Urinary incontinence is usually classified into four types: stress, urge, reflex and overflow incontinence. The first three types of incontinence are due to urine storage dysfunction and the latter is due to urine emptying dysfunction. To improve urine storage dysfunction treatment should be aimed at decreasing detrusor overactivity, increasing bladder capacity and/or increasing outlet resistance, whereas to improve emptying dysfunction, increasing detrusor contractility and/or decreasing outlet resistance are required. This review summarizes the various drugs currently in clinical use and new drugs under investigation.

Introduction
Urinary incontinence is a condition in which involuntary loss of urine is a social or hygienic problem and is usually classified into stress incontinence, urge incontinence, reflex incontinence and overflow incontinence. Stress incontinence is involuntary loss of urine during coughing, sneezing or physical exertion such as sports activities, sudden changes of position, etc., and occurs when the intravesical pressure exceeds the maximum urethral pressure but in the absence of detrusor activity. Urge incontinence is involuntary loss of urine associated with a sudden, strong desire to void due to detrusor overactivity. Reflex incontinence is involuntary loss of urine due to abnormal reflex activity in the spinal cord in the absence of the sensation usually associated with the desire to micturate. Overflow incontinence is involuntary loss of urine when the intravesical pressure exceeds the maximum urethral pressure due to an elevation of intravesical pressure associated with bladder distention but in the absence of detrusor activity (1, 2).

The lower urinary tract constitutes a functional unit which is controlled by a complex interplay
between the central and peripheral nervous systems and local regulatory factors (3). As the lower urinary tract has two basic functions, the storage and emptying of urine, disturbances at various levels may result in disorders of storage or emptying of urine. Most incontinence is due to failure to store urine, and only overflow incontinence is due to failure to empty urine. Pharmacological interventions have been used in treating these disorders, although often with limited success. To improve storage dysfunction, the treatment should be aimed at decreasing detrusor overactivity, increasing bladder capacity and/or increasing outlet resistance. On the other hand, to improve emptying dysfunction, increasing detrusor contractility and/or decreasing outlet resistance are required. Various drugs shown in Table I are clinically used for the treatment of urinary incontinence.

**Failure to Store Urine**

**Decreasing detrusor overactivity**

Detrusor overactivity is an involuntary detrusor contraction, and has many synonyms such as bladder hyperactivity, detrusor hyperreflexia, detrusor instability, uninhibited contraction, unstable bladder or reflex contraction, although they may be used in slightly different ways. Drugs that decrease detrusor overactivity are usually associated with increased bladder capacity.

1) Anticholinergic agents

Muscarinic receptors mediate not only normal bladder contractions but also the main part of contractions in hyperactive bladders. Atropine and other anticholinergic drugs are known to produce an almost complete paralysis of the normal bladder when injected intravenously (4, 5). Several studies suggest that blockade of detrusor contractions can also be achieved in patients with bladder hyperactivity (6). In such patients the volume to the first involuntary contraction increases, the amplitude of the contractions decrease and the total bladder capacity increases, with a proportionate reduction in symptomatology. On the other hand, there are several reports of insufficient efficacy of anticholinergic drugs given orally to patients with involuntary detrusor contractions (7-9). It is unclear to what extent this can be attributed to low bioavailability or to side effects, or if atropine resistance actually occurs in some cases of unstable bladder.

The most widely used drugs for the treatment of unstable bladder are probably propantheline, oxybutynin, tolterodine and propiverine. Propantheline is a synthetic quaternary ammonium analog of atropine and has potent antimuscarinic activity together with some ganglion blocking activity. Intravenous administration of 15 mg was shown to decrease or inhibit the contractions induced by hypogastric or pelvic nerve stimulation (10). In 6 normal individuals, intramuscular administration of 30 mg propantheline increased bladder capacity by an average of 53%, and abolished the uninhibited bladder activity (11). Oral propantheline was also effective for urinary incontinence due to uninhibited bladder contractions (12, 13). Propantheline is usually given at a dose of 15-30 mg, 3-4 times daily. To obtain an optimal effect, individual titration of the drug is necessary; the dose should be increased until incontinence is eliminated or until untoward side effects preclude further increase. Anticholinergic side effects such as dry mouth, blurred vision, constipation, headache and tachycardia are frequent and often preclude use of the drug despite its clinical efficacy.
Oxybutynin is a moderately potent anticholinergic agent with a strong independent musculotropic relaxant activity, as well as local anesthetic activity (14, 15). It has been demonstrated that oxybutynin is effective in controlling bladder hyperactivity with improvement of urinary frequency, urgency and urge incontinence, in addition to increasing bladder volume at first desire to void, enhancing maximum bladder capacity and reducing maximum detrusor pressure during filling (16, 17). Oxybutynin is usually administered at a dose of 2-5 mg, 2-3 times daily. During oxybutynin therapy, residual urine volume increased significantly (18). These findings appear to confirm that oxybutynin ameliorates symptoms of detrusor overactivity but increases residual urine volume. Anticholinergic side effects are common, and according to Gajewski et al. (16), intolerance occurs in approximately 20% of patients during treatment.

