

# Is there an effect of oral anticholinergics on the clinical and molecular parameters of prostate and bladder of patients with benign prostatic hyperplasia and overactive bladder?

<b>Submission date</b> 09/04/2017	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered
<b>Registration date</b> 18/04/2017	<b>Overall study status</b> Completed	<input type="checkbox"/> Protocol
<b>Last Edited</b> 23/01/2019	<b>Condition category</b> Urological and Genital Diseases	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
		<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Benign prostatic hyperplasia (also known as prostate enlargement) is a common condition in men after the age of 50. It usually causes people to have to urinate (pee) often and urgently. This can be very difficult to handle. An overactive bladder (where urine is collected and held) could be a symptom of an enlarged prostate. A prostatectomy is a surgical procedure that removes either part of or the whole prostate is done to try to help relieve an overactive bladder. However, research has shown that people who have undergone a prostatectomy still have overactive bladder symptoms. Therefore it is unclear if only the prostate should be treated or both the prostate and the bladder should be treated to help relieve the symptoms. There are medications that can be used to treat the symptoms such as tamsulosin which help improve urination and solifenacin which helps treat the muscle movement in the bladder. The aim of this study is to explore whether the medications used in the treatment of benign prostatic enlargement-associated Lower Urinary Tract Symptoms (LUTS) has an effect on the prostate as well as on the bladder.

### Who can participate?

Adults who are aged 50 and older who have lower urinary tract symptoms and adults who are 50 years or older who do not have symptoms.

### What does the study involve?

This study involves two parts. Participants in the first part of the study are randomly allocated to one of two groups. Those in the first group receive a single tablet taken by mouth of tamsulosin (0.4mg) that they take nightly for six months. Those in the second group receive a tablet of tamsulosin (0.4mg) that also includes solifenacin (5mg) that they take nightly for six months. Participants are assessed at the start of the study and at the end of the study for their bladder and urine symptoms as well as quality of life and blood tests. After the six months, participants are asked if they would like to continue with the medicine or undergo a prostatectomy. The second part of the study includes the samples taken from participants, who agreed to undergo a

prostatectomy, and compares their samples with participants (with both symptoms of overactive bladder and those without) who have agreed to provide tissue samples during other procedures.

What are the possible benefits and risks of participating?

Participants may benefit from receiving additional diagnostic tests. There are risks associated with the tamsulosin medication including blurred vision, hypotension (low blood pressure), retrograde ejaculate (where the semen enters the bladder as it cannot leave through the penis). There are also risks with solifenacin which include dry mouth, dry eyes, constipation (unable to have a bowel movement), cognitive dysfunction (mental problems) and hypertension (high blood pressure). There are risks with some of the diagnostic procedures including bleeding, infection, painful urination, and discomfort. There are also risks associated with prostatectomy which include bleeding, infection, retrograde ejaculation, incontinence (leakage of urine or feces).

Where is the study run from?

1. Hippokrateion General Hospital of Thessaloniki (Greece)
2. Papageorgiou Hospital of Thessaloniki (Greece)

When is the study starting and how long is it expected to run for?

January 2013 to June 2015

Who is funding the study?

1. European Social Fund (EU)
2. Greece National Resources (Greece)

Who is the main contact?

Dr Vasileios Sakalis

## Contact information

### Type(s)

Scientific

### Contact name

Dr Vasileios Sakalis

### ORCID ID

<http://orcid.org/0000-0003-0132-224X>

### Contact details

2nd Department of Urology  
Aristotele University of Thessaloniki  
Papageorgiou University Hospital of Thessaloniki  
Ring Road  
Nea Efkarpia  
Thessaloniki  
Greece  
54603  
+30 2310991476  
[vsakkalis@hotmail.com](mailto:vsakkalis@hotmail.com)

# Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

71/13.03.2014

## Study information

### Scientific Title

Changes in lower urinary tract cholinergic pathways in patients with Benign Prostatic Hyperplasia-associated Lower Urinary Tract Symptoms and Overactive Bladder symptoms: The effect of oral antimuscarinics

### Study objectives

The aim of this study is to explore whether the antimuscarinics used in the treatment of benign prostatic enlargement-associated Lower Urinary Tract Symptoms (LUTS) have an effect on the prostate as well as on the bladder.

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Aristotele University of Thessaloniki, Greece, School of Medicine, Ethics Committee, 13/03/2014, ref: 71/13.03.2014

### Study design

Prospective multi-centre open-label active comparator randomised controlled study

### Primary study design

Interventional

### Secondary study design

Randomised controlled trial

### Study setting(s)

Hospital

### Study type(s)

Other

### Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

### Health condition(s) or problem(s) studied

## Benign prostatic hyperplasia, Overactive Bladder

### Interventions

This study involves two study arms, one clinical and one molecular.

