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COMBINED USE OF α -ADRENERGIC AND MUSCARINIC ANTAGONISTS FOR THE TREATMENT OF VOIDING DYSFUNCTION

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Abstract

Purpose—We provide an overview of the medical literature supporting the combined use of muscarinic and α -adrenergic antagonist therapy for the treatment of voiding dysfunction.

Materials and Methods—The MEDLINE database (1966 to 2004) of the United States National Library of Medicine was searched for pertinent studies.

Results—Although the mechanism of action of α -adrenergic antagonist therapy for voiding dysfunction has traditionally been assumed to be relaxation of the periurethral, prostatic and bladder neck smooth muscle, substantial evidence supports action at extraprostatic sites involved in micturition, including the bladder dome smooth muscle, peripheral ganglia, spinal cord and brain. Likewise the mechanism of action of anticholinergic therapy has been traditionally assumed to be inhibition of the M₃ muscarinic receptor subtypes that mediate normal bladder contractions. However, M₂ receptor mediates hypertrophied bladder contractions and there is evidence for an M₂ component to the suprasacral control of voiding.

Conclusions—Based on the physiology of α -adrenergic and muscarinic receptors the inhibition of each one would be expected to be more beneficial than that of either alone because they would work on 2 components of detrusor function. Patients who would likely benefit from this combination therapy are men with lower urinary tract symptoms, women with urgency/frequency syndrome (overactive bladder), patients with uninhibited bladder contractions due to neurogenic bladder, and patients with pelvic pain and voiding symptoms, ie interstitial cystitis and chronic prostatitis/chronic pelvic pain syndrome.

Keywords

bladder; prostate; adrenergic alpha-antagonists; muscarinic antagonists; urination disorders

The wide range of patients who might benefit from this type of treatment combination is considered to be large, perhaps several times the estimated 17 million patients in the United States with overactive bladder.¹ A patent application has been filed for the treatment of lower urinary tract (LUT) symptoms (LUTS) in men with benign prostatic hyperplasia (BPH) with this combination.²

A-ADRENERGIC RECEPTORS

Signal transduction mechanisms

All known adrenergic receptors (ARs) are members of the G-protein coupled receptor family. They are single amino acid chains with 7 trans-membrane spanning α helices, of which the physiological effects are mediated through heterotrimeric G-proteins, so named for their ability to bind and hydrolyze guanine triphosphate. Receptor activation with agonist molecules induces dissociation of the $G\alpha$ subunit from the $G\beta\gamma$ subunits, of which each has effects on intracellular events. The wide range of cellular physiological processes affected by this signal transduction mechanism is partly due to the finding of at least 23 $G\alpha$ subunits, 6 $G\beta$ subunits and 14 $G\gamma$ subunits.³ In addition to G-protein diversity, a given receptor may be able to couple with several different types of G-proteins and, thus, mediate several cellular signals.⁴

As an oversimplification of this complex signal transduction process, there are 2 major mediators, namely cyclic adenosine monophosphate and inositol triphosphate. All 3 β -ARs are known to couple to $G_{\alpha s}$ and, thus, increase adenylyl cyclase activity, whereas all α_2 ARs couple preferentially with $G_{\alpha i}$ and, thus, inhibit adenylyl cyclase, activate receptor operated K^+ channels and inhibit voltage sensitive Ca^{++} channels. For the α_1 ARs as well as M_1 , M_3 and M_5 muscarinic receptors signaling is thought to be mediated by coupling with $G_{\alpha q}$, which activates PLC (phosphatidylinositol specific phospholipase C). This enzyme acts on the membrane lipid PIP_2 (phosphatidylinositol 4,5-bisphosphate) to generate IP_3 (inositol 1,4,5-triphosphate), which acts on a sarcoplasmic reticulum bound IP_3 receptor that induces Ca^{++} release from this intracellular store. The other product of PLC action on PIP_2 is diacyl glycerol. This activates protein kinase C, which through mechanisms not completely understood can activate the contractile process, perhaps in the absence of an increase in intracellular Ca^{++} . Other mechanisms activated by α_1 ARs and the odd numbered muscarinic receptor subtypes are phospholipase A_2 and D, and the activation of Ca^{++} and K^+ channels. These receptors may also stimulate cell growth through the mitogen activated protein kinase and rho kinase pathways.⁵

α_1 Receptor nomenclature

There has been some degree of confusion over nomenclature, although only 3 distinct α_1 -adrenoceptors have been cloned and sequenced.⁶ By convention upper case letters are used to denote α_1 receptors characterized by subtype selective drugs in tissues, while lower case letters denote α_1 receptors defined by molecular sequence data. Peculiar pharmacology was found for a bovine brain α -adrenoceptor originally designated α_{1c} but, because differences in experimental conditions explained this, the α_{1c} designation has now been discontinued. In the rat there are functional models for each of the 3 α_1 receptor subtypes. Contraction of the epididymal end of the vas deferens is mediated by the α_{1A} subtype, contraction of the spleen is mediated by the α_{1B} subtype and contraction of the portal vein is mediated by the α_{1D} subtype.⁷

