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Role of Trospium chloride and tamsulosin therapy for treating patients with symptoms of over-active bladder related to benign prostatic enlargement

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ABSTRACT

To assess the benefit and safety of composite therapy (Tamsulosin and Trospium drugs) in treating benign prostatic enlargement complain, mainly overactive urinary bladder symptoms. The study has been designed to estimate the benefit and safety of Trospium and Tamsulosin in processing of symptoms of excessive bladder and benign prostate hyperplasia (BPH). Prospective clinical trial study conducted at Al-Diwaniya teaching hospitals and private clinics from march 2016 to march 2017, to patients BPH and bothersome symptoms. 60 patients were treated with Tamsulocin and 60 patients were treated by Tamsulocin and Trospium. Median scores of IPSS, OABSS, and QOL proved no big difference between two study sets before staring treatment (P = 0.544), (P = 0.287) , (P = 0.668) consecutively. After one month, both treatments led to a big reduction in IPSS, OABSS median score; (P < 0.001), (P < 0.001). Following three months, both treatments resulted in significant reduction in IPSS (P < 0.001), OABSS (P < 0.001), QOLresult, (P < 0.001) consecutively. These results suggest which treatment with Trospium and tamsulosin therapy provides benefit for men with natural - Syndrome of the acute urinary tract and benignenlarged prostate.

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INTRODUCTION

Benign prostatic hyperplasia (histological term) or benign prostatic enlargement (clinical term) is a common benign epithelial and stromal overgrowth disease in the old men. Prevalence is between 60-80% of male aged more than 65 years (Dhingra and Bhagwat, 2011; Garraway *et al.*, 1991).

Symptoms of prostatic enlargement are due to the obstructive effect of the prostate to the bladder and called lower urinary tract symptoms (LUTS) (Speakman, 2001).

LUTS categorized into stockpiling/ irritating, invalid/obstructive symptoms, which in turn adversely effect on actions and kind of life(QOL) (Jolleys *et al.*, 1994; Peters *et al.*, 1997).

Storage symptoms are due to the inability to store urine and include frequency, nocturia/frequency at night, urgency, and urge incontinence. They are occurring in about 50% of patients with BOO (Roehrborn, 2005; Dmochowski, 2005).

Voiding symptoms are due to the obstructive effect of BPH and include weak stream, incomplete emptying, intermittency, and strained voiding.

Overactive bladder syndrome(OABS) includes (Depending on International Continence Society(ICS): repeat urine, urination at night, instancy or urge incontinence (Demaagd and Davenport,

2012). LUTS and OABS are usually related together in patients with BPH, especially with increasing age (Knutson *et al.*, 2001; Gomelsky and Dmochowski, 2009).

30% of patients having overactive bladder and obstruction of bladder outlet continue to have storage symptoms despite treating bladder outlet obstruction (Price *et al.*, 1980).

BPH patients can be assessed by using scores such as OABSS (overactive bladder symptom score), IPSS (International Prostate Symptom Score), and QOL (quality of life) questionnaire (Chou *et al.*, 2014). IPSS involves 7 questions, 4 voiding and 3 storage symptoms, as mentioned above (Jindal, 2014). The total score ranged from 0-35. (0-7) illustrates moderate symptoms, (8-19) indicate mild symptoms, (20-35) indicate strong symptoms (Homma *et al.*, 2006).

OABSS is the score used to qualify the storage symptoms only and include 4 questions: frequency, nocturia, urgency and/or urge incontinence. Score range from 0-15. $\leq$5 is mild, 6-11 moderate, and $\geq$12 severe (Homma *et al.*, 2006).

QoL score includes 6 questions whether the patient is delighted, pleased, mostly satisfied, mixed, mostly not satisfied or unhappy.

The voiding symptoms are usually relieved by α-blockers and/or 5-alpha reductase inhibitors or by surgery but 50% of patients still complain from storage symptoms (Abrams *et al.*, 2003).

