

**Editorial Comment on: Cizolirtine Citrate, an Effective Treatment for Symptomatic Patients with Urinary Incontinence Secondary to Overactive Bladder: A Pilot Dose-Finding Study**

Florian May, Ricarda Bauer

Department of Urology, Ludwig-Maximilians-University (LMU), Marchioninstr. 15, 81377 Munich, Germany  
florian.may@med.uni-muenchen.de

Antimuscarinic agents represent the first-line therapy for overactive bladder (OAB). Objective clinical data and systematic reviews confer a high level of evidence and strong recommendations [1]. Many urologists, however, believe that pharmacologic management of OAB is not satisfactory. 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 [2]. Pharmacologic research tries to answer these open questions and is looking for more efficacious alternatives to antimuscarinic agents.

This paper reports a multicentre, double blind, phase II study investigating the efficacy and safety of a new agent in overactive bladder with urinary incontinence [3]. This trial gives evidence for the therapeutic potential of cizolirtine citrate, which functions as a substance-P and calcitonin gene-related peptide release modulator at the spinal cord level. Due to the pilot nature of this trial,

the sample size was limited and placebo was chosen as the comparator. The results achieved by cizolirtine seem to be similar to antimuscarinic drugs currently used for OAB treatment. The different therapeutic mechanism suggests the use of cizolirtine both in patients nonresponsive to antimuscarinics and in combination with these drugs so as to achieve a stronger effect. Subsequent studies including a higher number of patients and a positive control treatment are necessary to get more information on this promising agent.

## References

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Massimo Lazzeri

Department of Urology, Casa di Cura Santa Chiara (GIOMI Group), p.zza Indipendenza 11, 50129 Firenze, Italy  
lazzeri.m@tiscali.it

As overactive bladder (OAB)-related symptoms are extremely distressing and have a significant negative impact on quality of life and health care costs, treatment and management remains the main challenge for health care professionals [1]. At present, primary pharmacologic treatment for OAB consists of antimuscarinic agents. Objective clinical data, systematic reviews, and adjusted indirect comparisons confer a high level of evidence and strong recommendations for old antimuscarinics even while new ones are available on the market [2].

In the past, the simple, “easy to accept” idea of antagonistic parasympathetic cholinergic and sympathetic adrenergic control of the lower urinary tract (LUT) discouraged extensive research into new drugs for the treatment of OAB. In recent years, LUT neuropharmacology has progressed. Immunohistochemical and pharmacologic studies of the bladder wall showed that many neuronal terminal endings do not correspond to

cholinergic and adrenergic innervation leading to the identification of noradrenergic, noncholinergic (NANC) pathways [3]. These nerves are peptide-containing fibres that are thought to be “silent” in normal conditions, but might play a major role in regulating LUT functions in pathologic conditions such as neurogenic bladder, OAB, and bladder outlet obstruction. The observation at the level of CNS as well as at peripheral organs of the synthesis and release of multiple neurotransmitters such as monoamines, purines, amino acid, peptides, and nitric oxide was another step forward in understanding the micturition reflex. Experimental studies in animals suggested that substance P (SP), calcitonine gene-related peptide (CGRP), and neurokinins A and B may play a role in the micturition reflex by the activation of specific receptors (NK<sub>1</sub>, NK<sub>2</sub>). NK<sub>1</sub> receptor antagonists may inhibit sensorial bladder-spinal cord input, thus increasing the threshold for initiating micturition and increasing bladder capacity without blocking the voiding phase.

Recently oral aprepitant, an NK<sub>1</sub> receptor antagonist, has been reported to significantly decrease the average daily micturition episodes of urgency, although the urgency urinary incontinence and total urinary incontinence were not significantly decreased [4].

In this issue of *European Urology*, Martínez-García and coworkers reported the effects of cizolirtine citrate, a SP and CGRP release modulator at the spinal cord level, in 79