Based on the response to prazosin and other antagonists α_1 -adrenoceptors may be functionally differentiated into 3 groups, namely α_{1H} —high affinity for prazosin, α_{1L} —low affinity for prazosin and α_{1N} —neither α_{1H} nor α_{1L} .⁸ The α_{1A} , α_{1B} and α_{1D} receptors have high affinity for prazosin and, thus, they are members of the α_{1H} family.⁶ To our knowledge α_{1L} and α_{1N} -adrenoceptors have yet to be cloned and they may not be different in their molecular sequence from the α_{1a} subtype. Rather, they may exist in different conformations, which results in the different affinity states. Some tissues, including the human LUT (periurethral, prostatic and bladder neck smooth muscle), have α_1 receptors with relatively low affinity for prazosin but functional properties that are closest to those of the α_{1A}

subtype. The human α_{1a} receptor gene product can display the pharmacological properties of α_{1L} -AR, which is found in the human LUT, as well as α_{1A} -AR, depending on assay conditions.⁹

Splice variants of α_{1a} receptor

The α_{1b} and α_{1d} -ARs are each expressed as single isoforms, although at least 12 different and distinct splice variants of the carboxy terminal tail of human α_{1a} -AR have been described, in addition to the original WT. Four of them give rise to fully functional α_{1a} -ARs that display ligand binding and signal transduction characteristics that are almost identical to WT α_{1a} -AR, designated α_{1a-1} -AR, α_{1a-2a} -AR, α_{1a-3} -AR and α_{1a-4} -AR.¹⁰ All tissues express several of these carboxy terminal splice variants and in the human prostate α_{1a-4} -AR has the most abundant mRNA.¹¹ Although the carboxyl terminus of the α_{1b} -AR mediates the decreased expression, phosphorylation, internalization and desensitization of the receptor, the carboxyl terminus of α_{1a} -AR does not.¹² When expressed in CHO-K1 cells, all 4 functional splice variants as well as the WT of the α_{1a} -AR display the pharmacological properties of so-called α_{1L} -AR.¹³ This finding proves that the distinct pharmacology of α_{1L} -AR in human LUT is not a function of the differential tissue expression of α_{1a} -AR splice variants and it strongly supports the concept that the distinct α_{1L} pharmacology of the human LUT is not the result of tissue expression of a different α_1 -AR, but rather a functional conformation of α_{1a} -AR. To our knowledge the cellular events that may induce a shift between α_{1a} -AR high and low affinity states have not yet been elucidated.

ROLE OF α -ADRENERGIC RECEPTORS IN VOIDING DYSFUNCTION

Traditionally the target of α -blockers for voiding symptoms in males with bladder outlet obstruction (BOO) resulting from BPH has been assumed to be the bladder neck and prostatic urethra. Norepinephrine contracts the prostate capsule and enucleated adenoma, which can be blocked by phentolamine, an α -adrenergic antagonist.¹⁴ Each α -adrenergic subtype is present in the human prostate, bladder neck and proximal urethra but the α_1 subtype is responsible for contraction.¹⁵ These findings have led to the assumption that α -blockers improve voiding symptoms by relaxing prostatic and urethral smooth muscle tone, which decreases outlet resistance, the dynamic component of BPH.

There are several problems with this concept. One is that many men without outlet obstruction respond to α -blocker therapy for LUTS and men can show persistent bladder outlet obstruction despite significant subjective improvement.¹⁶ Surgery that relieves obstruction does not relieve irritative voiding symptoms as much as obstruction symptoms.¹⁷ Thus, the mechanism of action of α -adrenergic antagonist therapy for the relief of LUTS secondary to BPH is not via decreased outlet obstruction.

Considerable evidence indicates that α -blockers act at extraprostatic sites, such as the bladder, ganglia and spinal cord. The bladder neck has abundant α receptors but the bladder body has only 20% of this density. This is still 3 times higher than the human coronary artery, which contracts in response to adrenergic stimulation.¹⁸ Outlet obstruction changes bladder α -adrenoceptor subtypes.¹⁹ α_1 -AR subtype density in the human detrusor consist of 60% to 70% α_{1D} , 30% to 40%, α_{1A} and undetectable α_{1B} .²⁰ A quarter of bladder specimens from patients with outlet obstruction have conversion of normally β induced relaxation to α mediated contraction, which correlates with detrusor instability.²¹ After 6 weeks of surgically induced outlet obstruction in the female rat the protein and mRNA for the α subtypes change from 70% α_{1A} to 75% α_{1D} ,²² resulting in greater α -adrenergic responsiveness because norepinephrine has 10 to 100-fold higher affinity for α_{1D} -adrenoceptors than for the α_{1A} or α_{1B} subtypes. In the detrusor of patients with bladder hyperactivity in the absence of neurological disorders there is a 4-fold increase in α -

adrenergic receptor density.²³ In 12 spinal cord injured patients the α_{1A}/α_{1D} selective antagonist terazosin improved bladder compliance and continence, suggesting that terazosin may have an effect on α receptors in the detrusor muscle or spinal cord and improved bladder compliance is not due to decreased outlet resistance.²⁴

α Receptors may also modulate voiding function at the level of the spinal cord or peripheral ganglia. There appear to be different effects of adrenergic stimulation on the afferent and efferent pathways in micturition. In the cat bladder parasympathetic cholinergic ganglion cells are surrounded by adrenergic terminals that originate from neurons located in the ganglia. Electrical stimulation of the hypogastric nerves elicits initial inhibition, followed by the facilitation of cholinergic transmission in the parasympathetic efferent pathways to the bladder. α_1 -Adrenoceptors, which facilitate acetylcholine release, have been demonstrated at the vesical ganglia and at cholinergic nerve terminals.²⁵ Adrenergic stimulation facilitates neural evoked bladder contractions in old and young rats, and increases basal tone in older rats.²⁶ Therefore, α -blockers could decrease acetylcholine release.