The anticholinergic drugs are currently used to overcome storage symptoms despite of AUA and EAU guidelines do not encourage its use in patients with severe BOO or urine retention (Anonymous, 2006).

Many of anticholinergics, such as (Tolterodine, Oxybutynin, Solifenacin, and Trospium). Act as blockers on all muscarinic senses (M1 to M5) and despite bladder having (M2 and M3), so they have side influences contained blurred vision, dry mouth, constipation, dizziness, drowsiness) (Hesch, 2007; Macdiarmid, 2003).

Trospium chloride is a quadrilateral ammonium compound and so it did not cross the blood-brain barrier, hence decreasing side effects on CNS. Also, it has a high affinity to block M1, M2, and M3 senses. Comparison with Oxybutynin it has similar efficacy and effects as many randomized controlled trial studies (Halaska *et al.*, 2003; Zellner *et al.*, 2009).

PATIENTS AND METHODS

A prospective clinical trial study conducted at Al-Diwaniya teaching hospitals and private clinics from march 2016 to march 2017 to patients BPH and bothersome symptoms with approval of the ethical committee of the hospital.

120 patients were had no attacks of urine retention, current UTI, previous prostatic intervention, no abnormal S.PSA, no abnormal DRE, abnormal renal function and categorized into 2 groups:

Group 1

60 patients were treated by Tamsulocin 0.4 mg at night and followed by 1 and 3 months.

Group 2

60 patients were treated by Tamsulocin 0.4 mg at night and Trospium 20 mg twice per day.

All patients were assessed. Taking the name, age, complete history.

IPSS, OABSS and QOL score were done for included patients

RESULTS AND DISCUSSION

The general features of the patients are shown in Table 1. There was no big distinction in mean age in both groups. Median scores of IPSS proved no big difference between two study sets before staring treatment, 23.50 versus 23.50, respectively (P = 0.544). Also, no significant difference in median OABSS between both sets, 11 versus 11, consecutively (P = 0.287). Moreover, also no big difference in median QOL between two sets, 4 opposite 4, respectively (P = 0.668).

Following one month, both treatments resulted in a significant reduction in IPSS median score; however, the magnitude of score reduction caused by combined treatment was significantly greater than using tamsulosin alone, the final median score of 10.5 versus 11, consecutively (P < 0.001), as shown in Table 2 and Figure 1. In addition, both treatments resulted in a significant reduction in OABSS median score; however, the magnitude of score reduction caused by combined treatment was significantly greater than using tamsulosin alone, the final median score of 4 versus 8, consecutively (P < 0.001), as shown in Table 2 andFigure 2. Both modalities of treatment were able to improve quality of life by reducing QOL score, but the amount of reduction caused by combined treatment was greater; however, the difference in final median score following one month of treatment was

