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The Challenge of the Overactive Bladder: From Laboratory to New Drugs

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Abstract

Antimuscarinic agents are currently the first-line therapy for overactive bladder (OAB). Many urologists believe the pharmacologic management of OAB is not altogether satisfactory. Pharmacologic research is trying to provide answers to the issues of efficacy, tolerability, and convenience of new drugs. This paper discusses the rationale underlying the development of new compounds, provides an update of progress in the search for new therapies for OAB, and tracks their translation into clinical practice. It offers an insight into the mechanism of action, efficacy, side-effects, and ''market status'' of several drug categories targeting the central nervous system (adrenoceptor modulators, serotonin/norepinephrine reuptake inhibitors, tachykinin modulators, opioids), neuromuscular blocking agents (botulinum toxin A), selective modulators of the afferent branch of micturition reflex (vanilloid, nociceptin/orphanin FQ), autonomic nervous system modulators (β_3-agonists), potassium and calcium channel openers, and nonsteroidal anti-inflammatory drugs.

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1. Introduction

Overactive bladder (OAB) is a complex clinical syndrome that the International Continence Society (ICS) defines as characterised by urgency (sudden, compelling desire to pass urine, which is difficult to defer), urinary incontinence (involuntary urine leakage with or without urgency), frequency, and nocturia (waking to void more than once at night), in absence of genitourinary pathologies or metabolic factors that could explain these symptoms (www.icsoffice.org). OAB may be associated with, but needs to be distinguished from, detrusor overactivity (DO), which refers to an uninhibited, involuntary rise in detrusor pressure during the filling phase of filling cystometry during urodynamic assessment in a conscious cooperative patient.

European and North American surveys reported that OAB is found in about 16% of the general population aged 40 yr and over; one third of patients with a clinical diagnosis of OAB present urgency urinary incontinence [1]. Interestingly, OAB rates are

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similar in men and women. In a cross-sectional population-based survey of adults (>18 yr old), Irwing et al reported a 12.2% total prevalence of OAB in four European countries and confirmed that it is common in men and women of all adult age groups [2].

Because OAB-related symptoms are extremely distressing and have a significant negative impact on quality of life and health care costs, treatment and management remain the main challenges for health care professionals [3]. At present, the primary pharmacologic treatment for OAB uses antimuscarinic agents; objective clinical data, systematic reviews, and adjusted indirect comparisons confer a high level of evidence and strong recommendations [4]. Urologists are, however, aware that caution should be exercised when evaluating, interpreting, or prescribing antimuscarinics. Attention should focus on the natural history of OAB, choice of appropriate study design, trial duration, restricted population, economic issues, unrealistic patient expectations, high placebo response rates, and diverse methods of outcome assessment in different trials. Currently there is no consensus on how long patients should be treated, whether treatment should be continuous, intermittent, or on demand, and why only relatively few patients remain on medication for >4–6 mo [5]. Many urologists are systematically searching for appropriate answers to these open questions and looking for more efficacious alternatives to antimuscarinic agents.

This paper discusses the pharmacologic rationale underlying the development of new compounds, provides an update of progress in the search for new therapies for OAB, and tracks their translation into clinical practice.

2. Pathophysiology of the micturition reflex

The lower urinary tract (LUT) serves two main functions: (1) urine storage without leakage (storage phase) and (2) release of urine (voiding phase). These two functions depend on central, peripheral autonomic, and somatic neuronal pathways and local peripheral factors.

During the storage phase afferent impulses, which reach the central nervous system (CNS) from the bladder, send information to the pons. In the pontine tegmentum in animals, positron emission tomography (PET) studies visualised a medial region (M-region), corresponding to Barrington's nucleus or pontine micturition center, which is involved in micturition reflex coordination, and a lateral region (L-region), which suppresses bladder contractions and improves external sphincter muscle activity during the storage phase [6]. PET and functional magnetic resonance imaging (fMRI) recently detected several suprapontine centers that modulate the micturition reflex in humans [7]. These areas are under the chemical control of different ligands (neurotransmitters) and receptors (Table 1).

The micturition reflex involves the parasympathetic, sympathetic, and somatic peripheral neuronal systems. The parasympathetic system, originating in the spinal cord sacral area (S2–4) controls bladder contractions. It provides an excitatory input to the bladder through post-ganglion nerve terminal release of acetylcholine (ACh), which excites muscarinic receptors (M_2, M_3) in the detrusor smooth muscle and leads to contraction. The sympathetic system originating in the thoracolumbar cord (Th11–L2) is involved in bladder relaxation and urethral closure through, respectively, post-ganglion nerve terminal release of norepinephrine (NE). NE provides

Table 1 – Central nervous system ligands and receptors involved in the regulation of micturition reflex

Ligands	Receptors	Function
Norepinephrine	ARs (α, β)	Micturition reflex • Excitatory: α_1 • Inhibitory: α_2 • β (?)
γ-aminobutyric acid (GABA)	$GABA_A$ and $GABA_B$	Inhibition of micturition reflex
Glycine	GlyR	Inhibition of micturition reflex
Opioids	μ, δ, κ	Inhibition of micturition reflex
Serotonin	$5\text{-}HT_{1\text{–}7}$	Inhibition of micturition reflex
Dopamine	D_1 and D_2	Inhibition of micturition reflex
Glutamate	NMDA and AMPA	Excitatory/inhibitory function
N/OFQ	NOP	Excitatory/inhibitory function

AR = adrenoreceptor; GlyR = glycine receptor; HT = hydroxytryptamine; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; N/OFQ = heptadecapeptide nociceptin/orphanin FQ; NOP = N/OFQ peptide receptor.