Central neural pathways are also under α -adrenergic control. Stimulation of the locus coeruleus causes bladder contractions, which are inhibited by the α -adrenergic antagonists phentolamine (nonselective) and prazosin (α_1 selective). Destruction of catecholamine containing neurons in the same area leads to urinary retention.²⁷ Central facilitatory α_1 -adrenoceptors appear to be involved in the sympathetic and somatic neural control of the cat LUT.²⁸ Intrathecal doxazosin decreases detrusor hyperactivity in the spontaneously hypertensive rat, acting on visceral afferent fibers, whereas peripherally administered doxazosin does not.²⁹ Thus, action at the central nervous system could increase bladder capacity and decrease the sensation to void, thereby, affecting nocturia and the feeling of incomplete emptying. In the human spinal cord α_1 mRNA localizes to ventral gray matter only, where levels are highest in the sacral segment, comparable to those in the lumbar and thoracic areas, and lowest in the cervical region. All 3 subtypes are found but α_{1d} predominates with the others at approximately half the mRNA expression.³⁰

Two other mechanisms may be involved in the clinical efficacy of α -adrenergic antagonists. One is modulation of sensory nerves at the urothelium. There are α and β receptors present on uroepithelial cells of the animal bladder and α_1 activation evokes the release of nitric oxide (NO).³¹ NO released from sensory nerves can affect sensation and modulate sensory nerve function. Thus, α -blockers may modulate sensory responses to bladder filling. Another possible mechanism for decreasing frequency and especially nocturia is animal studies showing that α antagonists decrease urine output.³²

Use of anticholinergics for the treatment of LUTS

The use of anticholinergic medications to treat urinary frequency, urgency and uninhibited bladder contractions is based on the fact that bladder contraction occurs from acetylcholine stimulation of bladder smooth muscle muscarinic receptors. However, it is not entirely clear that the mechanism of action of anticholinergic medications for the treatment of LUTS is by the inhibition of bladder contractions. Complete inhibition of bladder contraction resulting in urinary retention would be a serious unwanted side effect and one that occurs rarely, if ever, with anticholinergic drugs at doses that are clinically effective for treating LUTS. At least 3 classes of muscarinic receptors (M_1 , M_2 and M_3) can be distinguished based on the actions of relatively subtype selective anticholinergic agents. Agents are available that are at least 10-fold selective for each of the M_1 to M_3 subtypes and MT_3 toxin is at least 30-fold selective for the M_4 subtype.³³ Affinity values of these antagonists for inhibiting bladder contractions are consistent with M_3 receptors mediating contractility, although M_2 receptors are the predominant subtype.^{4, 34, 35} Binding studies as well as immunoprecipitation in

human and animal bladder membranes also indicate that M₂ is the predominant subtype (approximately 80%).^{4, 35}

There are limited published functional data on the human bladder. Contraction in the normal human bladder is mediated through the M₃ subtype because high affinity was found for the M₃ selective antagonist darifenacin and low affinity was found for pirenzepine and methoctramine (M₁ and M₂ selective, respectively).³⁶ However, the exact source of the human tissue and patient characteristics were not specified in this abstract. Similarly in a series of bladder specimens from 10 males and 11 females undergoing cystectomy for bladder cancer the affinity of 6 muscarinic antagonists (pirenzepine, methoctramine, 4-diphenylacetoxy-N-methylpiperidine methiodide, tropicamide, oxybutynin and tolterodine) were consistent with M₃ mediated contractions.³⁷ Muscarinic receptor stimulation of human bladder tissue induces phosphatidyl inositol hydrolysis, which is consistent with the M₃ subtype, because the M₁, M₃ and M₅ subtypes preferentially couple to phosphatidyl inositol turnover.³⁸ However, the inhibition of phospholipase C or D, which are enzymes that generate inositol triphosphate from membrane phospholipids, have no effect on carbachol induced contractions of human bladder muscle strips, whereas the inhibitor of rho-associated kinases Y 27,632 (trans-4-[(1R)-1-aminoethyl]-N-4-pyridinylcyclohexanecarboxamide) attenuates carbachol contractions in a dose dependent manner.⁵

Role of the M₂ receptor subtype in bladder contraction

Although studies in the normal bladder of all species studied to date indicate that M₃ mediates bladder contraction, there are multiple reports of M₂ contribution to bladder contraction in different pathological states. Bilateral removal of the major pelvic ganglia in rats denervates the bladder since, unlike in other mammalian species, the rat bladder does not contain intramural ganglia.³⁹ Antagonist affinities in denervated bladders is intermediate between that reported for M₂ and M₃ receptors, while in control bladders all affinities are consistent with M₃ mediated contraction. After denervation there is a 60% increase in M₂ receptor density with no change in M₃ receptor density.³⁴ M₂ receptors also contribute to bladder contraction in rats with a T9 level spinal cord that do not spontaneously regain the ability to urinate, whereas those that were able to spontaneously urinate and control animals demonstrate M₃ mediated bladder contractions.⁴⁰ Rat bladder obstruction for 3 days results in a hypertrophied bladder, some degree of functional denervation and up-regulation of M₂ receptors, including an M₂ mediated component of contraction. In aging rats there is down-regulation of M₃ receptors and the appearance of some M₂ mediated component of contraction but no denervation is seen.⁴¹