The clinical efficacy of oxybutynin and propantheline in the treatment of symptoms related to detrusor hyperactivity have been studied. Results indicated that oxybutynin was more effective than propantheline (16, 18-20), although it was less well tolerated (17).

Intravesical administration of oxybutynin has been investigated as a means of decreasing anticholinergic side effects while maintaining clinical efficacy. This approach is an option in patients who do not respond to oral medications or who experience intolerable systemic side effects. To administer oxybutynin, 5 mg tablets were crushed and dissolved in 10 ml room temperature sterile saline. This solution was instilled via a catheter and left in the bladder until the next catheterization. The instillation is performed 1-3 times daily depending on the symptoms. The safety and usefulness of intravesical oxybutynin has been demonstrated in several clinical trials (21-24). This mode of therapy is recommended in patients who are on clean intermittent catheterization.

Terodiline is a drug with anticholinergic and calcium antagonistic properties. Both effects have been shown to inhibit bladder contractions and therefore are important for the treatment of urge incontinence. In addition, terodiline has local anesthetic and spasmytic properties which might contribute to its total effect. Terodiline is eliminated slowly from the body with a mean serum elimination half-life of about 60 h. Consequently, steady-state plasma levels are not reached until after 10-14 days of treatment, which also indicates that there are very small fluctuations in the serum concentration between doses (25). The most common adverse events are related to the anticholinergic effects of terodiline, and dry mouth is the most prominent event. Bogentoft et al. (26) reported the results of worldwide safety studies in which adverse events were compared in 735 terodiline-treated patients and 433 placebo-treated patients. During treatment with terodiline, 290 patients (39%) reported adverse events compared with 128 patients (30%) on placebo. The difference was only 9%, and the relatively high incidence of adverse events for both groups was probably due to specific questions about the adverse events. Clinical studies, including 17 double-blind studies, show terodiline to be effective with a side effect profile that appears to be less than that of oxybutynin (27). Terodiline is usually given at doses of 25-50 mg/day.

Propiverine hydrochloride is a benzylid acid derivative with musculotropic antispasmodic activity and moderate anticholinergic effects. In a number of clinical trials propiverine was shown to be an effective therapy in urinary incontinence with a moderate incidence of adverse drug reactions. The most common side effects were anticholinergic symptoms. Mazur et al. (28) found that bladder capacity and compliance increased and bladder pressure decreased in a dose-dependent manner following therapy with 15, 30, 45 and 60 mg/day, and 15 and 30 mg were the daily doses with the most favorable ratio of efficacy in micturition frequency to tolerability.

Tolterodine, a novel compound intended for treatment of urgency and urge incontinence, has been characterized as a potent muscarinic receptor antagonist in in vitro and in vivo studies (29). The drug was shown to reduce bladder pressure at doses significantly lower than those affecting salivation (30), in contrast to oxybutynin, which was significantly more potent in inhibiting salivary secretion than urinary bladder contractions (29). Thus, tolterodine seems to have high affinity and selectivity for the urinary bladder over salivary gland, and would offer a superior performance in terms of both efficacy and safety compared to currently available pharmacotherapies.

All of the above drugs have anticholinergic side effects such as dry mouth, blurred vision, tachycardia, facial flushing, constipation, stomal ulcers, drowsiness, auditory and visual hallucinations, agitation, confusion, delirium and nightmares.
Because of the side effects, dosage reductions or discontinuation of the medication are often necessary. Anticholinergic agents are generally contraindicated in patients with narrow-angle glaucoma and should be used with caution in patients with single bladder outlet obstruction, as complete urinary retention may be precipitated.