#### Arm 1: Clinical

Potential participants are identified during an assessment in the male Lower Urinary Tract Symptoms (LUTS) clinic. They are given a study information pack and asked to return a three-day bladder diary within two weeks. Those who documented the required number of daily urgent episodes are asked to join the study. Participants are randomly allocated using SPSS software (1:1) into one of two groups.

**Group 1 Tamsulosin monotherapy:** Participants receive tamsulosin 0.4mg tamsulosin once at night (Tamsulosin OCAS 0.4mg, Astellas) for six months.

**Group 2 Tamsulosin & Solifenacin Combination therapy:** Participants receive solifenacin 5mg plus tamsulosin 0.4mg to take once at night (Astellas) for six months.

Titration of solifenacin dose (10mg) is possible in the combination therapy patients who have inadequate symptom control after 4 weeks. Patients are followed up at baseline and at 26 weeks to assess their urinary symptoms, quality of life and to complete tests including transrectal and transabdominal ultrasonography, free uroflowmetry and pressure-flow study, basic biochemistry, PSA and Testosterone blood tests. At week 26 they are asked to repeat a bladder diary. Participants have interim follow-up assessments at four and 12 weeks that include questionnaires, uroflowmetry and transabdominal ultrasonography. At study completion participants are asked whether they would like to continue on medical therapy or undergo prostatectomy (transurethral resection, for prostates <80mls or open procedure, for prostates >80mls). If they choose the prostatectomy they are included in the second arm of the study.

#### Arm 2: Molecular

This arm compares tissue samples from different symptomatic patients. Participants in this group include those from the first arm of the study who have agreed to a prostatectomy and from three control groups. Participants from the first arm of the study undergo a prostatectomy. This is done using a transurethral resection for prostates <80mls or an open procedure for >80mls.

The control groups consist of the following:

**Control group 1:** Treatment naive patients with benign prostatic hyperplasia (BPH) and Overactive Bladder (OAB). Participants in this group are asked to provide a tissue sample during a procedure for another problem (typically ureteroscopic lithotripsy or small volume bladder tumour disease).

**Control group 2:** Asymptomatic men (Bladder biopsies). Participants are recruited based on their IPSS (International prostate symptom score questionnaire) score. These participants undergo a procedure for another problem (usually to treat ureteric stones and small volume bladder tissue). The sample is obtained from a macroscopically healthy bladder area.

Control group 3: Asymptomatic men (Prostate biopsies) Participants are recruited based on their IPSS (International prostate symptom score questionnaire) score. Participants in this group provide a undergo a transrectal biopsy of their prostate, and are asked to provide an additional biopsy for this study.

The samples collected from the treatment group are compared to samples from the control groups (the symptomatic group, asymptomatic bladder tissue and one asymptomatic prostate tissue).

### **Intervention Type**

Drug

### **Phase**

Not Applicable

### **Drug/device/biological/vaccine name(s)**

Tamsulosin, Solifenacin

### **Primary outcome measure**

Muscarinic receptor expression is measured using the immunohistochemistry (Western Blot and RT-PCR) at 6 months

### **Secondary outcome measures**

1. Urinary symptoms are measured using IPSS Questionnaire at three and six months
2. Storage ability is measured using IPSS Questionnaire Storage subscale at three and six months
3. Amount of prostate specific antigen (PSA) in the blood is measured using standard laboratory biochemistry tests at three and six months
4. Semen parameters are measured using standard laboratory biochemistry tests at three and six months
5. Total prostate and adenoma volume is measured using Transabdominal and transrectal ultrasonography at three and six months
6. Quality of life is measured using the QoL question of the IPSS at three and six months
7. Adrenergic receptor expression in prostate and bladder is measured using immunohistochemistry (Western Blot and RT-PCR) at six months
8. Sensory receptor TRPV1 expression is measured using immunohistochemistry (Western Blot and RT-PCR) at six months
9. eNOS and VEGF expression in prostate and bladder using immunohistochemistry (Western Blot and RT-PCR) at six months

### **Overall study start date**

01/01/2013

### **Completion date**

30/06/2015

## **Eligibility**

### **Key inclusion criteria**

Treatment arms (Group 1 and 2):

1. Treatment-naïve men

2. Age 50 years or older
3. Predominantly storage LUTS as defined by the IPSS (storage subscore  $\geq$  voiding subscore and score  $\geq 3$  in the urgency question) and at least 3 urgency episodes per 24h as documented in a 3-day bladder diary
4. Prostate volume  $\geq 30$ ml
5. Maximum flow rate ( $Q_{max}$ )  $\geq 10$ ml/s
6. Post-void residual (PVR)  $\leq 100$ ml
7. PSA value  $\leq 4$  ng/ml. Patients with positive DRE and/or PSA values 4-10ng/ml are included only after negative prostate biopsy.

