# *EFFICACY OF SOLIFENACIN IN "DE NOVO" URGENCY FREQUENCY SYNDROME AFTER TRANS-OBTURATOR-TAPE SURGERY*

# EFFICACIA DELLA SOLIFENACINA NELLA SINDROME URGENZA FREQUENZA DOPO INTERVENTO CHIRURGICO CON TRANS-OBTURATOR-TAPE Y

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**ABSTRACT**

Our study evaluates the efficacy of Solifenacin in the cases of "de novo" urgency-frequency syndrome after the placing of transobturator tape (TOT). A sample of 106 women, treated by TOT, were followed in postoperative course for one month. We selected 13 patients (12.3%) with "de novo" urgency frequency syndrome, excluding cases of cystitis, who started Solifenacin 5mg/day, administered orally, for three months. Our study showed that these patients reported significant improvements in urge incontinence, frequency and nocturia, on the VAS ($p < 0.001$), all OAB-q and KHQ domains ($p < 0.001$) and bladder diaries. After the therapy, we highlighted that only 3 (2.8%) of the 13 patients continued to present, even if in a minimized manner, a pseudo-irritant symptomatology; in the other 10 patients (9.4%), we obtained a complete resolution of the symptomatology. Our study is one of the few in medical literature that has proven the efficacy of a selective M3 antimuscarinic for the cure of the pseudo-irritant symptomatology after anti-incontinence surgery. We got the regression of symptoms of urgency in 100% of patients with a meaningful improvement of quality of life.
**Key words:** *Solifenacin; De novo" urgency-frequency syndrome; transobturator tape*

**RIASSUNTO**

Il nostro studio valuta l'efficacia della solifenacina nei casi di sindrome urgenza-frequenza "de novo", dopo l'apposizione di un transobturator tape (TOT). Un campione di 106 donne, trattate con TOT, è stato seguito nel decorso post-operatorio per un mese. Abbiamo selezionato 13 pazienti (12,3%), con sindrome urgenza frequenza "de novo", esclusi i casi di cistite, che hanno iniziato la terapia con 5mg/die di solifenacina, con somministrazione orale, per tre mesi. Lo studio ha mostrato che queste pazienti hanno riportato miglioramenti significativi nell'incontinenza da urgenza, nella frequenza, nella nicturia, nella VAS ($p <0,001$), in tutti i domini OAB q e KHQ ($p <0,001$) e nei diari minzionali. Dopo la terapia, abbiamo evidenziato che solo 3 (2,8%) delle 13 pazienti ha continuato a presentare, anche se ridotta al minimo, una sintomatologia pseudo-irritante; nelle altre 10 pazienti (9,4%), abbiamo ottenuto una completa risoluzione della sintomatologia. Il nostro studio è uno dei pochi in letteratura medica che ha dimostrato l'efficacia di un antimuscarinico selettivo M3 per la cura della sintomatologia pseudo-irritante dopo l'intervento anti-incontinenza. Abbiamo ottenuto la regressione dei sintomi di urgenza nel 100% delle pazienti con un miglioramento significativo della qualità della vita.
**Parole chiave:** *Solifenacina; Sindrome urgenza-frequenza "de novo"; sling transotturatorio*