Receptor subtyping is an important concept for the future development of antimuscarinic compounds. At least five different genetically established muscarinic subtypes (M1-M5) are known (31). Cerebral cortex and parotid gland have mainly M1, whereas smooth muscle of the ileum has M3, and smooth muscle of the ileum or bladder has M5 (17). Human detrusor seems to contain M2 and M3 subtypes (32). At present no anticholinergics in clinical use have particular affinity to human detrusor muscle. Therefore, anticholinergics which would selectively block human detrusor muscarinic receptors and have fewer side effects, thus being more effective for the treatment of detrusor hyperreflexia, are eagerly awaited.

2) Direct smooth muscle relaxants
Flavoxate hydrochloride is a flavone derivative used in the treatment of urinary urge syndrome and urge incontinence. The drug and its major active metabolite, 3-methylflavone-8-carboxylic acid (MFCA), are thought to exert a direct smooth muscle relaxation of the lower urinary tract, probably through the inhibition of cAMP phosphodiesterase (33, 34), and weak anticholinergic activity (35). Flavoxate does not interfere with neuromuscular transmission and is therefore able to interact with the predominantly noncholinergic phase of urinary storage, thus reducing the rate of pressure formation in the bladder without interfering with the voiding mechanism, which is mainly under cholinergic control (36). Clinical studies showed a decrease in uninhibited detrusor contractions and an increase in bladder capacity with flavoxate (37, 38). However, some reports showed that the drug had no effects in patients with incontinence due to massive uninhibited contractions (39), or that it was not superior to placebo in patients with symptomatic benign prostatic hyper trophy (40). No significant increase of residual urine occurs during treatment with flavoxate. Furthermore, the drug has the particular advantage of having fewer and milder side effects compared with other drugs (36). The side effects of flavoxate are similar to those of anticholinergics (dry mouth, constipation, etc.), although the overall incidence is much lower (in only approx. 5% of patients). Studies have shown that treatment with flavoxate rarely needs to be interrupted due to side effects, whereas 10-30% of patients receiving other anticholinergics require a change in medication (35). Flavoxate is usually given at a dose of 100-200 mg, 3-4 times daily, and superior efficacy has been shown with doses up to 1200 mg/day (38).

3) Calcium antagonists
It is known that neurotransmitters act on the smooth muscle through activation of one or several calcium ion channels changing intracellular Ca²⁺ concentration and distribution. The movement of Ca²⁺ is essential for excitation-contraction coupling. Therefore, blocking the Ca²⁺ entrance is a logical way of controlling muscle activity. Hassouna et al. (41) studied the effects of three commonly used Ca²⁺ antagonists, verapamil, nifedipine and segontin, on detrusor contractility in vitro and found that all three drugs dose-dependently inhibited detrusor-induced contractions. Favaeus et al. (42) studied the effects of nifedipine on carbachol-induced contractions of isolated bladder smooth muscle from both rabbit and man. They showed that the contractions induced by muscarinic receptor stimulation were highly dependent on extracellular calcium, and that combined blockade of muscarinic receptors and calcium channels was an effective way of inhibiting bladder contraction.

Palmer et al. (43) studied the effects of flunarizine in 14 patients with urinary frequency and incontinence due to detrusor instability. The results showed statistically significant efficacy of flunarizine as compared to placebo, with mild side effects. Intravesical instillation of verapamil was investigated by Mattiason et al. (44) in patients with detrusor hyperactivity of neurogenic and non-neurogenic origin. The results showed that verapamil produced a significant increase in bladder capacity in patients with neurogenic detrusor hyperreflexia, but not in patients with nonneurogenic detrusor instability, suggesting that pathophysiological differences between hyperactivity of neurogenic and nonneurogenic origin may be responsible for the differences observed. Although the clinical usefulness has not yet been established, calcium antagonists have potential for the treatment of urinary incontinence due to detrusor overactivity.
4) β-Adrenergic agonists