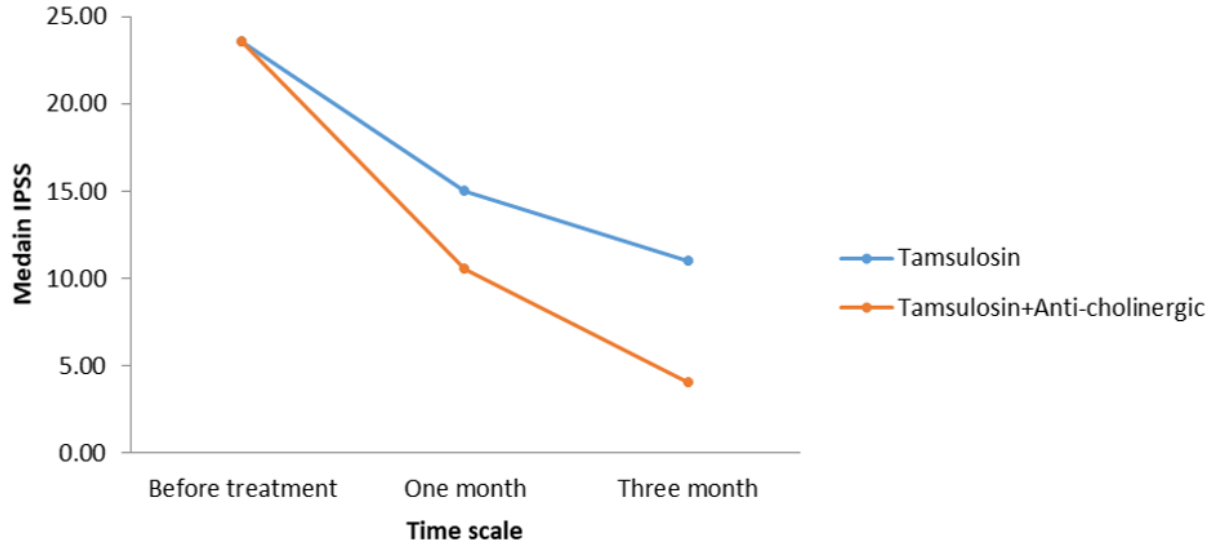

Figure 1: Median IPSS in both groups during 3 months of follow up

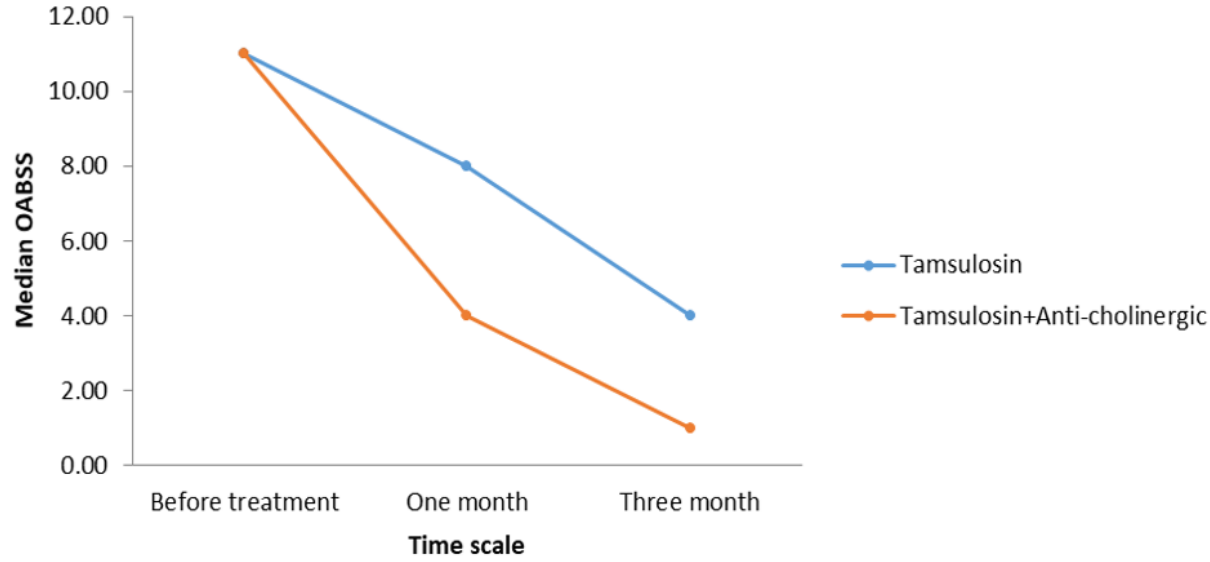

Figure 2: Median OABSS in both groups during 3 months of follow up

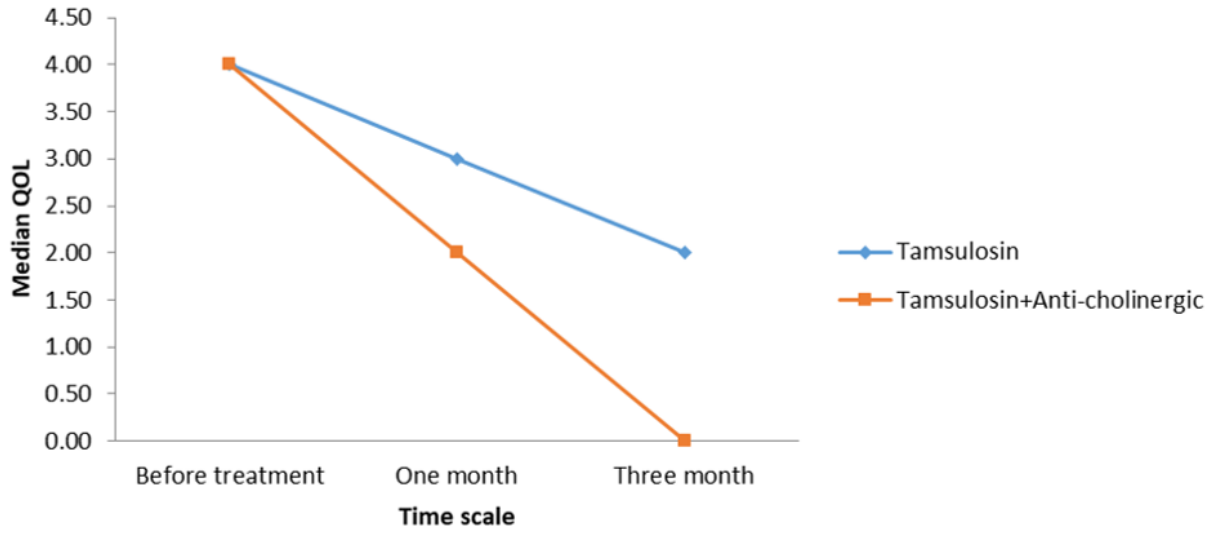

Figure 3: Median QOL in both groups during 3 months of follow up

Table 1: Characteristics of patients before the onset of starting treatment

Characteristics	Statistic	Tamsulosin *n* = 60	Tamsulosin+Anti-cholinergic *n* = 60	*p*
Age	Mean ±SD	67.38 ±9.68	67.08 ±7.42	0.849
	Range	47.00 -90.00	56.00 - 83.00	†
IPSS	Median (IQR)	23.50 (12.00)	23.50 (10.00)	0.544
	Range	9.00 -34.00	9.00 -35.00	¥
OABSS	Median (IQR)	11.00 (4.00)	11.00 (5.00)	0.287
	Range	6.00 -15.00	4.00 -15.00	¥
QOL	Median (IQR)	4.00 (2.00)	4.00 (2.00)	0.668
	Range	1.00 -6.00	1.00 -6.00	¥

IPSS: International Prostatic Symptom Score; OABSS: Over Active Bladder Symptom Score; QOL: Quality Of Life; n: Number of cases; SD:Standard Deviation; †: Independent samples t-test; ¥: Mann Whiney U test

Table 2: Indexes of symptoms and QOL one month after starting treatment

Characteristics	Statistic	Tamsulosin	Tamsulosin+Anti-cholinergic	*p*
IPSS	Median (IQR)	15.00 (8.00)	10.50 (6.00)	<0.001 ¥
	Range	2.00 -32.00	2.00 - 20.00	HS
OABSS	Median (IQR)	8.00 (3.00)	4.00 (3.00)	<0.001 ¥
	Range	4.00 -13.00	0.00 -11.00	HS
QOL	Median (IQR)	3.00 (1.00)	2.00 (1.00)	0.077 ¥
	Range	0.00 -6.00	0.00 -5.00	

IPSS: International Prostatic Symptom Score; OABSS: Over Bbladder Symptom Score; QOL: Quality Of Life; n: Number of cases; SD:Standard Deviation; †: independent samples t-test; ¥: Mann Whiney U test