## INTRODUCTION

International continence society (ICS) defines urge incontinence as: involontary loss of urine associated with or immediately preceded by a strong desire to urinate which correspond with uncontrollable overactivity of the urinary bladder smooth muscle with an intravesical pressure > 15 cmH2O.
Symptoms such as urgency, urge urinary incontinence and urinary frequency, instead, configure the overactive bladder (OAB) syndrome. OAB (mean of > or = 8 voids/24 h, plus > or = 1 incontinence episode or > or = 1 urgency episode/24 h) [1] has been recognised by the ICS as an important symptom syndrome that affects millions of people worldwide, particularly women. It's a highly prevalent symptom complex that may be extremely distressing to the patient, and can be associated with co-morbidities and reduced quality of life (QoL). Urgency is the defining symptom of OAB, yet a significant proportion of patients also suffer from incontinence, which is the most distressing symptom to the patient. As such, restoration of continence should be a primary treatment goal. [2]
A study shows that the prevalence for Maori women (46.8%) was significantly greater than for either Pacific Island (29.2%) or European women (31.2%). Increasing age, and parity were associated with increasing prevalence of incontinence for all ethnic groups. Of the incontinent women, 9% were continually incontinent, 28% once or more daily, and 37% more than twice monthly. A further 26% were incontinent less than twice monthly. The most reported type of incontinence was stress incontinence (48% of incontinent women), with 27% reporting urge incontinence, and 21% a mixed picture of stress and urge. [3]
The prevalence of UI in women has been intensively studied in a number of cross-sectional studies, all of which have shown that the prevalence increases with age. In fact it's sure that the risk factors for stress UI are: age > or = 40 years, pregnancy, previous vaginal delivery, postpartum incontinence and hysterectomy. There are no relationship between stress UI and obesity or previous Caesarean delivery. Gynaecological and obstetric events (pregnancy, particularly previous vaginal delivery and hysterectomy) are the most prominent risk factors, expecially for stress UI. [4]
In the last twenty years numerous surgical techniques (Burch, Raz, anterior colporraphy etc.) have been put forward as the cure for this pathology; nowadays the most common therapeutic option, supported by numerous random studies and follow-ups, is a new minimally invasive surgical procedure: the Trans-obturator Vaginal Tape (TOT).
TOT is safe with a low rate of complications. The mean operative time is about 12 min (range 6-30) with a catheterisation time of 0,9 day (range 0-2) and no severe bleeding.
This innovative technique is characterized by the use of molded rubber prosthesis of the hammock or sling type in a synthetic material such as polypropylene or, in alternative, acellular collagen of porcine origin to be positioned in a "tension free" manner corresponding to the suburethral area (third medium) in the exact position where the urethral sphincter is found.
After having ascertained the success percentage, which ranges from 88% to 93%, and researched materials with the characteristics that render these prosthesis always more "bio-compatible", the problem of complications arose, with the primary one being erosion, then the accentuation of the urgency-frequency syndrome prior to the operation and finally the appearance of a "de novo" urgency or even worse an urge incontinence.
For this reason it's useful to analyze the features of each patient by preoperative urodynamic exam, in order to assess the risk, even if the patient history is only minimally helpful in the identification of women at increased risk for the development of de novo urge urinary incontinence postoperatively.
Expecially detrusor pressure > 15 cm $H_2O$ may help identify patients at increased risk. [5]
One of the pathophysiological causes of OAB is overactivity of the detrusor muscle, mediated via muscarinic receptors in the bladder.
Some researchers suggest that it is because of a damage to central inhibitory pathways or sensitisation of peripheral afferent terminals in the bladder, others suggest that it is a bladder muscle problem; the reality is probably a spectrum encompassing these two main explanations.
Efficacy of OAB therapy needs to be balanced against tolerability, as a low incidence of adverse events (AEs) improves compliance with treatment. This balance between efficacy and tolerability should provide palpable benefits from a patient's perspective, and promote persistence with a therapy, which is of course an important issue in chronic conditions, such as OAB, that require continued therapy.
However, effective treatments should not only alleviate incontinence but also impact on the other key symptoms of OAB, such as micturition frequency

and urgency. Non-pharmacologic interventions to treat OAB can be effective but require patients to be highly motivated. In terms of pharmacologic therapy, treatment with an antimuscarinic agent is the mainstay of current therapy.
Unfortunately, many antimuscarinics, especially older agents, have modest clinical efficacy and are associated with unfavourable side effects, leading to poor persistence with therapy.
Therefore, treatment is difficult and is aimed at alleviating symptoms (being those of urgency, with or without urge incontinence, usually with frequency and nocturia) rather than treating the cause. Once a presumptive diagnosis is made, conservative management forms the first line of treatment and includes lifestyle modifications, bladder training, pelvic floor exercises and electrostimulation. If this fails, pharmacotherapy, in the form of anticholinergic drugs, is initiated.
The pharmaceutical therapy used for urinary incontinence from urgency and symptoms associated with a hyperactive bladder chiefly aims at discouraging detrusor activity, which, for reasons that are still not entirely clear, is "released" from the fine and complex neuro-muscular-visceral system that is the pavement of the female pelvis.
The most important drugs that have a proven clinical efficacy are the antimuscarinics/ anticolinergics.
These act by relaxing the detrusor, increasing the capacity of the bladder through a reduction of uncontrolled contractions.
There are many antimuscarinic drugs, for example oxybutynin, tolterodine and trospium chloride. Each has a different specificity to bladder muscarinic receptors, thus producing different adverse effect profiles (e.g. dry mouth, blurred vision and constipation). Different individuals experience these adverse effects to different extents. New anticholinergic drugs, more specific to the muscarinic M3 human bladder receptor, were introduced to the market in 2004 (e.g. solifenacin succinate and darifenacin). [6]
In addition to adverse effect profile, cost and improvement in quality of life are important factors in choosing treatment. Further research is being conducted on other types of drugs and different administration modalities, for example intravescical botulinum toxin A, electrostimulation, biofeedback, percutaneous stimulation of the tibial nerve (PTNS) and definite pacemaker insertion on the sacral roots; these represent the therapeutic options available to hospital personnel in handling a syndrome that certainly has an important impact on the quality of life, especially after having placed so much hope in the surgery that has resolved the incontinence stress but has caused, in certain cases, a not less annoying "urgency".