Control group 1:

1. Treatment-naïve men
2. Age 50 years or older
3. Predominantly storage LUTS as defined by the IPSS (storage subscore  $\geq$  voiding subscore and score  $\geq 3$  in the urgency question) and at least 3 urgency episodes per 24h as documented in a 3-day bladder diary
4. Prostate volume  $\geq 30$ ml
5. Maximum flow rate ( $Q_{max}$ )  $\geq 10$ ml/s
6. Post-void residual (PVR)  $\leq 100$ ml
7. PSA  $\leq 4$ ng/ml. Patients with positive DRE and/or PSA values 4-10bng/ml are included only after negative prostate biopsy
8. Consent to provide prostate or bladder tissue

Control group 2 and 3: Asymptomatic men

1. Treatment-naïve men
2. Age 50 years or older
3. Total IPSS  $< 7$  and/or a score of 0-1 in the IPSS 'urgency' question.
4. Prostate volume  $\geq 30$ ml
5. Maximum flow rate ( $Q_{max}$ )  $\geq 10$ ml/s
6. Post-void residual (PVR)  $\leq 100$ ml
7. PSA  $\leq 4$ ng/ml. Patients with positive DRE and/or PSA values 4-10 ng/ml were included only after negative prostate biopsy.

**Participant type(s)**

Mixed

**Age group**

Adult

**Sex**

Male

**Target number of participants**

Treatment groups (Group 1 & 2) 30 patients each. Control groups (Group 3,4 & 5) 15 subjects each.

**Key exclusion criteria**

1. Patients with neurogenic lower urinary tract dysfunction
2. Patients with a history of urinary tract malignancy
3. Any contraindication to the use of  $\alpha$ -blockers or antimuscarinics
4. Metabolic conditions that may affect lower urinary tract (LUT) function

5. Psychiatric illnesses
6. Chronic kidney, hepatic or cardiac failure
7. History of urinary stone disease
8. History of urethral instrumentation
9. Urethral stricture
10. Acute urinary tract infection (UTI) or history of recurrent UTI's
11. Use of medications known to affect LUT function including PDE-5 inhibitors
12. Positive urine culture
13. Microscopic haematuria, proteinuria or glucosuria. Subjects with pyuria were included only after a negative urine culture.

**Date of first enrolment**

01/10/2013

**Date of final enrolment**

01/02/2015

## **Locations**

**Countries of recruitment**

Greece

**Study participating centre**

**Hippokrateion General Hospital of Thessaloniki**

Thessaloniki

Greece

54642

**Study participating centre**

**Papageorgiou Hospital of Thessaloniki**

2nd Urology Department of Aristotele University of Thessaloniki

Thessaloniki

Greece

56403

## **Sponsor information**

**Organisation**

Aristotele University of Thessaloniki

**Sponsor details**

2nd Department of Urology

Aristotele University of Thessaloniki

Papageorgiou University Hospital of Thessaloniki  
Ring road  
Nea Efkarpia  
Thessaloniki  
Greece  
54603

**Sponsor type**

University/education

**ROR**

<https://ror.org/02j61yw88>

## **Funder(s)**

**Funder type**

Government

**Funder Name**

European Social Fund

**Alternative Name(s)**

Европейският социален фонд, Evropský sociální fond, Den Europæiske Socialfond, Europäischer Sozialfonds, Euroopa Sotsiaalfond, Ευρωπαϊκό Κοινωνικό Ταμείο, Fondo Social Europeo, Fonds social européen, Europejski socjalni fond, Fondo sociale europeo, Eiropas Sociālais fonds, Europos socialinis fondas, Európai Szociális Alap, Fond Soċjali Ewropew, Europees Sociaal Fonds, Europejski Fundusz Społeczny, Fundo Social Europeu, Fondul Social European, Európsky sociálny fond, Evropski socialni sklad, Euroopan sosiaalirahasto, Europeiska socialfonden, European Social Fund, Fondo Social Europeo Plus, Европейски социален фонд плюс, Evropský sociální fond plus, Europæiske Socialfond Plus, Europäische Sozialfonds+, Euroopa Sotsiaalfond+, Ευρωπαϊκό Κοινωνικό Ταμείο+, Fonds social européen+, Europejski socjalni fond plus, Fondo sociale europeo Plus, Eiropas Sociālais fonds Plus, Europos socialinis fondas +, Európai Szociális Alap Plusz, Europees Sociaal Fonds Plus, Europejski Fundusz Społeczny Plus, Fundo Social Europeu Mais, Fondul social european Plus, Európsky sociálny fond +, Evropski socialni sklad +, Euroopan sosiaalirahasto plus, Europeiska socialfonden+, ESF, ЕСФ, EKT, FSE, ESZA, EFS, ESS, ESR, ESF+, ESZA+, EFS+, FSE+, ESS+, ESR+

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

**Funder Name**



## Results and Publications

### Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal.

### Intention to publish date

31/12/2017

### Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Vasileios Sakalis MSc, FEBU at [vsakkalis@hotmail.com](mailto:vsakkalis@hotmail.com)

### IPD sharing plan summary

Available on request

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	01/08/2018	23/01/2019	Yes	No