Wrong publication type (review)
Rossanese M, Novara G, Challacombe B, Iannetti A, Dasgupta P, Ficarra V. 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 Jan;115(1):32-40. doi: 10.1111/bju.12730. Epub 2014 Jul 27. PMID: 24602031.	Wrong publication type (review)
Sebastianelli A, Russo GI, Kaplan SA, McVary KT, Moncada I, Gravas S, Chapple C, Morgia G, Serni S, Gacci M. Systematic review and meta-analysis on the efficacy and tolerability of mirabegron for the treatment of storage lower urinary tract symptoms/overactive	Less recent and complete compared to Mostafaei (2022)

bladder: Comparison with placebo and tolterodine. Int J Urol. 2018 Mar;25(3):196-205. doi: 10.1111/iju.13498. Epub 2017 Dec 3. PMID: 29205506.	
Shi H, Chen H, Zhang Y, Cui Y. The efficacy and safety of Vibegron in treating overactive bladder: A systematic review and pooled analysis of randomized controlled trials. Neurourol Urodyn. 2020 Jun;39(5):1255-1263. doi: 10.1002/nau.24387. Epub 2020 May 18. PMID: 32421908.	Less recent and complete compared to Mostafaei (2022)
Su S, Liang L, Lin J, Liu L, Chen Z, Gao Y. Systematic review and meta-analysis of the efficacy and safety of vibegron vs antimuscarinic monotherapy for overactive bladder. Medicine (Baltimore). 2021 Feb 5;100(5):e23171. doi: 10.1097/MD.0000000000023171. PMID: 33592817; PMCID: PMC7870164.	Wrong intervention (wrong doses of vibegron)
Wang J, Zhou Z, Cui Y, Li Y, Yuan H, Gao Z, Zhu Z, Wu J. Meta-analysis of the efficacy and safety of mirabegron and solifenacin monotherapy for overactive bladder. Neurourol Urodyn. 2019 Jan;38(1):22-30. doi: 10.1002/nau.23863. Epub 2018 Oct 23. PMID: 30350884.	Less recent and complete compared to Mostafaei (2022)
Wu T, Duan X, Cao CX, Peng CD, Bu SY, Wang KJ. The role of mirabegron in overactive bladder: a systematic review and meta-analysis. Urol Int. 2014;93(3):326-37. doi: 10.1159/000361079. Epub 2014 Aug 7. PMID: 25115445.	Less recent and complete compared to Mostafaei (2022)
Yi W, Yang Y, Yang J. Monotherapy with mirabegron had a better tolerance than the anticholinergic agents on overactive bladder: A systematic review and meta-analysis. Medicine (Baltimore). 2021 Oct 15;100(41):e27469. doi: 10.1097/MD.0000000000027469. PMID: 34731124; PMCID: PMC8519252.	Less recent and complete compared to Mostafaei (2022)
Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd PN Jr. International Phase III, Randomized, Double-Blind, Placebo and Active Controlled Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder: EMPOWUR. J Urol. 2020 Aug;204(2):316-324. doi: 10.1097/JU.0000000000000807. Epub 2020 Feb 18. PMID: 32068484.	Extension study included (Staskin, 2021)
Staskin D, Herschorn S, Fialkov J, Tu LM, Walsh T, Schermer CR. A prospective, double-blind, randomized, two-period crossover, multicenter study to evaluate tolerability and patient preference between mirabegron and tolterodine in patients with overactive bladder (PREFER study). Int Urogynecol J. 2018 Feb;29(2):273-283. doi: 10.1007/s00192-017-3377-5. Epub 2017 Jun 15. PMID: 28620791; PMCID: PMC5780540.	Published prior to February 2021 (search period Mostafaei, 2022)
Torimoto K, Matsushita C, Yamada A, Goto D, Matsumoto Y, Hosokawa Y, Miyake M, Aoki K, Hirayama A, Tanaka N, Fujimoto K. Clinical efficacy and safety of mirabegron and imidafenacin in women with overactive bladder: A randomized crossover study (the MICRO study). Neurourol Urodyn. 2017 Apr;36(4):1097-1103. doi: 10.1002/nau.23050. Epub 2016 Jun 6. PMID: 27265880.	Published prior to February 2021 (search period Mostafaei, 2022)
Varano S, Staskin D, Frankel J, Shortino D, Jankowich R, Mudd PN Jr. Efficacy and Safety of Once-Daily Vibegron for Treatment of Overactive Bladder in Patients Aged ≥65 and ≥75 Years: Subpopulation Analysis from the EMPOWUR Randomized, International, Phase III Study. Drugs Aging. 2021 Feb;38(2):137-146. doi: 10.1007/s40266-020-00829-z. Epub 2021 Jan 20. PMID: 33469832; PMCID: PMC7882560.	Wrong population (elderly)
Vasudeva P, Kumar A, Yadav S, Kumar N, Chaudhry N, Prasad V, Nagendra Rao S, Yadav P, Patel S. Neurological safety and efficacy of darifenacin and mirabegron for the treatment of overactive bladder in patients with history of cerebrovascular accident: A prospective study. Neurourol Urodyn. 2021 Nov;40(8):2041-2047. doi: 10.1002/nau.24793. Epub 2021 Sep 13. PMID: 34516666.	Wrong intervention (mirabegron 25 mg)
Vecchioli Scaldazza C, Morosetti C. Comparison of Therapeutic Efficacy and Urodynamic Findings of Solifenacin Succinate versus Mirabegron in Women with Overactive Bladder Syndrome: Results of	Published prior to February 2021 (search period Mostafaei, 2022)

a Randomized Controlled Study. Urol Int. 2016;97(3):325-329. doi: 10.1159/000445808. Epub 2016 Apr 20. PMID: 27092789.	
Wagg A, Staskin D, Engel E, Herschorn S, Kristy RM, Schermer CR. Efficacy, safety, and tolerability of mirabegron in patients aged ≥65yr with overactive bladder wet: a phase IV, double-blind, randomised, placebo-controlled study (PILLAR). Eur Urol. 2020 Feb;77(2):211-220. doi: 10.1016/j.eururo.2019.10.002. Epub 2019 Nov 13. PMID: 31733990.	Wrong population (elderly)
Weber MA, Chapple CR, Gratzke C, Herschorn S, Robinson D, Frankel JM, Ridder AM, Stoelzel M, Paireddy A, van Maanen R, White WB. A strategy utilizing ambulatory monitoring and home and clinic blood pressure measurements to optimize the safety evaluation of noncardiovascular drugs with potential for hemodynamic effects: a report from the SYNERGY trial. Blood Press Monit. 2018 Jun;23(3):153-163. doi: 10.1097/MBP.0000000000000320. PMID: 29578880; PMCID: PMC5959217.	Wrong outcome (evaluating blood pressure measurements)
Weber MA, Haag-Molkenteller C, King J, Walker A, Mudd PN Jr, White WB. Effects of vibegron on ambulatory blood pressure in patients with overactive bladder: results from a double-blind, placebo-controlled trial. Blood Press Monit. 2022 Apr 1;27(2):128-134. doi: 10.1097/MBP.0000000000000572. PMID: 34699409; PMCID: PMC8893125.	Wrong population (elderly)
White, W.B., Chapple, C., Gratzke, C., Herschorn, S., Robinson, D., Frankel, J., Ridder, A., Stoelzel, M., Paireddy, A., van Maanen, R. and Weber, M.A. (2018), Cardiovascular Safety of the β3-Adrenoceptor Agonist Mirabegron and the Antimuscarinic Agent Solifenacin in the SYNERGY Trial. The Journal of Clinical Pharmacology, 58: 1084-1091. https://doi.org/10.1002/jcph.1107	Published prior to February 2021 (search period Mostafaei, 2022)
Yamaguchi O, Kakizaki H, Homma Y, Igawa Y, Takeda M, Nishizawa O, Gotoh M, Yoshida M, Yokoyama O, Seki N, Okitsu A, Hamada T, Kobayashi A, Kuroishi K. Long-term safety and efficacy of antimuscarinic add-on therapy in patients with overactive bladder who had a suboptimal response to mirabegron monotherapy: A multicenter, randomized study in Japan (MILAI II study). Int J Urol. 2019 Mar;26(3):342-352. doi: 10.1111/iju.13868. Epub 2018 Dec 13. PMID: 30548692; PMCID: PMC7379522.	Published prior to February 2021 (search period Mostafaei, 2022)
Yoshida M, Takeda M, Gotoh M, Nagai S, Kurose T. Vibegron, a Novel Potent and Selective β3-Adrenoreceptor Agonist, for the Treatment of Patients with Overactive Bladder: A Randomized, Double-blind, Placebo-controlled Phase 3 Study. Eur Urol. 2018 May;73(5):783-790. doi: 10.1016/j.eururo.2017.12.022. Epub 2018 Feb 1. PMID: 29366513.	Wrong intervention (vibegron 50, 100 mg)
Yoshida M, Takeda M, Gotoh M, Yokoyama O, Kakizaki H, Takahashi S, Masumori N, Nagai S, Hashimoto K, Minemura K. Efficacy of novel β3 -adrenoreceptor agonist vibegron on nocturia in patients with overactive bladder: A post-hoc analysis of a randomized, double-blind, placebo-controlled phase 3 study. Int J Urol. 2019 Mar;26(3):369-375. doi: 10.1111/iju.13877. Epub 2018 Dec 17. PMID: 30557916; PMCID: PMC6912249.	Wrong intervention (vibegron 50, 100 mg)
Yoshida M, Takeda M, Gotoh M, Yokoyama O, Kakizaki H, Takahashi S, Masumori N, Nagai S, Minemura K. Efficacy of vibegron, a novel β3-adrenoreceptor agonist, on severe urgency urinary incontinence related to overactive bladder: post hoc analysis of a randomized, placebo-controlled, double-blind, comparative phase 3 study. BJU Int. 2020 May;125(5):709-717. doi: 10.1111/bju.15020. Epub 2020 Feb 23. PMID: 31991511; PMCID: PMC7318146.	Wrong intervention (vibegron 50, 100 mg)
Yoshida M, Takeda M, Gotoh M, Yokoyama O, Kakizaki H, Takahashi S, Masumori N, Nagai S, Minemura K. Cardiovascular safety of vibegron, a new β3-adrenoceptor agonist, in older patients with overactive bladder: Post-hoc analysis of a randomized, placebo-controlled, double-blind comparative phase 3 study. Neurourol Urodyn. 2021 Aug;40(6):1651-1660. doi: 10.1002/nau.24732. Epub 2021 Jun 17. PMID: 34139038; PMCID: PMC8362047.	Wrong intervention (vibegron 50, 100 mg

Zubiaur Líbano C, Poza-Barrasús JL, Valero Fernández EM. Quality of life and treatment persistence evaluation in Spanish patients treated with mirabegron. Results of the BELIEVE study. Actas Urol Esp (Engl Ed). 2020 May;44(4):224-232. English, Spanish. doi: 10.1016/j.acuro.2020.01.003. Epub 2020 Mar 4. PMID: 32145942.	Wrong outcome (QoL and treatment persistence)

Module Medicamenteuze behandeling ouderen

Uitgangsvraag

Wat is de waarde van medicamenteuze behandeling bij ouderen met UI in de tweede- en derdelijnszorg?

Inleiding

Medicamenteuze behandeling van aandrang urine-incontinentie is, na of naast conservatieve therapie, de eerste behandeling van keuze. Er zijn verschillende medicamenteuze behandelingen beschikbaar, waarbij de meeste ervaring is met antimuscarinica (ook vaak anticholinergica genoemd). Deze preparaten verschillen in farmacokinetische eigenschappen, maar hebben in meer of mindere mate (anticholinerge) vergelijkbare bijwerkingen, zoals droge mond, wazig zien of een veranderde cognitieve functie. Deze bijwerkingen zijn belangrijk om mee te nemen in de keuze voor deze medicatie, met name bij oudere patiënten . Onder ouderen wordt in vrijwel alle studies mensen boven de 65 verstaan.

Daarnaast is er sinds de laatste herziening van de richtlijn ('urine-incontinentie voor de 2^{e} / 3de lijns zorg') meer ervaring opgedaan met sympathicomimetica (beta3-agonisten) bij urine incontinentie. Zo is Mirabegron sinds 1 april 2014 in Nederland op de markt, waardoor er nu significant meer praktische ervaring met dit middel is opgedaan. Daardoor kan er een afgewogen advies gegeven worden over de plaats van dit middel in de behandeling van aandrang urine-incontinentie bij ouderen. Daarnaast is er toenemend literatuur over het ook in Nederland te verwachten sympathiomimeticum Vibegron. Kortom het is belangrijk om de plaatsbepaling van de verschillende medicamenteuze behandelmogelijkheden opnieuw te beoordelen voor oudere patiënten met aandrang urine-incontinentie. Bovenstaande ligt ten grondslag aan de herziening van deze module.

Search and select

A systematic review of the literature was performed to answer the following question:

What is the effectivity and safety of antimuscarinic treatment or mirabegron/vibegron in elderly patients with urine incontinence, compared to placebo or no treatment?

P: Elderly with urine incontinence
I1: Antimuscarinic treatment
I2: Mirabegron
C1: Placebo, no treatment
C2: Placebo, no treatment or antimuscarinic treatment
O: reduced urge urine incontinence episodes, quality of life, adverse events/complications (in particular cognitive decline)

<u>Relevant outcome measures</u>

The guideline development group considered improvement/cure of urge urine incontinence episodes and quality of life as critical outcome measures for decision making; and adverse events/complications as important outcome measures for decision making.

A priori, the working group defined adverse events as dry mouth, obstipation, and cognitive decline. Quality of life data was extracted when a validated questionnaire was used. For other outcomes, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the following minimal clinically (patient) important differences:

- Cognitive functioning:
    - Montreal Cognitive Assessment (MoCA, 0-30): ≥ 4 points (Feeney, 2016)
- Improvement/cure of overactive bladder complaints:
    - Urinary Distress Inventory (UDI-6): ≥ 8 points (Barber, 2009)

In all other cases, the working group defined a 25% difference for dichotomous outcomes (RR < 0.8 or > 1.25), and 0.5 SD or -0.5 < SMD > 0.5 for continuous outcomes as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until 10th May 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 450 hits. Studies were selected based on the following criteria:

- Systematic review (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available) or randomized controlled trial comparing antimuscarinic treatment (with or without bladder training?) with placebo or no treatment (with or without bladder training), or comparing mirabegron with placebo, no treatment or antimuscarinic treatment (with or without bladder training?);
- Elderly patients with urine incontinence;
- Full-text English language publication;
- Studies including ≥ 20 (ten in each study arm) patients; and
- Studies according to PICO.

Seventy studies were initially selected based on title and abstract screening. After reading the full text, 61 studies were excluded (see the table with reasons for exclusion under the tab Methods), and nine studies were included (Dubeau, 2014; Griebling 2020; Kosilov, 2015; Lackner, 2011; Samuelsson, 2015; Varano, 2021; Wagg, 2013; Wagg, 2020; Yoshida, 2021). In case measurements of dispersion were not reported but could be derived from reported mean differences, an estimated SMD was developed using Revman version 5.4.1.

Results

One systematic review and eight RCTs were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

PICO 1: Antimuscarinic treatment versus placebo

Summary of literature

Description of studies

Samuelsson (2015) performed a systematic review to assess the effects of pharmacotherapy for urinary incontinence in elderly and frail elderly populations. Randomized controlled trials and prospective controlled observational studies that evaluated interventions for drug treatment of urinary incontinence in the elderly and frail elderly population were included. PubMed, EMBASE, Cochrane library and Cinahl databases were searched up to October 2013. In total, 13 studies were included in the review. The review by Samuelsson (2015) was used for the description of all published studies up until 2010. For the purpose of this guideline, the results of these four RCTs matching de predefined PICO are summarized below (Chapple, 2007; Ouslander, 1995; Szony, 1995, Zinner, 2002). Chapple (2007) compared darifenacin with placebo, Ouslander (1995) and Szonyi (1995) compared oxybutynin with placebo, and Zinner (2002) compared tolterodine with placebo. Outcomes included urinary leakage, quality of life and adverse events.

1. *Darifenacin versus placebo*
   Samuelsson (2015) included one RCT that compared darifenacin versus placebo (Chapple, 2007). Patients received 7.5 mg darifenacin daily with voluntary up-titration to 15 mg after 2 weeks for 12 weeks.

2. *Fesoterodine versus placebo*
   Dubeau (2014) performed a randomized, double-blind, placebo controlled, parallel group, multicentre trial to assess the efficacy and safety of flexible dose fesoterodine in medically complex vulnerable elderly subjects with urgency urinary incontinence (UUI). Men or women who were 65 years old or older with self-reported UUI symptoms for 3 or more months, a mean of 2 to 15 UUI episodes (voids that subjects rated with a score of 5 on the Urinary Sensation Scale), 8 or more micturitions per 24 hours on baseline 3-day bladder diary, and at least some moderate bladder related problem on the Patient Perception of Bladder Condition (PPBC) who were determined to be vulnerable (at risk of deteriorating health) by a score of 3 or more on the VES-13 at screening were included. Besides, subjects had to be capable of adequate mobility for independent toileting (could use cane or walker) and independent completion of bladder diaries and study related questionnaires. Exclusion criteria were:
   - Any condition contraindicating the use of fesoterodine
   - Clinically significant hepatic disease or liver enzymes greater than 2 times the upper limit of normal
   - Clinically significant renal disease and/or estimated creatinine clearance less than 30 ml per minute
   - Neurological conditions that may specifically affect bladder function
   - Previous surgery that might alter bladder function
   - Advanced malignancy
   - Clinically significant bladder outflow obstruction
   - Post-void residual urinary volume (PVR) greater than 200 ml
   - Predominant stress urinary incontinence
   - Recurrent urinary tract infection
   - Significant constipation
   - Mini-Mental State Examination (MMSE) score less than 20
   - Behavioural interventions or electrical stimulation within 8 weeks

- Antimuscarinic medication use within 3 weeks
- Initiation or variable dose of tricyclic antidepressants, α-blockers, oestrogens (within 4 weeks) or diuretics (within 2 weeks)
- An unstable medical condition
- Average resting heart rate of 90 beats per minute or greater

In total, 281 subjects were randomized to fesoterodine treatment, and 281 subjects received a placebo once daily for 12 weeks. Subjects started at a dose of 4 mg, and this could be increased to 8 mg at the 4-week visit. For subjects that escalated their dose to 8 mg, it could be returned to 4 mg at any time but could not increase it again to 8 mg. Groups were comparable at baseline. Outcomes of interest were mean number of UUI episodes per 24 hours, quality of life and adverse events.

Wagg (2013) performed a randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of flexible-dose fesoterodine in elderly adults with overactive bladder (OAB). Men and women aged 65 years or older with OAB symptoms for 3 months or longer, a mean of eight or more micturitions and three or more urgency episodes per 24 hours on a 3-day bladder diary at baseline who self-reported at least some moderate problems on the Patient Perception of Bladder Condition (PPBC) questionnaire and had a MMSE score of 20 or greater were included. Besides, participants need to be able to complete micturition diaries and study-related questionnaires and adhere to study procedures. Exclusion criteria were:

- Hypersensitivity to the active substance (fesoterodine fumarate) or to peanut, soya, or any of the excipients
- Predominant stress incontinence as determined according to the investigator
- Significant bladder outlet obstruction
- Previous history of acute urinary retention requiring catheterization, severe voiding difficulties, or active urinary tract infection
- Clinically significant renal disease
- Multiple sclerosis or spinal cord injury
- Treatment with other antimuscarinics within 2 to 3 weeks before baseline
- Treatment with potent CYP3A4 inhibitors
- Intermittent or unstable use of diuretics or alpha-blockers or initiation of treatment within 2 weeks of baseline

In total, 392 patients received fesoterodine and 393 patients received placebo for 12 weeks. Subjects started at a fesoterodine dose of 4 mg, and this could be increased to 8 mg at 4 and 8 weeks. For subjects that escalated their dose to 8 mg, it could be de-escalated to 4 mg at 8 weeks. Groups were comparable at baseline. Outcomes of interest were urgency urinary incontinence episodes per 24 hours, quality of life, and adverse events.

3. *Oxybutynin versus placebo*

Lackner (2011) performed a randomized controlled trial to assess the efficacy of oral extended-release oxybutynin for urge urinary incontinence in older female nursing home residents with mild to severe cognitive impairment. Female nursing home residents of 65 years or older with urge urinary incontinence and mild to severe cognitive impairment (no delirium or diagnosis of dementia with Lewy bodies) were included. Besides, participants were ambulatory, able to communicate, had a post void residual urine volume of less than 150 mL and remain incontinent following a 2-day prompted voiding program conducted by investigators. Exclusion criteria were males, participants with unstable or severe medical conditions that precluded the

use of oxybutynin, a terminal illness and the use of antimuscarinic, bisphosphonate, or acetylcholinesterase inhibitors during the month before or during treatment. In total, 26 subjects were allocated to extended-release oxybutynin 5 mg/day and 24 subjects received placebo for 4 weeks. Groups were comparable at baseline. The outcome of interest were urinary incontinence episodes.

Samuelsson (2015) included two RCTs that compared oxybutynin versus placebo (Ouslander, 1995; Szonyi, 1995). Patients included in Ouslander (1995) received oxybutynin 2.5-5 mg three times daily with prompted voiding for 20 days. Patients included in Szonyi (1995) received oxybutynin 2.5 mg twice daily and bladder training or a placebo and bladder training for 6 weeks.

4. *Solifenacin versus placebo*

Kosilov (2015) performed a randomized controlled trial to assess the effectiveness and safety of mirabegron and solifenacin for managing heavy symptoms of overactive bladder. Patients with severe symptoms of overactive bladder (the frequency of episodes of incontinence (EI) ≥3/day) with an age over 65 years were included. Exclusion criteria were chronic active diseases including hypertension and intolerance to antimuscarinics and agonists of β3-adrenoreceptors. Sixty-three patients were treated with mirabegron (50 mg/day), 52 patients were treated with solifenacin (10 mg/day), and 59 patients were treated with placebo for 6 weeks. Outcomes of interest were the frequency of episodes of incontinence and adverse events.

5. *Tolterodine versus placebo*

Samuelsson (2015) included one RCT that compared tolterodine with placebo (Zinner, 2002). Patients received tolterodine extended release capsules 4 mg once daily for 12 weeks.

Results

1. Darifenacin versus placebo

1.1 *Improvement of urine incontinence complaints (critical)*

Chapple (2007) reported the urgency urinary incontinence episodes per week after 12 weeks of treatment. Patients receiving darifenacin experienced between 14 and 19.8 episodes/week as compared to 13 to 21 episodes/week for patients treated with placebo. However, since no standard deviations were presented, no GRADE-assessment could be performed.

1.2 *Quality of life (critical)*

Chapple (2007) reported the quality of life with the overactive bladder questionnaire (OABq). The mean change at week 12, was 22.9 (estimated SD 17.44) for patients receiving darifenacin (n= 266) and 16.8 (estimated SD 17.44) for patients receiving placebo (n= 133). This resulted in a mean difference of 6.10 (95%CI 2.47 to 9.73), translating in an SMD of 0.35 (95% CI 0.14 to 0.56), which was not clinically relevant.

1.3 *Adverse events (important)*

1.3.1. Dry mouth

Chapple (2007) reported that 59 of the 266 patients (22.2%) who received darifenacin had a dry mouth as compared to 5 of the 133 patients (3.8%) who received placebo (RR=9.83, 95%CI 3.14 to 30.78). This difference is clinically relevant favouring placebo.

1.3.2. Obstipation

Chapple (2007) reported that 41 of the 266 patients (15.4%) who received darifenacin had constipation as compared to 11 of the 133 patients (8.3%) who received placebo (RR=1.86, 95%CI 0.99 to 3.51). This difference is clinically relevant favouring placebo.

1.3.3. Cognitive decline

Not reported.

2. Fesoterodine versus placebo

2.1 Improvement of urine incontinence complaints (critical)

Dubeau (2014) reported the reduction in UUI episodes per 24 hours. At 4 weeks, a mean change of -2.36 episodes was found for patients treated with fesoterodine as compared to a mean change of -1.54 episodes for patients receiving placebo ($p<0.001$). At 12 weeks, a mean change of -2.84 episodes was found for patients who received treatment with fesoterodine as compared to a mean change of -2.20 episodes for patients who received placebo ($p=0.002$). Since no standard deviations have been reported, no GRADE assessment can be performed.

Wagg (2013) reported that the median number of UUI episodes per 24 hours decreased from 1.3 at baseline to 0.0 at week 12 for patients receiving fesoterodine and from 1.7 at baseline to 0.0 at week 12 for patients treated with placebo. Since no interquartile ranges were reported, no GRADE assessment can be performed.

2.2 Quality of life (critical)

Dubeau (2014) reported the total health-related quality of life (HRQL) score measured with the Overactive Bladder Questionnaire (OAB-q) which contained a 25-item HRQL scale with 4 domains. Higher scores indicated improvements. At 4 weeks, a mean HRQL of 17.8 (SE=1.4) was reported for patients treated with fesoterodine, as compared to a mean HRQL of 12.0 (SE=1.4) for patients who received placebo, resulting in an SMD of 0.25 (95% CI 0.08 to 0.41). At 12 weeks, a mean HRQL of 23.1 (SE=1.5) was reported for patients treated with fesoterodine, as compared to a mean HRQL of 17.6 (SE=1.5) for patients who received placebo, resulting in an SMD of 0.22 (95% CI 0.05 to 0.38). This difference is not clinically relevant.

Wagg (2013) reported the least squares (LS) mean change in HRQL from baseline to week 12. For patients receiving fesoterodine, the LS mean change for total HRQL was 11.6 as compared to 7.1 for patients receiving placebo. Since no standard deviations have been reported, no GRADE assessment can be performed.

2.3 Adverse events (important)

2.3.1. Dry mouth

Dubeau (2014) reported that 66 of the 281 patients (23.5%) who received fesoterodine had a dry mouth as compared to 17 of the 281 patients (6.0%) who received placebo (RR=3.88, 95%CI 2.34 to 6.44). This difference is clinically relevant favouring placebo.

Wagg (2013) reported that 133 of the 392 patients (33.9%) who received fesoterodine had a dry mouth as compared to 21 of the 393 patients (5.3%) who received placebo (RR=6.35, 95%CI 4.10 to 9.84). This difference is clinically relevant favouring placebo.

2.3.2. Obstipation

Dubeau (2014) reported that 31 of the 281 patients (11.0%) who received fesoterodine had constipation as compared to 12 of the 281 patients (4.3%) who received placebo (RR=2.58, 95%CI 1.35 to 4.93). This difference is clinically relevant favouring placebo.

Wagg (2013) reported that 35 of the 392 patients (8.9%) who received fesoterodine had constipation as compared to 10 of the 393 patients (2.5%) who received placebo (RR=3.51, 95%CI 1.76 to 6.99). This difference is clinically relevant favouring placebo.

2.3.3. Cognitive decline

Dubeau (2014) reported the Mini-Mental State Examination (MMSE) score. The MMSE is scored on a scale from 0 to 30 with scores ≥27 considered as normal cognition, scores from 20 to 26 were considered as some cognitive impairment, scores from 10 to 19 were considered as moderate to severe cognitive impairment and less than 10 was considered as very severe cognitive impairment. No deterioration in mean MMSE scores from baseline to week 12 were found. For patients receiving fesoterodine (n= 281), the LS mean MMSE score from baseline to week 12 was 0.15 (SE=0.12) as compared to 0.33 (SE=0.12) for patients receiving placebo (n= 281). This resulted in an SMD of -0.09 (95% CI -0.25 to 0.08). This difference is not clinically relevant. Subjective memory impairment was reported in two subjects treated with fesoterodine with onset after increase to the 8 mg dose.

Wagg (2013) reported no meaningful change in MMSE score from baseline to week 12. Mean MMSE scores at week 12 were 28.4 (range 20 to 30) for patients receiving fesoterodine and 28.3 (range 19 to 30) for patients treated with placebo. For patients receiving fesoterodine (n= 392), the mean change was 0.24 (SE=1.76) as compared to 0.23 (SE=1.82) in the placebo-group (n= 393), resulting in an SMD of 0.00 (95% CI -0.14 to 0.14). This difference is not clinically relevant.