The discovery of the presence of β-adrenergic receptors in human bladder muscle led to the idea of increasing bladder capacity by β-adrenergic stimulation. In in vivo animal studies, the administration of β-adrenergic stimulating agents resulted in increased bladder capacity and decreased intravesical pressure, thus facilitating the storage of urine (45, 46). Lidholm et al. (47) reported the results of a clinical study of terbutaline, a β₂-agonist, in patients with idiopathic urge incontinence and found subjective as well as objective improvement. They noted decreased detrusor instability and statistically significant increase in the volume of first desire to void, but not maximum cystometric capacity. Clenbuterol is another β₂-agonist which was found in vivo to dose-dependently relax bladder smooth muscle (48). Clenbuterol was also found to be effective in patients with urge incontinence (49, 50). The side effects such as palpitations, increased pulse rate and/or tremor were common but were transient in most patients. Although further clinical studies are needed, β-adrenergic agonists appear to have potential value in the pharmacological treatment of urge incontinence.

5) Prostaglandin inhibitors

The rationale for using prostaglandin inhibitors in the treatment of detrusor overactivity is that prostaglandins produced in bladder tissue and contribute to maintaining spontaneous contractile activity (51). Prostaglandins E₁, E₂, F₂α, F₃α, all produce contraction of human bladder muscle in vitro, PGF₂α being the most potent (52). The use of prostaglandin synthetase inhibitors in the treatment of irritative bladder symptoms has generated some controversy as well. Cardozo and Stanton (53) reported on a clinical trial of indomethacin and bromocriptine in 32 female patients with detrusor instability. They noted decreased detrusor instability and found subjective as well as objective improvement. But the incidence of side effects was also high, including nausea and/or vomiting, dizziness, headache, constipation, indigestion and aggression, although no patients discontinued treatment. Their results – only subjective response (urodynamic changes). Flurbiprofen, a prostaglandin synthetase inhibitor, was administered at a dose of 50 mg 3 times daily. It was concluded that the drug did not abolish involuntary bladder contractions but did delay the intravesical pressure rise to a greater degree of distention. Side effects were reported in 43% of the patients, primarily nausea, vomiting, headache, indigestion, gastric distress, constipation and rash. Because of the high rate of side effects, the use of prostaglandin inhibitors, so-called nonsteroidal antiinflammatory drugs, seems to be limited to the treatment of detrusor instability.

6) Tricyclic antidepressants

Tricyclic antidepressants, particularly imipramine, have come to be accepted for the treatment of urinary storage disorders including enuresis. Clinical observations and laboratory studies on animal preparations and in vitro tissue studies have suggested a myriad of possible mechanisms, including local anesthetic, musculotropic smooth muscle relaxant, inhibition of noradrenaline reuptake, α-adrenergic blockade, β-stimulation and anticholinergic (54-56). Empirically, this agent appears to decrease bladder contractility and increase outlet resistance (54).

Imipramine has been found to be highly effective in eliminating nocturnal enuresis and is widely used for symptomatic control of enuresis and diurnal urinary incontinence in children (57). In addition to having an effect on lower urinary tract, the drug also decreases deep night sleep and has some antiuric effects (58).

The successful treatment of enuresis with imipramine is directly correlated to serum drug levels. No linear relationship between serum imipramine levels and urinary incontinence was demonstrated (59). However, the incidence of side effects is uncommon, but include anxiety, insomnia, dry mouth, nausea and personality changes (60). Overdoses can cause cardiac arrhythmias, hypotension, respiratory complications and convulsions (61), and sometimes can be fatal.
Increasing outlet resistance

1) α-Adrenergic agonists

It is known that α-adrenoceptors are predominantly present in the bladder neck and prostate smooth muscle. Administration of α-adrenergic agonists increases the resistance of these structures and relieves urinary symptoms, particularly stress urinary incontinence (62, 63).

Ephedrine directly stimulates α- and β-adrenoceptors and releases noradrenaline from nerve terminals. It also possesses some central nervous system stimulating activity. It has been reported to be effective in patients with incontinence secondary to transurethral resection of the prostate, neurogenic bladder disease or stress incontinence. Urethral pressure measurements revealed increased pressure over the entire length of the urethra. It was concluded that ephedrine improves urinary incontinence provided that the wetting is minimal to moderate and related to decreased urethral resistance (64). Ephedrine is of little benefit in patients with uninhibited neurogenic bladders or severe stress incontinence (64, 65). The normal dose is 50-100 mg, 2-3 times daily. Side effects include epigastric distress, nervousness, insomnia, palpitations and cardiac arrhythmias. Ephedrine should be used with caution in patients with cardiovascular disease, hypertension, hyperthyroidism, prostatic hyperplasia or glaucoma (66).