Table 3: Indexes of symptoms and QOL one month after starting treatment

Characteristics	Statistic	Tamsulosin	Tamsulosin+Ant cholinergic	*p*
IPSS	Median (IQR)	11.00 (8.00)	4.00 (2.75)	<0.001 ¥
	Range	2.00 -21.00	0.00 -11.00	HS
OABSS	Median (IQR)	4.00 (3.00)	1.00 (2.00)	<0.001 ¥
	Range	0.00 -7.00	0.00 -5.00	HS
QOL	Median (IQR)	2.00 (2.00)	0.00 (2.00)	<0.001 ¥
	Range	0.00 -5.00	0.00 -4.00	HS

IPSS: International Prostatic Symptom Score; OABSS: Overactive Bladder Symptom Score; QOL: Quality Of Life; n: Number of cases; SD: Standard Deviation;†: Independent samples t-test; ¥: Mann Whiney U test

insignificant, 2 versus 3 (0.077), Table 2 and Figure 3.

Following three months, both treatments resulted in a significant reduction in IPSS median score; however, the magnitude of score reduction caused by combined treatment was significantly greater than using tamsulosin alone, the final median score of 4 versus 11, consecutively (P < 0.001), as shown in Table 3 and Figure 1. Also, both treatments resulted in a significant reduction in OABSS median score; however, the magnitude of score reduction caused by combined treatment was significantly greater than using tamsulosin alone, the final median score of 1 versus 4, consecutively (P < 0.001), as shown in Table 3 and Figure 2. Both modalities of treatment were able to improve quality of life by reducing QOL score, but the amount of reduction caused by combined treatment was greater; and, the difference in final median score following one month of treatment was highly significant, 0 versus 2 (*P* < 0.001), Table 3, Figure 3.

Overactive(OAB) bladder is a name for a col-

lection of urinary symptoms. It is a sudden, uncontrolled need or urge to urinate (Abed *et al.*, 2019). Clinical symptoms of OAB contain repeat urine and instancy, sometimes accompanied by urge incontinence which influences on quality of life(QOL) (Arora *et al.*, 2017).

Treatment of non-neurogenic OAB is classified simply into 3 ways,

1-Behavioral and education therapy.

2-Medications such as anticholinergics, β-3 agonist, and transdermal oxybutynin.

3-Treatment of the primary cause of BOO (bladder outlet obstruction): α-blockers, TURP, and laser prostatectomy (Abrams *et al.*, 1979; Abed and Salim, 2019).

Due to the obstructive effect of adenoma, with coexisting inflammation, the bladder blood flow is tending to decrease causing bladder low blood perfusion and repeated low perfusion and reperfusion during emptying might produce oxidative stress and this cause decrease sensitivity of nerves of the bladder with increasing the efferent nerve signals that may be answerable for expansion of bladder overactivity and then underactivity. The effect of α-blockers and anticholinergic drugs is for increases the bladder blood flow and decrease ischemia indirectly (Nomiya *et al.*, 2015).

In patients with benign enlarged prostate and hyperactive bladder, the blocker with anticholinergic therapy is common mixing compounds in the improvement of symptoms of BPH and slightly improvement of OAB symptoms (Homan *et al.*, 2013).

Quaternary ammonium compound (Trospium chloride) blocks the muscarinic receptors (the effect of Acetylcholine), so increasing the maximum bladder capacity.

Trospium have reduced central nervous system side influences due to the low ability to exceed BBB (blood-brain barrier) (Abdulhussein and Al-Awsi, 2019).

In our study, we evaluate the efficacy of combined α-blocker(Tamsulosin) and anticholinergic drug(Trospium) in treatment of BPH and OAB symptoms and followed by one and three months using IPSS (International Prostate Symptom Score), OABSS (Overactive Bladder Symptom Score), and QOL (Quality of Life) results (Shamran *et al.*, 2018).

We compare our results with other studies. Canadian Expert Drug Advisory Committee(CEDACC) recommends that Trospium be listed for patients who cannot tolerate immediate release Oxybutynin or Tolterodine. The committee reviewed 12 randomized controlled trials of Trospium in the treatment of overactive bladder (Han *et al.*, 2008).