3. Oxybutynin versus placebo

3.1 *Improvement of urine incontinence complaints (critical)*

Lackner (2011) reported the median number of urinary incontinence episodes after 4 weeks of treatment. For patients who received extended-release oxybutynin, the median number of urinary incontinence episodes was 6 (range 2 to 12) at baseline and 4 (range 0 to 11) after treatment. For patients receiving placebo, the median number of urinary incontinence episodes was 4.5 (range 3 to 10) at baseline and 2.5 (range 0 to 14) after treatment. Since no means or measures of dispersion were reported, these results were not GRADE evaluated.

Ouslander (1995) reported the number of incontinence episodes per 3 days at day 20. Patients receiving oxybutynin (n= 75) had 6.8 episodes (estimated SD 4.03) as compared to 7.7 episodes (estimated SD 4.03) for patients receiving placebo (n= 75). This resulted in a mean difference of -1.10 (95%CI -2.39 to 0.19), translating in an SMD of -0.22 (95% CI -0.54 to 0.10), which was not clinically relevant.

Szonyi (1995) reported the change in incontinence episodes/day during first 14 days versus last 14 days. Patients receiving oxybutynin had a difference of 8 (IQR=8 to 10) as compared to a difference of 7 (IQR = 7 to 7) for patients receiving placebo. No GRADE assessment could be performed.

Due to heterogeneity in reporting of data, it was not possible to pool the results.

3.2 *Quality of life (critical)*

Not reported.

3.3 *Adverse events (important)*

3.3.1 Dry mouth

Ouslander (1995) reported that 22 of the 52 patients (42%) who received oxybutynin had a dry mouth as compared to 19 of the 54 patients (35%) who received placebo (RR=1.20, 95%CI 0.74 to 1.95). This difference is not clinically relevant.

Szonyi (1995) reported that 93% of the patients who received oxybutynin had a dry mouth as compared to 85% of the patients who received placebo. However, since the number of patients is not reported, no GRADE assessment could be performed.

3.3.2 Obstipation

Ouslander (1995) reported that 16 of the 53 patients (30%) who received oxybutynin had constipation as compared to 13 of the 52 patients (25%) who received placebo (RR=0.83, 95%CI 0.48 to 1.42). This difference is not clinically relevant.

Szonyi (1995) reported that 50% of the patients who received oxybutynin had constipation as compared to 45% of the patients who received placebo. However, since the number of patients is not reported, no GRADE assessment could be performed.

3.3.3 Cognitive decline

Not reported.

4. <u>Solifenacin versus placebo</u>

4.1 Improvement of urine incontinence complaints (critical)

Kosilov (2015) reported the average number of episodes of incontinence. Patients who received solifenacin had a change of 2.2 episodes from baseline to 6 weeks, as compared to 0.2 episodes for patients treated with placebo. Since no standard deviations have been reported, no GRADE assessment can be performed.

4.2 Quality of life (critical)

Not reported.

4.3 Adverse events (important)

4.3.1 Dry mouth

Kosilov (2015) reported that 5 of the 52 patients (9.6%) who received solifenacin had a dry mouth as compared to 2 of the 59 patients (3.4%) who were treated with placebo (RR=2.84, 95%CI 0.57 to 14.01). This difference is clinically relevant favouring placebo.

4.3.2. Obstipation

Not reported.

4.3.3. Cognitive decline

Kosilov (2015) reported that cognitive impairment occurred in 1 of the 59 patients (1.7%) that received placebo and did not occur in patients who received solifenacin (RR=0.38, 95%CI 0.02 to 9.07). This difference is clinically relevant favouring solifenacin.

5. <u>Tolterodine versus placebo</u>

5.1 Improvement of urine incontinence complaints (critical)
Zinner (2002) reported the mean reduction in incontinence episodes per week. At baseline, mean frequency of incontinence episodes over both groups was 23. Patients who received tolterodine (n= 214) had a mean reduction of 11.5 (SD 18.2) episodes, as compared to a reduction of 6.3 (SD 15) episodes for patients treated with placebo (n= 223). This resulted in a SMD of -0.31 (95% CI -0.50 to -0.12), which is not clinically relevant.

5.2 Quality of life (critical)
Not reported.

5.3 Adverse events (important)
5.3.1 Dry mouth
Zinner (2002) reported that 52 of the 214 patients (24.3%) who received tolterodine had a dry mouth as compared to 16 of the 223 patients (7.2%) who were treated with placebo (RR=3.39, 95%CI 2.00 to 5.74). This difference is clinically relevant favouring placebo.

5.3.2. Obstipation
Zinner (2002) reported that 13 of the 214 patients (6.1%) who received tolterodine had constipation as compared to 10 of the 223 patients (4.5%) who were treated with placebo (RR=1.35, 95%CI 0.61 to 3.02). This difference is clinically relevant favouring placebo.

5.3.3. Cognitive decline
Not reported.

Level of evidence of the literature
According to GRADE, the level of evidence start at high because it was based on RCTs.

1. Darifenacin versus placebo

1.1. *Improvement of urine incontinence complaints (critical)*
The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* could not be assessed with GRADE.

1.2. *Quality of life (critical)*
The level of evidence regarding the outcome measure *quality of life* was downgraded by two levels to low because the optimal information size has not been reached and the upper limit of the 95% confidence interval crossed the line of a clinically relevant effect (-2, imprecision).

1.3. *Adverse events (important)*
1.3.1. *Adverse event: dry mouth*
The level of evidence regarding the adverse event *dry mouth* was downgraded by two levels to low because the upper limit of the 95% confidence interval was >3 times higher than the point estimate (-2, imprecision).

1.3.2. *Adverse event: obstipation*
The level of evidence regarding the adverse event *obstipation* was downgraded by two levels to low because of the low number of events and the 95% confidence interval crossed the line of no (clinically relevant) effect (-2, imprecision).

1.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* could not be assessed with GRADE.

2. Fesoterodine versus placebo

2.1. *Improvement of urine incontinence complaints (critical)*

The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* could not be assessed with GRADE.

2.2. *Quality of life (critical)*

The level of evidence regarding the outcome measure *quality of life* was downgraded by two levels to low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias) and the optimal information size has not been reached (-1, imprecision).

2.3. *Adverse events (important)*

2.3.1. *Adverse event: dry mouth*

The level of evidence regarding the adverse event *dry mouth* was downgraded by two levels to low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias) and the optimal information size has not been reached (-1, imprecision).

2.3.2. *Adverse event: obstipation*

The level of evidence regarding the adverse event *obstipation* was downgraded by two levels to low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias) and the optimal information size has not been reached (-1, imprecision).

2.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* was downgraded by two levels to low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias) and the optimal information size has not been reached (-1, imprecision).

3. Oxybutynin versus placebo

3.1. *Improvement of urine incontinence complaints (critical)*

The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* was downgraded by two levels to low because the optimal information size has not been reached and the lower limit of the 95% confidence interval crossed the line of a clinically relevant effect (-2, imprecision).

3.2. *Quality of life (critical)*

The level of evidence regarding the outcome measure *quality of life* could not be assessed with GRADE.

3.3. *Adverse events (important)*

3.3.1. *Adverse event: dry mouth*

The level of evidence regarding the adverse event *dry mouth* was downgraded by three levels to very low because the study population consisted of severely cognitive impaired patients (-1, indirectness) and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

3.3.2. *Adverse event: obstipation*

The level of evidence regarding the adverse event *obstipation* was downgraded by three levels to very low because the study population consisted of severely cognitive impaired patients (-1, indirectness) and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

3.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* could not be assessed with GRADE.

4. Solifenacin versus placebo

4.3. Adverse events (important)

4.3.1 Adverse event: dry mouth

The level of evidence regarding the adverse event *dry mouth* was downgraded by three levels to very low because of study limitations regarding blinding and selective outcome reporting (-1, risk of bias) and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

4.3.3 Adverse event: cognitive decline

The level of evidence regarding the adverse event *cognitive decline* was downgraded by three levels to very low because of study limitations regarding blinding and selective outcome reporting (-1, risk of bias) and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

4.1.*Improvement of urine incontinence complaints (critical); 4.2. Quality of life (critical); 4.3.2. Adverse event: obstipation (important)*

The level of evidence regarding the outcome measures *improvement of urine incontinence complaints*, *quality of life, and obstipation* could not be assessed with GRADE.

5. Tolterodine versus placebo

5.1.*Improvement of urine incontinence complaints (critical)*

The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* was downgraded by one level to moderate because the optimal information size has not been reached (-1, imprecision).

5.2.*Quality of life (critical)*

The level of evidence regarding the outcome measure *quality of life* could not be assessed with GRADE.

5.3.*Adverse events (important)*

5.3.1. *Adverse event: dry mouth*

The level of evidence regarding the adverse event *dry mouth* was downgraded by one level to moderate because the optimal information size has not been achieved (-1, imprecision).

5.3.2. *Adverse event: obstipation*

The level of evidence regarding the adverse event *obstipation* was downgraded by three levels to very low because of the low number of events and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

5.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* could not be assessed with GRADE.

Conclusions

1. Darifenacin versus placebo

1.1. Improvement of urine incontinence complaints (critical)

No GRADE	It was not possible to draw conclusions or grade the level of evidence for improvements from urine incontinence complaints in the comparison darifenacin and placebo, due to the absence of data.

1.2. Quality of life (critical)

Low GRADE	The evidence suggests that darifenacin results in little to no difference in quality of life when compared with placebo in elderly with urine incontinence. *Source: Chapple, 2007*

1.3. Adverse event (important)

1.3.1. Adverse event: dry mouth

Low GRADE	The evidence suggests darifenacin increases the adverse event dry mouth when compared with placebo in elderly with urine incontinence. *Source: Chapple, 2007*

1.3.2. Adverse event: obstipation

Low GRADE	The evidence suggests darifenacin increases the adverse event obstipation when compared with placebo in elderly with urine incontinence. *Source: Chapple, 2007*

1.3.3. Adverse event: cognitive decline

No GRADE	No evidence was found regarding the effect of darifenacin on the adverse event cognitive decline when compared with placebo in elderly with urine incontinence.

2. Fesoterodine versus placebo

2.1. Improvement of urine incontinence complaints (critical)

No GRADE	It was not possible to draw conclusions or grade the level of evidence for improvements from urine incontinence complaints in the comparison fesoterodine and placebo, due to the absence of data.

2.2. Quality of life (critical)

Low GRADE	The evidence suggests fesoterodine result in little to no difference in quality of life when compared with placebo in elderly with urine incontinence. *Source: Dubeau, 2014*

2.3. Adverse event (important)

2.3.1. Adverse event: dry mouth

Low GRADE	The evidence suggests fesoterodine increases the adverse event dry mouth when compared with placebo in elderly with urine incontinence. *Source: Dubeau, 2014; Wagg, 2013*

2.3.2. Adverse event: obstipation

Low GRADE	The evidence suggests fesoterodine increases the adverse event obstipation when compared with placebo in elderly with urine incontinence. *Source: Dubeau, 2014; Wagg, 2013*

2.3.3. Adverse event: cognitive decline

Low GRADE	The evidence suggests fesoterodine results in little to no difference in cognitive decline when compared with placebo in elderly with urine incontinence. *Source: Dubeau, 2014; Wagg, 2013*

3. <u>Oxybutynin versus placebo</u>

3.1. Improvement of urine incontinence complaints (critical)

Low GRADE	The evidence suggests oxybutynin results in little to no difference in improvement of urine incontinence complaints when compared with placebo in elderly with urine incontinence. *Source: Ouslander, 1995*

3.2. Quality of life (critical)

No GRADE	No evidence was found regarding the effect of oxybutynin on quality of life when compared with placebo in elderly with urine incontinence.

3.3. Adverse events (important)

3.3.1. Adverse event: dry mouth

Very low GRADE	The evidence is very uncertain about the effect of oxybutynin on the adverse event dry mouth when compared with placebo in elderly with urine incontinence. *Source: Ouslander, 1995; Szonyi, 1995*

3.3.2. Adverse event: obstipation

Very low GRADE	The evidence is very uncertain about the effect of oxybutynin on the adverse event obstipation when compared with placebo in elderly with urine incontinence. *Source: Ouslander, 1995; Szonyi, 1995*

3.3.3. Adverse event: cognitive decline

No GRADE	No evidence was found regarding the effect of oxybutynin on the adverse event cognitive decline when compared with placebo in elderly with urine incontinence.

4. Solifenacin versus placebo

4.1. Improvement of urine incontinence complaints (critical)

No GRADE	It was not possible to draw conclusions or grade the level of evidence for improvements from urine incontinence complaints in the comparison solifenacin and placebo, due to the absence of data.

4.2. Quality of life (critical)

No GRADE	No evidence was found regarding the effect of solifenacin on the quality of life when compared with placebo in elderly with urine incontinence.

4.3. Adverse events (important)

4.3.1. Adverse event: dry mouth

Very low GRADE	The evidence is very uncertain about the effect of solifenacin on the adverse event dry mouth when compared with placebo in elderly with urine incontinence. *Source: Kosilov, 2015*

4.3.2. Adverse event: obstipation

No GRADE	No evidence was found regarding the effect of solifenacin on the adverse event obstipation when compared with placebo in elderly with urine incontinence.

4.3.3. Adverse event: cognitive decline

Very low GRADE	The evidence is very uncertain about the effect of solifenacin on the adverse event cognitive decline when compared with placebo in elderly with urine incontinence. *Source: Kosilov, 2015*

5. Tolterodine versus placebo

5.1. Improvement of urine incontinence complaints (critical)

Moderate GRADE	Tolterodine likely results in little to no difference in the improvement of urine incontinence complaints when compared with placebo in elderly with urine incontinence. *Source: Zinner, 2002*

5.2. Quality of life (critical)

No GRADE	No evidence was found regarding the effect of tolterodine on the quality of life when compared with placebo in elderly with urine incontinence.

5.3. Adverse events (important)

5.3.1. Adverse event: dry mouth

Moderate GRADE	Tolterodine likely increases the adverse event dry mouth when compared with placebo in elderly with urine incontinence.

	Source: Zinner, 2002

5.3.2. Adverse event: obstipation

Very low GRADE	The evidence is very uncertain about the effect of tolterodine on the adverse event obstipation when compared with placebo in elderly with urine incontinence. *Source: Zinner, 2002*

5.3.3. Adverse event: cognitive decline

No GRADE	No evidence was found regarding the effect of tolterodine on the adverse event cognitive decline when compared with placebo in elderly with urine incontinence.

5

PICO 2: Mirabegron versus placebo or antimuscarinic treatment

Summary of literature

Description of studies

1. *Mirabegron versus placebo*

Griebling (2020) performed a pre-planned analysis of a phase 4 placebo-controlled study (PILLAR) to assess differences in cognitive function between mirabegron and placebo for treatment of wet overactive bladder (OAB) in patients aged ≥65 years. Community-dwelling patients with an age of 65 years or older with wet OAB (≥1 incontinence episode and ≥3 urgency episodes during the 3-day diary, plus an average of ≥8 micturitions/24 h) were included. There were no specific exclusion criteria regarding cognitive status, but subjects needed to be able to complete the micturition diaries and questionnaires. In total, 445 subjects received mirabegron and 442 subjects received placebo. Subjects were initially treated with 25 mg/day and could enhance the dose to 50 mg/day after week 4/8. The treatment duration was 12 weeks. Groups were similar at baseline. The outcome of interest was the Montreal Cognitive Assessment (MoCA) test score and adverse events.

Kosilov (2015) performed a randomized controlled trial to assess the effectiveness and safety of mirabegron and solifenacin for managing heavy symptoms of overactive bladder. Patients with severe symptoms of overactive bladder (the frequency of episodes of incontinence (EI) ≥3/day) with an age over 65 years were included. Exclusion criteria were chronic active diseases including hypertension and intolerance to antimuscarinics and agonists of β3-adrenoreceptors. Sixty-three patients were treated with mirabegron (50 mg/day), 52 patients were treated with solifenacin (10 mg/day), and 65 patients were treated with placebo for 6 weeks. Comparisons between these different treatments were conducted. Outcomes of interest were the frequency of episodes of incontinence and adverse events.

Wagg (2020) performed a double-blind, randomised, placebo-controlled trial to study the efficacy, safety and tolerability of mirabegron in patients ≥65 years. Community-dwelling patients aged ≥65 years with one or more incontinence episodes, three or more urgency episodes, and an average of eight or more micturition episodes per day based on a 3 day micturition diary were included. Besides, subjects needed to be mental capable to complete the study or consent procedures. Exclusion criteria were nursing home residence, bladder outlet obstruction, predominant stress incontinence, postvoid residual volume >150 ml, neurogenic detrusor overactivity, acute urinary tract infection, recent initiation of conservative/invasive therapy for OAB, permanent or intermittent catheterisation, severe renal or hepatic impairment, or uncontrolled hypertension. In total, 445 subjects received mirabegron and 443 subjects received a placebo for 3 months. Patients started with an initial dose of 25 mg/day mirabegron or matched placebo and the dose could be increased to 50 mg/day after 4 or 8 weeks. Outcomes of interest were urgency incontinence episodes/24 hours and adverse events.

2. *Vibegron versus placebo*

Varano (2021) performed a subpopulation analysis from the phase 3 double-blind controlled EMPOWUR trial to determine the efficacy and safety of vibegron in patients aged ≥65 and ≥75 years. Adults with a history of OAB for at least 3 months before the screening visit and met prespecified criteria for wet or dry OAB were included. Exclusion criteria were:

- History of 24-h urine volume > 3000 mL in the past 6 months
- Lower urinary tract pathology (e.g., bladder outlet obstruction) that could account for OAB symptoms
- History of stress urinary incontinence surgery within 6 months of screening
- Intradetrusor injection of botulinum toxin within 9 months of screening, or electrostimulation within 28 days of screening
- Diabetes insipidus
- Uncontrolled hyperglycemia (fasting blood glucose > 150 mg/dL or 8.33 mmol/L and/or non-fasting blood glucose > 200 mg/dL or 11.1 mmol/L or, if in the opinion of the investigator, was uncontrolled)
- Current history or evidence of stage ≥ 2 pelvic organ prolapse or use of pessary for the treatment of pelvic organ prolapse
- History of neurodegenerative diseases (e.g., multiple sclerosis, Parkinson disease) that could affect the lower urinary tract or its nerve supply.

In total, 647 participants aged ≥65 were randomized to either placebo (n=228), vibegron 75 mg (n=247) or tolterodine extended release 4 mg (n=172). Besides, 183 participants aged ≥75 years were randomized to either placebo (n=60), vibegron 75 mg (n=75) or tolterodine extended release 4 mg (n=48). Outcomes of interest were the number of urge urinary incontinence episodes and adverse events.

Yoshida (2021) performed a post-hoc subgroup analysis of a randomized, placebo-controlled, double-blind comparative phase 3 study to assess the safety and efficacy of vibegron in patients aged ≥65 years. Patients with overactive bladder with ≥8 micturitions/day and either ≥1 urgency episodes/day or ≥1 urgency incontinence episodes/day were included. Exclusion criteria were urinary tract infection, bladder cancer, bladder calculus, interstitial cystitis, enlarged prostate, residual urinary volume >100 ml, and systolic blood pressure ≥ 160 mmHg, diastolic blood pressure ≥ 100 mmHg, or pulse rate ≥110 bpm. Subjects ≥65 years were randomized to vibegron 50 mg (n=131), vibegron 100 mg (n=130) or placebo (n=131) for 12 weeks. The outcomes of interest were the change in urgency urinary incontinence and adverse events.

3. *Vibegron versus tolterodine*

In the study of **Varano (2021)**, the efficacy and safety of vibegron was also compared with tolterodine. The description of this study can be found under "Vibegron versus placebo".

4. *Mirabegron versus solifenacin*

In the study of **Kosilov (2015)**, the effectiveness and safety of mirabegron was also compared with solifenacin. The description of this study can be found under "Mirabegron versus placebo".

Results

1. Mirabegron versus placebo

1.1 *Improvement of urine incontinence complaints (critical)*

Kosilov (2015) reported the average number of episodes of incontinence. Patients who received mirabegron had a change of 2.3 episodes from baseline to 6 weeks, as compared to 0.2 episodes for patients treated with placebo. Since no standard deviations have been reported, no GRADE assessment can be performed.

Wagg (2020) reported the mean number of incontinence episodes per 24 hours. Patients who received mirabegron (n= 445) had an adjusted mean change of -2.0 episodes (SE=0.1) from baseline to 12 weeks, as compared to -1.5 episodes (SE=0.1) for patients receiving placebo (n= 443), translating into a SMD of -0.24 (95% CI -0.37 to -0.11). This difference is not clinically relevant.

1.2 *Quality of life (critical)*
Not reported.

1.3 *Adverse events (important)*
1.3.1. Dry mouth
Griebling (2020) reported that 6 of the 445 patients (1.3%) who received mirabegron had a dry mouth as compared to 7 of the 442 patients (1.6%) who were treated with placebo (RR=0.85, 95%CI 0.29 to 2.51). This difference is not clinically relevant.

Kosilov (2015) reported that 1 of the 63 patients (1.6%) who received mirabegron had a dry mouth as compared to 2 of the 59 patients (3.4%) who were treated with placebo (RR=0.47, 95%CI 0.04 to 5.03). This difference is clinically relevant favouring mirabegron.

1.3.2. Obstipation
Griebling (2020) reported that 3 of the 445 patients (0.7%) who received mirabegron had constipation as compared to 4 of the 442 patients (0.9%) who were treated with placebo (RR=0.74, 95%CI 0.17 to 3.31). This difference is clinically relevant favouring mirabegron.

1.3.3. Cognitive decline
Griebling (2020) reported cognitive function with the Montreal Cognitive Assessment (MoCA). The MoCA consists of 30-items and higher scores indicates better cognitive function. A MoCA score <26 indicates impaired cognitive function. For patients treated with mirabegron, the mean MoCA score was 26.9 (SE=0.1) after 12 weeks as compared to a mean MoCA score of 27.0 (SE=0.1) for patients receiving placebo. This difference is not clinically relevant. An impaired cognitive function at 12 weeks was reported in 104 of the 425 patients (24.5%) receiving mirabegron as compared to 106 of the 411 patients (25.8%) receiving placebo (RR=0.95, 95%CI 0.75 to 1.20). This difference is not clinically relevant.

Kosilov (2015) reported that cognitive impairment occurred in 1 of the 59 patients (1.7%) that received placebo and did not occur in patients who received mirabegron (RR=0.31, 95%CI 0.01 to 7.52). This difference is clinically relevant favouring mirabegron.

Wagg (2020) reported no statistically significant change in MoCA score from baseline to 12 weeks of treatment. An adjusted mean change of -0.2 points (SE=0.1) was found for patients treated with mirabegron (n= 445) as compared to -0.1 points (SE=0.1) for patients receiving placebo (n= 443), translating into a SMD of -0.05 (95% CI -0.18 to 0.08) This difference is not clinically relevant.

Due to heterogeneity in reporting of data, it was not possible to pool the results.

2. Vibegron versus placebo

2.1 *Improvement of urine incontinence complaints (critical)*

Varano (2021) reported the change in average daily number of urge urinary incontinence episodes for patients aged ≥65 years and ≥75 years from baseline to 12 weeks of treatment. For patients ≥65 years, the LS mean change was -2.0 episodes for patients receiving vibegron as compared to -1.2 episodes for patients receiving placebo at 12 weeks of treatment. For patients ≥75 years, the LS mean change was -2.0 episodes for patients receiving vibegron as compared to -0.4 episodes for patients receiving placebo at 12 weeks of treatment. Since no standard deviations have been reported, no GRADE assessment can be performed.

Yoshida (2021) reported the change in the number of urgency urinary incontinence episodes per 24 hours from baseline to week 12 for patients treated with 50 mg vibegron and patients receiving 100 mg vibegron. For patients receiving 50 mg vibegron, the LS mean change was -0.36 (95%CI -0.66 to -0.06) episodes as compared with placebo. For patients receiving 100 mg vibegron, the LS mean change was -0.48 (95%CI -0.79 to -0.18) episodes as compared with placebo. Since no standard deviations have been reported, no GRADE assessment can be performed.

2.2 *Quality of life (critical)*

Not reported.

2.3 *Adverse events (important)*

2.3.1. Dry mouth

Varano (2021) reported that 9 of the 545 patients (1.7%) who received vibegron had a dry mouth as compared to 5 of the 540 patients (0.9%) who were treated with placebo (RR=1.78, 95%CI 0.60 to 5.29). This difference is clinically relevant favouring placebo.

Yoshida (2021) reported that 3 of the 261 patients (1.1%) who received vibegron had a dry mouth as compared to 2 of the 131 patients (1.5%) who were treated with placebo (RR=0.75, 95%CI 0.13 to 4.45). This difference is clinically relevant favouring vibegron.

2.3.2. Obstipation

Yoshida (2021) reported that 5 of the 261 patients (1.9%) who received vibegron had constipation, while no constipation was experienced by patients treated with placebo (RR=5.54, 95%CI 0.31 to 99.47). This difference is clinically relevant favouring placebo.

2.3.3. Cognitive decline

Not reported.

3. Vibegron versus tolterodine

3.1 *Improvement of urine incontinence complaints (critical)*

Varano (2021) reported the change in average daily number of urge urinary incontinence episodes for patients aged ≥65 years and ≥75 years from baseline to 12 weeks of treatment. For patients ≥65 years, the LS mean change was -2.0 episodes for patients receiving vibegron as compared to -1.8 episodes for patients receiving tolterodine at 12 weeks of treatment. For patients ≥75 years, the LS mean change was -2.0 episodes for patients receiving vibegron as compared to -2.0 episodes for patients receiving placebo at 12 weeks of treatment. Since no standard deviations have been reported, no GRADE assessment can be performed.

Quality of life (critical)

Not reported.

3.3 Adverse events (important)
3.3.1. Dry mouth
Varano (2021) reported that 9 of the 545 patients (1.7%) who received vibegron had a dry mouth as compared to 28 of the 430 patients (6.5%) who were treated with tolterodine (RR=0.25, 95%CI 0.12 to 0.53). This difference is clinically relevant favouring vibegron.

3.3.2. Obstipation
Not reported.

3.3.3. Cognitive decline
Not reported.

4. Mirabegron versus solifenacin

4.1 Improvement of urine incontinence complaints (critical)
Kosilov (2015) reported the average number of episodes of incontinence. Patients who received mirabegron had a change of 2.3 episodes from baseline to 6 weeks, as compared to 2.3 episodes for patients treated with solifenacin. Since no standard deviations have been reported, no GRADE assessment can be performed.

4.2 Quality of life (critical)
Not reported.

4.3 Adverse events (important)
4.3.1. Dry mouth
Kosilov (2015) reported that 1 of the 63 patients (1.6%) who received mirabegron had a dry mouth as compared to 5 of the 52 patients (9.6%) who were treated with solifenacin (RR=0.17, 95%CI 0.02 to 1.37). This difference was clinically relevant favouring mirabegron.

4.3.2. Obstipation
Not reported.

4.3.3. Cognitive decline
Kosilov (2015) reported no cognitive impairments for patients receiving mirabegron or solifenacin.

Level of evidence of the literature
According to GRADE, the level of evidence start at high because it was based on RCTs.

1. Mirabegron versus placebo

1.1. *Improvement of urine incontinence complaints (critical)*
The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* was downgraded by two levels to low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias), discrepancy of results between Wagg (2020) and Kosilov (2015) (-1, inconsistency) and the optimal information size has not been reached (-1, imprecision).

1.2. *Quality of life (critical)*
The level of evidence regarding the outcome measure *quality of life* could not be assessed with GRADE.

1.3.*Adverse events (important)*

1.3.1. *Adverse event: dry mouth*

The level of evidence regarding the adverse event *dry mouth* was downgraded by three levels to very low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias), and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

1.3.2. *Adverse event: obstipation*

The level of evidence regarding the adverse event *obstipation* was downgraded by three levels to very low because of study limitations regarding allocation concealment (-1, risk of bias), and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

1.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* was downgraded by three levels to very low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias), difference in the direction of the effect (-1, inconsistency), and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-1, imprecision).

2. <u>Vibegron versus placebo</u>

2.1.*Improvement of urine incontinence complaints (critical)*

The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* could not be assessed with GRADE.