The aim of our study was to evaluate the efficacy of a new antimuscarinic drug – Solifenacin (which has an affinity for M3 receptors 30-fold higher than that for M2 ones) – using the dose of 5mg per day, in the treatment of the "de novo" pseudo-irritant symptomatology, or indeed after anti-incontinence surgery, and in particular after the placing of a transobturator (TOT) "tension free" sling and it's based on the evaluation of its possible causes.

## MATERIALS AND METHODS

The present study was conducted at the Urogynaecological Unit of the Gynaecology and Obstetrics Clinic of the University of Catania, at the Santo Bambino Hospital, in the period from November 2008 to January 2010. The sample taken into consideration was made up of 106 women affected with urinary incontinence from pure strain (IUS) with the following characteristics:

- Age: 44 – 63 years old;
- Body Mass Index (BMI): 24.3 (range 18 – 45.2);
- Average Parity: 1.7;
- Urodynamic Diagnosis of urinary incontinence from strain;
- Patients excluded were affected by mixed incontinence and prolapse, so as to evaluate the efficacy of Solifenacin 5mg 1 cpr/day in the cases of "de novo" urgency-frequency syndrome after TOT.

The institutional ethical committee of the department approved the study. All the subjects provided written informed consent before entering the study, which was conducted in accordance with the Declaration of Helsinki.
The study was not advertised and no remuneration was offered.

We carried out an urogynecological work-up, an accurate urodynamic examination and chose these patients because of their TOT surgery.
The prosthesis used were 49 Safyre T Promedon Cordoba Argentina, 36 Pelvilace TO Bard-USA, 21 Monarc AMS.
One necessary requisite for being chosen was the

exclusion of a glaucoma diagnosis or mellito diabetes in that there are absolute contrary indications for antimuscarinic treatment.
We estimated three follow-ups: the first after 15 days, the second after three months and the third after six months. The patients that developed a subjective urge or urge-frequency with incontinence were started on Solifenacin 5mg/day for three months and we administered the visual analog scale (VAS) for assessing individual symptoms, the Overactive Bladder Questionnaire (OAB-q), the King's Health Questionnaire (KHQ) and bladder diaries.

## RESULTS

At the second follow-up, after 3 months, 13 women (12.3%) presented "de novo" pseudo-irritant symptoms that were urgency, frequency, and urge incontinence. In these patients, after having excluded cystitis, we started the administration of Solifenacin at the dosage of 5mg/day for 3 months. These patients reported significant improvements from the second follow-up (3 months) at the third follow-up (6 months) in urinary urgency, urge incontinence, frequency, and nocturia on the VAS ($p < 0.001$), all OAB-q and KHQ domains (symptom severity, coping, concern, sleep, social, health-related quality of life; $p < 0.001$) and bladder diaries (a statistically significant reduction in the number of voids, incontinence episodes and urgency episodes per 24 hrs). At the end of the therapy, we were able to highlight that only 3 (2.8%) of the 13 patients in the study continued to present, even if in a minimized manner, a pseudo-irritant symptomatology not pre-existent to surgery. In the other 10 (9.4%) patients, on the other hand, we obtained a resolution of the symptomatology with an optimum tolerance to the medicine. We tried to associate topic estrogenotherapy to all 13 patients only after the third follow-up and we verified a further improvement of the symptomatology even in the 3 non-responder patients.

