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Novel findings continue to challenge researchers and clinicians

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Abstract

2015 has seen advances in various bladder conditions. MicroRNAs might become therapeutic targets, the MAPP network characterized central neurological changes in chronic pelvic pain syndrome, and urologists were reminded to consider cognitive effects of long-term anticholinergics use. A study of obstetric vesicovaginal fistula repair shows how evidence-based research might improve public health in poorly resourced countries.

Despite urologists' best efforts to relieve bladder outlet obstruction, bothersome symptoms of urinary frequency, urgency and nocturia often persist. The reasons for this inadequacy in treatment are unclear, but an emerging hypothesis might provide an explanation: maybe pharmacological interventions are currently given too late, at a point when the bladder has already undergone substantial remodelling and drugs are ineffective.

Current management strategies used in the treatment of hypertension might provide a model to improve the treatment paradigm in bladder dysfunction¹. Both heart and bladder undergo repeated cycles of filling and contraction and respond to pathological pressure overload by developing hypertrophy and fibrosis, eventually resulting in dysfunction. In the bladder, as outlet resistance increases, distinct phases of decompensation occur, starting with inflammatory responses and smooth muscle hypertrophy, resulting in fibrosis². For hypertension, physicians are trained to identify symptoms early and begin therapy promptly in the hope of delaying life-threatening consequences of long-term high blood pressure. In patients with bladder dysfunction, better identifying prognostic factors related to bladder problems and intervening before reaching a point of no return might similarly be critical to improving patient outcomes.

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Competing interest statement

The authors declare no competing interests.

FURTHER INFORMATION

MAPP Network: <http://www.mappnetwork.org/>

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MicroRNAs (miRNAs) might be a resource for the discovery of such new prognostic factors and could also be targets for therapeutic intervention. A review by Koek *et al.*¹ published in 2015 summarizes common signalling pathways the role of miRNAs. These small, noncoding, single-stranded RNAs regulate gene expression by a post-transcriptional mechanism and have critical functions in cell proliferation, differentiation and death. In the bladder and the heart, miRNAs are involved in various signalling pathways activated in pathological smooth-muscle hypertrophy, hypoxia, the renin–angiotensin system, protein remodelling and fibrosis. For example, miR-199a-5p, which seems to be one of the key players upregulated in the bladder and heart during pathological pressure overload, contributes to increased urothelial permeability, smooth-muscle differentiation and hypertrophy. Another interesting miRNA is miR-29, which is downregulated in the heart and bladder during pathological pressure overload as a fibrotic response, reducing collagen expression and bladder wall stiffness.

Restoring or inhibiting expression of specific miRNAs could become a therapeutic strategy. Polymeric nanoparticles that deliver miRNAs effectively have already been explored in reducing fibrosis in cystic fibrosis and renal fibrosis. In addition, miRNAs circulate freely in the urine and can be collected noninvasively and in large quantities, possibly enabling their use as diagnostic or prognostic factors of bladder dysfunction. Intriguingly, the bladder is easily accessible for therapeutic drug instillation and could be the ideal site for exploration of miRNA-based treatment options.

Interestingly, the first miRNA profiling in the context of lower urinary tract dysfunction, which was already published in 2010, was performed to study bladder pain syndrome³. Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition characterized by pelvic pain associated with urinary urgency and frequency. Urological chronic pelvic pain syndrome (UCPPS) comprises a combination of pelvic disorders, including IC/BPS and chronic prostatitis/chronic pelvic pain syndrome, with poorly understood pathophysiology — central and peripheral disturbances in the processing of pain and viscerosensory signals are thought to be involved.

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network was created to study the pathophysiology and treatment options for patients with UCPPS ([MAPP Research Network](#)). As part of the Trans-MAPP neuroimaging study to characterize differences in brain activity and pathway connectivity in patients with UCPPS structural and resting functional MRI was used at five MAPP network sites across the USA. The most recent report arising from this study is particularly interesting. Woodworth *et al.*⁴ focused on microstructural changes in the brain of patients with UCPPS. Control groups of this study included healthy individuals, but also patients with irritable bowel syndrome (a common gastrointestinal pain disorder) to strengthen the study's comparisons and results. The investigators used detrusor tension imaging and track density imaging analysis techniques, concluding that patients with UCPPS have extensive microstructural changes within white matter areas of the brain that are responsible for the processing and integration of sensory information from pelvic areas. These alterations seemed specific to patients with UCPPS and were not observed in patients with irritable bowel syndrome. The direct clinical implications of these findings are not yet entirely clear; however, brain plasticity could be

related to symptom severity and pain duration, and might be a target for specific intervention in the future.