2.2.*Quality of life (critical)*

The level of evidence regarding the outcome measure *quality of life* could not be assessed with GRADE.

2.3.*Adverse events (important)*

2.3.1. *Adverse event: dry mouth*

The level of evidence regarding the adverse event *dry mouth* was downgraded by three levels to very low because of study limitations regarding allocation concealment and substantial loss to follow up (-1, risk of bias), difference in the direction of the effect (-1, inconsistency), and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-1, imprecision).

2.3.2. *Adverse event: obstipation*

The level of evidence regarding the adverse event *obstipation* was downgraded by three levels to very low because of study limitations regarding blinding (-1, risk of bias), and the upper limit of the 95% confidence interval was >3 times higher than the point estimate (-2, imprecision).

2.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* could not be assessed with GRADE.

3. Vibegron versus tolterodine

3.1. *Improvement of urine incontinence complaints (critical)*

The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* could not be assessed with GRADE.

3.2. *Quality of life (critical)*

The level of evidence regarding the outcome measure *quality of life* could not be assessed with GRADE.

3.3. *Adverse events (important)*

3.3.1. *Adverse event: dry mouth*

The level of evidence regarding the adverse event *dry mouth* was downgraded by two levels to low because of study limitations regarding substantial loss to follow up (-1, risk of bias) and the optimal information size has not been reached (-1, imprecision).

3.3.2. *Adverse event: obstipation*

The level of evidence regarding the adverse event *obstipation* could not be assessed with GRADE.

3.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* could not be assessed with GRADE.

4. Mirabegron versus solifenacin

4.1. *Improvement of urine incontinence complaints (critical)*

The level of evidence regarding the outcome measure *improvement of urine incontinence complaints* could not be assessed with GRADE.

4.2. *Quality of life (critical)*

The level of evidence regarding the outcome measure *quality of life* could not be assessed with GRADE.

4.3. *Adverse events (important)*

4.3.1. *Adverse event: dry mouth*

The level of evidence regarding the adverse event *dry mouth* was downgraded by three levels to very low because of study limitations regarding blinding (-1, risk of bias) and the 95% confidence interval crossed both lines of no (clinically relevant) effect (-2, imprecision).

4.3.2. *Adverse event: obstipation*

The level of evidence regarding the adverse event *obstipation* could not be assessed with GRADE.

4.3.3. *Adverse event: cognitive decline*

The level of evidence regarding the adverse event *cognitive decline* was downgraded by three levels to very low because of study limitations regarding blinding (-1, risk of bias) and the optimal information size has not been reached (-2, imprecision).

Conclusions

1. Mirabegron versus placebo

1.1. Improvement of urine incontinence complaints (critical)

Very low GRADE	The evidence is very uncertain about the effect of mirabegron on improvement of urine incontinence complaints when compared with placebo in elderly with urine incontinence. *Source: Wagg, 2020, Kosilov, 2015*

1.2. Quality of life (critical)

No GRADE	No evidence was found regarding the effect of mirabegron on quality of life when compared with placebo in elderly with urine incontinence.

1.3. Adverse events (important)

1.3.1. Adverse event: dry mouth

Very low GRADE	The evidence is very uncertain about the effect of mirabegron on the adverse event dry mouth when compared with placebo in elderly with urine incontinence. *Source: Griebling, 2020; Kosilov, 2015*

1.3.2. Adverse event: obstipation

Very low GRADE	The evidence is very uncertain about the effect of mirabegron on the adverse event obstipation when compared with placebo in elderly with urine incontinence. *Source: Griebling, 2020*

1.3.3. Adverse event: cognitive decline

Very low GRADE	The evidence is very uncertain about the effect of mirabegron on the adverse event cognitive decline when compared with placebo in elderly with urine incontinence. *Source: Griebling, 2020; Kosilov, 2015; Wagg, 2020*

2. Vibegron versus placebo

2.1. Improvement of urine incontinence complaints (critical)

No GRADE	It was not possible to draw conclusions or grade the level of evidence for improvements from urine incontinence complaints in the comparison vibegron and placebo, due to the absence of data.

2.2. Quality of life (critical)

No GRADE	No evidence was found regarding the effect of vibegron on quality of life when compared with placebo in elderly with urine incontinence.

2.3. Adverse events (important)

2.3.1. Adverse event: dry mouth

Very low GRADE	The evidence is very uncertain about the effect of vibegron on the adverse event dry mouth when compared with placebo in elderly with urine incontinence. *Source: Varano, 2021; Yoshida, 2021*

2.3.2. Adverse event: obstipation

Very low GRADE	The evidence is very uncertain about the effect of vibegron on the adverse event obstipation when compared with placebo in elderly with urine incontinence. *Source: Yoshida, 2021*

2.3.3. Adverse event: cognitive decline

No GRADE	No evidence was found regarding the effect of vibegron on the adverse events cognitive decline when compared with placebo in elderly with urine incontinence.

3. <u>Vibegron versus tolterodine</u>

3.1. Improvement of urine incontinence complaints (critical)

No GRADE	It was not possible to draw conclusions or grade the level of evidence for improvements from urine incontinence complaints in the comparison vibegron and tolterodine, due to the absence of data.

3.2. Quality of life (critical)

No GRADE	No evidence was found regarding the effect of vibegron on quality of life when compared with tolterodine in elderly with urine incontinence.

3.3. Adverse events (important)

3.3.1. Adverse event: dry mouth

Low GRADE	The evidence suggests that vibegron results in a reduction in the adverse event dry mouth when compared with tolterodine in elderly with urine incontinence. *Source: Varano, 2021*

3.3.2. Adverse event: obstipation; 3.3.3. Adverse event: cognitive decline

No GRADE	No evidence was found regarding the effect of vibegron on the adverse events obstipation or cognitive decline when compared with tolterodine in elderly with urine incontinence.

4. <u>Mirabegron versus solifenacin</u>

4.1. Improvement of urine incontinence complaints (critical)

No GRADE	It was not possible to draw conclusions or grade the level of evidence for improvements from urine incontinence complaints in the comparison mirabegron and solifenacin, due to the absence of data.

4.2. Quality of life (critical)

No GRADE	No evidence was found regarding the effect of mirabegron on quality of life when compared with solifenacin in elderly with urine incontinence.

4.3. Adverse events (important)

4.3.1. Adverse event: dry mouth

Very low GRADE	The evidence is very uncertain about the effect of mirabegron on the adverse event dry mouth when compared with solifenacin in elderly with urine incontinence. *Source: Kosilov, 2015*

4.3.2. Adverse event: obstipation

No GRADE	No evidence was found regarding the effect of mirabegron on the adverse event obstipation when compared with solifenacin in elderly with urine incontinence.

4.3.3. Adverse event: cognitive decline

Very low GRADE	The evidence is very uncertain about the effect of mirabegron on the adverse event cognitive decline when compared with solifenacin in elderly with urine incontinence. *Source: Kosilov, 2015*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

In de literatuuranalyse werd onderzocht wat de waarde is van medicamenteuze behandeling bij ouderen met UI in de tweede- en derdelijnszorg. De effectiviteit en veiligheid van behandeling met antimuscarinica of mirabegron/vibegron werden onderzocht.

Antimuscarinica versus placebo

1. *Darifenacine of fesoterodine versus placebo*

Voor de vergelijking tussen darifenacine en placebo en fesoterodine en placebo werd de bewijskracht voor de cruciale uitkomstmaat kwaliteit van leven beoordeeld als laag vanwege beperkingen in de studiepopulatie, methodologische beperkingen en populatiegrootte. Er werd geen bewijs gevonden voor de cruciale uitkomstmaat verbetering van aandrang urine-incontinentie klachten. Dit leidt tot een zeer lage overall bewijskracht. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Het gebruik van darifenacine bij ouderen met UI leidt mogelijk tot meer bijwerkingen zoals een droge mond en obstipatie. Het gebruik van fesoterodine bij ouderen met UI leidt mogelijk tot meer bijwerkingen zoals een droge mond en obstipatie, maar mogelijk geen verschil in cognitief functioneren in vergelijking met placebo. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van darifenacine of fesoterodine bij ouderen met UI in de tweede- en derdelijnszorg.

2. *Oxybutynine versus placebo*

Voor de vergelijking tussen oxybutynine en placebo werd de bewijskracht voor de cruciale uitkomstmaat verbetering van aandrang urine-incontinentie klachten beoordeeld als laag vanwege beperkingen in de studiepopulatie. Er werd geen bewijs gevonden voor de cruciale uitkomstmaat kwaliteit van leven. Dit leidt tot een zeer lage overall bewijskracht. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van oxybutynine bij ouderen met UI in de tweede- en derdelijnszorg.

3. *Solifenacine versus placebo*

Voor de vergelijking tussen solifenacine en placebo werd er geen bewijs gevonden voor de cruciale uitkomstmaten verbetering van aandrang urine-incontinentie klachten en kwaliteit van leven. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van solifenacine bij ouderen met UI in de tweede- en derdelijnszorg.

4. *Tolterodine versus placebo*

Voor de vergelijking tussen tolterodine en placebo werd de bewijskracht voor de cruciale uitkomstmaat verbetering van urine-incontinentie klachten beoordeeld als gemiddeld vanwege beperkingen in de studiepopulatie. Er werd geen bewijs gevonden voor de cruciale uitkomstmaat kwaliteit van leven. Dit leidt tot een zeer lage overall bewijskracht. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Het gebruik van tolterodine bij ouderen met UI leidt waarschijnlijk tot meer bijwerkingen zoals een droge mond. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van tolterodine bij ouderen met UI in de tweede- en derdelijnszorg.

Mirabegron versus placebo of antimuscarinica

1. *Mirabegron of vibegron versus placebo*

Voor de vergelijking tussen mirabegron en placebo werd de bewijskracht voor de cruciale uitkomstmaat verbetering van urine incontinentie klachten beoordeeld als laag vanwege

methodologische beperkingen en de populatie grootte. Er werd geen bewijs gevonden voor de cruciale uitkomstmaat kwaliteit van leven. Voor de vergelijking tussen vibegron en placebo werd geen bewijs gevonden voor de cruciale uitkomstmaten verbetering van urine incontinentie klachten en kwaliteit van leven. Dit leidt tot een zeer lage overall bewijskracht. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van mirabegron of Vibegron bij ouderen met UI in de tweede- en derdelijnszorg. Extra aandacht dient besteed te worden aan het feit dat voornoemde studies bekende bijwerkingen van antimuscarinica als uitgamngspunt namen, bijwerkingen waarop sympaticomimetica inderdaad veelal beter scoorden. Daar stonden wel andere bijwerkingen, typisch voor sympaticomimetica, tegenover. Men denke hierbij vooral aan verhoging van de bloeddruk en tachycardie.

2. *Vibegron versus tolterodine en mirabegron versus solifenacine*

Voor de vergelijking tussen vibegron en tolterodine werd er geen bewijs gevonden voor de cruciale uitkomstmaten verbetering van urine incontinentie klachten en kwaliteit van leven. Ditzelfde geldt voor de vergelijking tussen mirabegron en solifenacine. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten. Het gebruik van vibegron bij ouderen met UI leidt mogelijk tot minder bijwerkingen zoals een droge mond vergeleken met tolterodine. Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over de waarde van vibegron vergeleken met tolterodine, of over de waarde van mirabegron vergeleken met solifenacine bij ouderen met UI in de tweede- en derdelijnszorg.

Er zijn twee beperkende factoren bij deze analyse. Er zijn weinig studies naar kwetsbare ouderen gedaan, ten eerste omdat onderzoek doen in deze patiënten groep niet eenvoudig is vanwege hun kwetsbaarheid en ten tweede omdat er geen consensus is om cognitieve achteruitgang eenduidig te meten.

Op basis van de huidige literatuur is er weinig evidentie betreffende de werkzaamheid van de antimuscarinica op de primaire uitkomstmaat aandrang urine-incontinentie en op kwaliteit van leven. Voor een deel van de studies geldt dat de kwaliteit matig is, waarbij het niet mogelijk is via het GRADE systeem om tot duidelijke conclusies te komen. Antimuscarinica geven daarbij wel significant meer bijwerkingen, zoals droge mond en obstipatie, wat volgens de werkgroep een reden kan zijn tot staken van deze middelen. In de literatuur wordt in de onderzochte studie populaties geen cognitieve achteruitgang beschreven bij het gebruik van de verschillende antimuscarinica. Gezien het werkingsmechanisme is echter wel de verwachting dat de anticholinerge bijwerkingen inclusief cognitieve achteruitgang vaker zullen voorkomen wanneer er een verminderde cholinerge functie is, zoals bij kwetsbare ouderen. Derhalve adviseert de werkgroep om terughoudend te zijn met antimuscarinica bij deze kwetsbare groep.
De literatuur laat wat betreft de sympathicomimetica mirabegron en – het nu nog niet in Nederland beschikbare- vibegron ook geen duidelijk positief effect zien op de uitkomstmaten urine-incontinentie en kwaliteit van leven. Wel lijkt vooral vibegron minder bijwerkingen zoals droge mond te laten zien dan bijvoorbeeld tolterodine.

Gezien de positieve significante effecten van niet-farmacologische interventies, zoals blaastraining (vanzelfsprekend zonder de betreffende medicamenteuze bijwerkingen), zijn dit de eerst aangewezen behandelopties, ook bij oudere patiënten. Op basis van deze literatuur search zou behandeling met anticholinergica en sympathicomimetica niet als eerste keuze worden geadviseerd bij ouderen. De huidige module beschrijft de plaats van

farmacotherapeutische interventies bij ouderen met aandrang urine-incontinentie. Voor meer informatie over de conservatieve behandeling, zie de module 'Conservatieve behandeling UI bij ouderen'.

In de Europese richtlijn (EAU) female non-neurogenic lower urinary tract symptoms (F-LUTS), herzien in 2022, wordt medicatie gebruik bij oudere patiënten met aandrang urine incontinentie ook separaat geanalyseerd en beschreven. Hierbij dient te worden opgemerkt dat de EAU-richtlijn een andere systematiek voor het beoordelen van literatuur hanteert en naast de resultaten van reviews en RCTs ook studies met een andersoortige designs in de literatuur searches betrekt. Hierdoor kunnen de uitkomsten soms afwijken van de in de uw voorliggend richtlijn gebruikte systematiek. Samengevat wordt in de EAU-richtlijn gesteld dat:

- Antimuscarinica even effectief zijn bij ouderen, vergeleken met jongere patiënten;
- In cohortstudies gezien werd dat Oxybutinine mogelijk de cognitieve functie kan verslechteren bij oudere patiënten;
-Solifenacine, darifenacine en fesoterodine geen cognitieve dysfunctie veroorzaken in korte termijn studies;
- De impact van medicatie met anticholinergische effecten cumulatief is en vergroot bij langduriger exposure bij ouderen;
- Mirabegron effectief en veilig is bij ouderen boven de 65 jaar, waarbij een gunstiger bijwerkingenprofiel wordt gezien ten opzichte van antimuscarinica. Onbehandelde hypertensie is wel een contra-indicatie voor deze medicatie.

In de praktijk ziet de werkgroep ook verbetering bij specifieke patiëntengroepen die onvoldoende effect ervaren van de conservatieve maatregelen, of niet in aanmerking komen voor meer invasieve behandelingen. Het valt dan te overwegen om in het kader van 'shared decision making' de optie voor behandeling met deze medicatie te bespreken, waarbij men alert dient te zijn op eventuele bijwerkingen, zoals droge mond en obstipatie. Terughoudendheid bij kwetsbare ouderen lijkt hierbij geïndiceerd gezien kans op anticholinerge bijwerkingen. Mirabegron wordt in de internationale EAU richtlijn wel geadviseerd bij ouderen, maar hierbij wordt aangeraden om bloeddruk te controleren indien er gelijktijdig gebruik is van antihypertensiva, in ieder geval een keer in de eerste weken na start van het gebruik. Daarnaast wordt er in de samenvatting van de literatuur geen eenduidig positief effect op aandrang urine incontinentie beschreven, aangezien er nog onvoldoende studies zijn verricht naar dit onderwerp.

Kwaliteit van leven is een belangrijke uitkomstmaat, maar wordt regelmatig niet meegenomen in de studies; wellicht kan dit in toekomstig onderzoek meer worden meegenomen, aangezien dit een zeer belangrijke maat is voor de patiënten.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>

De tolerantie van antimuscarinica en mirabegron is onderzocht in o.a. de PREFER studie (Staskin, 2018) waarbij patiënten met aandrang urine incontinentie mirabegron met tolterodine in een cross-over design als monotherapie gedurende 3 maanden gebruikten. De 'medication tolerability score' en klinische verbetering was meer uitgesproken in de mirabegron groep dan bij de tolterodine groep en meer uitgesproken bij vrouwen, patiënten ouder dan 65 jaar en patiënten zonder incontinentie bij start van de studie. In de richtlijn van de EAU wordt het volgende beschreven over waarden en voorkeur voor patiënten; 1) naleving aan antimuscarinische behandeling is laag en verminderd over tijd door gebrek aan effect, bijwerkingen en kosten, 2) de meeste patiënten stoppen de antimuscarinische medicijnen in de 1^{e} 3 maanden. Hierbij wil de werkgroep aanraden de anticholinerge

effecten bij kwetsbare ouderen in ogenschouw te nemen. Bespreek vooraf met de patiënt de uit de literatuur bekende (mogelijke) bijwerkingen van de medicatie en beslis samen met de patiënt tot starten van medicatie, met inachtname het geslacht, de leeftijd en de medicatie-tolerantie-score.

Kosten (middelenbeslag)

Zeker door het generiek geworden zijn van meerdere van de onderzochte medicijnen ligt de prijs van behandeling niet hoog: De prijs van antimuscarinica/sympathicomimetica varieert per dag tussen de € 0,24 (solifenacine 10mg/oxybutinine 5 mg) en de € 0,90 (fesoterodine 4mg/mirabegron 50mg). Op jaarbasis kan dit evenwel een behoorlijke impact geven op het eigen risico (www.farmacotherapeutischkompas.nl)). De prijs van het nog in Nederland toe te laten vibregon is nog niet bekend.

Aanvaardbaarheid, haalbaarheid en implementatie

Gezien de brede beschikbaarheid van de medicatie, ziet de werkgroep geen problemen voor haalbaarheid en implementatie van de geformuleerde aanbevelingen. In de dagelijkse praktijk wordt deze medicatie al voorgeschreven.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Geen van de antimuscarinica of sympaticomimetica is superieur ten opzichte van een ander ten aanzien van het genezen of verbeteren van aandrang urine incontinentie. De zorgen rondom bijwerkingen aangaande de cognitie kan bij de keuze tussen antimucarinica en sympathicomimetica een rol spelen. De meeste patiënten stoppen met het gebruik van antimuscarinica in de eerste 3 maanden. Dit hoge aantal kan worden verklaard door een ervaren gebrek aan effectiviteit, bijwerkingen en kosten van het geneesmiddel. De werking van antimuscarinica is maximaal na 4 weken. Bij mirabegron is de tijd tot maximaal effect langer, namelijk rond de 6 weken. Gezien de mogelijke anticholinerge bijwerkingen zoals beschreven in de module over beta-3 receptor agonisten, gaat de voorkeur van de werkgroep uit naar antimuscarinica. Raadzaam is het recept voor maximaal 6 weken voor te schrijven met het oog op duurzaamheid en na 6 weken de behandeling te evalueren ten aan zien van effect en bijwerkingen, met instructie om eerder contact op te nemen bij hinderlijke bijwerkingen. Bloeddrukcontrole is noodzakelijk bij gebruik van mirabegron bij patiënten die antihypertensiva gebruiken.

Kies bij het behandelen van ouderen met UI zoveel mogelijk voor niet-farmacologische behandelingen alvorens antimuscarinica voor te schrijven.

Overweeg bij ouderen met UI antimuscarinica voor te schrijven indien conservatieve behandelingen onvoldoende effectief zijn, waarbij aandacht voor ontwikkelen van bijwerkingen zoals droge mond en obstipatie, en cognitieve achteruitgang.

Wees terughoudend met het voorschrijven van antimuscarinica bij kwetsbare oudere patiënten die at risk zijn voor cognitieve disfunctie of met hoge anticholinerge load.

De keuze van het antimuscarinicum maakt geen relevant verschil betreffende kans op anticholinerge bijwerkingen, mogelijk met uitzondering van oxybutynine.

Overweeg mirabegron als alternatief voor antimuscarinica. Monitor bijwerkingen, met name hypertensie.

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5 Implementatieplan

Aanbeveling	**Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar**	**Verwacht effect op kosten**	**Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)**	**Mogelijke barrières voor implementatie[1]**	**Te ondernemen acties voor implementatie[2]**	**Verantwoordelijken voor acties[3]**	**Overige opmerkingen**
1 - 5	<1 jaar	Geen effect	Geen, sluit grotendeels aan bij de klinische praktijk	n.v.t.	n.v.t.	n.v.t.	Geen

Table of excluded studies

Reference	Reason for exclusion
Abreu-Mendes, 2021	No subgroup of elderly patients
Cardozo, 2013	Wrong population: not specific elderly patients with dose escalation
Cartwright, 2011	Wrong population: no elderly
Castro-Diaz, 2015	Wrong study design: post-hoc analysis of three studies
Chapple, 2013a	Wrong population: no elderly
Chapple, 2013b	Wrong population: no elderly
Chapple, 2013c	Wrong population: no elderly
Chapple, 2014a	Wrong population: no elderly
Chapple, 2014b	Wrong population: no elderly
Chapple, 2015	No meta-analysis, not only RCTs and older study
Corcos, 2011	Wrong population: no elderly
Dell'Utri, 2012	Wrong population: no elderly
Dmochowski, 2010	Wrong population: no elderly
Duong, 2021	No subgroup of elderly patients
Goldfischer, 2015	Wrong population: no elderly
Herschorn, 2010	Wrong population: no elderly
Herschorn, 2013	Wrong population: no elderly
Herschorn, 2017	Wrong population: no elderly
Herschorn, 2018	Wrong population: no elderly
Herschorn, 2020	Same registration number and outcomes as Wagg 2020
Huan, 2012	Wrong population: no elderly
Inoue, 2019	Wrong population: no elderly
Kaplan, 2011	Wrong population: no elderly
Kaplan, 2014	Wrong population: no elderly
Kessler, 2011	Wrong population: no elderly
Khullar, 2011	Wrong population: no elderly
Khullar, 2013	Wrong population: no elderly
Khullar, 2016	Wrong population: no elderly
Kobayashi, 2018	Wrong population: no elderly
Kuo, 2015	Wrong population: no elderly
Leone Roberti, 2012	Wrong population: no elderly
Lozano-Ortega, 2020	Conflicts of interest
Mahapatra, 2022	Wrong population: no elderly
Meek, 2011	Wrong population: no elderly
Micheson, 2019	Wrong population: no elderly
Mueller, 2019	Subgroup analysis of Gratzke 2018, observational study
Newman, 2010	Wrong population: no elderly
Nitti, 2010	Wrong population: no elderly
Nitti, 2013	Wrong population: no elderly
Orešković, 2012	Wrong population: no elderly
Paquette, 2011	No meta-analysis for elderly, older study
Rana, 2016	Wrong population: no elderly
Rangganata, 2020	Systematic review with only two suitable RCTs
Robinson, 2018	Wrong population: no elderly
Rosa, 2018	Wrong study design: narrative review
Rossanese, 2015	Wrong population: no elderly
Sand, 2012	Wrong population: no elderly
Serels, 2010	Wrong population: no elderly
Shin, 2019	Wrong population: no elderly
Staskin, 2018	Wrong population: no elderly
Staskin, 2020	Wrong population: no elderly
Vecchioli Scaldazza, 2016	Wrong population: no elderly
Vouri, 2017	Older systematic review only about adverse events
Wagg, 2014	Not matching with PICO: no comparison between fesoterodine and placebo
Wani, 2021	Wrong population: no elderly
Yamaguchi, 2011	Wrong population: no elderly
Yamaguchi, 2014	Wrong population: no elderly
Yamaguchi, 2015	Wrong population: no elderly

Yamaguchi, 2016	Wrong population: no elderly
Yi, 2021	Wrong population: no elderly
Yoshida, 2018	Wrong population: no elderly

Modules Urine-incontinentie in de 2e/3e lijn – organisatie van zorg

Uitgangsvragen
Hoe optimaliseren we de zorg omtrent urine-incontinentie in de 2e/3e lijn?

De uitgangsvraag omvat de volgende deelvragen:
7.1 Hoe betrekken we de patiënt optimaal bij het maken van de therapiekeuze?
7.2 Hoe organiseren we de juiste zorg op de juiste plek?
7.3 Wat is de rol van de PROMS bij het evalueren van effectiviteit van de zorg?

Inleiding
Veel continentiezorg in de tweede en derde lijn is al goed georganiseerd. In toenemende mate zijn continentieverpleegkundigen betrokken bij de eerste contacten en/of de begeleiding. Daarnaast is er op veel plekken sprake van een goede samenwerking tussen urologen en gynaecologen in de vorm van laagdrempelig overleg, geüniformeerde zorgpaden, MDO's en/of gezamenlijke spreekuren. Met het oog op de modules die in 2023 zijn geüpdatet zijn er echter nog aanvullende stappen te zetten.

Samenvatting literatuur
Er is geen search uitgevoerd, omdat het niet de verwachting was dat er onderzoek beschikbaar is die deze uitgangsvraag beantwoord. Als deze onderzoeken er wel zouden zijn, dan is echter de kans groot dat de resultaten van dit onderzoek niet van toepassing zijn op de Nederlandse situatie. De uitgangsvraag is daarom beantwoord met behulp van 1) expert opinion en expertise van de werkgroep, 2) leerartikelen, 3) consensus artikelen en 4) bestaande afspraken met betrekking tot de inrichting van zorg in Nederland.

Hoe betrekken we de patiënt optimaal bij het maken van de therapiekeuze?

Overwegingen – van bewijs naar aanbeveling
<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>
Er is bij de werkgroep geen internationale literatuur bekend over de voor- en nadelen van 'shared decision making' bij de zorg omtrent urine-incontinentie, die een reflectie biedt op de Nederlandse praktijk.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Naast dat patiënten kunnen meebeslissen over de beste behandeling, is er ook toenemend behoefte van patiënten om mee te bepalen wat 'beste behandeling' voor hen betekent. Mede aangezwengeld door de discussie over het gebruik van synthetische mesh bij de chirurgische behandeling van stressincontinentie is er een herbezinning gekomen van wat als gewenste uitkomst wordt nagestreefd. Daarbij kan bijvoorbeeld een patiënt kiezen voor een minder effectieve behandeling met minder bijwerkingen in plaats van een effectievere behandeling met een groter risico op bijwerkingen. De keuze voor een behandeling van de overactieve blaas en urge-incontinentie (OAB/UUI) wordt bepaald door de te verwachten effectiviteit en de tolerantie van bijwerkingen. Omdat het succes van een behandeling in een individuele patiënt met OAB/UUI lastig te voorspellen is, is ook deze behandeling voorkeurssensitief (Seinen, 2021; Paudel, 2022).

<u>Kosten (middelenbeslag)</u>
Nieuw ontwikkelde keuzehulpen worden kosteloos aangeboden.

Aanvaardbaarheid, haalbaarheid en implementatie
Ontwikkeling van vaardigheden van zorgverleners en van hulpmiddelen, zoals begrijpelijke patiëntinformatie en keuzehulpen om tot echte 'shared decision making' (SDM) te komen zijn van belang. Uiteraard kan dit slechts als patiënten goed zijn geïnformeerd, waarbij de informatie op maat, aangepast naar behoefte en vaardigheden, wordt aangeboden. Het is belangrijk dat de patiëntinformatie en keuzehulpen alle behandelingen omvatten, goed te begrijpen zijn en vrij toegankelijk zijn voor patiënten en zorgverleners. Echt 'samen beslissen' vloeit voort uit goed 'samen bespreken'. Daarnaast is het van belang om betrokken zorgverleners te trainen in 'shared decision making', omdat zorgverleners wel het belang van SDM inzien, maar vaak moeite hebben met de uitvoering hiervan (Driever, 2020).