## DISCUSSION

Pathogenesis of detrusorial instability after TOT surgery may be connected with weakness of the internal urethral sphincter; in fact, even if the sling type prothesy is correctly positioned, some urine may penetrate in the urethra stimulating, consequently, detrusorial contractions.
Another theory is based on the minor compliance of the bladder due to the previous condition of stress incontinence. Detrusorial instability would be, in this case, secondary to the restablished continence. [7]
Several authors underlined that patients affected by SUI have longer times of nervous conduction; they always are > 2,4 msec in fact. [8]
Another possible cause of de novo urge incontinence can be associated with paraurethral sclerosis stimulated by the sling. [9]
Antimuscarinic agents are the mainstay of OAB pharmacotherapy, and exert their effects by competitively blocking acetylcholine binding at the muscarinic receptors within the various histological compartments of the bladder.
Among the first medicines used in the treatment for urinary incontinence from urgency *Ossibutinina,* at a dosage of 2.5 – 5 mg 2-3 times a day, is the best medicine that has been documented in terms of efficacy and safety and should be considered as a reference.
It is a myolitic with anticolinergic properties and a bland local anaesthetic effect. Despite the fairly good percentage of success, the medicine is often suspended because of its side effects(like mouth dryness, confused vision, dryness of the eyes, nausea, constipation diarrhea, abdominal pain, cephalalgy, dizziness, drowsiness, skin dryness and difficulty in urination.
Another antimuscarinic used in this form of incontinence, recently commercialized, is *Tolterodina.* It has a greater specificity for the muscarinic M2 receptors with respect to the M3, resulting, for this reason, more tolerable than Ossibutinina. Both medicines have to be taken for 5 – 10 weeks so as to obtain the maximum benefits. The undesirable side effects are the same as for ossibutinina.
New molecules have recently been introduced, such as *Trospio chloride,* with a dosage of 20mg twice a day, which blocks in a non-selective mode the muscarinic receptors.
*Solifenacin succinat,* the latest generation antimuscarinic, has shown a good therapeutic efficacy for "de novo" urinary incontinence and, compared to the molecules that were analyzed before, a reduced incidence of undesirable side effects. Solifenacin succinate is a once daily, bladder selective antimuscarinic available in two doses (5 and 10 mg). The recommended dose is 5 mg once daily and can be increased to 10 mg once daily if 5 mg is well tolerated.
The medicine under test is a specific competitive antagonist to the muscarinic M3 receptors; its affinity was higher for the M3 receptors at the bladder level, compared to those of the salivary glandular tissue.
Solifenacin is highly lipophilic (50:1 octanol:water distribution at pH 7.0), completely orally bioavailable, and 98% protein bound. It is metabolized by

the cytochrome P450 3A isozyme. Approximately 70% of a dose is eliminated renally as parent compound, with 1 active and 3 inactive metabolites and the rest through the feces.
Taken orally, Solifenacin has a bio-disposability of 90%, which is not influenced by the presence of food in the stomach. It is absorbed well and reaches peak plasmatic levels in 3 – 6 h. Its half-life is from 45 to 65 h.
Several trials show that solifenacin 5 and 10 mg once daily is significantly more effective than placebo at reducing urgency, incontinence, micturition frequency and nocturia and at increasing volume voided per micturition.
Adverse events were mainly mild-to-moderate in all treatment groups.
In a study of pooled data from two 12-week studies, patients who received SOL 5 or 10 mg reported significant improvements in a number of quality-of-life domains (P< or = 0.05).
In a pooled analysis of 4 studies, the most common adverse effects (occurring in > or =3% of any group) in patients receiving SOL 5 mg (n = 266) and 10 mg (n = 612) were dry mouth (10.9% and 27.1%, respectively), constipation (5.3% and 12.9%), and blurred vision (4.5% and 4.7%). [10]
Long-term efficacy in the treatment of overactive bladder (OAB) syndrome depends, of course, in part on the patient's persistence with pharmacologic therapy.
40-week open-label extension of two 12-week, placebo-controlled, double-blind studies show that a total of 81% of patients completed 40 weeks of open-label treatment. Solifenacin treatment was safe and well tolerated, and rates of anticholinergic side effects were relatively low. Only 4.7% of patients discontinued treatment owing to adverse events. Improvements in major symptoms of OAB were noted for all patients for up to 52 weeks of treatment.
Efficacy was confirmed when outcomes were assessed as a function of total solifenacin exposure. Patient satisfaction with solifenacin tolerability (85%) and efficacy (74%) were high. Long-term therapy with solifenacin resulted in a favourable tolerability profile, and was associated with improvements in efficacy parameters based on diary data recorded over a 12-month period. This balance of tolerability and efficacy with solifenacin was associated with excellent persistence with therapy. These results suggest that solifenacin may be useful for the long-term treatment of the chronic symptoms associated with OAB. [11]
Another study, that lasted 12 weeks, compared Solifenacin (5 and 10 mg/day) to Tolterodina (2mg twice a day) and a placebo in 1,081 patients with hyperactive bladder symptoms. [12]
The average reduction of immediate urgency urinations in a 24 h period was statistically significant in favor of Solifenacin [ -2.85 (5mg) and 3.07 (10mg) compared to 2.05 with the Tolterodina], without appreciable differences in the average reduction of the episodes of incontinence in the 24 h period (1.42 and 1.45 with 5 and 10mg of Solifenacin compared to 1.14 with Tolterodina).
The side effects are those typical of the anticolinergics and are usually of a slight or moderate form. The frequency of the undesirable side effects is dependant on the dose. Compliance is generally very high (99%) and about 90% of the patients treated completed the foreseen period of study of about 12 weeks.
Different other studies were made to evaluate the antimuscarinic properties of solifenacin and to compare the results with those obtained for tolterodine, oxybutynin, darifenacin, propiverine and atropine. In radioligand receptor binding assay, Ki values of solifenacin for human muscarinic M1, M2, M3, M4 and M5 receptors were 26, 170, 12, 110 and 31 nM, respectively. In anesthetized rats, solifenacin and oxybutynin increased the maximum bladder capacity in a dose-dependent manner and also ecreased the maximum intravesical pressure. The dosages required to produce a 30% increase in maximum bladder capacity (ED30 values) of solifenacin and oxybutynin were 0.35 and 0.30 mg/kg i.v., respectively, indicating approximately equal efficacies.
These results support the fact that solifenacin, similarly to currently used antimuscarinic agents, is an effective agent in the treatment of overactive bladder symptoms such as urinary frequency and urge incontinence. [13]
In the urinary bladder smooth muscle although muscarinic M2 receptors are numerically predominant, muscarinic M3 receptors are considered to predominate in the mediation of bladder contraction. [14]
In radioligand receptor binding assay, solifenacin showed the highest affinity for the muscarinic M3 receptor, which mediates the urinary bladder contraction, but its affinity for the M3 receptor was only marginal over those for the M1 and M5 receptor subtypes. The antimuscarinic action of solifenacin was more potent than that of propiverine, and less potent than those of tolterodine, oxybutynin and darifenacin. These results were considered to nearly reflect the rank order of affinity for the muscarinic M3 receptor. However, the antagonistic potencies of solifenacin, oxybutynin and propiverine were