We recently reported data on patients with suprasacral spinal cord injury or uninhibited contractions associated with spina bifida, in whom the affinity of the M₃ selective antagonists darifenacin and para fluoro hexahydro siladifenadol was determined. The affinity was consistent with M₂ mediated contractions in 4 of these 6 specimens, intermediate between M₂ and M₃ in 1 and within the M₃ range in 1. The other specimen, which was tested with the M₂ selective antagonist methoctramine, showed M₃ affinity.⁴² Therefore, whereas normal detrusor contractions are thought to be mediated by the M₃ receptor subtype, in patients with neurogenic bladder dysfunction contractions can be mediated by the M₂ muscarinic receptor subtype. Antimuscarinic medications may also affect bladder function by a suprasacral mechanism. Intrathecal atropine and tolterodine decrease micturition pressure and increase bladder capacity in female rats, while oxybutynin only decreases micturition pressure and darifenacin has no effect.⁴³ This indicates that there may be also an M₂ component to the suprasacral control of voiding.

PATIENTS MOST LIKELY TO BENEFIT FROM COMBINED ANTIMUSCARINIC AND ANTI- α_1 -ADRENERGIC THERAPY

Men with LUTS

As stated, this includes men with and without urodynamic evidence of BOO or overactive bladder (OAB), that is involuntary detrusor contractions. The combination of α -blockers and anticholinergics could be useful in either group. In men with BOO there are changes that make the α -adrenergic component of bladder function and spinal cord regulation of the bladder more important. Given that the changes include up-regulation of α_{1D} receptors, an α antagonist that is effective against α_{1D} in addition to α_{1A} , which seems to be involved in BOO, would be advisable. Because there may be M_2 mediated contractions with BOO, an anticholinergic with M_2 activity as opposed to a selective M_3 antagonist would also be advisable. This was verified in a recently published study, in which 68 of 144 men with BOO also had OAB. Of the 76 men without OAB 60 (79%) had clinical improvement with doxazosin alone and 6 of the 16 who did not respond had improvement with the combination of doxazosin and tolterodine. Of the 68 patients with BOO plus OAB 24 (35%) improved with doxazosin alone and 23 of 44 nonresponders (73%) improved with the combination.⁴⁴ In another study of 43 men with BPH and LUTS in whom α -blocker therapy failed and who were changed to tolterodine, significant decreases in American Urological Association symptom score, frequency, nocturia, post-void residual volume and increased urinary flow were found with no patients in urinary retention.⁴⁵ Combination therapy with the α -blocker tamsulosin and the anticholinergic tolterodine in 25 men with BOO and detrusor instability was shown to improve quality of life over treatment in 25 patients with α -blocker alone.⁴⁶

A risk of using anticholinergics in men with LUTS secondary to BOO is precipitating urinary retention. This question was recently addressed in a study in which 221 men with BOO were randomized to tolterodine immediate release compared with placebo.⁴⁷ Although post-void residual volume increased to a significantly greater extent in the tolterodine immediate release group relative to placebo (25 ml), this was not accompanied by an increase in adverse events. Volume to first contraction and maximum cystometric capacity were increased. Thus, tolterodine immediate release therapy in men with BOO appears to be safe, well tolerated and efficacious. In addition to men with BOO and LUTS, approximately 20% to 45% of men with LUTS have symptoms in the absence of obstruction.^{48, 49} The pathophysiology of these symptoms is not clear, but it likely involves changes in the bladder and central nervous system. α -Blockers are also widely and successfully used in this group of patients.

Women with overactive bladder

OAB symptoms are thought to be due to involuntary bladder contractions with detrusor filling. Because bladder contractions are mediated by acetylcholine, antimuscarinic therapy with behavioral therapy has been the main treatment.¹ However, data on α -blockers would support their use for symptoms of urgency and frequency, whether in male or female patients. Certainly symptoms in men and women with aging are similar, if not indistinguishable. American Urological Association symptom scores in women and men between ages 50 and 79 years are equivalent.⁵⁰ In a study of doxazosin combined with hyoscyamine for treating women with LUTS 68% responded to hyoscyamine alone, 68% responded to doxazosin alone and 77% responded to combination treatment.⁵¹ There was no increase in side effects using the 2 medications combined compared to each drug alone. An interesting finding was that there were different responses among women to the types of drugs. Overall 50% of women not responding to hyoscyamine responded to doxazosin or the combination, while 38% not responding to doxazosin responded to hyoscyamine or the

combination. This implies that there are likely different subgroups with different underlying pathological conditions but common symptoms.