Aanbeveling 1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Naar aanleiding van de herziene modules van de richtlijn Urine-incontinentie in de 2e/3e lijn zijn organisatorische aspecten beschreven die tot verdere optimalisatie van zorg kunnen leiden. Omdat de behandeling van incontinentie voorkeurssensitief is, is het van belang om de voor- en nadelen van alle behandelingen te bespreken en af te stemmen op de voorkeuren en waarden van de patiënt, ook als behandelingen niet lokaal worden aangeboden. Hiervoor zijn middelen nodig zoals o.a. uit duidelijke patiënteninformatie, keuzehulpen en trainingen van dokters in 'shared decision making'.

Aanbeveling
Bespreek voor- en nadelen van alle behandelingen voor urine-incontinentie en stem deze af op de voorkeuren en waarden van de patiënt. Maak hierbij gebruik van goede patiëntinformatie op maat, vrij toegankelijke keuzehulpen en trainingen voor professionals SDM.

Hoe organiseren we de juiste zorg op de juiste plek?

Overwegingen – van bewijs naar aanbeveling
Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Er is bij de werkgroep geen internationale literatuur bekend over de voor- en nadelen van juiste zorg op de juiste plek bij de zorg omtrent urine-incontinentie, die een reflectie biedt op de Nederlandse praktijk.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
De juiste zorg op de juiste plek betekent dat laag complexe zorg dichtbij huis georganiseerd wordt en hoog complexe zorg in de tweede of derde lijn georganiseerd wordt. Idealiter worden niet invasieve en laag complexe behandelingen, zoals leefstijladviezen, bekkenfysiotherapie en medicatie in de eerste lijn uitgevoerd door huisartsen en bekkenfysiotherapeuten. Bij therapie falen kunnen patiënten worden doorverwezen naar de tweede of derde lijn voor meer invasieve behandelingen, zoals intravesicale Botox injecties of sacrale neuromodulatie. Door deze aanpak wordt de patiënt dichter bij huis geholpen en wordt overbelasting van de tweede en derde lijn voorkomen.
In de tweede en derde lijn zorgen multidisciplinaire aanpak en centralisatie voor onnodige (over)diagnostiek en interne doorverwijzingen en voor geoptimaliseerde behandeling met de hoogste kans op succesvolle uitkomst. Een grotere reisafstand kan een keerzijde zijn.

Kosten (middelenbeslag)
Met goede aandacht voor juiste zorg op de juiste plek zullen kosten voor continentiezorg kunnen afnemen. Dit door onnodige verwijzing van zorg naar de tweede en derde lijn enerzijds, en te verwachten efficiëntie en kwaliteitsverbetering van deels gecentraliseerde zorg anderzijds.

Aanvaardbaarheid, haalbaarheid en implementatie
In veel ziekenhuizen is incontinentiezorg doorgaans goed georganiseerd. Is de patiënt het beste af bij de bekkenfysiotherapeut, uroloog of gynaecoloog? En voor welk deel is de continentieverpleegkundige het meest geschikt? Hierover zijn veelal goede afspraken gemaakt en wordt goed samengewerkt in multidisciplinaire bekkenbodemspreekuren. In de meeste gevallen levert deze samenwerking efficiëntere zorg op voor patiënten en zorgverleners. Echter, blijkt het in sommige gevallen niet noodzakelijk om door een volledig bekkenbodemteam gezien te worden. Denk hierbij aan primaire stress-incontinentie of eenvoudige urge-incontinentie. Goede triage en regelmatige evaluatie van bekkenbodemteams blijft hiervoor nodig, waarbij naast aandacht voor juiste zorg op de juiste plek er ook aandacht is voor juiste diagnostiek voor de juiste indicatie.
Een deel van de in de richtlijn aanbevolen behandelingen zijn niet in elk ziekenhuis aanwezig. Denk hierbij vooral aan prothesechirurgie en aan sacrale neuromodulatie. Voor beide behandelingen geldt dat gecentraliseerde expertise, begeleiding van patiënten op lange termijn en afspraken met zorgverzekeraars van belang zijn. Onder optimale omstandigheden worden patiënten geïnformeerd over de behandelingen die er zijn en worden aanbevolen in de richtlijn, ook wanneer betreffende behandeling lokaal niet voorhanden is. Laagdrempelig overleg of doorverwijzing naar regionale partners waar specifieke behandelingen worden aangeboden zou kunnen helpen om te voorkomen dat patiënten een behandeloptie onthouden wordt, omdat een zorgverlener de behandeling onvoldoende kent en niet kan inschatten wat de waarde voor de patiënt kan zijn.

Niet ondenkbaar echter is dat behandelingen die nu nog niet gecentreerd zijn, al of niet opgelegd dat in de toekomst wel zullen worden. Dit geldt bijvoorbeeld voor behandeling van stressincontinentie bij de man, maar kan ook gelden voor de midurethrale sling bij vrouwen. Aantallen discussies, door beroepsverenigingen geformuleerde kwaliteitseisen, gedefinieerde subspecialismen: goede centralisatie kan ertoe leiden dat als zorg ingewikkelder wordt, ook deze op de goede plek komt. De in 2023 geupdate modules in deze richtlijn geven aanleiding hier nader naar te kijken. Maar juiste zorg op de juiste plek betekent ook dat continentiezorg in de tweede en derde lijn, die daar niet thuishoort, aandacht verdient. Aandacht dient te worden besteed aan het onnodig verwijzen vanuit de eerste lijn, bijvoorbeeld omdat leefstijl aanpassingen, bekkenfysiotherapie bij zuivere stressincontinentie of het uitproberen van een medicijn bij overactieve blaas niet werden uitgeprobeerd. Initiatieven ter verbetering van kennis in de eerste lijn, het naleven van de NHG richtlijn en goede afspraken met huisartsen over wanneer eventueel wel te verwijzen en andere initiatieven ter verbetering dienen derhalve te worden omarmd. Laagdrempelig overleg en kaderhuisartsen kunnen hierbij een belangrijke rol spelen.

Aanbevelingen 2 en 3
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Bovenstaande samengevat betekent dat er gestreefd dient te worden naar aandacht voor centralisatie van expertise enerzijds, maar ook uit de tweede/derde lijn houden wat daar niet heen hoeft.

Aanbevelingen

Onderhoud contact met de eerste lijn om te stimuleren dat conservatieve behandelingen (o.a. leefstijladviezen, bekkenfysiotherapie, medicatie) eerst zijn uitgevoerd voordat verwezen wordt naar de tweede lijn (de juiste zorg op de juiste plek).

Verwijs naar centra waar expertise is in specifieke behandelingen zoals sacrale neuromodulatie of prothesiologie, indien deze behandelingen lokaal niet beschikbaar zijn. Patiënten moeten geen behandelingen onthouden worden, omdat deze lokaal niet beschikbaar zijn.

Wat is de rol van de PROMS bij het evalueren van effectiviteit van de zorg?

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is buiten het ICHOM-document wat hieronder wordt besproken bij de werkgroep geen internationale literatuur bekend over de voor- en nadelen van PROMS bij de zorg omtrent urine-incontinentie, die een reflectie biedt op de Nederlandse praktijk.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

De evaluatie van de effectiviteit van incontinentiebehandeling kan lastig zijn. In de praktijk verschillen de subjectieve en objectieve effectiviteit tussen patiënten. Evaluatie met bijvoorbeeld een mictiedagboek is tijdsintensief en niet gemakkelijk voor patiënten. Daarnaast is het lastig om sterk subjectieve klachten zoals urgency te objectiveren met een mictiedagboek, waardoor deze vorm minder betrouwbaar is. Bij de evaluatie van een therapie moet ook de tolerantie geëvalueerd worden, zoals bijwerkingen van medicatie en tolerantie van invasieve behandelingen. Hiervoor kan gebruik gemaakt worden van ‘patient related outcome measures’ (PROMs). Een recent rapport van de aandoeningswerkgroep ‘Overactieve Blaas’ van het programma Uitkomstgerichte Zorg adviseert om de generieke en OAB specifieke patiënt gerapporteerde uitkomsten te meten met respectievelijk de OAB-q-SF, PROMIS Global 01, ICIQ-OAB en de PGI-I. Door effectiviteit van de behandeling zorgvuldiger te evalueren verwacht met minder praktijkvariatie en betere patiënttevredenheid. Hierbij is ook van belang de evaluatie binnen een redelijk termijn te doen, zoals voor medicatie en intravesicale Botox injecties binnen 4-6 weken en PTNS na 12 wekelijkse behandelingen. In het geval van sacrale neuromodulatie is een evaluatie van tussen de 2 tot 4 weken voldoende.

Kosten (middelenbeslag)

Er zijn bij de werkgroep geen effecten van het gebruik van PROMS op de zorgkosten bekend. Echter is de verwachting dat het gebruik van PROMS niet zal leiden tot meer zorgkosten.

Aanvaardbaarheid, haalbaarheid en implementatie

Belangrijk is dan wel dat overeenstemming wordt bereikt over zowel wat er uitgevraagd wordt als de manier waarop. Het ICHOM-document hierover kan als houvast dienen. Tijdens de ontwikkeling van deze richtlijn is door een andere werkgroep een document ‘Uitkomstgerichte zorg voor de overactieve blaas’ gemaakt. Voor de plaatsbepaling en evaluatie van verschillende PROMS verwijzen we naar dit document.

Aanbeveling 4

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Het is de verwachting dat investeren in een goede set PROMS kan leiden tot een uniformere manier van meten van kwaliteit van continentiezorg in de ruimste zin. Hiervoor verwijzen we naar het document in ontwikkeling 'Uitkomstgerichte zorg voor de overactieve blaas'.

Aanbeveling Evalueer klachten voor en na een behandeling gestructureerd met PROMs om uitkomst- en praktijkvariatie te verminderen.

Literatuur

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Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1	< 1 jaar	Het is onduidelijk of shared decision making een kosteneffectieve methode is om patiënten met een overactieve blaas te behandelen. Gezien de steeds ruimere beschikbaarheid van kosteloze keuzehulpen is echter de verwachting dat dit geen extra kosten met zich meebrengt.	Geen, sluit grotendeels aan bij de klinische praktijk.	-	-	-	n.v.t.
2 en 3	< 1 jaar	Door meer zorg op de juiste plek verwacht de werkgroep dat dit een kostenbesparing met zich meebrengt.	Organisatie van laagdrempelig overleg tussen de 1e en 2e/3e lijn	Storing in communicatie tussen de 1e en 2e/3e lijn.	-	NVU	n.v.t.
4	< 1 jaar	Het is de werkgroep niet bekend of het gebruik van PROMS de kosten zal verminderen. Hiermee zijn echter geen meerkosten gemoeid.	Verspreiding van het document 'Uitkomstgerichte zorg voor de overactieve blaas'	-	de aandoeningswerkgroep 'Overactieve Blaas' van het programma Uitkomstgerichte Zorg	NVU	n.v.t.

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Bijlage 1 Kennislacunes

Module SUI en prolaps chirurgie

Deze module is gebaseerd om tekortkomingen in de literatuur voor onze primaire zoekvraag: wat is de toegevoegde waarden van de gecombineerde chirurgische behandeling bij vrouwen met stress-urineincontinentie en prolaps ten opzichte van enkel plaatsen van een midurethrale sling.

What is the effect of combined surgery (SUI and prolapse surgery) in women with SUI and prolapse compared to single surgery (SUI or prolapse surgery)?

P: Women with SUI and primary prolapse (main complain incontinence)
I: Combined surgery (SUI surgery and prolapse surgery (mesh for prolapse excluded))
C: Only SUI surgery (i.e., only slings); only prolapse surgery (mesh excluded)
O: Post-operative SUI (persistence of complaints), reoperation due to persistence of complaints, post-operative prolapse symptoms (persistence of prolapse symptoms), complications, serious complications, patient experience, quality of life

How do existing prediction models (internally validated) perform in predicting (de novo) SUI after surgery perform in an external population?

P: Patients undergoing surgery for prolaps and/or SUI
I: Prediction model x
C: No prediction model/ prediction by clinical expert
O: Predictive values and/or clinical outcome

What is the cost effectiveness of combined surgery compared to single surgery?

P: Women with SUI and primary prolapse (main complain incontinence)
I: Combined surgery (SUI surgery and prolapse surgery (mesh for prolapse excluded))
C: Only SUI surgery (i.e., only slings); only prolapse surgery (mesh excluded)
O: Cost-effectiveness

Module Injectie bulkmateriaal vrouwen

What is the effectiveness of bulk injection in women with stress urinary incontinence compared to no treatment, physical therapy, or midurethal sling?

P: Women with stress urinary incontinence (SUI)
I: Injection with bulking material as primary treatment
C: No treatment, physiotherapy, tape
O: Effect on/cure of complaints of SUI, quality of life, adverse events

What is the cost-effectiveness of bulk injection in women with stress urinary incontinence compared to no treatment, physical therapy, or midurethal sling?

P: Women with stress urinary incontinence (SUI)
I: Injection with bulking material as primary treatment
C: No treatment, physiotherapy, tape
O: Costs

Module male-sling postprostatectomie

Definitie van mate van incontinentie en de relatie met behandelopties

Direct vergelijk tussen sling en AUS op basis van succes van de behandeling, lange termijn resultaten, kwaliteit van leven en complicaties

P: Men with postprostectatomy urine incontinence
I: Sling
C: AUS
O: Long term effects, quality of life, complications

De waarde van bulk in de behandeling van PPSUI

P: Men with postprostectatomy urine incontinence
I: Bulking materials
C: AUS, Sling, other treatment
O: Long term effects, quality of life, complications

Module botox volwassenen

- *Er is onduidelijkheid over de noodzaak van antibiotica profylaxe voorafgaand aan intravesicale BoNT-a- injecties.*
- *Er is onduidelijkheid over het staken van antistollingsmedicatie voorafgaand aan intravesicale BoNT-a- injecties.*
- *Er is onduidelijkheid over de optimale intravesicale verdoving voor intravesicale BoNT-A injecties.*
- *Er ontbreken sham-gecontroleerde studies naar de effectiviteit van SNM bij patiënten met refractaire OAB.*
- *Er ontbreken vergelijkende studies naar de effectiviteit van SNM en andere doses intravesicale BoNT-A injecties, zoals 100IE en 300IE, in patiënten met refractaire OAB. Er ontbreken kosteneffectiviteitsstudies naar intravesicale BoNT-A injecties en SNM met internal pulse generators (IPG's) met een langere levensduur.*
- *Er ontbreken studies naar de kosteneffectiviteit van 'samen beslissen'.*
- *Er ontbreken gerandomiseerde studies naar BoNT-A en SNM in de mannelijke patiënten met OAB.*

Module bèta-3 receptor agonisten

What is the efficacy of a beta-3 receptor agonist (sympathomimetic) in adults with UI compared to placebo/no treatment, antimuscarinic or a combination?

P: Adults with urine incontinence (UI)
I: Beta-3 receptor agonist (sympathomimetic: mirabegron [50 mg] or vibegron [75 mg])
C_1: Placebo/no treatment
C_2: Antimuscarinic (e.g., oxybutynin, solifenacin, tolterodine, darifenacin, fesoterodine)
C_3: Combination of an antimuscarinic and beta-3 receptor agonist
O: Volume voided per micturition, number of micturitions per 24h, number of urinary incontinence episodes per 24h, number of urgency episodes per 24h, adverse events, blood pressure, hypertension, pulse rate, tachycardia, palpitations

Module medicamenteuze behandeling ouderen

What is the effectivity and safety of antimuscarinic treatment or mirabegron/vibegron in elderly patients with urine incontinence, compared to placebo or no treatment?

P: Elderly with urine incontinence

I1: Antimuscarinic treatment (i.e.darifenacine, fesoterodine, tolterodine, solifenacine, oxybutinine) with or without bladder training/pelvic floor training
I2: Beta3-agonist (i.e. Mirabegron/vibegron) with or without bladder training/pelvic floor training
C1: Placebo, no treatment with or without bladder training/pelvic floor training
C2: Placebo, no treatment or antimuscarinic treatment with or without bladder training/pelvic floor training
O: reduced urge urine incontinence episodes, quality of life, adverse events/complications (in particular cognitive decline)

Modules organisatie van zorg

1. *Het is onduidelijk of shared decision making een kosteneffectieve methode is om patiënten met een overactieve blaas te behandelen.*

P: Patients treated for OAB
I: Shared decision making
C: Standard care with less/no elements of shared decision making
O: Effectiveness/costs/cost-effectiveness

2. *Het is onduidelijk of de gedefinieerde PROMs uitkomst en praktijkvariatie kunnen verminderen.*

P: Patients treated for OAB
I: Evaluation of care using patient reported outcome measures
C: Evaluation of care using unstandardized outcome measures
O: Uniformity in provided care, clinical outcomes

Bijlage 2 Zoekstrategieën

Module SUI en prolaps chirurgie

Richtlijn: NVU Urine-incontinentie 2e en 3e lijn	
Uitgangsvraag: Wat is de waarde van gecombineerde chirurgische ingreep (SUI en prolaps chirurgie) bij vrouwen met SUI en prolaps vergeleken met een enkele ingreep (SUI of prolaps chirurgie)?	
Database(s): Medline (OVID), Embase	Datum: 03-08-2022
Periode: >2010	Talen: Geen beperking
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting en opmerkingen: → Voor deze vraag is gezocht op de elementen **chirurgie bij (stress) urine incontinentie** (in het blauw) en **prolaps chirurgie** (in het groen). → De genoemde sleutelartikelen van Van der Ploeg (2018), Van der Ploeg (2014) en Van der Ploeg (2019) zitten in de zoekopbrengst. Van der Ploeg (2021) valt er buiten op studiedesign. → Resultaten staan in Rayyan.	
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 03-08-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews en RCT's over (gecombineerde) chirurgische ingreep bij vrouwen met (stress) urine incontinentie en prolaps. De literatuurzoekactie leverde 415 unieke treffers op.	

5

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	89	70	106
RCTs	277	94	309
Totaal	366	164	**415**

Zoekstrategie

Database	Zoektermen		
Embase	*No.*	*Query*	*Results*
	#1	('stress incontinence'/exp OR 'urodynamic stress incontinence'/exp OR 'stress urge incontinence':ti,ab,kw OR 'stress urgency incontinence':ti,ab,kw OR 'stress urinary incontinence':ti,ab,kw OR 'stress urine incontinence':ti,ab,kw OR 'stress incontinence*':ti,ab,kw OR (((urge OR urgency OR urinary OR urine) NEAR/3 incontinence):ti,kw)) AND ('surgery'/exp/mj OR surger*:ti,ab,kw)	16075
	#2	('pelvic organ prolapse'/exp/mj OR ((prolapse NEAR/4 surger*):ti,ab,kw)) AND ('surgery'/exp/mj OR surger*:ti,ab,kw)	10323
	#3	#1 AND #2 AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1041
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	822466
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3531947

	#8 #3 AND #5 – **SR's**	89
	#9 #3 AND #6 NOT #8 – **RCT's**	277
	#10 #8 OR #9	366
Medline (OVID)	1 (exp Urinary Incontinence, Stress/ or 'stress urge incontinence'.ti,ab,kf. or 'stress urgency incontinence'.ti,ab,kf. or 'stress urinary incontinence'.ti,ab,kf. or 'stress urine incontinence'.ti,ab,kf. or 'stress incontinence'.ti,ab,kf. or ((urge or urgency or urinary or urine) adj3 incontinence*).ti,kf.) and (exp General Surgery/ or exp Urologic Surgical Procedures/ or surger*.ti,ab,kf.) (8399) 2 (exp Pelvic Organ Prolapse/ or (prolaps* adj4 surger*).ti,ab,kf.) and (exp General Surgery/ or exp Urologic Surgical Procedures/ or surger*.ti,ab,kf.) (5854) 3 1 and 2 (1375) 4 limit 3 to yr="2010-Current" (862) 5 4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (824) 6 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (582217) 7 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1398429) 9 5 and 6 (70) – **SRs** 10 (5 and 7) not 9 (94) - **RCTs** 11 9 or 10 (164)	

Module 2 injectie bulkmateriaal vrouwen

Literature search strategy

5 ***Algemene informatie***

Richtlijn: NVU Urine-incontinentie 2e en 3e lijn

Uitgangsvraag: Wat is de effectiviteit van een injectie met bulkmateriaal bij vrouwen met SUI vergeleken met geen behandeling, fysiotherapie of tape?	
Database(s): Medline (OVID), Embase	Datum: 17-05-2022
Periode: >2010	Talen: Geen beperking
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting en opmerkingen: → Voor deze vraag is gezocht op de elementen **(stress) urine incontinentie** (in het blauw) en **bulkmateriaal** (in het groen). → De genoemde sleutelartikelen van Leone Roberti Maggiore (2015), Kirchin (2017), Ghoniem (2012), Siddiqui (2017), Matsuoka (2016) en Itkonen (2021) zitten allen in de zoekopbrengst. → Eventueel zijn er nog 111 observationele studiedesigns beschikbaar. → Resultaten staan in Rayyan.	
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 18-05-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews en RCT's over injectie met bulkmateriaal bij vrouwen met (stress) urine incontinentie. De literatuurzoekactie leverde 181 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	78	54	84
RCTs	98	22	97
Observationele studies	(104)	(70)	(111)
Totaal	176	76	**181**

Zoekstrategie

Database	**Zoektermen**		
Embase	*No.*	*Query*	*Results*
	#1	'stress incontinence'/exp OR 'urodynamic stress incontinence'/exp OR 'stress urge incontinence':ti,ab,kw OR 'stress urgency incontinence':ti,ab,kw OR 'stress urinary incontinence':ti,ab,kw OR 'stress urine incontinence':ti,ab,kw OR 'stress incontinence*':ti,ab,kw OR (((urge OR urgency OR urinary OR urine) NEAR/3 incontinence):ti,kw)	41042

	#2	'bulking agent'/exp OR 'injectable incontinence implant'/exp OR 'glutaraldehyde cross linked collagen'/exp OR ((bulk* NEAR/3 (injection* OR material OR agent*)):ti,ab,kw) OR (((transurethral OR intraurethral OR urethral OR paraurethral OR periurethral) NEAR/3 (injection* OR bulk*)):ti,ab,kw) OR ((glutaraldehyde NEAR/3 collagen):ti,ab,kw) OR contigent:ti,ab,kw OR ((porcine NEAR/3 implant*):ti,ab,kw) OR permacol:ti,ab,kw OR 'silicone elastomer':ti,ab,kw OR macroplastique:ti,ab,kw OR 'autologous fat':ti,ab,kw OR 'pyrolytic carbon':ti,ab,kw OR durasphere:ti,ab,kw OR 'calcium hydroxylapatite':ti,ab,kw OR coaptite:ti,ab,kw OR 'polyacrylamide hydrogel':ti,ab,kw OR bulkamid:ti,ab,kw OR 'dextran polymer':ti,ab,kw OR zuidex:ti,ab,kw	118442
	#3	#1 AND #2 AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	501
	#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	822466
	#5	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti	3531947

	#6	OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti 'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR	13092713

	aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) #7 #3 AND #4 **– SR's** 78 #8 #3 AND #5 NOT #7 **– RCT's** 98 #9 #3 AND #6 NOT (#7 OR #8) **- observationeel** 104 #10 #7 OR #8 OR #9 280 #11 #7 OR #8 176
Medline (OVID)	1 exp Urinary Incontinence, Stress/ or 'stress urge incontinence'.ti,ab,kf. or 'stress urgency incontinence'.ti,ab,kf. or 'stress urinary incontinence'.ti,ab,kf. or 'stress urine incontinence'.ti,ab,kf. or 'stress incontinence'.ti,ab,kf. or ((urge or urgency or urinary or urine) adj3 incontinence).ti,ab,kf. (24702) 2 (bulk* adj3 (injection* or material* or agent*)).ti,ab,kf. or ((transurethral OR intraurethral OR urethral OR paraurethral OR periurethral) adj3 (injection* OR bulk*)).ti,ab,kf. OR ((glutaraldehyde adj3 collagen).ti,ab,kf.) OR contigent.ti,ab,kf. OR ((porcine adj3 implant*).ti,ab,kf.) OR permacol.ti,ab,kf. OR 'silicone elastomer'.ti,ab,kf. OR macroplastique.ti,ab,kf. OR 'autologous fat'.ti,ab,kf. OR 'pyrolytic carbon'.ti,ab,kf. OR durasphere.ti,ab,kf. OR 'calcium hydroxylapatite'.ti,ab,kf. OR coaptite.ti,ab,kf. OR 'polyacrylamide hydrogel'.ti,ab,kf. OR bulkamid.ti,ab,kf. OR 'dextran polymer'.ti,ab,kf. OR zuidex.ti,ab,kf. (12618) 3 1 and 2 (768) 4 limit 3 to yr="2010-Current" (390) 5 4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (336) 6 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (565862) 7 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1376733)

	8 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5158952) 9 5 and 6 (54) **– SRs** 10 (5 and 7) not 9 (22) **- RCTs** 11 (5 and 8) not (9 or 10) (70) **- observationeel** 12 9 or 10 or 11 (146) 13 9 or 10 (76)

Module Male-sling postprostatectomie

Literature search strategy

5 ***Zoekverantwoording***

Algemene informatie

Richtlijn: NVU Urine-incontinentie 2e en 3e lijn	
Uitgangsvraag: Wat is de waarde van een male sling bij mannen met post-prostatectomie SUI?	
Database(s): Medline (OVID), Embase	Datum: 07-06-2022
Periode: >2010	Talen: Geen beperking
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	

Toelichting en opmerkingen: → Voor deze vraag is gezocht op de elementen **(stress) urine incontinentie** (in het blauw), (**male) sling** (in het groen) en **mannen óf prostatectomie** (in het oranje). → De genoemde sleutelartikelen van Abrams (2021) en Meisterhofer (2020) zitten in de zoekopbrengst. Wenjin (2022) is een conference abstract/supplement en Silva (2014) gaat niet over male sling. → Eventueel zijn er nog 157 observationele studiedesigns beschikbaar. → Resultaten staan in Rayyan.
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 07-06-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews en RCT's over male slings bij mannen met (stress) urine incontinentie. De literatuurzoekactie leverde 130 unieke treffers op.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	26	36	39
RCTs	80	19	91
Observationele studies	(87)	(168)	(157)
Totaal	106 (193)	55 (223)	**130 (287)**

Zoekstrategie

Database	Zoektermen		
Embase	*No.*	*Query*	*Results*
	#1	'stress incontinence'/exp OR 'urodynamic stress incontinence'/exp OR 'stress urge incontinence':ti,ab,kw OR 'stress urgency incontinence':ti,ab,kw OR 'stress urinary incontinence':ti,ab,kw OR 'stress urine incontinence':ti,ab,kw OR 'stress incontinence*':ti,ab,kw OR 'postprostatectomy incontinence':ti,ab,kw OR (((urge OR urgency OR urinary OR urine) NEAR/3 incontinence*):ti,kw)	41282
	#2	'male sling'/exp OR (((male OR transobturator OR retropubic OR quadratic OR bulbourethral) NEAR/4 sling*):ti,ab,kw)	2678
	#3	'prostate surgery'/exp OR Male/ OR 'prostatectomy'/exp OR 'male'/exp OR ((prostate NEAR/3 surger*):ti,ab,kw) OR prostatectom*:ti,ab,kw OR male:ti,ab,kw OR men:ti,ab,kw	11157783
	#4	#1 AND #2 AND #3 AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	302
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	822466

	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3531947
	#7	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR	13092713

	versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR (('or' OR 'rr') NEAR/6 ci):ab))) #8 #4 AND #5 **– SR's** 26 #9 #4 AND #6 NOT #8 **– RCT's** 80 #10 #4 AND #7 NOT (#8 OR #9) **- observationeel** 86 #11 #8 OR #9 OR #10 193 #12 #8 OR #9 106
Medline (OVID)	1 exp Urinary Incontinence, Stress/ or 'stress urge incontinence'.ti,ab,kf. or 'stress urgency incontinence'.ti,ab,kf. or 'stress urinary incontinence'.ti,ab,kf. or 'stress urine incontinence'.ti,ab,kf. or 'stress incontinence'.ti,ab,kf. or 'postprostatectomy incontinence'.ti,ab,kf. or ((urge or urgency or urinary or urine) adj3 incontinence*).ti,kf. (24835) 2 exp Suburethral Slings/ or ((male or transobturator or retropubic or quadratic or bulbourethral) adj4 sling*).ti,ab,kf. (3913) 3 exp Prostatectomy/ or Male/ or ((prostate adj3 surger*) or prostatectom* or (male or men)).ti,ab,kf. (9488409) 4 1 and 2 and 3 (579) 5 limit 4 to yr="2010-Current" (474) 6 5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (421) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (569795) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1381879) 9 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or

	single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5172605) 10 6 and 7 (36) **– SRs** 11 (6 and 8) not 10 (19) **- RCTs** 12 (6 and 9) not (10 or 11) (168) **- observationeel** 13 10 or 11 or 12 (223) 14 10 or 11 (55)

Module Botox volwassenen

Literature search strategy

5 ***Searchtabel***

Richtlijn: NVU Urine-incontinentie 2e en 3e lijn	
Uitgangsvraag: Wat is de plaats van behandeling met intravesicale botulinetoxine injecties ten opzichte van neuromodulatie bij volwassenen met een refractaire overactieve blaas?	
Database(s): Medline (OVID), Embase	Datum: 03-01-2022
Periode: >2010	Talen: Geen beperking
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting en opmerkingen: → Voor deze vraag is gezocht op de elementen **refractaire overactieve blaas** (in het blauw), **botulinetoxine injecties** (in het groen) en **neuromodulatie** (in het oranje). → De genoemde sleutelartikelen van Amundsen (2014), Amundsen (2018), Niu (2018) en He (2021) zitten in de zoekopbrengst.	