Trospium was found to be more favourable than a placebo and equivalent to Oxybutynin with the advantage of CNS reduction side effects and high cost in comparison to immediate release Oxybutynin and low cost in comparison to extended-release Oxybutynin or Tolterodine (Ann *et al.*, 2015; Abed, 2017). Many authors like Kaplan and others., Abrams, and Athanosopoulos and others (Al-Grawi and Al-Awsi, 2018).

Used combinations of Tamsulosin and anticholinergic drugs to the treatment of patients with BOO and OAB stated that an amendment in bladder capacity, QOL, with very low percent of urine retention. Safety for a long time of combination has been proven through Matsukawa and others (Al-Zaidy *et al.*, 2019). Liao, Lee and others have stated which Trospium chloride is most valuable in patients with BOO, OAB (Ovsag *et al.*, 2008).

And many studies showed low negative effects on detrusor contraction or retention. Our study baseline parameters are age, prostate size and pretreatment IPSS, OABSS, and QOL for 2 groups (Gray *et al.*, 2015; Ewaid and Abed, 2017).

The first group are patients with BPH and Tamsulosin and the second group are patients with BPH, Tamsulosin and Trospium. We exclude patients with attacks of urine retention and any abnormal PSA or DRE, no vesical stone (Chalap, 2019).

At the time of initiation of therapy, there was no big distinction in both sets regarding the age of patients. After one month of therapy, there was great amelioration in IPSS, OABSS, and QOL with magnified improvement in combined treatment (Ewaid *et al.*, 2019b,a).

After three months, also there was great amelioration in IPSS, OABSS, and QOL with magnified improvement in combined treatment. We have some limitations in our study because we were not use Urodynamic study for assessment. We depend on the clinical improvement of patients (Chillab *et al.*, 2019; Al-Awsi *et al.*, 2019).

CONCLUSIONS

A prospective clinical trial study conducted at Al-Diwaniya teaching hospitals and private clinics from march 2016 to march 2017, to patients BPH and bothersome symptoms. 60 patients were treated with Tamsulocin and 60 patients were treated by Tamsulocin and Trospium. Median scores of IPSS, OABSS, and QOL proved no big difference between

two study sets before staring treatment (P = 0.544), (P = 0.287), (P = 0.668) consecutively. After one month, both treatments led to a big reduction in IPSS, OABSS median score; (P < 0.001), (P < 0.001). Following three months, both treatments resulted in significant reduction in IPSS (P < 0.001), OABSS (P < 0.001), QOL result, (P < 0.001) consecutively. Conclusion: These results suggest which treatment with Trospium and tamsulosin therapy provides benefit for men with natural - Syndrome of the acute urinary tract and benign enlarged prostate.

REFERENCES

Abdulhussein, H., Al-Awsi 2019. Comparing the Effectiveness of the Antibiotics and Medicinal Plants to Influence the Bacteria Propionibacterium Acne Which Causing Acne. *International Journal of Research in Pharmaceutical Sciences*, 10(1):515–518.

Abed, S. A. 2017. An occurrence of Anatidae in Sawa Lake: A Ramsar Wetland Site in Southern Iraq. *Journal of Advanced Zoology*, 38(1):43–51. J. Adv. Zool.

Abed, S. A., Ewaid, S. H., Al-Ansari, N. 2019. Evaluation of Water Quality in the Tigris River within Baghdad, Iraq, using Multivariate Statistical Techniques. *Journal of Physics*, 1294:72025–72025.

Abed, S. A., Salim, M. A. 2019. The first record of Asian Pied starling gracupica contra Linnaeus, 1758 (Aves, Sturnidae) in Iraq. *Eco. Env. & Cons*, 25. 1) : ; pp. (106-110.

Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U., Wein, A. 2003. The standardization of terminology in lower urinary tract function: a report from the standardization sub-committee of the International Continence Society. *Urology*, (1):37–49.

Abrams, P. H., Farrar, D. J., Turner-Warwick, R. T., Whiteside, C. G., Feneley, R. C. L. 1979. The Results of Prostatectomy: A Symptomatic and Urodynamic Analysis of 152 Patients. *Journal of Urology*, 121(5):640–642.

Al-Awsi, G. R., Challap, A. D., Hamzah, H. 2019. Investigation of Tumor Necrosis Factor-Alpha (TNF A) Gene Polymorphism in Patients with Hypertension in Al-Diwaniyah City Iraq. *Journal of Global Pharma Technology*, 11(2):144–148.

Al-Grawi, E. D. C., Al-Awsi, G. R. L. 2018. Expression of CDKN2A (p16/Ink4a) among Colorectal Cancer Patients: A cohort study. *Journal of Pharmaceutical Sciences and Research*, 10(5):1145–1147.

Al-Zaidy, K. J., Parisi, G., Abed, S. A., Salim, M. A. 2019. Classification of The Key Functional Diversity of the Marshes of Southern Iraq Marshes. *Journal of Physics: Conference Series*, 1294:72021–72021.

Ann, G. E., Martha, L. D., Prasan, F. 2015. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment. *Journal of Urology*, 193(5):1572–1580.

Anonymous 2006. British National. *Formulary*, 5. edition.

Arora, H. C., Eng, C., Shoskes, D. A. 2017. Gut microbiome and chronic prostatitis/chronic pelvic pain syndrome. *Ann Transl Med*, 5:30–30.

Chalap, G. R. L. A.-A. E. D. 2019. A General Overview of the Genetic Effects of Extracellular Polymers For Enterococcus Faecium in Cancer Cells. *International Journal of Research in Pharmaceutical Sciences*, 10(1):436–479.

Chillab, E. D., Talib, R. A., Al-Awsi, G. R. L. 2019. Genetics of Sickle Cell Anemia Disorders in Baghdad City Iraq. *Indian Journal of Public Health Research & Development*, 10(2):817–822.

Chou, E. C., Hung, M. J., Yen, T. W., Chuang, Y. C., Huang, E., Huang, S. T., Kuo, H. C. 2014. The translation and validation of the Chinese overactive bladder symptom score for assessing overactive bladder syndrome and response to solifenacin treatment. *Journal of the Formosan Medical Association*, 113(8):506–512.

Demaagd, G. A., Davenport, T. C. 2012. Management of urinary incontinence. *Journal for Formulary Management*, 37(6):345–361.

Dhingra, N., Bhagwat, D. 2011. Benign prostatic hyperplasia: An overview of existing treatment. *Indian Journal of Pharmacology*, 43(1).

Dmochowski, R. R. 2005. Bladder outlet obstruction: etiology and evaluation. *Reviews in Urology*, 7(Suppl 6):S3–S13.

Ewaid, S., Abed, S., Al-Ansari, N. 2019a. Water Footprint of Wheat in Iraq. *Water* , 11(3):535.

Ewaid, S. H., Abed, S. A. 2017. Water quality index for Al-Gharraf river, southern Iraq. *Egypt. J. Aquatic Res*, 43(2):117–122.

Ewaid, S. H., Abed, S. A., Al-Ansari, N. 2019b. Crop Water Requirements and Irrigation Schedules for Some Major Crops in Southern Iraq. *Water*, 11(4):756.

Garraway, W. M., Lee, R. J., Collins, G. N. 1991. High prevalence of benign prostatic hypertrophy in the community. *The Lancet*, 338(8765):469–471.

Gomelsky, A., Dmochowski, R. R. 2009. Overactive bladder in males. *Therapeutic Advances in Urology*, 1(4):209–221.

Gray, S. L., Anderson, M. L., Dublin, S., Hanlon, J. T., Hubbard, R., Walker, R., Larson, E. B. 2015. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Internal Medicine*, 175(3):401–407.