Phenylpropanolamine, an α-receptor stimulant, was shown to be effective in 11 of 13 female and 6 of 7 male patients with sphincteric incontinence. In all of the male patients except 1, the incontinence followed prostatectomy (67). Beisland et al. (68) also noted the efficacy of oral administration of 50 mg of phenylpropanolamine in patients suffering from postmenopausal urinary incontinence. Urodynamic investigations demonstrated increased maximal urethral closure pressure and continence area. Another potent α-receptor stimulant, midodrine, also increased the intraurethral pressure and subjective improvement or cure in patients with stress incontinence (69).

There is reason to believe that the predominating postjunctional α-adrenoceptor subtype in the human lower urinary tract is α₂ (70). α₂-Adrenoceptors have been demonstrated on adrenergic nerve terminals in both detrusor and urethral smooth muscle, which when stimulated by noradrenaline inhibit further release of the amine (71). Although there are none in clinical use so far, selective α₁-agonists seem to be more appropriate for the treatment of stress incontinence.

2) β-Adrenergic agonists

It has been shown in vitro that the β₂-agonist, clenbuterol, relaxes bladder smooth muscle in a dose-dependent manner while increasing maximal urethral closure (48). The urethral sphincter consists of smooth and striated muscle, each of which is responsible for the intraurethral pressure. The increase in intraurethral pressure by clenbuterol was not due to its effect on smooth muscle but on striated muscles (72). Yamanishi et al. (73) demonstrated in animal studies that clenbuterol enhanced the contractility of fatigued urethral sphincter and suggested that β₂-agonists act on fast-contracting fibers in the urethral sphincter. Clenbuterol was found to be effective on stress incontinence in open (50, 74, 75) and double-blind, placebo-controlled (76) trials. Clenbuterol is usually given in a dose of 10-30 µg/kg b.i.d.

3) Estrogens

Sex steroids may influence morphology and function of the lower urinary tract. In animal experiments, estrogen treatment increases tissue mass and the sensitivity of the smooth muscles of both the bladder and urethra to autonomic drugs (77, 78). Increasing sensitivity of α-agonist receptors potentiates their effect on urinary continence (79, 80). Estrogen has been used clinically for the treatment of urinary stress incontinence in women. The results of estrogen therapy in postmenopausal women with urogenital changes are controversial because of the different evaluation criteria, types of hormones, administration routes and doses employed (81). Although there are studies reporting unsatisfactory clinical response compared with placebo (82, 83), other studies have reported considerable improvement of urinary symptoms and urodynamic data (81, 84, 85). Hormone replacement therapy may be a useful treatment for stress urinary incontinence in postmenopausal women.

Failure to Empty Urine

Increasing bladder contractility

1) Cholinergic agents

In the normal human detrusor, the emptying contraction in vivo and the contraction evoked by electrical stimulation of nerves in vitro have been
suggested to be mediated mainly through muscarinic receptor stimulation (5, 86). The drugs that imitate the action of acetylcholine might be expected to be useful in the management of patients who cannot empty because of inadequate bladder contractility. Acetylcholine itself cannot be used for therapeutic purposes because of its actions at central and ganglionic levels and because of its rapid hydrolysis by acetylcholinesterase.

Among the many acetylcholine-like drugs, only bethanechol chloride was found to be both long-acting due to resistance to hydrolysis and purely muscarinic. Subcutaneous administration of bethanechol was shown to produce bladder and gastrointestinal effects with only minor effects in other systems (87). In normal individuals, bethanechol produces a decrease in bladder capacity, an increase in detrusor tone and an increase in maximum voluntary voiding pressure within 5 min of administration (88). However, these effects may not cause a change in urine flow rate during voiding.