→ Resultaten staan in Rayyan.
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 03-01-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews, RCT's, en observationele studiedesigns over botulinetoxine injecties ten opzichte van neuromodulatie bij patiënten met een refractaire overactieve blaas. De literatuurzoekactie leverde 92 unieke treffers op.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	25	17	29
RCTs	20	16	25
Observationele studies	38	17	38
Totaal	83	50	**92**

Zoekstrategie

Database	Zoektermen		
Embase	*No.*	*Query*	*Results*
	#1	('overactive bladder'/exp OR 'urinary urgency'/exp OR 'urge incontinence'/exp OR 'nocturia'/exp OR (((bladder OR detrusor) NEAR/4 overactiv*):ti,ab,kw) OR incontinence:ti,ab,kw OR urge:ti,ab,kw OR nocturia*:ti,ab,kw) AND refract*:ti,ab,kw	3263
	#2	'botulinum toxin a'/exp OR botox*:ti,ab,kw OR botulinum*:ti,ab,kw OR onabotulinum*:ti,ab,kw OR dysport:ti,ab,kw	39513
	#3	'neuromodulation'/exp OR 'tibial nerve stimulation'/exp OR 'transcutaneous electrical nerve stimulation'/exp OR neuromodulation*:ti,ab,kw OR electrostimulation*:ti,ab,kw OR (((transcutaneous OR percutaneous OR sacral OR tibial) NEAR/3 'nerve stimulation*'):ti,ab,kw) OR ptns:ti,ab,kw OR tens:ti,ab,kw	83391
	#4	#1 AND #2 AND #3 AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	175
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	786610
	#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical	1857772

		trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	
	#7	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR	12775070

	aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) #8 #4 AND #5 **– SR's** 25 #9 #4 AND #6 NOT #8 **– RCT's** 20 #10 #4 AND #7 NOT (#8 OR #9) **- observationeel** 38 #11 #8 OR #9 OR #10 83
Medline (OVID)	1 (exp Urinary Bladder, Overactive/ or exp Urinary Incontinence, Urge/ or exp Nocturia/ or ((bladder or detrusor) adj4 overactiv*).ti,ab,kf. or incontinence.ti,ab,kf. or urge.ti,ab,kf. or nocturia.ti,ab,kf.) and refract*.ti,ab,kf. (1535) 2 exp Botulinum Toxins, Type A/ or (botox* or botulinum* or onabotulinum* or dysport).ti,ab,kf. (24032) 3 exp Transcutaneous Electric Nerve Stimulation/ or exp Electric Stimulation Therapy/ or (neuromodulation* or electrostimulation* or ptns or tens).ti,ab,kf. or ((transcutaneous or percutaneous or sacral or tibial) adj3 'nerve stimulation*').ti,ab,kf. (113477) 4 1 and 2 and 3 (137) 5 limit 4 to yr="2010-Current" (125) 6 5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (119) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (1340806) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (538789) 9 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or

	masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5048882) 10 6 and 7 (17) **– SRs** 11 (6 and 8) not 10 (16) **- RCTs** 12 (6 and 9) not (10 or 11) (17) **- observationeel** 13 10 or 11 or 12 (50)

Module 5 bèta-3 receptor agonisten

5 Literature search strategy

Zoekverantwoording

Algemene informatie

Richtlijn: NVU Urine-incontinentie 2e en 3e lijn	
Uitgangsvraag: Wat is de waarde van een bèta-3-receptor agonist (sympathicomimeticum) bij UI in de tweede- en derdelijnszorg in vergelijking met een placebo/geen behandeling of antimuscarinica dan wel een combinatie?	
Database(s): Medline (OVID), Embase	Datum: 18-08-2022
Periode: >2010	Talen: Geen beperking
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting en opmerkingen: → Voor deze vraag is gezocht op de elementen **urine incontinentie** (in het blauw) en **bèta-3-receptor agonist (mirabegron/vibegron)** (in het groen). → De genoemde sleutelartikelen van Cui (2014) en Wu (2014) zitten in de zoekopbrengst. → Eventueel zijn er nog 172 observationele studiedesigns beschikbaar. → Resultaten staan in Rayyan.	

Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 18-08-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews en RCT's over het gebruik van bèta-3-receptor agonist/mirabegron bij patiënten met urine incontinentie. De literatuurzoekactie leverde 479 unieke treffers op.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	143	82	149
RCTs	324	128	330
Observationele studies	(161)	(138)	(172)
Totaal	467	210	**479**

Zoekstrategie

Database	**Zoektermen**		
Embase	*No.*	*Query*	*Results*
	#1	'overactive bladder'/exp/mj OR 'urge incontinence'/exp OR 'bladder overactivity':ti,ab,kw OR 'overactive bladder':ti,ab,kw OR 'detrusor overactivity':ti,ab,kw OR 'overactive detrusor':ti,ab,kw OR 'overactive urinary bladder':ti,ab,kw OR 'urge incontinence':ti,ab,kw OR 'urgency incontinence':ti,ab,kw OR 'urinary incontinence':ti,ab,kw OR 'urine incontinence':ti,ab,kw	63491
	#2	'mirabegron'/exp OR 'vibegron'/exp OR 'beta 3 adrenergic receptor'/exp OR mirabegron:ti,ab,kw OR vibegron:ti,ab,kw OR ((('beta 3' OR β3) NEAR/3 (adrenoceptor* OR receptor* OR adrenergic)):ti,ab,kw)	6358
	#3	#1 AND #2 AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	921
	#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature')	849935

		NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
	#5	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3600457
	#6	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR	13366696

	control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) #7 #3 AND #4 **– SR's** 143 #8 #3 AND #5 NOT #7 **– RCT's** 324 #9 #3 AND #6 NOT (#7 OR #8) **- observationeel** 161 #10 #7 OR #8 OR #9 628 #11 #7 OR #8 467
Medline (OVID)	1 exp Urinary Bladder, Overactive/ or exp Urinary Incontinence, Urge/ or exp Urinary Incontinence/ or ((bladder or detrusor) adj4 overactiv*).ti,ab,kf. or 'urge incontinence'.ti,ab,kf. or 'urgency incontinence'.ti,ab,kf. or 'urinary incontinence'.ti,ab,kf. or 'urine incontinence'.ti,ab,kf. (1535) 2 exp Receptors, Adrenergic, beta-3/ or (mirabegron or vibegron).ti,ab,kf. or (beta-3 adj3 (adrenoceptor* or receptor* or adrenergic)).ti,ab,kf. (24032) 3 1 and 2 (696) 4 limit 3 to yr="2010-Current" (669) 5 4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (567) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data

	source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (1400653) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (583929) 9 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5225241) 10 5 and 7 (82) **– SRs** 11 (5 and 8) not 10 (128) **- RCTs** 12 (5 and 9) not (10 or 11) (138) **- observationeel** 13 10 or 11 or 12 (348) 14 10 or 11 (210)

Medicamenteuze behandeling ouderen

Literature search strategy

Richtlijn: NVU Urine-incontinentie 2e en 3e lijn
Uitgangsvraag: Wat is de waarde van medicamenteuze behandeling bij ouderen met UI in de tweede- en derdelijnszorg?
Database(s): Medline (OVID), Embase
Periode: >2010
Literatuurspecialist: Linda Niesink
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.
Toelichting en opmerkingen: → Voor deze vraag is gezocht op de elementen **urine incontinentie** (in het blauw), **ouderen** (in het groen) en **antimuscarinica/mirabegron** (in het oranje). → De genoemde sleutelartikelen van Chapple (2020), Mueller (2019), Dubeau (2014) en Wagg (2013) zitten in de zoekopbrengst. → Eventueel zijn er nog 140 observationele studiedesigns beschikbaar. → Resultaten staan in Rayyan.
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 10-05-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews en RCT's over antimuscarinica/mirabegron bij ouderen met urine incontinentie. De literatuurzoekactie leverde 450 unieke treffers op.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	35	40	46
RCTs	344	228	404
Observationele studies	(100)	(151)	(140)
Totaal	379	268	**450**

5

Zoekstrategie

Database	**Zoektermen**		
Embase	*No.*	*Query*	*Results*
	#1	'overactive bladder'/exp OR 'urge incontinence'/exp OR 'bladder overactivity':ti,ab,kw OR 'overactive bladder':ti,ab,kw OR 'detrusor overactivity':ti,ab,kw OR 'overactive detrusor':ti,ab,kw OR 'overactive urinary bladder':ti,ab,kw OR 'urge	64610

		incontinence':ti,ab,kw OR 'urgency incontinence':ti,ab,kw OR 'urinary incontinence':ti,ab,kw OR 'urine incontinence':ti,ab,kw	
	#2	'aged'/exp OR 'geriatrics'/exp OR 'elderly care'/exp OR elder*:de,ab,ti OR eldest:de,ab,ti OR frail*:de,ab,ti OR geriatri*:de,ab,ti OR ((old NEXT/1 age*):de,ab,ti) OR ((oldest NEXT/1 old*):de,ab,ti) OR senior*:de,ab,ti OR senium:de,ab,ti OR ((very NEXT/1 old*):de,ab,ti) OR septuagenarian*:de,ab,ti OR octagenarian*:de,ab,ti OR octogenarian*:de,ab,ti OR nonagenarian*:de,ab,ti OR centarian*:de,ab,ti OR centenarian*:de,ab,ti OR supercentenarian*:de,ab,ti OR 'older people':de,ab,ti OR ((older NEXT/1 subject*):de,ab,ti) OR ((older NEXT/1 patient*):de,ab,ti) OR ((older NEXT/1 age*):de,ab,ti) OR ((older NEXT/1 adult*):de,ab,ti) OR 'older man':de,ab,ti OR 'older men':de,ab,ti OR 'older male*':de,ab,ti OR 'older woman':de,ab,ti OR 'older women':de,ab,ti OR 'older female*':de,ab,ti OR ((older NEXT/1 population*):de,ab,ti) OR ((older NEXT/1 person*):de,ab,ti)	3859407
	#3	'mirabegron'/exp/mj OR 'darifenacin'/exp/mj OR 'fesoterodine'/exp/mj OR 'tolterodine'/exp/mj OR 'solifenacin'/exp/mj OR 'oxybutynin'/exp/mj OR darifenacin:ti,ab,kw OR fesoterodine:ti,ab,kw OR tolterodine:ti,ab,kw OR solifenacin:ti,ab,kw OR oxybutynin:ti,ab,kw OR mirabegron:ti,ab,kw	6025
	#4	#1 AND #2 AND #3 AND [2010-2022]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	551
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study	822466

		selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3531947
	#7	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter	13092713

	study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) #8 #4 AND #5 **– SR's** 35 #9 #4 AND #6 NOT #8 **– RCT's** 344 #10 #4 AND #7 NOT (#8 OR #9) **- observationeel** 100 #11 #8 OR #9 OR #10 479 #12 #8 OR #9 379
Medline (OVID)	1 exp Urinary Bladder, Overactive/ or exp Urinary Incontinence, Urge/ or exp Urinary Incontinence/ or ((bladder or detrusor) adj4 overactiv*).ti,ab,kf. or 'urge incontinence'.ti,ab,kf. or 'urgency incontinence'.ti,ab,kf. or 'urinary incontinence'.ti,ab,kf. or 'urine incontinence'.ti,ab,kf. (1535) 2 exp Adrenergic beta-Agonists/ or (darifenacin or fesoterodine or tolterodine or solifenacin or oxybutynin or mirabegron).ti,ab,kf. (24032) 3 exp "Aged"/ or exp "Aged, 80 and over"/ or exp "Frail Elderly"/ or exp "Geriatrics"/ or exp "Geriatric Psychiatry"/ or exp "Geriatric Nursing"/ or exp "Geriatric Dentistry"/ or exp "Dental Care for Aged"/ or exp "Health Services for the Aged"/ or (elder* or eldest or frail* or geriatri* or old age* or oldest old* or senior* or senium or very old* or septuagenarian* or octagenarian* or octogenarian* or nonagenarian* or centarian* or centenarian* or supercentenarian* or older people or older subject* or older patient* or older age* or older adult* or older man or older men or older male* or older woman or older women or older female* or older population* or older person*).ti,ab,kf. (113477) 4 1 and 2 and 3 (137) 5 limit 4 to yr="2010-Current" (125) 6 5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (119) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data

	source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (1340806) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (538789) 9 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5048882) 10 6 and 7 (40) **– SRs** 11 (6 and 8) not 10 (228) **- RCTs** 12 (6 and 9) not (10 or 11) (151) **- observationeel** 13 10 or 11 or 12 (419) 14 10 or 11 (268)

Bijlage 3 Risk of bias tables en evidence tables

Module SUI en prolaps chirurgie

5 **Research question: What is the effect of combined surgery (SUI and prolapse surgery) in women with SUI and prolapse compared to single surgery (SUI or prolapse surgery)?**

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Baessler, 2018 [individual study characteristics deduced from [Baessler, 2018]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to November 2017* Four RCT's selected for data extraction **A**: Borstad, 2010 **B:** Van der Ploeg, 2015 Study design: RCT. Setting and Country: **A**: regional hospitals and University clinics, Norway	Inclusion criteria SR: - Randomised controlled trials (RCTs) with a sample size of at least 20 in each group and follow-up time of at least six months - Adult women seeking treatment for symptomatic pelvic organ prolapse with or without symptomatic or occult SUI - Comparing any type of abdominal or vaginal surgery for pelvic organ prolapse with or without concomitant or	Describe intervention: **A**: TVT performed at the same time as prolapse repair surgery **B:** vaginal prolapse repair with MUS	Describe control: **A**: TVT performed 3 months after prolapse repair surgery if still clinically indicated (of 99 participants randomised to this group, 53 underwent TVT 3 months post prolapse repair) **B**: vaginal prolapse repair without MUS	End-point of follow-up: **A**: 12 months **B:** 12 months For how many participants were no complete outcome data available? Not reported.	Outcome measure 1: subjective postoperative SUI *Additional MUS vs vaginal repair alone* **A**: 0.19 (0.07 to 0.52) **B**: 0.37 (0.22 to 0.60) Outcome measure 2: reoperation **B**: 0.05 (0 to 0.74)	Brief description of author's conclusion In women with POP and SUI (symptomatic or occult), a concurrent MUS probably reduces postoperative SUI and should be discussed in counselling. It might be feasible to postpone the MUS and perform a delayed (two-stage) continence procedure, if required. Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question The limited data available were not suitable for meta-analysis. Level of evidence: GRADE GRADE assessed for each individual study.

	B: multi-centre, Netherlands <u>Source of funding and conflicts of interest:</u> **A**: study authors state no conflicts of interest; no details provided of trial funding **B**: Jan-Paul W.R. Roovers: medical consultant for American Medical Systems (AMS). C. Huub van der Vaart: medical consultant for BARD Medical. Funding from Academic Medical Center (AMC) Department of Gynaecology	delayed continence surgery <u>Exclusion criteria SR:</u> Not reported. *Nineteen studies included, but four studies included in literature analysis* <u>Important patient characteristics at baseline</u>: *Mean age (mean ± SD or range)* **A:** 57.2 (31 to 89) vs. 59.9 (38 to 85) **B**: NR Unknown if groups were comparable at baseline					**A**: high risk for blinding **D**: high risk for blinding <u>Sensitivity analyses:</u> - studies without high risk of bias - a random-effects model <u>Heterogeneity</u>: Study authors considered whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. Statistical heterogeneity was assessed by measuring I^2. An I^2 measurement greater than 50% was defined as indicating substantial heterogeneity. For comparison additional MUS vs vaginal repair alone: I^2 =28%
Van der Ploeg, 2018 [individual study characteristics deduced from [Van der Ploeg, 2018]]	SR and meta-analysis of RCTs *Literature search up to January 2017* Four RCT's selected for data extraction **A**: Borstad, 2010 **B**: Van der Ploeg, 2015	<u>Inclusion criteria</u> - Randomized trials comparing prolapse surgery with and without an incontinence procedure and describing at least one of the following outcomes with a follow-up of at least 3 months: urinary	<u>Describe intervention:</u> **A**: TVT performed at the same time as prolapse repair surgery **B:** vaginal prolapse repair with MUS	<u>Describe control:</u> **A**: TVT performed 3 months after prolapse repair surgery if still clinically indicated (of 99 participants randomised to this group, 53 underwent TVT 3 months post prolapse repair) **B**: vaginal prolapse repair without MUS	<u>End-point of follow-up</u>: **A**: 12 months **B:** 12 months <u>For how many participants were no complete outcome data available?</u> Not reported.	<u>Outcome measure-1:</u> <u>Adverse events</u> *Vaginal prolapse repair with or without MUS* **A**: 1.92 (0.90 to 4.12) **B**: 1.55 (1.04 to 2.32) <u>Outcome measure-2:</u> <u>Serious adverse events</u> *Vaginal prolapse repair with or without MUS* **B**: 2.82 (0.93 to 8.54)	<u>Brief description of author's conclusion</u> Vaginal prolapse repair with MUS reduced the risk of postoperative SUI in women with preoperative SUI symptoms or occult SUI, but serious adverse events were more frequent <u>Personal remarks on study quality, conclusions, and other issues (potentially)</u>

PS., study characteristics and results are extracted from the SR (unless stated otherwise)	Study design: RCT. Setting and Country: See description of Baessler 2018. Source of funding and conflicts of interest: See description of Baessler 2018	incontinence (e.g. SUI or treatment for UI); bladder storage symptoms (e.g. frequency or nocturia); voiding symptoms (e.g. incomplete emptying or retention); or adverse events (e.g. bladder injury or blood loss). - English literature - Publication date: January 1995 until January 2017 Exclusion criteria Excluded interventions: - Incontinence procedures: Kelly plication, fascia slings etc. - Trials that only studies obliterative procedures as prolapse surgery *Ten studies included, but four studies included in literature analysis* Important patient characteristics at baseline:					relevant to the research question Quality of the individual studies. Level of evidence: GRADE GRADE assessed for each individual study. **A**: moderate **B**: moderate Sensitivity analyses: No Heterogeneity: Statistical heterogeneity assessed: substantial statistical heterogeneity considered as I^2 of more than 25%

		See description of Baessler 2018 Unknown if groups were comparable at baseline					

Risk of bias table

Research question: What is the effect of combined surgery (SUI and prolapse surgery) in women with SUI and prolapse compared to single surgery (SUI or prolapse surgery)?

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns**

	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	**HIGH**
Borstad, 2010	Definitely yes; Reason: Department of Epidemiology and Biostatistics (investigator not involved in the clinical treatment of patients) performed the randomization, consisting of permuted block randomization stratified by centre.	Definitely yes; Reason: Sealed, opaque envelopes for each hospital were generated.	Definitely no; Reason: Participants and personnel were aware of allocation. Preoperative and postoperative assessors were also not blinded to allocation.	Definitely yes; Reason: For TVT with prolapse repair, four women were lost to follow-up and no lost to follow-up occurred for only TVT repair.	Probably no; Reason: The outcome measure complications were not mentioned as outcome in the protocol or methods section and were not pre-specified. Subjective and objective measures combined for measuring post-operative SUI.	Probably yes; Reason: No other problems for risk of bias.	LOW (post-operative SUI, adverse events)
Van der Ploeg, 2015	Definitely yes; Reason: Randomization sequence generated by central computer random number generator using blocks of four and stratified for centre and the leading edge of the POP in a 1:1 ratio for the two comparison groups.	Definitely yes; Reason: Sequence list was concealed from the investigators and those groups including participants.	Definitely no; Reason: The study was not blinded.	Definitely yes; Reason: Minimal loss to follow-up.	Probably yes; Reason: Outcomes reported in protocol were also reported in the article.	Probably yes; Reason: No other problems for risk of bias.	Some concerns (post-operative SUI) LOW (reoperation due to persistence of SUI complaints, adverse events, serious adverse events)

Module 2 Injectie bulkmateriaal vrouwen

Research question: What is the effectiveness of bulk injection in women with stress urinary incontinence compared to no treatment, physical therapy, or tape?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kirchin, 2017 [individual study characteristics deduced from [Kirchin, 2017]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to November 2010* Three RCT's selected for data extraction **A**: Corcos, 2005 **B**: Maher, 2005 **C**: Ter Meulen, 2009 Study design: RCT. Setting and Country: Not described. Source of funding and conflicts of interest: Not described for individual studies.	Inclusion criteria SR: All randomised or quasi-randomised controlled trials in the treatment of urinary incontinence in women, in which at least one management arm involved urethral injection therapy. Exclusion criteria SR: Studies were excluded from the review if they were not randomised or quasi randomised controlled trials of treatment for urinary incontinence, or if they made	Describe intervention: **A**: Collagen injection **B**: Macroplastique **C**: Macroplastique	Describe control: **A**: Open surgery (bladder neck suspension, sling or Burch) **B**: Pubovaginal sling **C**: Pelvic floor muscle exercises	End-point of follow-up: **A**: 12 months **B**: 6 months, 12 months, ± 62 months (range 43-71 months) **C:** 3- and 12-months (12 months only for Macroplastique) For how many participants were no complete outcome data available? Not reported.	Outcome measure-1: *Number not cured (worse, unchanged or improved) at three months* Effect measure: RR (95% CI): **C**: 0.7 (0.52 to 0.94) *Number not cured (subjectively) within first year* Effect measure: RR (95% CI): **B**: 2.39 (0.52 to 10.99) *Number not cured (objectively) within first year* Effect measure: RR (95% CI): **A:** 1.69 (1.02 to 2.79) **B:** 4.77 (1.96 to 11.64) Outcome measure-2: *Number not improved (worse or unchanged) at three months* Effect measure: RR (95% CI): **C**: 0.22 (0.03 to 1.81) Outcome measure-3: *Disease-specific measures*	Brief description of author's conclusion The available evidence base remains insufficient to guide practice. One small trial comparing silicone particles with pelvic floor muscle training was suggestive of benefit at three months but it is not known if this was sustained, and the treatment was associated with high levels of postoperative retention and dysuria. Greater symptomatic improvement was observed with surgical treatments, though the advantages need to be set against likely higher risks. Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question The limited data available were not suitable for meta-analysis.

		comparisons other than those prespecified. *Fourteen studies included, but three studies included in literature analysis* <u>Important patient characteristics at baseline</u>: *N, mean age* **A**: 66 vs 67; age NR **B**: 23 vs 22; median age 65 yrs vs 63 yrs **C**: 24 vs 21; age NR Unknown if groups were comparable at baseline				Effect measure: mean difference (95% CI): **A**: 3.6 (-2.91 to 10.11) **C**: 0.54 (0.16 to 0.92) <u>Outcome measure-4:</u> *Peri- and postoperative complications* Effect measure: RR (95% CI): **C**: 34.32 (2.2 to 535.8) <u>Outcome measure-5:</u> *Presence of urinary urgency and urge incontinence* Effect measure: RR (95% CI): **A**: 0.32 (0.01 to 7.45) <u>Outcome measure-6:</u> *Numbers not satisfied* Effect measure: RR (95% CI): **A:** 0.9 (0.48 to 1.7) **B:** 2.15 (0.78 to 5.92)	<u>Level of evidence: GRADE</u> For all outcome measures, low to very low GRADE. <u>Sensitivity analyses:</u> None. <u>Heterogeneity</u>: Not applicable.

Research question: What is the effectiveness of bulk injection in women with stress urinary incontinence compared to no treatment, physical therapy, or tape?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Itkonen Freitas, 2020	Type of study: Randomized controlled parallel group trial Setting and country: Helsinki University Hospital (Finland) Funding and conflicts of interest: Supported by grants. No direct or indirect commercial, personal, academic, political, religious, or ethical incentive is associated with publishing this article.	Inclusion criteria: - SUI not responsive to conservative treatment - Patient age > 18 years - No previous incontinence procedure - Positive cough stress test without urge-type leakage - PVR volume <100 ml - Bladder capacity >300 ml Exclusion criteria: - Body mass index >35 kg/m^2 - Neurogenic disease - Use of anticholinergics or mirabegron - Illness or another condition causing a risk of	Describe intervention (treatment/procedure/test): TVT (tension-free vaginal tape) The Gynecare TVT Exact system was used as mid-urethral sling. The TVT was inserted with the patient under local anesthesia using 70 to 100 ml 0.25% prilocaine with epinephrine. Cystoscopy with a 70-degree optic was performed during the operation to detect possible bladder perforation. The sling was adjusted to avoid retention using the cough test (200 to 300 ml saline in the bladder), allowing a few drops of saline to escape on vigorous coughing. The study nurse telephoned the patients 1 month after the initial procedure. After the 3-month visit, patients were instructed to contact the	Describe control (treatment/procedure/test): PAHG (polyacrylamide hydrogel) PAHG (Bulkamid) was injected with the patient under local anesthesia with periurethral lidocaine (10 ml) injections. Under endoscopic control at 1.5 cm from the vesicourethral junction hydrogel was injected at the 10, 2, 5 and 7 o'clock locations with the aim that the hydrogel cushions would meet at the midline. The study nurse telephoned the patients 1 month after the initial procedure. One more PAHG injection (an addition or top up) after the initial PAHG treatment was offered if the patient was not satisfied. PAHG additions were scheduled for the first postoperative visit at 3 months and done based on filling up or	Length of follow-up: 12 months Loss-to-follow-up: Intervention: N=3 (2.9%) Reasons: unable to contact (n=1) and interviewed only by phone (n=2) Control: N=1 (1%) Reasons: interviewed only by phone (n=1) Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): *Patient satisfaction (measured with VAS)* Score of 80 or greater: I: 96 (95.0%) C: 64 (59.8%) Difference = 35.2% (24.4 to 45.1) p <0.001 Median satisfaction score: I: 99 (IQR 94-100) C: 85 (IQR 65-98) *Cure* Objective (cough stress test negative): I: 96 (95.0%) C: 71 (66.4%) Difference = 28.7% (18.4 to 38.5%) Subjective cure (Likert scale): I: 84 (83.2%) C: 25 (23.4%)	Author's conclusion: At the 12-month follow-up PAHG did not show noninferior patient satisfaction compared to TVT in women with primary SUI. While TVT treatment provides higher satisfaction and cure rates than PAHG, complications were almost exclusively associated with TVT. Since most PAHG treated women also reported high satisfaction and were objectively cured, women with primary SUI can be offered PAHG as an alternative therapy with subsequent TVT in the event of failure. However, in women who expect to be completely cured by the initial treatment and who are willing to accept the complication risks, TVT should be offered as first line treatment.