Patients with neurogenic bladder

Standard therapy in these patients is the use of antimuscarinic agents and self-intermittent catheterization. These patients typically have detrusor-sphincter dyssynergia with increased activity in the external urethral sphincter, which results in functional outlet obstruction.⁵² The use of α -blockers would not be expected to reverse dyssynergia, but rather increase bladder capacity, in addition to antimuscarinic medications. Tamsulosin and terazosin have been shown to improve cystometric capacity and volume at first contraction in men with suprasacral spinal cord injury.⁴⁷ Patients with multiple sclerosis may have detrusor hyperreflexia with or without dyssynergia, urgency, urge incontinence and urinary frequency, and they routinely receive antimuscarinic therapy. α -Blockers have also been used in this population, of whom the majority are women.⁵³

Patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPP) and interstitial cystitis (IC)

IC and CP/CPPS are clinical conditions characterized by pelvic pain with or without voiding symptoms in the absence of other identifiable pathological conditions. Given the assumption that CP/CPPS is somehow related to the prostate, men with such symptoms can be labeled as having IC or CP/CPPS, while women are said to have IC.⁵⁴ α Antagonists and antimuscarinics are widely used for CP/CPPS⁵⁵ and antimuscarinics are used for IC.⁵⁶ α -Blockers may also be useful for IC based on the data suggesting activity in the bladder and spinal cord. A limitation to treating IC and CP/CPPS is a lack of understanding of the pathophysiology of the conditions. However, it is known that when spinal reorganization occurs due to injury that results in pain, some new neurons are under α -adrenergic control.⁵⁷

POTENTIAL ADVERSE EFFECTS

Potential cardiovascular interactions

α_1 -Adrenergic activation in the heart induces a positive inotropic effect, likely due to increases in IP_3 . In human failing hearts the positive inotropic response of α_1 -AR activation may have greater physiological importance due to a decrease in the β -adrenergic effect.⁵⁸ Blockade of α_1 -AR receptors by doxazosin in hypertensive patients lowers blood pressure with increased peripheral vascular resistance, causes a small increase in the standing heart rate and causes little change in cardiac output. In double-blind, placebo controlled studies doxazosin treatment in normotensive men with BPH did not result in a clinically significant blood pressure lowering effect.⁵⁹

α -Adrenergic blockers can cause marked hypotension, syncope, dizziness and lightheadedness or vertigo, especially when the patient is standing. In placebo controlled trials of BPH the incidence of these symptoms with doxazosin was low (0.3%) and it did not increase with increasing the dose to 8 mg daily. The incidence of discontinuation due to hypotension or orthostatic symptoms was 3.3%. Other adverse reactions to doxazosin with less than a 1% incidence but of possible clinical interest are angina pectoris, postural hypotension, syncope and tachycardia. These cardiovascular effects are much less often observed with tamsulosin.^{60, 61}

Muscarinic activation in the heart induces a negative inotropic response due to the induction of K^+ conductance mediated by G_i . Regardless, no safety concerns have been found with tolterodine with regard to cardiac function in healthy volunteers, patients on concomitant thiazide diuretic therapy or elderly individuals.¹ However, in phase III clinical studies 1.5%

of subjects receiving tolterodine vs 0.6% of those receiving placebo showed an incidence of hypertension. Similarly cardiovascular side effects with oxybutynin treatment are not frequent. However, the cardiovascular side effects observed in 2% to 5% of patients include hypertension, palpitation and vasodilation with tachycardia reported less frequently.⁶² Hypertension is likely due to the blockade of M_1 or M_3 receptors on the arterial endothelium and the blockade of NO release because muscarinic stimulation can relax pulmonary arteries that are pre-contracted with noradrenaline.⁶³ Therefore, in general the cardiovascular side effects associated with anticholinergic medications at doses that are clinically effective for LUTS are minor and they are rarely, if ever, a reason for discontinuing the medication.

Potential interaction effects on intraocular pressure (glaucoma)

Currently the pathophysiological processes involved in the optic nerve damage due to glaucoma and its relationship to the dynamics of the aqueous humor are not understood, although glaucoma is the leading cause of blindness in black Americans and the third leading cause in white individuals.⁶⁴ The most serious potential side effect is the precipitation of acute angle closure glaucoma, formerly known as narrow angle glaucoma, which can be precipitated in anatomically predisposed individuals by anticholinergic and sympathomimetic drugs as a result of drug induced mydriasis (pupil dilation). This is a result of anticholinergic drug induced relaxation of the sphincter muscle and α -adrenergic induced contraction of the dilator muscle of the pupil. By far the most common form of glaucoma is open angle glaucoma and treatment is aimed at decreasing aqueous humor production and/or increasing aqueous humor outflow. Neither anticholinergics nor α -adrenergic antagonists pose any danger to these patients.⁶⁴ However, antimuscarinics should be used with caution in patients being treated for angle closure glaucoma.

CONCLUSIONS

Given the physiology of α -AR and muscarinic receptors, the combined use of adrenergic antagonists and anticholinergic medications to treat voiding symptoms would potentially be more beneficial than either alone because they work on 2 components of detrusor function. Their use may be especially effective in certain patient populations, given the changes in receptor function seen with some pathological conditions. Also, based on these receptor changes certain medications may be more effective than others. Because α_{1B} -AR has been reported to increase with age in the human mammary artery,¹⁸ selective antagonism of this subtype may be a useful way to treat hypertension in the elderly population but it may also be responsible for orthostatic hypotension side effects. In addition, because α_{1D} -AR predominates in the human spinal cord³⁰ and bladder detrusor,²⁰ whereas α_{1A} -AR (α_{1L} -AR) is the predominant receptor subtype controlling adrenergic mediated contraction of the human prostatic urethra and bladder neck smooth muscle, use of an α_1 -AR blocker with subtype selectivity for α_{1D} -AR alone may be advantageous or 1 with selectivity for α_{1D} -AR and α_{1A} -AR (α_{1L} -AR) subtypes if the relief of BOO is desired. Unfortunately none of the Food and Drug Administration approved α_1 -AR antagonists currently available are completely selective for 1 of the 3 (or 4) α_1 -ARs. Tamsulosin has 2.5 to 12-fold greater selectivity for the α_{1A} -AR than for the α_{1B} -AR subtype.⁹ However, to our knowledge whether this translates into clinically relevant selectivity for treating voiding dysfunction is not known.