weaker than their affinities for the muscarinic M3 receptor. This discrepancy was probably caused by restricted drug diffusion into structured tissues, which hinders equilibrium conditions.
In the previous studies, solifenacin exhibited greater selectivity for urinary bladder over salivary gland than tolterodine, oxybutynin, darifenacin and atropine. [15] Since the muscarinic M3 receptor mediates both bladder contraction and salivary secretion, the bladder selectivity demonstrated for solifenacin is thus not considered to be attributable to its low affinity for the muscarinic M1 and M5 receptors.
Therefore, selectivity for the other non-M3 muscarinic receptor subtypes is not considered to contribute to the bladder selectivity. Thus, a great deal of investigation would be required to clarify the mechanism of bladder selectivity of solifenacin.
In conclusion in vitro studies confirm that solifenacin is a potent and competitive muscarinic receptor antagonist and increases the maximum bladder capacity. These findings support the fact that solifenacin is useful in the treatment of overactive bladder, similarly to currently used antimuscarinic agents. In this regard, we note with interest that solifenacin at 5 and 10 mg/man has been shown in clinical studies to be more effective than placebo in improving overactive bladder symptoms.
The data available to-date show that Solifenacin is more efficacious in the treatment of symptoms for a hyperactive bladder, compared to a placebo and similar to Tolterodina. There is no data that compare Solifenacin to Ossibutanina. Considering the fact that Solifenacin has a greater selectivity for the M3 receptors, compared to the other molecules of the same category, it theoretically presents a lower incidence of adverse side effects compared to the other antimuscarinics. With the data that are available to-date, this statement can only be made considering the lower incidence of the dryness of the fauces manifested with Solifenacin, compared to Tolterodina. Furthermore, the compliance is much higher than the other antimuscarinics and a high percentage of patients concludes the treatment in 12 weeks.
In conclusion, purpose of our study has been that to appraise the effectiveness of medical therapy based on Solifenacin succinate 5 mg/die in cases of urge incontinence that manifests de novo after surgical treatment of SUI by TOT sling and it's based on the evaluation of its possible causes. Our study is one of the few in medical literature that has proven the efficacy of a selective M3 antimuscarinic for the cure of the pseudo-irritant symptomatology after anti-incontinence surgery.
We got the regression of symptoms of urgency in 100% of patients with a meaningful improvement of quality of life.
We demonstrated that following the administration of Solifenacin at the dose of 5mg/day for 3 months the initial symptomatology reported (frequency, urgency, pelvic and perineal pain) improved even after the first 10 days of treatment.
Our intention now is to evaluate the efficacy of this molecule in the establishment of processes of "cellular memory and imprinting" so as to make full use of the effects even in periods when the drug is not taken.

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