	Financial interest and/or other relationship with Contura.	complications during the TVT operation - Active malignancy - Urinary tract infection - More than second degree urogenital prolapse - Pregnancy or future plans for pregnancy - Inability to understand the purpose of the study <u>N total at baseline</u>: Intervention: 104 Control: 108 <u>Important prognostic factors[2]</u>: *Median age (IQR):* *I: 48 (42 – 57)* *C: 49 (42 – 60)* *BMI* *I: 24 (22 – 26)* *C: 25 (22 – 27)* <u>Groups comparable at baseline</u>	study nurse if still unsatisfied.	replacing a missing cushion. Patients who elected TVT after the initial procedure were also treated within 3 months upon request. After the 3-month visit patients were instructed to contact the study nurse if still unsatisfied.		Difference = 59.8% (47.5 to 69.1) p <0.001 Subjective improved: I: 17 (16.8%) C: 73 (68.2%) Difference = -51.4 (-61.5 to -38.8) p <0.001 *Complications (perioperative and/or postoperative)* I: 45 (44.6%) C: 21 (19.6%) Difference = 24.9% (12.3 to 36.6) <u>Less than 3 months postoperative</u> Reoperation due to retention: I: 3 (3.0%) C: 0 Difference = 3.0 (-1.0 to 8.4) p = 0.113 Urinary tract infections I: 7 (6.9%) C: 9 (8.4%) Difference = -1.5 (-9.1 to 6.3) p = 0.689 <u>12 months postoperative</u> Pelvic/implantation site/tape pain I: 5 (5.0%) C: 0 Difference = 5.0 (0.5 to 11.1) p = 0.026	

Itkonen Freitas, 2021	Type of study: Randomized trial Setting and country: Helsinki University Hospital (Finland) Funding and conflicts of interest: Funded by a Helsinki University Hospital research grant and an unrestricted grant from Contura. The funders of the study had no influence in the study design, data collection, data analysis, data interpretation or writing of the report	Inclusion criteria: SUI with inadequate response to pelvic floor muscle training. Other inclusion criteria reported in Itkonen Freitas 2020 Exclusion criteria: Reported in Itkonen Freitas 2020 N total at baseline: Intervention: 104 Control: 108 Important prognostic factors[2]: *Age (±SD)):* *I: 50.4 ± 10.4* *C: 51.5 ± 11.0* *BMI* *I: 24.5 ± 3.5* *C: 24.8 ± 3.6* Groups comparable at baseline	Describe intervention (treatment/procedure/test): TVT (tension-free vaginal tape) Both procedures were performed in an outpatient setting using local anesthesia. The TVT was inserted as described in Itkonen Freitas 2020.	Describe control (treatment/procedure/test): PAHG (polyacrylamide hydrogel) PAHG injections (Bulkamid®, Contura, Denmark) were injected under endoscopic control 1.5 cm from the vesico-urethral junction to four sites with hydrogel cushions meeting at midline	Length of follow-up: 12 months Loss-to-follow-up: Six women in the TVT group and five women in the PAHG group withdrew their consent after randomization, one woman accidentally received two randomization envelopes, and four women were lost to follow-up. Incomplete outcome data: At baseline: I: 3/104 (2.9%) C: 1/108 (0.9%) After 1 year: I: 1/104 (1%) C: 0	Outcome measures and effect size (include 95%CI and p-value if available): *UDI-6 (total score max 100)* I: 7.89 ± 7.65 (95% CI 6.38–9.40), p = < 0.001 C: 18.96 ± 13.20 (95% CI 16.43–21.50), p = < 0.001 Between-group difference < 0.001 (95% CI -3.37–1.95) *IIQ-7 (total score max 100)* I: 3.49 ± 8.61 (95% CI 1.79–5.20), p = < 0.001 C: 19.34 ± 21.01 (95% CI 15.31–23.37), p = < 0.001 Between-group difference < 0.001 (95% CI -4.23–2.38)	Author's conclusion In primary SUI, TVT and PAHG treatments both improved QoL and sexual function at 1 year. However, incontinence and health-related QoL scores were better in the TVT group. More pain compared to the baseline was reported after TVT, although there was no difference between groups.

Risk of bias table

Research question: What is the effectiveness of bulk injection in women with stress urinary incontinence compared to no treatment, physical therapy, or tape?

5

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Corcos, 2005	Definitely yes Reason: Randomization was centralized and stratified by center with randomly	Probably no Reason: After verification of inclusion/exclusion criteria by coordinating center, the randomly	Definitely no Reason: Unblinded study in which surgeons and patients were aware of the therapy administered.	No information Reason: During the course of the study, 5 patients were lost to follow-up or withdrew their participation but unknown if this was in	Probably yes Reason: All relevant outcomes were reported.	Probably no Reason: Patients who were randomized to collagen treatment might have been less inclined to consider themselves 'satisfied'	High

	distributed blocks 4 and 6 in size.	allocated treatment was faxed back.		the intervention or control group.		because they knew they could still opt for surgery.	
Maher, 2005	Definitely yes Reason: Patients were randomly allocated using computer randomisation software.	No information Reason: No information about how the allocation was concealed.	Definitely no Reason: Blinding was impossible.	Probably no Reason: Loss to follow-up was infrequent in intervention and control group.	Probably yes Reason: All relevant outcomes were reported.	Probably no Reason: Small sample size.	High
Ter Meulen, 2009	Probably yes Reason: A table of random numbers was used; all 0–4 were assigned to MPQ and all 5–9 were assigned to control PFME home training program.	Definitely yes Reason: Sealed envelopes containing the treatment assignment.	No information Reason: Unclear if any blinding was performed.	Probably yes Reason: Loss to follow-up was infrequent in intervention and control group at 3-months follow-up.	Definitely no Reason: 12-month follow-up only for intervention group.	Probably no Reason: Study sponsored by uroplasty BV, makers of Macroplastique Implantation system	High
Itkonen Freitas, 2020 & Itkonen Freitas, 2021	Definitely yes Reason: Randomization was done using a computer assisted, random block system and R by an assistant outside the study.	Definitely yes Reason: Randomization cards were sealed in opaque, sequentially numbered envelops.	Definitely no Reason: Open-label trial (participants or investigators were not masked to treatment).	Probably yes Reason: Loss to follow-up was infrequent in intervention and control group.	Definitely yes Reason: All relevant outcomes were reported.	Probably yes Reason: No other problems noted	Some concerns

Module Male sling post-prostatectomie

5 **Risk of bias table**

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Abrams, 2020	Probably yes probabilistic algorithm to either a male sling or an AUS in a 1:1 ratio	Probably yes remote automated computer-allocated randomisation system	Defenitely no Reason: Patients were not blinded. Blinding of other staff not mentioned.	Defenitely no In the sling-group, 157 (83%) participant responded, in the AUS-group, 161 (85%) responded. “ appropriate imputation methods according to protocol. Objective improvement was measured in only 94/312 participants.	Probably no Trial protocol published, SF-12 described but not reported on. Pad-test alternatively reported	Unknown	**HIGH** (all outcomes)

Module botox volwassenen

Risk of bias table

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Amundsen, 2016	Defenitely yes Reason: Assigned 1:1 in blocks of 2 or 4	Probably yes Reason: All participants were blinded to sequence. One data coordinating center statistician was not masked to block sequence.	Defenitely no Reason: Open-label trial (patients and health care providers not blinded). Blinding of data collectors, outcome assessors and analysts not reported.	Probably no Reason: Reasons for withdrawal or lost to follow up unknown, but unbalanced due to treatment assignment. Adequate imputation methods (multiple imputation) were used.	Probably yes Reason: Registered at ClinicalTrials.gov (NCT01502956). Primary and secondary outcomes reported as prespecified in register.	Probably yes Reason: Modified intention to treat analysis on all outcomes; only participants with at least 1 post-baseline measurement were included in analysis.	**Some concerns** (urine incontinence episodes, quality of life, AE (urinary tract infection)
Amundsen, 2018	Defenitely yes	Probably yes	Defenitely no	Probably no	Probably yes	Probably yes	**Some concerns** (AE (urine tract infections))

	Reason: Assigned 1:1 in blocks of 2 or 4	Reason: All participants were blinded to sequence. One data coordinating center statistician was not masked to block sequence.	Reason: Open-label trial (patients and health care providers not blinded). Blinding of data collectors, outcome assessors and analysts not reported.	Reason: Reasons for withdrawal or lost to follow up unknown, but unbalanced due to treatment assignment.	Reason: Registered at ClinicalTrials.gov (NCT01502956). Primary and secondary outcomes reported as prespecified in register.	Reason: No other problems noted.	
Sherif, 2015	Unknown	Unknown	Defenitely no Reason: Open-label trial (patients and health care providers not blinded). Blinding of data collectors, outcome assessors and analysts not reported.	Probably no Reason: drop-out balanced, no reasons were given. No adequate imputation method was described.	Probably no No registration in Register of Clinical Trials known.	Unknown	**HIGH** (all outcomes)

Module Bèta-3 receptor agonisten

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Abrams, 2015	Type of study: Multicenter RCT. Setting and country: 141 sites in 20 European countries. Funding: The study was funded by Astellas.	Inclusion criteria: - 18 years or older. - Symptoms of OAB (urgency, urinary frequency, and/or urgency incontinence) for ≥3 months. - Eight or more micturitions per 24h and one urgency episode or more per 24h	Combinations of solifenacin (2.5/5/10 mg) and mirabegron (50 mg)	Solifenacin (2.5/5/10 mg) monotherapy Mirabegron (50 mg) monotherapy Placebo	Length of follow-up: 14 weeks Loss-to-follow-up: N (total) = 67 *Reasons:* Withdrawal by patient (n = 27) Adverse event (n = 18) Protocol violation (n = 14) Lack of efficacy (n = 3) Lost to follow-up (n = 3) Other (n = 2)	**Voided volume per micturition** *Adjusted mean change (SE) from baseline to end of treatment* *Placebo*: 14 (6) *Mira (50 mg)*: 35 (6) *Soli (2.5 mg)*: 36 (6) *Soli (5 mg)*: 36 (4) *Soli (10 mg)*: 36 (6) *Soli (2.5 mg) + Mira (50 mg)*: 42 (4) *Soli (5 mg) + Mira (50 mg)*: 54 (4)	*Authors conclusion:* a combination of mirabegron and solifenacin demonstrated significant improvements in mean voided volume, micturition frequency, and urgency over solifenacin (5 mg) monotherapy, without increasing adverse effects associated with AM therapy compared with mirabegron or solifenacin monotherapy. *Limitations*: 1) low proportion of incontinent individuals in the study population, 2) lack of power to detect a meaningful effect in secondary efficacy parameters (due to small sample sizes).

	Conflicts of interest: Potentially; several researchers received consultancy fees, grants, speaker fees, and patents and royalties from pharmaceutical companies. And some researchers involved in this study are employees of a pharmaceutical company.	(with or without incontinence) Exclusion criteria: - Average total daily urine volume >3000 ml. - Severe hypertension N total at baseline: *Placebo*: 81 *Mira (50 mg)*: 78 *Soli (2.5 mg)*: 79 *Soli (5 mg)*: 156 *Soli (10 mg)*: 78 *Soli (2.5 mg) + Mira (50 mg)*: 149 *Soli (5 mg) + Mira (50 mg)*: 153 *Soli (10 mg) + Mira (50 mg)*: 81 Important prognostic factors[2]: *Age ± SD* *Placebo*: 54.6 ± 13.4 *Mira (50 mg)*: 53.4 ± 14.0 *Soli (2.5 mg)*: 56.1 ± 11.7 *Soli (5 mg)*: 54.2 ± 15.5 *Soli (10 mg)*: 55.0 ± 12.8			Incomplete outcome data: Not reported, except loss of follow-up as above.	*Soli (10 mg) + Mira (50 mg)*: 62 (6) **Frequency of TEAEs** *no, (%)* *Placebo*: 32 (40) *Mira (50 mg)*: 41 (53) *Soli (2.5 mg)*: 32 (41) *Soli (5 mg)*: 70 (45) *Soli (10 mg)*: 47 (60) *Soli (2.5 mg) + Mira (50 mg)*: 61 (41) *Soli (5 mg) + Mira (50 mg)*: 67 (44) *Soli (10 mg) + Mira (50 mg)*: 48 (59) **Blood pressure** *Adjusted mean change (SE) from baseline to end of treatment* Systolic *Placebo*: -2.6 (1.1) *Mira (50 mg)*: 0.7 (1.1) *Soli (2.5 mg)*: -2 (1.1) *Soli (5 mg)*: -1.7 (0.8) *Soli (10 mg)*: -2.7 (1.1) *Soli (2.5 mg) + Mira (50 mg):* -0.6 (0.8) *Soli (5 mg) + Mira (50 mg)*: -2.1 (0.8) *Soli (10 mg) + Mira (50 mg)*: -0.4 (1.1) Diastolic *Placebo*: -1.2 (0.7) *Mira (50 mg)*: 0.3 (0.8) *Soli (2.5 mg)*: -1.2 (0.8) *Soli (5 mg)*: -0.6 (0.5) *Soli (10 mg)*: 0 (0.8) *Soli (2.5 mg) + Mira (50 mg):* 0.2 (0.6)	

		Soli (2.5 mg) + Mira (50 mg): 53.7 ± 14.6 *Soli (5 mg) + Mira (50 mg)*: 54.1 ± 14.1 *Soli (10 mg) + Mira (50 mg)*: 55.5 ± 13.8 *Sex (%female)* *Placebo*: 66.7 *Mira (50 mg)*: 66.7 *Soli (2.5 mg)*: 64.6 *Soli (5 mg)*: 66.0 *Soli (10 mg)*: 67.9 *Soli (2.5 mg) + Mira (50 mg)*: 67.1 *Soli (5 mg) + Mira (50 mg)*: 66.0 *Soli (10 mg) + Mira (50 mg)*: 66.7 <u>Groups comparable at baseline?</u> Yes, baseline characteristics were comparable, but incontinence, urgency and frequency were less severe in the placebo group.				*Soli (5 mg) + Mira (50 mg)*: -0.8 (0.6) *Soli (10 mg) + Mira (50 mg)*: -0.2 (0.7) **Hypertension** *no, (%)* *Placebo*: 7 (9) *Mira (50 mg)*: 11 (14) *Soli (2.5 mg)*: 8 (10) *Soli (5 mg)*: 18 (12) *Soli (10 mg)*: 5 (6) *Soli (2.5 mg) + Mira (50 mg)*: 11 (7) *Soli (5 mg) + Mira (50 mg)*: 7 (9) *Soli (10 mg) + Mira (50 mg)*: 11 (14) **Pulse rate** *Adjusted mean change (SE) from baseline to end of treatment* *Placebo*: 0.1 (0.85) *Mira (50 mg)*: 1.0 (0.87) *Soli (2.5 mg)*: 0.1 (0.87) *Soli (5 mg)*: 0.1 (0.62) *Soli (10 mg)*: 0.9 (0.87) *Soli (2.5 mg) + Mira (50 mg):* 1.1 (0.63) *Soli (5 mg) + Mira (50 mg)*: 0.6 (0.62) *Soli (10 mg) + Mira (50 mg)*: 1.3 (0.85) **Tachycardia** *no, (%)* *Placebo*: 1 (1) *Mira (50 mg)*: 2 (3) *Soli (2.5 mg)*: 2 (3) *Soli (5 mg)*: 6 (4) *Soli (10 mg)*: 2 (3)	

						Soli (2.5 mg) + Mira (50 mg): 7 (5) *Soli (5 mg) + Mira (50 mg)*: 3 (2) *Soli (10 mg) + Mira (50 mg)*: 3 (4)	
Herschorn, 2017	Type of study: Multicenter RCT. Setting and country: 435 sites in 42 countries. Funding: This study was funded by Astellas Pharma Europe B.V. Conflicts of interest: Potentially; several researchers received consultancy fees, grants, speaker fees, personal fees from pharmaceutical companies. And some researchers involved in this study are full-time employees of a pharmaceutical company.	Inclusion criteria: - 18 years or older - Symptoms of wet OAB for ≥3 months - In patients with mixed stress UI/UUI, UUI had to be the predominant factor - On average ≥8 micturitions/24h, ≥1 urgency episodes/24h, and ≥3 UI episodes over the 7-day micturition diary Exclusion criteria: - Evidence of a urinary tract infection (urine culture containing >100.000 cfu/ml). - Average total daily urine volume >3000 ml. - Serum creatinine > 150	Combinations of solifenacin (5 mg) and mirabegron (50 mg) daily	Daily: Solifenacin (5 mg) monotherapy Mirabegron (50 mg) monotherapy Placebo	Length of follow-up: 14 weeks Loss-to-follow-up: *Placebo: 43* Reasons: no study group (n = 2), AE (n = 13), lack of efficacy (n = 1), lost to follow-up (n = 4), protocol violation (n = 2), withdrawal by patient (n = 21). *Mira 50 mg: 50* Reasons: no study group (n = 4), AE (n = 12), lost to follow-up (n = 4), protocol violation (n = 3), withdrawal by patient (n = 23), other reasons (n = 4). *Soli 5 mg: 37* Reasons: no study group (n = 2), AE (n = 9), lack of efficacy (n = 2), lost to follow-up (n = 2), protocol violation (n = 5), withdrawal by patient (n = 16), other reasons (n = 1). *Soli 5 mg + Mira 50 mg: 85* Reasons: no study group (n = 13), AE (n = 26), lack	**Mean number of urinary incontinence episodes per 24h** *Adjusted change from baseline to end of treatment* *Placebo:* -1.3 *Mira 50 mg:* -1.8 *Soli 5 mg*: -1.8 *Soli 5 mg + Mira 50 mg:* -2.0 **Mean number of micturitions per 24h** *Adjusted change from baseline to end of treatment* *Placebo:* -1.6 *Mira 50 mg:* -2.0 *Soli 5 mg*: -2.2 *Soli 5 mg + Mira 50 mg:* -2.6 **Mean volume voided per micturition** *Adjusted change from baseline to end of treatment* *Placebo:* 8.4 *Mira 50 mg:* 22.0 *Soli 5 mg*: 31.0 *Soli 5 mg + Mira 50 mg:* 39.7 **Frequency of TEAEs** *no, (%)* *Placebo:* 145 (34) *Mira 50 mg:* 147 (35) *Soli 5 mg:* 149 (35) *Soli 5 mg + Mira 50 mg:* 314 (37)	*Authors conclusion*: combination therapy of mirabegron and solifenacin improved the most relevant OAB symptoms (urgency and UI episodes) compared with monotherapy. *Limitations*: study population was very comparable with populations of previous mirabegron monotherapy studies.

		µmol/l, AST and/or ALT >2 x ULN, or GGT >3 x ULN, or total bilirubin >2 ULN. <u>N total at baseline</u>: *Placebo:* 429 *Mira 50 mg:* 422 *Soli 5 mg:* 423 *Soli 5 mg + Mira 50 mg:* 848 <u>Important prognostic factors</u>[2]: *Age ± SD* *Placebo:* 57.9 ± 13.0 *Mira 50 mg:* 56.7 ± 13.3 *Soli 5 mg:* 58.2 ± 12.8 *Soli 5 mg + Mira 50 mg:* 57.6 ± 13.4 *Sex (%male)* *Placebo:* 23.3 *Mira 50 mg:* 23.5 *Soli 5 mg:* 21.7 *Soli 5 mg + Mira 50 mg:* 23.2 <u>Groups comparable at baseline?</u> Yes, no significant differences between the			of efficacy (n = 1), lost to follow-up (n = 3), protocol violation (n = 4), withdrawal by patient (n = 34), other reasons (n = 4). <u>Incomplete outcome data</u>: Not reported, except loss of follow-up as above.		

		groups regarding baseline.					
Khullar, 2013	Type of study: Multicenter RCT. Setting and country: 189 sites in 27 countries in Europe and Australia. Funding: Astellas Pharma Global Development sponsored this study. Conflicts of interest: Potentially; several researchers are member of the advisory board of pharmaceutical companies. Researchers also received consultancy fees, grants and payment for lectures from pharmaceutical companies, and some researchers involved are employees of a	Inclusion criteria: - 18 years or older - Symptoms of OAB for >3 months - Average micturition frequency of eight or more times per 24h period and at least three episodes of urgency, with or without incontinence. Exclusion criteria: - Stress incontinence or stress-predominant mixed incontinence - Average total daily urine volume >3000 ml N total at baseline: *Placebo:* 494 *Mira 50 mg:* 493 *Mira 100 mg:* 496 *Tol 4 mg:* 495	Mirabegron (50 mg) orally once daily	Placebo or tolterodine ER (4 mg) orally once daily	Length of follow-up: 12 weeks + 30 days Loss-to-follow-up: *Placebo: 44* Reasons: eligibility criterion not met (n = 5), adverse event (n = 13), lack of efficacy (n = 5), withdrew consent (n = 11), lost to follow-up (n = 4), protocol violation (n = 2), randomised but did not receive study drug (n = 2), other (n = 2). *Mira 50 mg: 57* Reasons: eligibility criterion not met (n = 8), adverse event (n = 25), lack of efficacy (n = 6), withdrew consent (n = 9), lost to follow-up (n = 3), protocol violation (n = 3), randomised but did not receive study drug (n = 1), other (n = 2). *Tol 4 mg: 50* Reasons: eligibility criterion not met (n = 4), adverse event (n = 24), lack of efficacy (n = 3), withdrew consent (n = 9), lost to follow-up (n = 5), protocol violation (n = 3), other (n = 2).	**Mean number of incontinence episodes per 24h** *Mean change (SE) from baseline to final visit* *Placebo:* -1.1 (0.13) *Mira 50 mg:* -1.6 (0.14) *Tol 4 mg:* -1.2 (0.14) **Mean number of micturitions per 24h** *Mean change (SE) from baseline to final visit* *Placebo:* -1.4 (0.12) *Mira 50 mg:* -1.9 (0.12) *Tol 4 mg:* -1.6 (0.12) **Volume voided per micturition** *Adjusted mean change (SE) from baseline to final visit* Placebo: 12 (2) Mira 50 mg: 24 (2) Tol 4 mg: 25 (2) **Mean number of urgency episodes per 24h** *Adjusted mean change (SE) from baseline to final visit* Placebo: -1.7 (0.2) Mira 50 mg: -2.3 (0.2) Tol 4 mg: -2.1 (0.2) **Frequency of TEAEs** *no, (%)* Placebo: 214 (43) Mira 50 mg: 211 (43) Tol 4 mg: 231 (47) **Hypertension**	*Authors conclusion:* mirabegron has a proven efficacy and good tolerability, and therefore represents a new class of treatment for OAB. *Limitations*: 1) long-term safety, efficacy and persistence of mirabegron cannot be extrapolated from this study, 2) head-to-head comparison of mirabegron and tolterodine was not allowed due to the study design, 3) a high placebo response diminished the treatment effect in this study, 4) this study included a significant proportion of patients who had previously discontinued antimuscarinic treatment, which may have influenced the tolterodine treatment effect.

	pharmaceutical company.	Important prognostic factors[2]: *Age ± SD* *Placebo:* 59.2 ± 12.3 *Mira 50 mg:* 59.1 ± 12.4 *Tol 4 mg:* 59.1 ± 12.9 *Sex (%male)* *Placebo:* 27.9 *Mira 50 mg:* 27.6 *Tol 4 mg:* 27.1 Groups comparable at baseline? Yes.			Incomplete outcome data: Not reported, except loss of follow-up as above.	*no, (%)* Placebo: 38 (8) Mira 50 mg: 29 (6) Tol 4 mg: 40 (8)	
Kuo, 2015	Type of study: Multicenter RCT. Setting and country: 67 sites in Taiwan, Korea, China and India. Funding: This study was funded by Astellas Inc. Conflicts of interest: Potentially; several researchers received consultancy	Inclusion criteria: - Symptoms of OAB for at least 12 weeks. - ≥8 micturitions per 24h on average - ≥1 episodes of urgency or urgency incontinence per 24h on average Exclusion criteria: - Stress urinary incontinence as a predominant symptom - Urinary tract infection, urinary stone, interstitial	Mirabegron (50 mg) orally, once daily after breakfast	Placebo or tolterodine ER (4 mg) orally, once daily after breakfast	Length of follow-up: 14 weeks *Placebo: 77* Reasons: eligibility criteria not met (n = 23), adverse event (n = 14), lack of efficacy (n = 7), withdrawal of consent (n = 21), lost to follow-up (n = 6), protocol deviation (n = 2), other (n = 4). *Mira: 61* Reasons: eligibility criteria not met (n = 18), adverse event (n = 9), lack of efficacy (n = 4), withdrawal of consent (n = 21), lost to follow-up (n = 3), protocol	**Frequency of TEAEs** *no, (%)* *Placebo*: 214 (59%) *Mira*: 191 (52%) *Tol*: 260 (70%) **Hypertension** *no, (%)* *Placebo*: 0 (0) *Mira*: 2 (0.5) *Tol*: 3 (0.8) **Blood pressure increased** no, (%) Placebo: 1 (0.3) Mira: 0 (0) Tol: 1 (0.3)	*Authors conclusion:* mirabegron is superior to placebo in reducing the frequency of micturitions in patients with symptoms of OAB. *Limitations*: 1) low amount of severely affected patients included.

	fees, speaker fees and grants from, and conducted clinical trials for pharmaceutical companies. Also, some researchers are employees of the study sponsor.	cystitis or a history of recurrent urinary tract infection - Postvoid residual volume of ≥100 ml or a clinically significant lower urinary tract obstructive disease - Average total daily urine volume >3000 ml - Uncontrolled hypertension sitting systolic blood pressure (≥180 mmHg or diastolic blood pressure ≥110 mmHg) - Pulse rate ≥110 beats per minute - Indwelling catheter or practices intermittent self-catheterization N total at baseline: *Placebo:* 323 *Mira:* 338 *Tol:* 333 Important prognostic factors[2]: *Age ± SD*			deviation (n = 4), other (n = 2). *Tol: 67* Reasons: eligibility criteria not met (n = 17), adverse event (n = 15), lack of efficacy (n = 2), withdrawal of consent (n = 24), lost to follow-up (n = 7), other (n = 2). Incomplete outcome data: Not reported, except loss of follow-up as above.		

		Placebo: 55.3 ± 13.6 *Mira:* 54.3 ± 14.2 *Tol:* 53.9 ± 14.5 *Sex (%male)* *Placebo:* 30.3 *Mira:* 32.5 *Tol:* 36.0 <u>Groups comparable at baseline?</u> Yes.					
Nitti, 2013	<u>Type of study</u>: Multicenter RCT. <u>Setting and country</u>: 132 sites in the United States and Canada. <u>Funding</u>: Medical writing assistance was supported by Astellas. <u>Conflicts of interest</u>: None reported.	<u>Inclusion criteria</u>: - 18 years or older - OAB symptoms for 3 or more months <u>Exclusion criteria</u>: - Clinically relevant stress incontinence or mixed stress/urgency incontinence with stress as the predominant factor - An indwelling catheter - Evidence of a symptomatic urinary tract infection - Chronic inflammation - Bladder stones	Once daily mirabegron (50 mg)	Once daily placebo	<u>Length of follow-up</u>: 12 weeks + 30 days <u>Loss-to-follow-up</u>: *Placebo:* 15.2% Reason: discontinuations due to adverse events (3.7%) *Mira 50 mg:* 13.3% Reason: discontinuations due to adverse events (4.1%) <u>Incomplete outcome data</u>: Not reported, except loss of follow-up as above.	**Number of incontinence episodes per 24h** *Change (SE) from baseline to final visit* *Placebo:* -1.1 (0.11) *Mira 50 mg:* -1.5 (0.11) **Number of micturitions per 24h** *Change (SE) from baseline to final visit* *Placebo:* -1.1 (0.13) *Mira 50 mg:* -1.7 (0.13) **Volume voided per micturition** *Change (SE) from baseline to final visit* *Placebo:* 7 (2.4) *Mira 50 mg:* 18 (2.4) **Number of urgency episodes per 24h** *Change (SE) from baseline to final visit* *Placebo:* -0.8 (0.16) *Mira 50 mg:* -1.6 (0.16)	*Authors conclusion*: mirabegron was shown to be efficacious across objective and subjective endpoints in OAB patients. Mirabegron could provide an alternative therapeutic option for OAB, particularly in patients whose OAB is inadequately treated with current antimuscarinic therapy.