References

1. Abrams P. Evidence for the efficacy and safety of tolterodine in the treatment of overactive bladder. *Expert Opin Pharmacother*. 2001; 2:1685. [PubMed: 11825311]
2. Wyllie, MG. Pharmaceutical combinations. United States Patent Application 09/778,290, Publication No. US 2001/0044438. A1,1–7. November 22. 2001

3. Balcueva EA, Wang Q, Hughes H, Kunsch C, Yu Z, Robishaw JD. Human G protein gamma(11) and gamma(14) subtypes define a new functional subclass. *Exp Cell Res.* 2000; 257:310. [PubMed: 10837145]
4. Wang P, Luthin GR, Ruggieri MR. Muscarinic acetylcholine receptor subtypes mediating urinary bladder contractility and coupling to GTP binding proteins. *J Pharmacol Exp Ther.* 1995; 273:959. [PubMed: 7752101]
5. Schneider T, Fetscher C, Krege S, Michel MC. Signal transduction underlying carbachol-induced contraction of human urinary bladder. *J Pharmacol Exp Ther.* 2004; 309:1148. [PubMed: 14769832]
6. Hieble JP, Bylund DB, Clarke DE, Eikenburg DC, Langer SZ, Lefkowitz RJ, et al. International Union of Pharmacology. X. Recommendation for nomenclature of alpha 1-adrenoceptors: consensus update. *Pharmacol Rev.* 1995; 47:267. [PubMed: 7568329]
7. Hussain MB, Marshall I. Characterization of alpha1-adrenoceptor subtypes mediating contractions to phenylephrine in rat thoracic aorta, mesenteric artery and pulmonary artery. *Br J Pharmacol.* 1997; 122:849. [PubMed: 9384500]
8. Muramatsu I, Ohmura T, Kigoshi S, Hashimoto S, Oshita M. Pharmacological subclassification of alpha 1-adrenoceptors in vascular smooth muscle. *Br J Pharmacol.* 1990; 99:197. [PubMed: 1970493]
9. Ford AP, Daniels DV, Chang DJ, Gever JR, Jasper JR, Lesnick JD, et al. Pharmacological pleiotropism of the human recombinant alpha1A-adrenoceptor: implications for alpha1-adrenoceptor classification. *Br J Pharmacol.* 1997; 121:1127. [PubMed: 9249248]
10. Coge F, Guenin SP, Renouard-Try A, Rique H, Ouvry C, Fabry N, et al. Truncated isoforms inhibit [3H]prazosin binding and cellular trafficking of native human alpha1A-adrenoceptors. *Biochem J.* 1999; 343:231. [PubMed: 10493934]
11. Chang DJ, Chang TK, Yamanishi SS, Salazar FH, Kosaka AH, Khare R, et al. Molecular cloning, genomic characterization and expression of novel human alpha1A-adrenoceptor isoforms. *FEBS Lett.* 1998; 422:279. [PubMed: 9490024]
12. Price RR, Morris DP, Biswas G, Smith MP, Schwinn DA. Acute agonist-mediated desensitization of the human alpha 1a-adrenergic receptor is primarily independent of carboxyl terminus regulation: implications for regulation of alpha 1aAR splice variants. *J Biol Chem.* 2002; 277:9570. [PubMed: 11781325]
13. Daniels DV, Gever JR, Jasper JR, Kava MS, Lesnick JD, Meloy TD, et al. Human cloned alpha1A-adrenoceptor isoforms display alpha1L-adrenoceptor pharmacology in functional studies. *Eur J Pharmacol.* 1999; 370:337. [PubMed: 10334511]
14. Caine M, Raz S, Zeigler M. Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. *Br J Urol.* 1975; 47:193. [PubMed: 1148621]
15. Marshall I, Burt RP, Chapple CR. Noradrenaline contractions of human prostate mediated by alpha 1A-(alpha 1c-) adrenoceptor subtype. *Br J Pharmacol.* 1995; 115:781. [PubMed: 8548177]
16. Gerber GS, Kim JH, Contreras BA, Steinberg GD, Rukstalis DB. An observational urodynamic evaluation of men with lower urinary tract symptoms treated with doxazosin. *Urology.* 1996; 47:840. [PubMed: 8677574]
17. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol.* 1999; 36:1. [PubMed: 10364649]
18. Rudner XL, Berkowitz DE, Booth JV, Funk BL, Cozart KL, D'Amico EB, et al. Subtype specific regulation of human vascular alpha(1)-adrenergic receptors by vessel bed and age. *Circulation.* 1999; 100:2336. [PubMed: 10587338]
19. Moore CK, Levendusky M, Longhurst PA. Relationship of mass of obstructed rat bladders and responsiveness to adrenergic stimulation. *J Urol.* 2002; 168:1621. [PubMed: 12352468]
20. Malloy BJ, Price DT, Price RR, Bienstock AM, Dole MK, Funk BL, et al. Alpha1-adrenergic receptor subtypes in human detrusor. *J Urol.* 1998; 160:937. [PubMed: 9720591]
21. Perlberg S, Caine M. Adrenergic response of bladder muscle in prostatic obstruction. Its relation to detrusor instability. *Urology.* 1982; 20:524. [PubMed: 7147531]