Bethanechol has been used extensively in patients with idiopathic hypotonic bladder without a critical look at the documentation of its efficacy (89, 90). In neurological lesions, bethanechol can be used during the recovery phase from spinal shock, but its beneficial effects have not yet been substantiated. According to Awad et al. (91), subcutaneous injection of bethanechol in lower motor neuron lesions was effective in initiating micturition and lowering postvoid residual urine. However, side effects such as sweating, hot flushes and palpitation with a general feeling of malaise were reported and appeared to worsen with repeated administration. Light and Scott (92) studied the effects of bethanechol in 28 men with neurogenic bladder secondary to spinal cord injury at various levels. The only statistically significant changes induced by bethanechol injection were an increase in maximum detrusor pressure and a decrease in peak urinary flow rate with the patient in the supine position. The authors concluded that although 5 mg of bethanechol administered subcutaneously was pharmacologically active, the drug’s effects were unpredictable. Bethanechol failed to improve voiding with the patient in a supine or sitting position, failed to induce detrusor contractions in patients with areflexia and aggravated functional bladder outlet obstruction.

Based on a comparison between the acute effects of subcutaneous and oral bethanechol on bladder pressure, Lapides et al. recommended increasing the oral dose to a maximum of 100 mg every 4-6 h (93, 94). Because only acute effects were monitored, this dose seems inappropriate to the current long-term use of oral bethanechol. The effects of oral administration of bethanechol are questionable (95, 96) and are probably rarely successful or ineffective (90, 97).

Distigmine bromide is a long-acting anticholinesterase compound which inactivates cholinesterase within a few hours, allowing the sustained action of acetylcholine on cholinergic nerve endings. It has been widely used for many years in the treatment of voiding difficulties experienced by patients after prostatectomy, abdominal surgery, spinal injuries and gynecological procedures (98). Parenteral administration of distigmine bromide, but not oral, was reported to be useful in enhancing detrusor activity in spinal cord injury patients (99). The results of a double-blind study of Shah et al. (98) showed that parenteral distigmine produced no statistically significant differences in voiding effectiveness after prostatectomy.

2) Prostaglandins

In 1976 Bultitude et al. (51) treated 21 female patients with varying degrees of urinary retention with intravesical administration of PGF$_{2\alpha}$. By comparing urodynamic parameters before and after instillation of the drug, they noted a significant improvement in 14 patients. Follow-up of these patients for up to 2 years revealed a long-lasting response in all but 3 of them. A few years later, Desmond et al. (100) in a study from the same institution evaluated 36 patients with poorly functioning detrusors and assessed the response to larger doses of intravesical PGF$_{2\alpha}$. They found improvement in 72% and a long-term therapeutic response in 39% of their patients. Their findings supported the clinical usefulness of prostaglandins. Subsequently, therapeutic efficacy of intravesical instillation of PGF$_{2\alpha}$ or PGE$_{2\alpha}$ was reported by others (101-103), but Delaere et al. (104) and Wagner et al. (105) found no therapeutic value in the treatment of voiding dysfunction. Although the pharmacological properties of prostaglandins are indicative of a promising potential for clinical application, more and better controlled studies are needed in order to elucidate their effects in humans.

3) Opioid antagonists

Naloxone, an opioid peptide antagonist, has been reported to facilitate voiding in neurologic
bladder disorders (106-108). Galeano et al. (109) studied the effects of naloxone on detrusor-sphincter dyssynergia in the spinal cat and found that it increased not only micturition reflex but also urethro-urethral contraction reflex, aggravating the spasmodyc contractions of the external sphincter. The results indicated that naloxone is contraindi-cated in cases of spinal cord lesions with detrusor-sphincter dyssynergia. Wheeler et al. (110) tested the urodynamic effects of naloxone (0.4-0.8 mg i.v.) in spinal cord injury patients and found no increase in detrusor-sphincter dyssynergia or cystometric changes. However, there was a decrease in electromyographic activity in 73% of the patients.

Decreasing outlet resistance

1) α-Adrenergic antagonists

It is known that α1-adrenoceptors are predomi-nantly present in the bladder neck and prostate smooth muscle. α1-Blocking agents have success-fully been used to decrease the pressure in the prostatic urethra and bladder neck and relieve symptoms in patients with lower urinary tract symptoms.