		- Previous pelvic radiation therapy - Previous or current malignant disease of the pelvic organs - Severe hypertension (sitting average SBP 180 mmHg or greater and/or average sitting DBP 110 mmHg or greater) - Use of OAB medications which could not be stopped safely at screening. <u>N total at baseline</u>: *Placebo:* 453 *Mira 50 mg:* 442 <u>Important prognostic factors</u>[2]: *Age ± SD* *Placebo: 60.1* ± 13.8 *Mira 50 mg:* 59.2 ± 13.5 *Sex (%male)* *Placebo:* 23.8 *Mira 50 mg:* 27.1				**Hypertension** *no, (%)* *Placebo*: 30 (7) *Mira 50 mg*: 27 (6) **Tachycardia** *no, (%)* *Placebo*: 2 (0.4) *Mira 50 mg*: 6 (1.4)	

		Groups comparable at baseline? Yes					
Shin, 2018	Type of study: Multicenter RCT Setting and country: Korea. Funding: This study was funded by Astellas Pharma Korea, Inc. Conflicts of interest: All authors completed the ICMJE form for the disclosure of potential conflicts of interest.	Inclusion criteria: - Males aged ≥20 years - Symptoms of OAB persistent for at least 12 weeks - Average of 8 or more micturition episodes per 24h - Score of 2 (one urgency episode or more per week) or greater in the urgency score section of the OAB symptoms scale Exclusion criteria: - Risk or history of acute urinary retention - PSA levels >10 ng/ml or suspected prostate cancer - Voiding volume over 3000 ml per day - Suspicion of stress urinary incontinence - Postvoid residual volume >200 ml, voided volume <125 ml	Once daily mirabegron (50 mg)	Once daily placebo	Length of follow-up: 12 weeks + 14 weeks extended treatment period Loss-to-follow-up: *Placebo:* 45 Reasons: lack of efficacy (n = 1), adverse event (n =3), withdrawal by patient (n = 10), lost to follow-up (n = 5), compliance <70%, >130% (n = 2), protocol violation (n = 21), other (n = 3). *Mira 50 mg:* 85 Reasons: lack of efficacy (n = 3), adverse event (n = 10), withdrawal by patient (n = 24), lost to follow-up (n = 6), compliance <70%, >130% (n = 3), protocol violation (n = 29), other (n = 10). Incomplete outcome data: Not reported, except loss of follow-up as above.	**Number of micturition episodes per 24h** *Mean change (SD) from baseline to final visit* Mirabegron: -1.8 (2.2) Placebo: -2.0 (2.7) **Frequency of AEs** *no, (%)* Mirabegron: 48 (15.5) Placebo: 18 (11.7) **Blood pressure** *Mean change (SD) from baseline to final visit* Systolic Mirabegron: -0.21 Placebo: 0.76 Diastolic Mirabegron: 0.13 Placebo: 0.7 **Pulse rate** *Mean change (SD) from baseline to final visit* Mirabegron: 0.58 Placebo: 1.12	*Authors conclusion:* a daily dose of 50 mg mirabegron for 12 weeks can be an effective treatment that alleviates urgency and storage symptoms in male patients with OAB. *Limitations*: 1) small study population, 2) short follow-up, 3) there was no wash-out period of combined drugs to treat lower urinary tract symptoms (might have confounded the results found), 4) large variation of the primary efficacy variables within each group.

		and Qmax <5 ml/sec - Subjects that received non-drug treatment, including bladder training or pelvic floor muscle exercise within the 4 weeks prior to screening N total at baseline: *Placebo:* 154 *Mira:* 310 Important prognostic factors[2]: *Age ± SD* *Placebo:* 65.2 ± 10.0 *Mira:* 66.4 ± 9.5 Groups comparable at baseline? Yes, but the mirabegron group had larger prostate volume and fewer 24h micturition episodes.					
Staskin, 2021	Type of study: RCT extension study. Setting and country:	Inclusion criteria: - 18 years or older - History of OAB diagnosed by a physician 3 or	Once daily vibegron (75 mg)	Once daily tolterodine ER (4 mg)	Length of follow-up: 40 weeks of extension (52 total weeks of treatment) Loss-to-follow-up:	**Daily number of micturitions** *LS mean change (95%CI) from baseline to final visit* *Vibe*: -2.4 (-2.9 to -2.0) *Tol*: -2.0 (-2.5 to -1.5)	*Authors conclusion*: vibegron treatment showed favorable long-term efficacy, safety and tolerability in OAB patients. Vibegron represents an interesting long-term treatment option for patients with OAB.

	109 sites in the United States. Funding: Editorial support was funded by Urovant Sciences. Conflicts of interest: None declared.	more months before screening - Meet the diary-based criteria for either wet or dry OAB (i.e., urinary urgency with or without urge incontinence) - Completion of the EMPOWER study - Demonstration of ≥80% compliance with self-administration of the study treatment in EMPOWUR and to have completed ≥4 diary days for EMPOWUR week 12 Exclusion criteria: - Urine volume output of greater than 3000 ml - Inability to complete EMPOWUR for any reason - Change in history or current evidence of any clinically significant condition that			*40 weeks* *Vibe:* 13 (14.1%) Reasons: withdrew consent (6.5%), lost to follow-up (4.3%), adverse event (1.1%), death (1.1%), other (1.1%). *Tol:* 19 (20.9%) Reasons: withdrew consent (7.7%), adverse event (4.4%), lost to follow-up (3.3%), withdrawal by investigator (1.1%), other (4.4%). *52 weeks* *Vibe:* 26 (14.3%) Reasons: withdrew consent (6.0%), adverse event (1.6%), lost to follow-up (3.3%), withdrawal by investigator (0.5%), lack of efficacy (0.5%), protocol deviation (0.5%), other (1.6%). *Tol:* 18 (12.8%) Reasons: withdrew consent (5.7%), adverse event (2.8%), lost to follow-up (1.4%), withdrawal by investigator (0.7%), withdrawal by sponsor (0.7%), lack of efficacy (0.7%), other (0.7%).	**Daily number of urgency episodes** *LS mean change (95%CI) from baseline to final visit* *Vibe*: -3.4 (-4.0 to -2.7) *Tol*: -3.2 (-4.0 to -2.5) **Daily number of urinary incontinence episodes** *LS mean change (95%CI) from baseline to final visit* *Vibe*: -2.5 (-2.8 to -2.2) *Tol*: -1.9 (-2.3 to -1.6) **Frequency of TEAEs** no, (%) Vibe: 171 (63) Tol: 126 (54) **Hypertension** no, (%) Vibe: 24 (9) Tol: 20 (9)	*Limitation*: potential for selection bias for patients who elected to enter the EMPOWUR extension

		could confound study results - Uncontrolled hyperglycaemia - Uncontrolled hypertension - Resting heart rate >100 beats per minute <u>N total at baseline</u>: *40 weeks* *Vibe*: 92 *Tol:* 91 *52 weeks* *Vibe:* 181 *Tol:* 141 <u>Important prognostic factors</u>[2]: *Age ± SD* *40 weeks* *Vibe:* 58.8 ± 13.7 *Tol:* 62.1 ± 12.1 *52 weeks* *Vibe:* 62.1 ± 12.4 *Tol:* 60.6 ± 13.0 *Sex (%female)* *40 weeks* *Vibe:* 79.3 *Tol:* 76.9 *52 weeks* *Vibe:* 77.3 *Tol:* 79.4			<u>Incomplete outcome data</u>: Not reported, except loss of follow-up as above.		

		Groups comparable at baseline? Yes					
Suzuki, 2021	Type of study: Multicenter RCT. Setting and country: 11 urology clinics and centers in Japan. Funding: This study was sponsored by Hisamitsu Pharmaceutical. Conflicts of interest: None declared.	Inclusion criteria: - Female patients aged ≥20 years - OAB symptoms for >8 weeks - Eight or more micturitions per 24h - One or more urinary urgency episodes per 24h - Two or more nocturnal micturitions per night Exclusion criteria: - ≥100 ml postvoid residual urine - Difficulty in walking by themselves - Urethral stricture - Bladder stone - Bladder tumor - Urinary tract infection - Pregnancy - Pelvic organ prolapse - Neuropsychiatric disorder associated with neurogenic	Mirabegron (50 mg) orally once daily	Oxybutynin (73.5 mg) patch placed on the lower abdomen or thighs once daily	Length of follow-up: 8 weeks Loss-to-follow-up: *Mira:* 5 Reasons: withdrew consent (n = 3), ineligible after enrolment (n = 1), adverse event (n = 1). *Oxy:* 10 Reasons: withdrew consent (n = 4), ineligible after enrolment (n = 1), adverse event (n = 5). Incomplete outcome data: Not reported, except loss of follow-up as above.	**24h urinary urgency** *Mean changes from baseline to end of treatment* *Mira*: -1.3 ± 1.6 *Oxy*: -1.7 ± 2.7 **24h urgency incontinence** *Mean changes from baseline to end of treatment* *Mira*: -0.6 ± 1 *Oxy*: -1.1 ± 2 **Total urine volume** *Mean changes from baseline to end of treatment* *Mira*: -57 ± 402 *Oxy*: -58 ± 491 **Mean voided urine volume** *Mean changes from baseline to end of treatment* *Mira*: 28 ± 36 *Oxy*: 37 ± 48 **Frequency of AEs** *no, (%)* *Mira*: 1 (2) *Oxy*: 26 (51)	*Authors conclusion*: the oxybutynin patch shows promising results for the treatment of OAB. *Limitations*: 1) not enough power to evaluate differences among groups but only to compare before and after administration of each drug, 2) only objective evaluation of bladder function was carried out, 3) only female OAB patients were included in this study, 4) statistical differences in age between the two groups were present, 5) statistical improvement of N-QOL could not be detected, so it remains unclear if the oxybutynin patch has therapeutic effects on nocturia in the long term.

		bladder, including cerebrovascular disorder - Use of medicines for urinary tract dysfunction within 2 weeks before enrolment N total at baseline: *Mira:* 49 *Oxy:* 51 Important prognostic factors[2]: *Age ± SD* *Mira:* 72.7 ± 11.3 *Oxy:* 68.2 ± 11.3 Groups comparable at baseline? Yes					
Yamaguchi, 2014	Type of study: Multicenter RCT. Setting and country: Japan. Funding: This study was sponsored by Astellas Pharma Inc.	Inclusion criteria: - 20 years or older - OAB symptoms for ≥24 weeks - On average ≥8 micturitions per 24h and ≥1 urgency episode per 24h and/or ≥1 urgency incontinence episode per 24h	Active mirabegron group: mirabegron (50 mg) tablet and tolterodine placebo capsule once daily	Active tolterodine control: tolterodine (4 mg) capsule and mirabegron placebo tablet once daily Placebo group: mirabegron placebo tablet and tolterodine placebo capsule once daily	Length of follow-up: 14 weeks Loss-to-follow-up: *Placebo:* 31 Reasons: adverse events (n = 9), inadequate efficacy (n = 3), withdrew consent (n = 12), protocol deviations (n = 5), other (n = 2). *Mira:* 31	**Volume voided per micturition** *Mean change (SD) from baseline to final assessment* *Placebo*: 10 ± 29 *Mira*: 24 ± 35 *Tol*: 29 ± 35 **Micturitions per 24h** *Mean change (SD) from baseline to final assessment* *Placebo*: -0.9 ± 2.3 *Mira*: -1.7 ± 2.2 *Tol*: -1.4 ± 2.2	*Authors conclusion*: this study supports mirabegron as an attractive treatment alternative in the management of OAB compared to antimuscarinic therapy. *Limitation*: low mean number of nocturia episodes at baseline.

	Conflicts of interest: Potentially; several researchers received grants, consultancy fees, speaker fees and payments for lectures from pharmaceutical companies. Also, one researcher is a member of the advisory boards of a pharmaceutical company.	Exclusion criteria: - Diagnosis of genuine stress incontinence - Average total daily urine volume >3000 ml - Postvoid residual urine volume of at least 100 ml N total at baseline: *Placebo:* 368 *Mira:* 369 *Tol:* 368 Important prognostic factors[2]: *Age ± SD* *Placebo:* 58.2 ± 14.2 *Mira:* 58.3 ± 13.9 *Tol:* 58.3 ± 13.7 *Sex (%male)* *Placebo:* 15.8 *Mira:* 15.7 *Tol:* 17.4 Groups comparable at baseline? Yes			Reasons: adverse events (n = 15), inadequate efficacy (n = 4), withdrew consent (n = 8), protocol deviations (n = 3), other (n = 1). *Tol:* 23 Reasons: adverse events (n = 13), inadequate efficacy (n = 2), withdrew consent (n = 1), protocol deviations (n = 2), other (n = 5). Incomplete outcome data: Not reported, except loss of follow-up as above.	**Urgency episodes per 24h** *Mean change (SD) from baseline to final assessment* *Placebo*: -1.4 ± 3.2 *Mira*: -1.9 ± 2.5 *Tol*: -1.7 ± 2.6 **Incontinence episodes per 24h** *Mean change (SD) from baseline to final assessment* *Placebo*: -0.7 ± 1.9 *Mira*: -1.1 ± 1.5 *Tol*: -1 ± 1.6 **Frequency of AEs** *no, (%)* *Placebo*: 91 (24) *Mira*: 93 (25) *Tol*: 131 (35) **Hypertension** *no, (%)* *Placebo*: 0 (0) *Mira*: 0 (0) *Tol*: 3 (0.8) **Tachycardia** *no, (%)* *Placebo*: 0 (0) *Mira*: 1 (0.3) *Tol*: 0 (0) **Blood pressure increased** *no, (%)* *Placebo*: 1 (0.3) *Mira*: 0 (0) *Tol*: 2 (0.5) **Pulse rate increased** *no, (%)* *Placebo*: 0 (0)	

						Mira: 1 (0.3) *Tol*: 1 (0.3)	
Yamaguchi, 2015	Type of study: Multicenter RCT. Setting and country: Japan. Funding: This study and editorial support were funded by Astellas Pharma Inc. Conflicts of interest: Potentially; several researchers received grants, consultancy fees, speaker fees and payments for lectures from pharmaceutical companies. Also, one researcher is a member of the advisory boards of a pharmaceutical company.	Inclusion criteria: - Outpatients aged ≥20 years - OAB symptoms for ≥24 weeks - An average of ≥8 micturitions per 24h and ≥1 urgency episode and/or ≥1 urgency incontinence episode per 24h Exclusion criteria: - Polyuria exceeding 3000 ml in mean daily micturition volume - Clear diagnosis of stress incontinence N total at baseline: *Placebo:* 211 *Mira 50 mg:* 208 Important prognostic factors[2]: *Age ± SD* *Placebo:* 55.7 ± 12.9 *Mira 50 mg:* 56.2 ± 13.6 *Sex (%male)*	Oral once daily mirabegron (50 mg) tablet	Oral once daily placebo tablet	Length of follow-up: 12 weeks Loss-to-follow-up: *Placebo:* 16 Reasons: adverse events (n = 6), insufficient therapeutic effect (n = 4), consent withdrawal (n = 1), protocol deviation (n = 5). *Mira 50 mg:* 13 Reasons: adverse events (n = 8), consent withdrawal (n = 2), protocol deviation (n = 2), other (n = 1). Incomplete outcome data: Not reported, except loss of follow-up as above.	**Micturitions per 24h** *Mean change (SD) from baseline to end of study* *Placebo:* -1.2 ± 2.2 *Mirabegron:* -2.1 ± 2.4 **Urgency episodes per 24h** *Mean change (SD) from baseline to end of study* *Placebo:* -1.8 ± 3 *Mirabegron:* -2.2 ± 3.1 **Incontinence episodes per 24h** *Mean change (SD) from baseline to end of study* *Placebo:* -0.6 ± 1.4 *Mirabegron:* -1.2 ± 1.5 **Volume voided per micturition** *Mean change from baseline to end of study* *Placebo:* 11.2 ± 36.9 *Mirabegron:* 27.3 ± 39.5 **Frequency of TEAEs** *no, (%)* *Placebo*: 157 (74) *Mirabegron*: 171 (82) **Pulse rate** *Mean change (SD) from baseline to end of study* *Placebo:* 0.22 ± 6.9 *Mirabegron:* 2.7 ± 6.4 **Hypertension** no, (%)	*Authors conclusion*: this study confirms the efficacy and safety of mirabegron, and support the recommended dose of 50 mg.

		Placebo: 19.9 *Mira 50 mg:* 14.9 <u>Groups comparable at baseline?</u> Yes				*Placebo*: 0 (0) *Mirabegron*: 1 (0.5) **Tachycardia** no, (%) *Placebo*: 0 (0) *Mirabegron*: 1 (0.5) **Palpitations** no, (%) *Placebo*: 1 (0.5) *Mirabegron*: 4 (1.9)	

Risk of bias tables

Study reference	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients/healthcare providers/data collectors/outcome assessors/data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
Abrams, 2015	Probably yes Reason: assigned in a 2:1 ratio for primary compared with secondary treatment groups.	Probably yes Reason: not specifically reported but no reason to doubt that the allocation was adequately concealed.	Definitely yes Reason: double-blind trial using a double-blind, double-dummy technique. Run-in period was single-blinded.	Definitely yes Reason: primary reasons for discontinuation were withdrawal of consent, adverse events and protocol violation. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	Probably yes Reason: registered at ClinicalTrials.gov (NCT01340027). Primary and (most) secondary outcomes reported as prespecified in register. No reason to doubt that study is free of selective outcome reporting.	Definitely yes Reason: no other problems reported.	LOW (some information is missing but it seems uncertain that it affected the outcomes)
Herschorn, 2017	Probably yes Reason: assigned to treatment in a 2:1 ratio between the combined therapy, monotherapy and placebo treatment arms.	Probably yes Reason: not specifically reported but no reason to doubt that the allocation was adequately concealed.	Definitely yes Reason: single-blind run-in period, double-blind treatment period, and single-blind run-out period.	Definitely yes Reason: primary reasons for discontinuation were adverse events or withdrawal by the patient. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	Definitely yes Reason: registered at ClinicalTrials.gov (NCT01972841). Primary and secondary outcomes reported as prespecified in register.	Probably yes Reason: primary objective of the study was not met.	Some concerns (some information is missing, and the primary objective of the study was not met)
Khullar, 2013	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	LOW (no reasons to suspect bias)

	Reason: computer-generated randomisation scheme with stratification by country was used.	Reason: allocation was accomplished via an interactive response system.	Reason: single-blind run-in period, followed by a double-blind treatment period.	Reason: primary reasons for discontinuation were adverse events and withdrawal of consent. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	Reason: registered at ClinicalTrials.gov (NCT01972841). Primary and (most) secondary outcomes reported as prespecified in register. No reason to doubt that study is free of selective outcome reporting.	Reason: no other problems reported.	
Kuo, 2015	Definitely yes Reason: computer-generated randomisation scheme with stratification by site was used.	Probably yes Reason: not specifically reported but no reason to doubt that the allocation was adequately concealed.	Definitely yes Reason: single-blind run-in period, followed by a double-blind treatment period.	Definitely yes Reason: primary reasons for discontinuation were not meeting the eligibility criteria and withdrawal of consent. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	Definitely yes Reason: registered at ClinicalTrials.gov (NCT01043666). Primary and secondary outcomes reported as prespecified in register.	Definitely yes Reason: no other problems reported.	LOW (no reasons to suspect bias)
Nitti, 2013	Definitely yes Reason: assigned to mirabegron (50/100 mg) or matching placebo in a 1:1:1 ratio using a computer-generated randomization scheme.	Probably yes Reason: not specifically reported but no reason to doubt that the allocation was adequately concealed.	Definitely yes Reason: single-blind run-in period, followed by a double-blind treatment period.	Definitely yes Reason: primary reason for discontinuation was adverse events. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	Probably yes Reason: registered at ClinicalTrials.gov (NCT00662909). Primary and (most) secondary outcomes reported as prespecified in register. No reason to doubt that study is free of selective outcome reporting.	Definitely yes Reason: no other problems reported.	LOW (no reasons to suspect bias)
Shin, 2018	Probably yes Reason: randomization in a 2:1 ratio into the	Probably yes Reason: not specifically reported but no reason to doubt that the	Definitely yes Reason: double-blinded trial	Definitely yes Reason: primary reasons for discontinuation were	Probably yes Reason: no registration in register of clinical trials known. Study	Probably no Reason: large baseline characteristic differences, and no	Some concerns (some problems reported that could have affected the outcomes)

	mirabegron or placebo group.	allocation was adequately concealed.		withdrawal by patient and protocol violation. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	protocol has been published but is not available.	appropriate statistical analysis was used.	
Staskin, 2021	Definitely yes Reason: central web-based randomization in a 1:1 ratio into the vibegron or tolterodine group	Definitely yes Reason: central web-based interactive response system.	Definitely yes Reason: double-blinded trial	Definitely yes Reason: the study completion rate was 85% overall, with similar completion rates for both treatment groups. Primary reason for discontinuation in both groups was withdrawal of consent, followed by adverse events.	Definitely yes Reason: registered at ClinicalTrials.gov (NCT03583372). Primary and secondary outcomes reported as prespecified in register.	Probably no Reason: potential selection bias for patients who elected to enter the EMPOWUR extension study, no sample size calculation.	Some concerns (some problems reported that could have affected the outcomes)
Suzuki, 2021	Definitely yes Reason: central web-based randomization in a 1:1 ratio into the oxybutynin or mirabegron group	Definitely yes Reason: alliance clinical research support system was used	Unknown	Probably yes Reason: six participants (9.8%) discontinued the study due to adverse events. Five patients in the oxybutynin group and one patient in the mirabegron group.	Probably yes Reason: no registration in register of clinical trials known. Study protocol has been published but is not available.	Probably no Reason: no sample size calculation was performed, small differences in baseline characteristics, objective evaluation for the effects of drugs.	Some concerns (crucial information about blinding is missing, and problems are reported that could have affected the outcomes)
Yamaguchi, 2014	Definitely yes Reason: randomization in a 1:1:1 ratio using a block size of six	Probably yes Reason: not specifically reported but no reason to doubt that the allocation was adequately concealed.	Definitely yes Reason: single-blind run-in period, followed by a double-blind treatment period.	Definitely yes Reason: primary reasons for discontinuation were adverse events and withdrawal of consent. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	Definitely yes Reason: registered at ClinicalTrials.gov (NCT00966004). Primary and secondary outcomes reported as prespecified in register.	Definitely yes Reason: no other problems reported.	LOW (no reasons to suspect bias)

Yamaguchi, 2015	Probably yes Reason: not specifically reported but no reason to doubt that the sequence was adequately generated.	Probably yes Reason: not specifically reported but no reason to doubt that the allocation was adequately concealed.	Definitely yes Reason: single-blind run-in period, followed by a double-blind treatment period.	Definitely yes Reason: primary reasons for discontinuation were adverse events, protocol deviation and withdrawal of consent. Missing outcome data is balanced in numbers across intervention groups, with similar reasons.	Definitely yes Reason: registered at ClinicalTrials.gov (NCT00527033). Primary and secondary outcomes reported as prespecified in register.	Definitely yes Reason: no other problems reported.	LOW (no reasons to suspect bias)

Evidence table for systematic review of RCTs and observational studies

Research question: What is the effectivity and safety of antimuscarinic treatment or mirabegron in elderly patients with urine incontinence, compared to placebo or no treatment?

PICO 1: Antimuscarinic treatment versus placebo

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments

Samuelsson, 2015 [individual study characteristics deduced from Samuelsson, 2015] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs and prospective controlled observational studies *Literature search up to October 2013* **A**: Chapple, 2007 **B**: Ouslander, 1995 **C**: Szonyi, 1995 **D**: Zinner, 2002 Study design: **A**: RCT **B**: RCT **C**: RCT **D**: RCT Setting and Country: **A**: USA, Poland, South Africa, Hungary, Sweden, UK, Germany **B**: USA **C**: UK **D**: Europe, USA, Canada, Australia, and New Zealand	Inclusion criteria SR: - Patients aged 65 years or older with urinary incontinence (elderly) - Patients living in nursing homes (frail elderly) - At least 20 patients in the intervention group and 20 in the control group - Treatment with one or more drugs for urinary Incontinence as intervention - Treatment with placebo or other specified treatment as control - Urinary leakage, quality of life or adverse events as outcomes - The study design should be a randomized controlled study or observational cohort study. - Studies written in English Exclusion criteria SR: - Outdated treatments *15 studies included* Important patient characteristics at baseline: N, mean age **A**: 399 patients, 72 ± 5 years **B**: 150 patients, 85.6 ± 8.6 years **C**: 60 patients, 82 ± 6 years **D**: 437 patients, 74 ± 6 years *Sex:* **A**: 77.4% women **B**: Not reported **C:** 95% women **D**: 74.4% women Groups not comparable at baseline	Describe intervention: **A**: Darifenacin 7.5 mg daily (voluntary up-titration to 15 mg after 2 weeks) **B**: Oxybutynin 2.5-5 mg x 3 + prompted voiding **C**: Oxybutynin 2.5 mg twice daily and bladder training **D**: Tolterodine ER capsules 4 mg once daily	Describe control: **A**: Placebo **B**: Placebo **C**: Placebo **D**: Placebo	End-point of follow-up: **A**: 12 weeks **B**: 20 days **C**: 6 weeks **D**: 12 weeks For how many participants were no complete outcome data available? (intervention/control) **A:** 22/16 **B**: 12/12 **C**: 8/5 **D:** 21/29	Urinary leakage Defined as urgency urinary incontinence episodes per week (12 weeks) **A**: I: 19.8–14.0 C: 21.0–13.0 Defined as incontinence episodes per week *Mean reduction* **D**: I: 23.2-11.5 C: 23.4-6.3 MD = -5.20 (-8.33, -2.07) Defined as incontinence episodes/3 days (day 20) **B**: I: 6.8 C: 7.7 MD = -1.10 (-2.39, 0.19) Defined as change in incontinence episodes/day during first 14 days vs last 14 days **C**: I: IQR = 10-8 (difference 8) C: IQR = 7-7 (difference 7) Quality of life Defined as OABq (mean change at week 12) **A**: I: 22.9 C: 16.8 MD = 6.10 (2.47, 9.73) Adverse events Any adverse event **A:** I: 149 (56.0%) C: 60 (45.1%) RD = 0.11 (0.01, 0.21) **B**: RD = 0.02 (-0.01, 0.05) **D**: I: 116 (54.2%) C: 102 (46.0%) RD = 0.08 (-0.01, 0.18)	Risk of bias (high, some concerns or low): **A**: Low **B**: Some concerns **C**: Some concerns **D**: Low Brief description of author's conclusion Anticholinergics have a small, but significant, effect on urinary leakage in older adults with UUI. Treatment with drugs for UUI in the frail elderly is not evidence based. Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question - Low number of studies on frail elderly individuals Level of evidence: **A**: High **B**: Moderate **C**: Moderate **D**: High Sensitivity analyses None Heterogeneity Due to clinical heterogeneity, random effects model was used.

	Source of funding and conflicts of interest: **A**: sponsored by Novartis Pharmaceuticals **B**: Not reported **C**: sponsored by Smith&Nephew Pharmaceuticals Ltd **D** sponsored by Pharmacia					*Dry mouth* **A**: I: 59 (22.2%) C: 5 (3.8%) RD = 0.18 (0.12, 0.24) **B**: I: 22 (42%) C: 19 (35%) RD = 0.07 (-0.11, 0.26) **C**: I: 93% C: 86% RD = 0.07 (-0.08, 0.22) **D**: I: 52 (24.3%) C: 16 (7.2%) RD = 0.17 (0.10, 0.24) *Constipation* **A**: I: 41 (15.4%) C: 11 (8.3%) RD = 0.07 (0.01, 0.14) **B**: I: 16 (30%) C: 13 (25%) RD =0.06 (-0.11, 0.23) **C**: I: 50% C: 45% RD=0.03 (-0.22, 0.29) **D**: I: 13 (6.1%) C: 10 (4.5%) RD = 0.02 (-0.03, 0.06)	

Evidence table for intervention studies

Research question: What is the effectivity and safety of antimuscarinic treatment or mirabegron in elderly patients with urine incontinence, compared to placebo or no treatment?