Through the MAPP Research Network, four landmark articles that use extensive anatomical and functional neuroimaging to establish a phenotype pattern of UCPPS have been published in the past year^{4–7}. Comprehensive evaluation of these results will enable clinicians to clearly recognize the implications of these costly, complex and technically challenging studies, and help to develop a clear understanding of how to use these data in patient phenotyping, diagnosis and management.

Unfortunately, current treatments offer limited effectiveness with considerable adverse effects, even when bladder dysfunction is appropriately evaluated and characterized. Antimuscarinic agents are the most commonly used oral therapeutics for bladder dysfunction associated with urgency, frequency and urge urinary incontinence, but these drugs have limited effectiveness and poor patient compliance. Antimuscarinics (a subcategory of anticholinergics) block the effect of acetylcholine at muscarinic receptors. Drugs with anticholinergic effects are found in a variety of medications, including antihistamines, tricyclic antidepressants and antipsychotics.

Findings published in 2015 indicate that cumulative exposure to anticholinergics might lead to cognitive impairment. Gray *et al.*⁸ reported on the cumulative use of anticholinergic medication and its association with the risk of dementia using a population-based prospective cohort of individuals 65 years of age. The investigators used pharmacy dispensing data to define cumulative anticholinergic exposure as total standardized daily doses (TSDD) prescribed over 10 years. Data on 3,434 patients were analysed and showed that 797 participants (23%) developed dementia (specifically, 637 participants developed Alzheimer disease) during a mean follow-up period of 7.3 years. The adjusted hazard ratio for developing dementia was 0.92 for 1–90 TSDD and increased with increasing cumulative anticholinergic use to a hazard ratio of 1.54 for >1,095 TSDD. The authors concluded that a sustained and increased risk of cognitive deficits with high cumulative use of anticholinergics exists, and suggest that an individual taking, for example, 5 mg oxybutynin daily is at greater risk of developing dementia.

This provocative comment should raise concerns among all clinicians managing patients with overactive bladder. We commonly prescribe anticholinergics over long periods of time (for example, in the treatment of neurogenic bladder) to manage persistent bladder problems and we need to be aware of the unintended adverse effects of these medications. Whether these negative effects are reversible or differ between different classes of antimuscarinics remains unclear and should be investigated in large randomized trials.

The final article of 2015 that we would like to highlight is the study by Barone *et al.*⁹, which has a direct clinical implication. In their prospective, open-label, controlled trial, the investigators randomized 524 women with simple obstetric vesicovaginal fistulas to 7 days versus 14 days of catheterization following fistula repair. Patients from eight hospitals across Africa treated by 17 surgeons were included. Results of 7-day bladder catheterization were not inferior to results of 14-day drainage, with no risk of significantly increasing fistula

breakdown, urinary retention or incontinence within 3 months following the repair. No standardization of surgical technique, anaesthesia, resources used or clinical care prior to randomization was performed, suggesting that the study outcomes can be generalized to all simple obstetric fistula repairs globally. Many consider obstetric vesicovaginal fistulas a historical concern restricted to developing countries, but, in Africa alone, 30,000–130,000 new fistulas are estimated to occur following a prolonged obstructed labour¹⁰. These women labour for days, experience ischaemic injuries to their pelvis, receive poorly skilled care during their delivery and are devastated by stillbirth and various forms of fistulas; eventually, they might be cast out by their families and communities. Any evidence-based intervention to improve fistula repair outcome, decrease hospital stay, cost of care and patient discomfort will have a tremendous effect on public health in the areas with highest rates of obstetric fistulas and poorest resources. The evidence provided by this important trial exemplifies a global approach to better care and is welcomed with enthusiasm by surgeons who treat fistulas.

In 2015, areas of new findings in various bladder-related conditions ranged from translation of pathogenetic signalling through pharmacological treatment to surgical repair. The discoveries continue to challenge researchers and clinicians alike to expand our understanding of the diverse set of disorders summarized as bladder dysfunction to provide best patient care.

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Key advances

- Similarities in pressure-overload-induced remodelling of the heart and bladder include changes in microRNA expression that influence tissue permeability, stiffness and smooth muscle differentiation, indicating novel therapeutic targets¹
- Results from a MAPP network study show that patients with urological chronic pelvic pain syndrome have extensive microstructural changes within brain white matter regions responsible for sensory information from pelvic areas⁴
- Findings that high cumulative use of anticholinergic drugs results in an increased risk of cognitive deficits and dementia should raise concerns among urologists prescribing these medications long-term for patients with overactive bladder⁸
- A study of obstetric vesicovaginal fistula repair in Africa shows that 7 day catheterization is not inferior to 14 day drainage, illustrating how evidence based research might have a tremendous effect on public health in areas of poorest resources⁹