Halaska, M., Ralph, G., Wiedemann, A., Primus, G., Ballering-Brühl, B., Höfner, K., Jonas, U. 2003. A controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World Journal of Urology*, 20(6):392–399.

Han, L., Agostini, J. V., Allore, H. G. 2008. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. *Journal of the American Geriatrics Society*, 56(12):2203–2210.

Hesch, K. 2007. Agents for treatment of overactive bladder: a therapeutic class review. *Baylor University Medical Center Proceedings*, 20:307–314.

Homan, T., Tsuzuki, T., Dogishi, K., Shirakawa, H., Oyama, T., Nakagawa, T., Kaneko, S. 2013. Novel mouse model of chronic inflammatory and overactive bladder by a single intravesical injection of hydrogen peroxide. *Journal of Pharmacological Sciences*, 121(4):327–337.

Homma, Y., Yoshida, M., Seki, N., Yokoyama, O., Kakizaki, H., Gotoh, M., Nishizawa, O. 2006. Symptom assessment tool for overactive bladder syndrome-overactive bladder symptom score. *Urology*, 68(2):318–323.

Jindal, T. 2014. Misinterpretation of the international prostate symptom score questionnaire by Indian patients. *Indian Journal of Urology*, 30:252–252.

Jolleys, J. V., Donovan, J. L., Nanachahal, K., Peters, T. J., Abrams, P. 1994. Urinary symptoms in the community: how bothersome are they? *British Journal of Urology*, 74(5):551–555.

Knutson, T., Edlund, C., Fall, M., Dahlstrand, C. 2001. BPH with coexisting overactive bladder dysfunction? An everyday urological dilemma. *Neurourology and Urodynamics*, 20(3):237–247.

Macdiarmid, S. 2003. Antimuscarinic therapy for the treatment of mixed incontinence. *Reviews in urology*, 5(Suppl 8):S18–S25.

Nomiya, M., Andersson, K. E., Yamaguchi, O. 2015. Chronic bladder ischemia and oxidative stress: New pharmacotherapeutic targets for lower urinary tract symptoms. *International Journal of Urology*, 22(1):40–46.

Ovsag, K., Hydery, S., Mousa, S. 2008. Preferred drug lists: Potential impact on healthcare economics. *Vascular health and risk management*, 4:403–413.

Peters, T. J., Donovan, J. L., Kay, H. E., Abrams, P., Rosette, J. J. M. C. H. D. L., Porru, D., Thuroff, J. W. 1997. The International Continence Society "Benign Prostatic Hyperplasia" Study: The Bothersomeness of Urinary Symptoms. *Journal of Urology*, 157(3):885–889.

Price, D. A., Ramsden, P. D., Stobbart, D. 1980. The Unstable Bladder and Prostatectomy. *British Journal of Urology*, 52(6):529–531.

Roehrborn, C. G. 2005. Benign prostatic hyperplasia: an overview. *Reviews in Urology*, 7(Suppl9):S3–S14.

Shamran, A. R., Shaker, Z. H., Al-Awsi, G., Khamis, A. S., Tolaifeh, Z. A. 2018. Rapd-PCR is a good DNA finger-printing technique to detect phylogenetic relationships among Staphylococcus. aureus isolated from different sources in Hilla city Iraq. *Biochem Cell Arch*, 18(suppl 1):1157–1161.

Speakman, M. J. 2001. Initial Choices and Final Outcomes in Lower Urinary Tract Symptoms. *European Urology*, 40:21–30. Suppl. 4.

Zellner, M., Madersbacher, H., Palmtag, H., Stöhrer, M., Bödeker, R. H. 2009. Trospium chloride and oxybutynin hydrochloride in a german study of adults with urinary urge incontinence: Results of a 12-week, multicenter, randomized, double-blind, parallel-group, flexible-dose noninferiority trial. *Clinical Therapeutics*, (11):2519–2539.