22. Hampel C, Dolber PC, Smith MP, Savic SL, Thüroff JW, Thor KB, et al. Modulation of bladder α 1-adrenergic receptor subtype expression by bladder outlet obstruction. *J Urol*. 2002; 167:1513. [PubMed: 11832780]
23. Restorick JM, Mundy AR. The density of cholinergic and alpha and beta adrenergic receptors in the normal and hyper-reflexic human detrusor. *Br J Urol*. 1989; 63:32. [PubMed: 2537674]
24. Swierzewski SJ 3rd, Gormley EA, Belville WD, Sweetser PM, Wan J, McGuire EJ. The effect of terazosin on bladder function in the spinal cord injured patient. *J Urol*. 1994; 151:951. [PubMed: 7907374]
25. Somogyi GT, Tanowitz M, de Groat WC. Prejunctional facilitatory alpha 1-adrenoceptors in the rat urinary bladder. *Br J Pharmacol*. 1995; 114:1710. [PubMed: 7599939]
26. Yamamoto T, Ghosh R, De Groat WC, Somogyi GT. Facilitation of transmitter release in the urinary bladders of neonatal and adult rats via alpha1-adrenoceptors. *Eur J Pharmacol*. 2001; 414:31. [PubMed: 11230992]
27. Yoshimura N, Sasa M, Ohno Y, Yoshida O, Takaori S. Contraction of urinary bladder by central norepinephrine originating in the locus coeruleus. *J Urol*. 1988; 139:423. [PubMed: 3339764]
28. Danuser H, Thor KB. Inhibition of central sympathetic and somatic outflow to the lower urinary tract of the cat by the alpha₁-adrenergic receptor antagonist prazosin. *J Urol*. 1995; 153:1308. [PubMed: 7869533]
29. Persson K, Pandita RK, Spitsbergen JM, Steers WD, Tuttle JB, Andersson KE. Spinal and peripheral mechanisms contributing to hyperactive voiding in spontaneously hypertensive rats. *Am J Physiol*. 1998; 275:R1366. [PubMed: 9756570]
30. Smith MS, Schambra UB, Wilson KH, Page SO, Schwinn DA. Alpha1-adrenergic receptors in human spinal cord: specific localized expression of mRNA encoding alpha1-adrenergic receptor subtypes at four distinct levels. *Brain Res Mol Brain Res*. 1999; 63:254. [PubMed: 9878769]
31. Birder LA, Apodaca G, De Groat WC, Kanai AJ. Adrenergic- and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. *Am J Physiol*. 1998; 275:F226. [PubMed: 9691011]
32. Lee JZ, Tillig B, Perkash I, Constantinou CE. Effect of alpha1 adrenoceptor antagonist on the urodynamics of the upper and lower urinary tract of the male rat. *Neurourol Urodyn*. 1998; 17:213. [PubMed: 9590473]
33. Caulfield MP, Birdsall NJ. International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacol Rev*. 1998; 50:279. [PubMed: 9647869]
34. Braverman AS, Luthin GR, Ruggieri MR. M2 muscarinic receptor contributes to contraction of the denervated rat urinary bladder. *Am J Physiol*. 1998; 275:R1654. [PubMed: 9791087]
35. Goepel M, Gronewald A, Kresse S, Michel MC. Muscarinic receptor subtypes in porcine detrusor: comparison with humans and regulation by bladder augmentation. *Urol Res*. 1998; 26:149. [PubMed: 9631949]
36. Newgreen DT, Naylor AM. Comparison of the functional muscarinic receptor selectivity of darifenacin with tolterodine and oxybutinin. *Br J Pharmacol*, suppl. 1996; 117:107P.
37. Chess-Williams R, Chapple CR, Yamanishi T, Yasuda K, Sellers DJ. The minor population of M3-receptors mediate contraction of human detrusor muscle in vitro. *J Auton Pharmacol*. 2001; 21:243. [PubMed: 12123469]
38. Ruggieri MR, Bode DC, Levin RM, Wein AJ. Muscarinic receptor subtypes in human and rabbit bladder. *Neurourol Urodyn*. 1987; 6:119.
39. Gabella G, Uvelius B. Urinary bladder of rat: fine structure of normal and hypertrophic musculature. *Cell Tiss Res*. 1990; 262:67.
40. Braverman A, Legos J, Young W, Luthin G, Ruggieri M. M2 receptors in genito-urinary smooth muscle pathology. *Life Sci*. 1999; 64:429. [PubMed: 10069506]
41. Braverman AS, Karlovsky M, Pontari MA, Ruggieri MR. Aging and hypertrophy change the muscarinic receptor subtype mediating bladder contraction from M₃ towards M₂. *J Urol*, suppl. 2002; 167:43, abstract 170.
42. Pontari MA, Braverman AS, Ruggieri MR Sr. The M2 muscarinic receptor mediates in vitro bladder contractions from patients with neurogenic bladder dysfunction. *Am J Physiol Regul Integr Comp Physiol*. 2004; 286:R874. [PubMed: 14751843]