PICO 1: Antimuscarinic treatment versus placebo

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Dubeau, 2014	Type of study: RCT Setting and country: 108 United States sites Funding and conflicts of interest: Supported by Pfizer. Authors have financial interest and/or other relationship with Pfizer or Astellas	Inclusion criteria: - Men or women ≥65 years old - Self-reported urgency urinary incontinence (UUI) symptoms for ≥3 months - Mean of 2 to 15 UUI episodes (voids that subjects rated with a score of 5 on the Urinary Sensation Scale) - 8 or more micturitions per 24 hours on baseline 3-day bladder diary - At least some moderate bladder related problem on the Patient Perception of Bladder Condition (PPBC) who were determined to be vulnerable (at risk of deteriorating health) by a score of 3 or more on the VES-13 at screening - Capable of adequate mobility for independent toileting (could use cane or walker) - Independent completion of bladder diaries and study related questionnaires	Describe intervention (treatment/procedure/test): Fesoterodine once daily for 12 weeks. Initiated on 4 mg but could be increased to 8 mg at 4 weeks (and returned back to 4 mg any time but not increase again).	Describe control (treatment/procedure/test): Placebo once daily for 12 weeks. Sham dose escalation and de-escalation between 4 mg and 8 mg.	Length of follow-up: 12 weeks Loss-to-follow-up: Intervention: 55 (20%) Reasons: adverse events, insufficient clinical response, withdrew consent, did not meet entrance criteria, had protocol violations, were lost to follow-up, and other reasons Control: 61 (22%) Reasons: adverse events, insufficient clinical response, withdrew consent, did not meet entrance criteria, had protocol violations, were lost to follow-up, and other reasons Incomplete outcome data: Not reported	Improvement UI complaints Defined as reduction in mean number of UUI episodes per 24 hours (UUS rating 5) *At 4 weeks:* I: -2.36 C: -1.54 P<0.001 *At 12 weeks:* I: -2.84 C: -2.20 P=0.002 Quality of life Defined as health-related quality of life (HRQL) *At 4 weeks:* I: 17.8 (SE=1.4) C: 12.0 (SE=1.4) P<0.05 *At 12 weeks:* I: 23.1 (SE=1.5) C: 17.6 (SE=1.5) P<0.05	Author's conclusion: Flexible dose fesoterodine significantly improved urgency urinary incontinence episodes and other outcomes vs placebo and was generally well tolerated. Limitations: - Population less cognitively impaired than other vulnerable elderly individuals - MMSE not sufficiently sensitive to small short-term changes in cognition - Patients may underreport mild cognitive changes

		Exclusion criteria: - Any condition contraindicating the use of fesoterodine - Clinically significant hepatic disease or liver enzymes >2 times the upper limit of normal - Clinically significant renal disease and/or estimated creatinine clearance <30 ml per minute - Neurological conditions that may specifically affect bladder function - Previous surgery that might alter bladder function - Advanced malignancy - Clinically significant bladder outflow obstruction - Post-void residual urinary volume (PVR) >200 ml - Predominant stress urinary incontinence - Recurrent urinary tract infection - Significant constipation - Mini-Mental State Examination (MMSE) score <20 - Behavioural interventions or electrical stimulation within 8 weeks - Antimuscarinic medication use within 3 weeks - Initiation or variable dose of tricyclic antidepressants, α-blockers, oestrogens				Adverse events: Dry mouth I: 66 (23.5%) C: 17 (6.0%) Obstipation: I: 31 (11.0%) C: 12 (4.3%) Cognitive decline MMSE (Mini-Mental State Examination) LS mean $\pm$ SE I: 0.15$\pm$0.12 C: 0.33$\pm$0.12 P=0.28	

		(within 4 weeks) or diuretics (within 2 weeks) - An unstable medical condition - Average resting heart rate of ≥90 beats per minute <u>N total at baseline</u>: Intervention: 281 Control: 281 <u>Important prognostic factors</u>: *Mean age (range)* I: 74.8 (65 to 91) C: 75.3 (65 to 90) *Sex:* I: 80% F C: 84% F Groups comparable at baseline					
Kosilov, 2015	<u>Type of study:</u> RCT <u>Setting and country:</u> Russia <u>Funding and conflicts of interest:</u> Authors declared no conflicts of interest. Funding not reported.	<u>Inclusion criteria</u>: - Age >65 years - Severe symptoms of overactive bladder (the frequency of episodes of incontinence (EI) ≥3/day) <u>Exclusion criteria</u>: - Chronic active diseases including hypertension - Intolerance to antimuscarinics and agonists of β3-adrenoreceptors <u>N total at baseline</u>: Intervention: 63 Control: 59	<u>Describe intervention (treatment/procedure/test):</u> Solifenacin 10 mg/day	<u>Describe control (treatment/procedure/test):</u> Placebo	<u>Length of follow-up</u>: 6 weeks <u>Loss-to-follow-up</u>: N=7 (2.9%) in total population because of intolerable side-effects <u>Incomplete outcome data</u>: Not reported	<u>Number of episodes of incontinence</u> I: 2.2 (5.5 → 3.3) C: 0.2 (4.3 → 4.1) <u>Adverse events</u> Dry mouth: I: 5 (9.6%) C: 2 (3.4%) Cognitive impairment: I: 0 C: 1 (1.7%)	<u>Author's conclusion</u> Taking any of these drugs separately for the treatment of severe malfunction of lower urinary tracts in elderly people may turn out to be insufficient for effective symptom management <u>Limitations:</u> - No direct comparison

		Important prognostic factors: Not reported Unclear if groups were comparable at baseline					
Lackner, 2011	Type of study: RCT Setting and country: 12 skilled nursing homes in the Twin Cities, Minnesota (US) Funding and conflicts of interest: Supported by a research grant from Ortho-McNeil Pharmaceuticals	Inclusion criteria: - Female nursing home residents with an age ≥ 65 years - Urge urinary incontinence - Mild to severe cognitive impairment (participants did not have delirium or a diagnosis of dementia with Lewy bodies) - Ambulatory - Able to communicate - Post void residual urine (PVR) volume <150 mL - Remain incontinent following a 2-day prompted voiding program conducted by investigators Exclusion criteria: - Males - Unstable or severe medical condition that precluded the use of oxybutynin - Terminal illness - Use antimuscarinic, bisphosphonate, or acetylcholinesterase inhibitors during the month before or during treatment N total at baseline: Intervention: 26	Describe intervention (treatment/procedure/test): Oxybutynin 5 mg/day	Describe control (treatment/procedure/test): Placebo	Length of follow-up: 4 weeks Loss-to-follow-up: Intervention: 1 (3.8%) Reasons: excessive post void residual urine volume Control: 2 (8.3%) Reasons: death and decline in medical condition Incomplete outcome data: Not reported	Urinary incontinence episodes After 4 weeks (median (range)) I: 4 (0-11) C: 2.5 (0-14) P = 0.75 Median change from baseline I: 38% C: 53% P=0.97	Author's conclusion: Extended-release oxybutynin 5 mg per day for 4 weeks in older cognitively impaired female nursing home residents did not significantly reduce urinary incontinence. Limitations: - Insufficient power

		Control: 24 <u>Important prognostic factors</u>: *Mean age ± SD* I: 89.2 ± 5.2 C: 88.0 ± 7.1 Groups comparable at baseline					
Wagg, 2013	<u>Type of study:</u> RCT <u>Setting and country:</u> 61 sites in Austria, Belgium, Denmark, Finland, Germany, Israel, Italy, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom <u>Funding and conflicts of interest:</u> Funded by Pfizer. Conflicts of interest with pharmaceutical companies (Pfizer/Astellas). Sponsor involved in design and	<u>Inclusion criteria</u>: - Men and women aged ≥65 years with OAB symptoms for ≥3 months, a mean of ≥8 micturitions and ≥3 urgency episodes per 24 hours on a 3-day bladder diary at baseline who self-reported at least some moderate problems on the Patient Perception of Bladder Condition (PPBC) questionnaire and had a Mini-Mental State Examination (MMSE) score of ≥20 - Need to be able to complete micturition diaries and study-related questionnaires - Adhere to study procedures. <u>Exclusion criteria</u>: - Hypersensitivity to the active substance (fesoterodine fumarate) or to peanut, soya, or any of the excipients - Predominant stress incontinence as	<u>Describe intervention (treatment/procedure/test):</u> Fesoterodine once daily for 12 weeks. Initiated on 4 mg but could be increased to 8 mg at 4 weeks and 8 weeks (and could return back to 4 mg at week 8).	<u>Describe control (treatment/procedure/test):</u> Placebo once daily for 12 weeks. Sham dose escalation and de-escalation.	<u>Length of follow-up</u>: 12 weeks <u>Loss-to-follow-up</u>: Intervention: 78 (20%) Reasons: adverse events, insufficient clinical response, no longer willing to participate Control: 52 (13%) Reasons: adverse events, insufficient clinical response, no longer willing to participate <u>Incomplete outcome data</u>: Not reported	<u>UUI episodes</u> Median change/24h at week 12 I: -1.0 C: -0.7 P = 0.73 Median number of UUI episodes per 24 hours (for those with UUI>0 at baseline) decreased from 1.3 to 0.0 in the fesoterodine group and from 1.7 to 0.0 in the placebo group. <u>HRQL</u> LS Mean (±SE) Change From Baseline at Week 12 I: 11.6 C: 7.1 P<0.05 <u>Adverse events</u> Dry mouth I: 133 (33.9%) C: 21 (5.3%)	<u>Author's conclusion:</u> Fesoterodine was associated with significantly greater improvements in most diary variables and participant-reported outcomes than placebo and was generally well tolerated in older people <u>Limitations:</u> - Limited generalizability because of relatively high level of functioning <u>Other remarks:</u> Subgroup 65–75 and >75

	conduct of study.	determined according to the investigator - Significant bladder outlet obstruction - Previous history of acute urinary retention requiring catheterization, severe voiding difficulties, or active urinary tract infection - Clinically significant renal disease - Multiple sclerosis or spinal cord injury - Treatment with other antimuscarinics within 2 to 3 weeks before baseline - Treatment with potent CYP3A4 inhibitors - Intermittent or unstable use of diuretics or alpha-blockers or initiation of treatment within 2 weeks of baseline <u>N total at baseline</u>: Intervention: 392 Control: 393 <u>Important prognostic factors</u>: *Mean age ± SD* I: 72.6 ± 5.8 C: 72.8 ± 5.7 *Sex (female)* I: 213 (54%) C: 205 (52%) Groups comparable at baseline				Obstipation I: 35 (8.9%) C: 10 (2.5%) <u>Cognitive decline</u> MMSE score (change from baseline to week 12) I: 0.24±1.76 C: 0.23±1.82 Mean MMSE scores at week 12 I: 28.4 (range 20–30) C: 28.3 (range 19–30)	

PICO 2: Mirabegron/vibegron versus placebo or antimuscarinic treatment

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Griebling, 2020	Type of study: Pre-planned analysis of phase 4 placebo-controlled study (PILLAR). Setting and country: Multicentre study in US and Canada. Funding and conflicts of interest: Funded by Astellas and authors are employees of Astellas.	Inclusion criteria: Community-dwelling patients aged ≥65 years with wet overactive bladder (OAB) (≥1 incontinence episode and ≥3 urgency episodes during the 3-day diary, plus an average of ≥8 micturitions/24 h. Exclusion criteria: Patients needed to be able to complete the micturition diaries and questionnaires. N total at baseline: Intervention: 445 Control: 442 Important prognostic factors: *Mean age ± SD* I: 71.7 ± 5.5 C: 71.9 ± 6.0 *Sex:* I: 71.2% F C: 71.9% F Groups comparable at baseline	Describe intervention (treatment/procedure/test): Mirabegron Initial 25 mg/day and optional to enhance to 50 mg/day after week 4/8	Describe control (treatment/procedure/test): Placebo	Length of follow-up: 12 weeks Loss-to-follow-up: Not reported Incomplete outcome data: The number of patients missing scores were 29 for placebo and 18 for the mirabegron total group.	Cognitive decline Defined by MoCA test (mean (SE)) I: 26.9 (0.1) C: 27.0 (0.1) Impaired cognitive function at 12 weeks: I: 24.5% (104/425) C: 25.8% (106/411) Adverse events Dry mouth: I: 6 (1.3%) C: 7 (1.6%)	Author's conclusion: Treatment with mirabegron for 12 weeks did not contribute to drug-related cognitive side effects in patients aged ≥65 years, as measured by the MoCA. Furthermore, the pattern of change in cognition over time in an older OAB trial population does not appear to differ from that of subjects receiving placebo. Limitations - Short study duration - Results to not apply to all elderly individuals with OAB

Kosilov, 2015	Type of study: RCT Setting and country: Russia Funding and conflicts of interest: Authors declared no conflicts of interest. Funding not reported.	Inclusion criteria: - Age >65 years - Severe symptoms of overactive bladder (the frequency of episodes of incontinence (EI) ≥3/day) Exclusion criteria: - Chronic active diseases including hypertension - Intolerance to antimuscarinics and agonists of β3-adrenoreceptors N total at baseline: Intervention: 63 Control: 59 Important prognostic factors: Not reported Unclear if groups were comparable at baseline	Describe intervention (treatment/procedure/test): Mirabegron 50 mg/day	Describe control (treatment/procedure/test): Placebo	Length of follow-up: 6 weeks Loss-to-follow-up: N=7 (2.9%) in total population because of intolerable side-effects Incomplete outcome data: Not reported	Number of episodes of incontinence I: 2.3 (5.2 → 2.9) C: 0.2 (4.3 → 4.1) Adverse events Dry mouth: I: 1 (1.6%) C: 2 (3.4%) Cognitive impairment: I: 0 C: 1 (1.7%)	Author's conclusion Taking any of these drugs separately for the treatment of severe malfunction of lower urinary tracts in elderly people may turn out to be insufficient for effective symptom management Limitations: - No direct comparison
Kosilov, 2015	Type of study: RCT Setting and country: Russia Funding and conflicts of interest: Authors declared no conflicts of interest. Funding not reported.	Inclusion criteria: - Age >65 years - Severe symptoms of overactive bladder (the frequency of episodes of incontinence (EI) ≥3/day) Exclusion criteria: - Chronic active diseases including hypertension - Intolerance to antimuscarinics and agonists of β3-adrenoreceptors	Describe intervention (treatment/procedure/test): Mirabegron 50 mg/day	Describe control (treatment/procedure/test): Solifenacin 10 mg/day	Length of follow-up: 6 weeks Loss-to-follow-up: N=7 (2.9%) in total population because of intolerable side-effects Incomplete outcome data: Not reported	Number of episodes of incontinence I: 2.3 (5.2 → 2.9) C: 2.2 (5.5 → 3.3) Adverse events Dry mouth: I: 1 (1.6%) C: 5 (9.6%)	Author's conclusion Taking any of these drugs separately for the treatment of severe malfunction of lower urinary tracts in elderly people may turn out to be insufficient for effective symptom management Limitations: - No direct comparison

		N total at baseline: Intervention: 63 Control: 52 Important prognostic factors: Not reported Unclear if groups were comparable at baseline					
Varano, 2021	Type of study: Subpopulation analysis from RCT Setting and country: 199 study sites in the USA, Canada, Poland, Hungary, Latvia, and Lithuania Funding and conflicts of interest: This study and medical writing and editorial support for the preparation of this manuscript were funded by Urovant Sciences (Irvine, CA). Conflicts of interests with pharmaceutical companies (Astellas/Pfizer).	Inclusion criteria: Adults with a history of OAB for at least 3 months before the screening visit and met prespecified criteria for wet or dry OAB Exclusion criteria: - History of 24-h urine volume > 3000 mL in the past 6 months - Lower urinary tract pathology (e.g., bladder outlet obstruction) that could account for OAB symptoms - History of stress urinary incontinence surgery within 6 months of screening Intradetrusor injection of botulinum toxin within 9 months of screening, or electrostimulation within 28 days of screening - Diabetes insipidus - Uncontrolled hyperglycemia (fasting blood glucose > 150 mg/dL or 8.33 mmol/L	Describe intervention (treatment/procedure/test): Vibegron 75 mg/day	Describe control (treatment/procedure/test): Placebo	Length of follow-up: 12 weeks Loss-to-follow-up: Intervention: 21 (6.5%) Reasons: withdrew consent and adverse events Control: 26 (9.0%) Reasons: withdrew consent, lack of efficacy, adverse event, and withdrawn by sponsor Incomplete outcome data: Not reported	UUI episodes Mean daily number of UUI episodes at 12 weeks *Least squares ≥65 years after 12 weeks* I: -2.0 C: -1.2 P <0.001 *Least squares ≥75 years after 12 weeks* I: -2.0 C: -0.4 P<0.0001 for patients ≥75 Adverse events Dry mouth I: 9 (1.7%) C: 5 (0.9%)	Author's conclusion: In this subpopulation analysis of patients with OAB aged ≥ 65 and ≥ 75 years from the EMPOWUR study, once-daily vibegron 75 mg showed rapid onset and robust efficacy versus placebo and was generally safe and well tolerated. Limitations: - Underpowered - Mostly female patients

		and/or non-fasting blood glucose > 200 mg/dL or 11.1 mmol/L or, if in the opinion of the investigator, was uncontrolled) - Current history or evidence of stage ≥ 2 pelvic organ prolapse or use of pessary for the treatment of pelvic organ prolapse - History of neurodegenerative diseases (e.g., multiple sclerosis, Parkinson disease) that could affect the lower urinary tract or its nerve supply. <u>N total at baseline</u>: Intervention: 322 (FAS n=317) Control: 288 (FAS n=277) <u>Important prognostic factors</u>: *Number of patients with mean age ≥65 and sex (based on FAS)* I: 242 (76.0%); 204 (84%) females C: 220 (79.4%); 178 (81%) females *Number of patients with mean age ≥75 and sex (based on FAS)* I: 75 (23.3%); 59 (79%) females C: 57 (20.6.0%); 43 (75%) females					

		Groups comparable at baseline					
Varano, 2021	Type of study: Subpopulation analysis from RCT Setting and country: See above Funding and conflicts of interest: See above	Inclusion criteria: See above Exclusion criteria: See above N total at baseline: Intervention: 322 (FAS n=317) Control: 220 (FAS n=213) Important prognostic factors: *Number of patients with mean age ≥65 and sex (based on FAS)* I: 242 (76.0%); 204 (84%) females C: 166 (77.9%); 132 (80%) females *Number of patients with mean age ≥75 and sex (based on FAS)* I: 75 (23.3%); 59 (79%) females C: 47 (22.1%); 35 (75%) females Groups comparable at baseline	Describe intervention (treatment/procedure/test): Vibegron 75 mg/day	Describe control (treatment/procedure/test): Tolterodine 4 mg extended release	Length of follow-up: 12 weeks Loss-to-follow-up: Intervention: 21 (6.5%) Reasons: withdrew consent and adverse events Control: 26 (11.8%) Reasons: adverse event, withdrew consent, withdrawn by principal investigator, lack of efficacy, protocol deviation, death Incomplete outcome data: Not reported	UUI episodes Mean daily number of UUI episodes at 12 weeks *Least squares ≥65 years after 12 weeks* I: -2.0 C: -1.8 *Least squares ≥75 years after 12 weeks* I: -2.0 C: -2.0 Adverse events Dry mouth: I: 9 (1.7%) C: 28 (6.5%)	Author's conclusion: See above Limitations: See above
Wagg, 2020	Type of study: RCT Setting and country: 103 sites in the USA and Canada	Inclusion criteria: - Community-dwelling patients aged ≥65 years with one or more incontinence episodes, three or more urgency	Describe intervention (treatment/procedure/test): Mirabegron Initial dose of 25 mg/day After week 4 or 8, the dose could be increased to 50 mg/day	Describe control (treatment/procedure/test): Matched placebo	Length of follow-up: 12 weeks Loss-to-follow-up: Intervention: 36 (8.1%)	Number of incontinence episodes/24 h Difference [SE]: –0.6 [0.1] 95% CI –0.8 to –0.3	Author's conclusion Mirabegron efficacy, safety, and tolerability over 12 wk were confirmed in patients

	Funding and conflicts of interest: Funded by Astellas. Conflicts of interest with pharmaceutical companies.	episodes, and an average of eight or more micturition episodes per day based on a 3 day micturition diary - Mental capable to complete the study or consent procedures Exclusion criteria: nursing home residence, bladder outlet obstruction, predominant stress incontinence, postvoid residual volume >150 ml, neurogenic detrusor overactivity, acute urinary tract infection, recent initiation of conservative/invasive therapy for OAB, permanent or intermittent catheterisation, severe renal or hepatic impairment, or uncontrolled hypertension N total at baseline: Intervention: 445 Control: 443 Important prognostic factors: *Mean age ± SD* I: 71.7 ± 5.5 C: 71.9 ± 6.0 *Sex (female)* I: 317 (71%)			Reasons: adverse events, lack of efficacy, protocol violation, withdrawal by patient or study terminated by sponsor Control: 42 (9.5%) Reasons: adverse events, lack of efficacy, protocol violation, or withdrawal by patient Incomplete outcome data: Intervention: 4 (1%) Control: 4 (1%)	Urgency incontinence episodes Difference [SE]: –0.56 [0.14] 95% CI –0.83 to –0.29 Montreal Cognitive Assessment There was no statistically significant change in MoCA score from baseline to end of treatment, with adjusted mean (standard error) changes of -0.1 (0.1) points for placebo and -0.2 (0.1) for mirabegron.	aged ≥65 years with OAB and incontinence Limitations: - Study was not designed to detect a difference between individual mirabegron doses and placebo, because patients were not randomly allocated to individual doses - Patients remaining on 25 mg had different baseline demographic and disease characteristics from those electing to increase their dose to 50 mg mirabegron at week 4 or 8

		C: 324 (73%) Groups comparable at baseline					
Yoshida, 2021	Type of study: Post-hoc analysis of RCT Setting and country: 109 sites in Japan Funding and conflicts of interest: Funding by Kyorin and Kissei Pharmaceutical. Conflicts of interests with pharmaceutical companies (Kyorin/Astellas/Pfizer).	Inclusion criteria: Patients with overactive bladder with ≥8 micturitions/day and either ≥1 urgency episodes/day or ≥1 urgency incontinence episodes/day Exclusion criteria: - Urinary tract infection - Bladder cancer - Bladder calculus - Interstitial cystitis - Enlarged prostate - Residual urinary volume >100 ml - Systolic blood pressure ≥ 160 mmHg, diastolic blood pressure ≥ 100 mmHg, or pulse rate ≥110 bpm N total at baseline: Intervention: 261 (I1=131 with 50 mg; I2=130 with 100 mg) Control: 131 Important prognostic factors: *Age (mean ± SD)* I1: 70.9 ± 4.4 I2: 71.2 ± 4.6 C: 71.7 ± 4.8 *Sex (number of females)*	Describe intervention (treatment/procedure/test): 1: Vibegron 50 mg/day 2: Vibegron 100 mg/day	Describe control (treatment/procedure/test): Placebo	Length of follow-up: 12 weeks Loss-to-follow-up: Not reported Incomplete outcome data: Missing data for systolic/diastolic blood pressure I1: n=5 (3.8%) I2: n=7 (5.4%) C: n=8 (6.1%)	UUI episodes/24h Difference from placebo on LS mean change I1: -0.36 (95% CI -0.66 to -0.06) I2: -0.48 (95% CI -0.79 to -0.18) Adverse events Dry mouth: I: 3 (1.1%) C: 2 (1.5%)	Author's conclusion: Vibegron exerts its efficacy on OAB symptoms with minimal influence on cardiovascular parameters in both patients aged ≥65 and <65 years, suggesting that vibegron may be useful in OAB treatment regardless of age. Limitations: - Mostly female patients included - No elderly ≥75 years

		I1: 123 (93.9%) I2: 117 (90.0%) C: 118 (90.1%) Groups probably comparable at baseline					

FAS: full analysis set

5

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

PICO 1: Antimuscarinic treatment versus placebo

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/not applicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Samuelsson, 2015	Yes. Clear description of participants, interventions and outcomes.	Yes. Search period and search strategy described. PubMed and Medline were searched.	No. List of excluded studies are provided, but no reasons for exclusion were given.	Yes. Characteristics of individual studies are reported.	Not applicable (only RCTs).	Yes. Risk of bias was assessed of individual studies.	Yes. Random effects model was applied to account for clinical heterogeneity and statistical heterogeneity was assessed when possible.	No. Publication bias was only considered in GRADE assessment.	No. Conflict of interest only reported for review.

Risk of bias table for intervention studies

Research question: What is the effectivity and safety of antimuscarinic treatment or mirabegron in elderly patients with urine incontinence, compared to placebo or no treatment?

PICO 1: Antimuscarinic treatment versus placebo

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Dubeau, 2014	Probably yes; Reason: Impala system (only for Pfizer-authorized users) was used for randomization. The randomization schedule was generated, secured, distributed and stored by Pfizer Global Clinical Data Services.	No information	Probably yes; Reason: Only mentioned that it was a double-blinded study, but not further elaborated.	Probably no; Reason: Loss to follow-up was frequent in intervention and control group.	Probably yes; Reason: Outcomes described in the protocol were also reported in the study.	Probably yes; Reason: No other problems noted.	**Some concerns**
Kosilov, 2015	Probably yes;	Probably yes;	Probably no;	Probably yes;	Probably no;	Probably no;	**Some concerns**

	Reason: Simple probability sampling with randomization by the method of sequential numbers was used.	Reason: Participants were not aware of pharmacological properties and names of the drugs.	Reason: Participants were blinded, but no information about blinding of other study personnel.	Reason: Loss to follow-up was infrequent.	Reason: One outcome measure was not reported in the methods section; the other outcomes were only mentioned in the analysis part.	Reason: No information about baseline characteristics of participants.	
Lackner, 2011	Definitely yes; Reason: Computer-generated randomization program was used by investigational pharmacy.	Probably yes; Reason: Identical-appearing sham tablet used for placebo.	Probably yes; Reason: Participants and study personnel were blinded.	Probably yes; Reason: Loss to follow-up was infrequent in intervention and control group.	Probably yes; Reason: Secondary outcomes of previous study.	Probably no; Reason: Insufficient power.	**Some concerns**
Wagg, 2013	Probably yes; Reason: Centralized system for randomization, but Pfizer Inc. generated and secured the randomization schedule.	Probably yes; Reason: Study drug and placebo were identical in appearance.	Probably yes; Reason: Participants and investigators were blinded.	Probably no; Reason: Loss to follow-up was frequent in intervention and control group	Probably yes; Reason: Outcomes mentioned in the protocol were also reported in the article.	Probably yes; Reason: No other problems noted.	**Some concerns**

PICO 2: Mirabegron versus placebo or antimuscarinic treatment

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Griebling, 2020	Probably yes; Reason: Computer-generated randomisation schedule prepared by the sponsor.	No information	Probably yes; Reason: Patients, investigators, and the sponsor were blinded to treatment allocation.	Probably yes; Reason: No loss to follow-up.	Probably yes; Reason: All relevant outcomes were reported.	Probably yes; Reason: No other problems noted.	**Some concerns**
Kosilov, 2015	Probably yes; Reason: Simple probability sampling with randomization by the method of	Probably yes; Reason: Participants were not aware of pharmacological	Probably no; Reason: Participants were blinded, but no information about	Probably yes; Reason: Loss to follow-up was infrequent.	Probably no; Reason: One outcome measure was not reported in the methods section; the	Probably no; Reason: No information about baseline characteristics of participants.	**Some concerns**

	sequential numbers was used.	properties and names of the drugs.	blinding of other study personnel.		other outcomes were only mentioned in the analysis part.		
Varano, 2021	Probably yes; Reason: Central, web based interactive response system.	Probably yes; Reason: Placebo capsules matching with intervention tablet.	Probably yes; Reason: Patients, investigators and sponsor were blinded.	Probably no; Reason: Loss to follow-up was frequent in intervention and control group.	Probably yes; Reason: All relevant outcomes were reported.	Probably no; Reason: Unpowered study.	**Some concerns**
Wagg, 2020	Probably yes; Reason: Computer-generated randomisation schedule prepared by the sponsor.	No information	Probably yes; Reason: Patients, investigators, and the sponsor were blinded to treatment allocation.	Probably no; Reason: Loss to follow-up was frequent in intervention and control group.	Probably yes; Reason: All relevant outcomes were reported.	Probably yes; Reason: No other problems noted.	**Some concerns**
Yoshida, 2021	No information	No information	Probably yes; Reason: Only mentioned that it was a double-blinded study, but not further elaborated.	Probably yes; Reason: Loss to follow-up was infrequent for intervention and control.	Probably no; Reason: All relevant outcomes were reported.	Probably yes; Reason: No other problems noted.	**HIGH**