Phenoxybenzamine is a prototypical α1-antagonist which has produced encouraging improvements in urinary flow and clinical symp-toms in most clinical studies (111-114), with few exceptions (115). The lack of efficacy reported in some studies was attributed to the blockade of presynaptic α2-adrenoceptors, which is thought to interfere with the normal negative feedback control of noradrenaline release at the presynaptic adren-ergic nerve terminal, resulting in high levels of cir-culating noradrenaline. Side effects are generally due to blocking of α2-receptors in organs other than the bladder and urethra. The loss of vasomotor control can lead to postural hypotension and reflex tachycardia. The drug-induced hypotension may be exaggerated by exercise, ingestion of alcohol and/or eating a large meal which diverts blood from the central vascular compartment.

Prazosin was introduced as an antihyperten-sive agent and was subsequently reported to pro-duce urinary incontinence in 10% of patients (116). This supported new findings that prazosin is a selective α1-adrenoceptor blocking agent and con-firmed the importance of α1-adrenoceptors in maintaining intraurethral pressure (117). Most of the studies have demonstrated that selective α1-adrenoceptor blockade can be effective with few adverse events. All of the contemporary alpha-blockers presently in clinical use appear to behave with similar pharmacological and clinical efficacy and safety, producing up to a 50% increase in urin-ary flow rate with significant improvement in patients’ symptoms (118). Other α1-adrenoceptors currently in clinical use are alfuzosin (119-121), terazosin (122-124) and doxazosin (125-127). The most common side effects of prazosin were headache, dizziness and drowsiness, occurring in up to 15% of patients, but they were usually mild and did not require discontinuation of therapy (118). Mild postural hypotension has also been reported, and particular caution should be taken when treating elderly patients.

Ligand binding studies initially suggested that there was a heterogeneity of α1-adrenoceptors, which were subsequently subclassified on a func-tional basis into three subtypes: α1a, α1b and α1d (there is no α1g). The subtype which is present at the greatest concentration in human prostate and which is responsible for contraction of prostate smooth muscle is α1a (128, 129). Although it is not certain which subtype is responsible for blood pressure regulation, it has been suggested that the α1a subtype is involved in smooth muscle contrac-tion of large human arteries (129). It has been post-ulated that a drug with a relatively high affinity for the α1a-adrenoceptor may be as effective as other α1-adrenoceptor antagonists but may have less effect on blood pressure and cause fewer vasodilatory side effects. Consequently, dose titra-tion may not be necessary to avoid side effects and may allow an optimal therapeutic dose to be used from the onset of therapy. Tamsulosin is the first selective α1a-adrenoceptor antagonist to demonstrate efficacy and good safety in patients with symptomatic benign prostatic enlargement (130, 131). The normal therapeutic dose of tamsu-losin is 0.4 mg/day, which can be administered from the beginning of therapy.

2) β-Adrenergic agonists

β- Receptors are found in bladder neck and ure-thra, although to a lesser extent than in detrusor muscle. Significant decrease in urethral pressure after infusion of isoproterenol was demonstrated by Raz et al. (132) Rao et al. (113) observed a 47.3% decrease in maximum urethral closure pressure after administration of orciprenaline in patients with neurogenic bladder dysfunction but...
cardiovascular adverse effects discouraged its frequent use. Vaidyanathan et al. (134) also noted a significant decrease in maximum urethral closure pressure after subcutaneous injection of terbutaline. Whether a decrease in maximum urethral closure pressure after β-adrenergic agonists could be used to promote vesical emptying awaits further studies.

3) Skeletal muscle relaxants

The purpose of skeletal muscle relaxants is to treat detrusor-sphincter dyssynergia, the main cause of voiding dysfunction in spinal cord diseases. Three different types of drugs, i.e., benzodiazepine, dantrolene and baclofen can be used for this purpose. However, no drug will selectively relax the striated musculature of the pelvic floor. In a study in patients with traumatic paraplegia (135), Hachen and Krucker found that intravenous administration of baclofen at a dose of 20 mg/day was highly effective on urethral sphincter spasticity, whereas oral administration was ineffective (136). Oral administration of dantrolene was reported to be beneficial in patients with neurogenic voiding dysfunctions (137, 138). These are the results of short-term studies. Since the side effects of skeletal muscle relaxants are common and may be life-threatening, the therapeutic application of these drugs in voiding disorders is limited.

Conclusions

The recent development in lower urinary tract pharmacology have led to new therapeutic approaches, as well as a great deal of confusion. Since our primary goal is to discover agents that have favorable effects on lower urinary tract functions, further results from properly conducted and executed clinical trials on the efficacy of drugs are awaited.

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