43. Gu B-J, Ishizuka O, Igawa Y, Nishizawa O, Andersson K-E. Suprasacral effects of antimuscarinic drugs on micturition in normal, conscious rats. *J Urol*, suppl. 2001; 165:276, abstract 1134.
44. Lee JY, Kim HW, Lee SJ, Koh JS, Sun HJ, Chancellor MB. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and overactive bladder. *BJU Int*. 2004; 94:817. [PubMed: 15476515]
45. Kaplan SA, Walmsley K, Te AE. Use of muscarinic receptor antagonists as monotherapy in men with lower urinary tract symptoms who failed previous therapy with alpha blockers. *J Urol*, suppl. 2004; 171:243, abstract 917.
46. Athanasopoulos A, Gyftopoulos K, Giannitsas K, Fisfis J, Perimenis P, Barbaliass G. Combination treatment with an α -blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol*. 2003; 169:2253. [PubMed: 12771763]
47. Abrams P. Tolterodine therapy in men with bladder outlet obstruction and symptomatic detrusor overactivity is not associated with urinary safety concerns. *J Urol*, suppl. 2002; 167:266, abstract 1048.
48. Ko DSC, Fenster HN, Chambers K, Sullivan LD, Jens M, Goldenberg LS. The correlation of multichannel urodynamic pressure-flow studies and American Urological Association symptom index in the evaluation of benign prostatic hyperplasia. *J Urol*. 1995; 154:396. [PubMed: 7541853]
49. Yalla SV, Sullivan MP, Lecamwasam HS, DuBeau CE, Vickers MA, Cravalho EG, et al. Correlation of American Urological Association symptom index with obstructive and nonobstructive prostatism. *J Urol*. 1995; 153:674. [PubMed: 7532231]
50. Lepor H, Machi G. Comparison of AUA symptom index in unselected males and females between fifty-five and seventy-nine years of age. *Urology*. 1993; 42:36. [PubMed: 7687078]
51. Serels S, Stein M. Prospective study comparing hyoscyamine, doxazosin, and combination therapy for the treatment of urgency and frequency in women. *Neurourol Urodyn*. 1998; 17:31. [PubMed: 9453690]
52. Kaplan SA, Chancellor MB, Blaivas JG. Bladder and sphincter behavior in patients with spinal cord lesions. *J Urol*. 1991; 146:113. [PubMed: 2056568]
53. Pontari MA, Mishra B, Ruggieri MR, Greenstein J. Use of doxazosin for voiding dysfunction from multiple sclerosis. *J Urol*, suppl. 1998; 159:79, abstract 301.
54. Moldwin RM. Similarities between interstitial cystitis and male chronic pelvic pain syndrome. *Curr Urol Rep*. 2002; 3:313. [PubMed: 12149163]
55. Schaeffer AJ, Landis JR, Knauss JS, Probert KJ, Alexander RB, Litwin MS, et al. Demographic and clinical characteristics of men with chronic prostatitis: the National Institutes of Health Chronic Prostatitis Cohort Study. *J Urol*. 2002; 168:593. [PubMed: 12131316]
56. Rovner E, Probert KJ, Brensinger C, Wein AJ, Foy M, Kirkemo A, et al. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. *Urology*. 2000; 56:940. [PubMed: 11113737]
57. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999; 353:1959. [PubMed: 10371588]
58. Schmitz W, Eschenhagen T, Mende U, Muller FU, Scholz H. The role of alpha 1-adrenergic and muscarinic receptors in cardiac function. *Eur Heart J*. 1991; 12:83. [PubMed: 1666557]
59. Lepor H, Kaplan SA, Klimberg I, Mobley DF, Fawzy A, Gaffney M, et al. Doxazosin for benign prostatic hyperplasia: long-term efficacy and safety in hypertensive and normotensive patients. *J Urol*. 1997; 157:525. [PubMed: 8996348]
60. Wilde MI, McTavish D. Tamsulosin. A review of its pharmacological properties and therapeutic potential in the management of symptomatic benign prostatic hyperplasia. *Drugs*. 1996; 52:883. [PubMed: 8957159]
61. Beduschi MC, Beduschi R, Oesterling JE. Alpha-blockade therapy for benign prostatic hyperplasia: from a non-selective to a more selective alpha1A-adrenergic antagonist. *Urology*. 1998; 51:861. [PubMed: 9609620]
62. Hashim H, Abrams P. Drug treatment of overactive bladder: efficacy, cost and quality-of-life considerations. *Drugs*. 2004; 64:1643. [PubMed: 15257626]
63. Norel X, Walch L, Costantino M, Labat C, Gorenne I, Dulmet E, et al. M1 and M3 muscarinic receptors in human pulmonary arteries. *Br J Pharmacol*. 1996; 119:149. [PubMed: 8872368]

64. Moroi, SE.; Lichter, PR. Ocular pharmacology. In: Hardman, JG.; Libmbird, LE.; Gilman, AG., editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10. New York: McGraw-Hill; 2001. p. 1821-1848.