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Overactive Bladder: Shortcomings of Current Diagnostic and Treatment Approaches and a New Etiological Paradigm

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Abstract

Aims: To examine the effectiveness of the current diagnostic and treatment approach of overactive bladder (OAB) and the relative impact of cognition on what is currently a bladder-centric condition. **Methods:** A review of the literature on OAB from the population to organ/brain level was conducted. The impact of age-induced bladder dysfunction via cognitive changes to sensory integration and attention control are discussed. **Results:** OAB uses bladder-centric terminology to represent a collection of symptoms with inconsistent and often unknown pathology. Proposed etiologies and therapeutic models for overactive bladder focus on the bladder organ, but evidence suggests that age-related degradation to inhibitory neural circuits and attentional switching mechanisms may enhance myogenic dysfunction or be implicated in idiopathic diagnoses. There is potential for cognitive-level interventions and research that may reduce the significant public health burden of OAB and related bladder dysfunctions. **Conclusions:** The influence of cognitive dysfunctions on bladder control emerges as a potentially substantial determinant of population OAB burden.

Introduction

Our population is aging and projections estimate that by 2030 there will be more adults over 65 than children under 10 for the first time in world history.[1] As people age, chronic diseases become more prevalent and often present simultaneously, with 62% of Americans over 65 having at least two chronic conditions.[2] Chronic diseases now account for over 87% of the disease burden in the over-60 population globally and are the most common causes of mortality.[3] The 21st century presents public health with the new challenge of accounting for the disproportionate ratio of life years to health years. Confronting the burden of disease in the aging population will prove to be an urgent consideration as the global over-60 population increases to two billion by 2050.[4]

Overactive bladder (OAB) is a common urological disorder consisting of urinary urgency accompanied by urgency incontinence, frequency or nocturia in which no precise cause can be identified.[5] OAB is highly prevalent and imposes significant burden to public health. In the U.S. adult population, the prevalence of experiencing OAB symptoms at least "sometimes" is 27.2% and 43.1% for men and women respectively.[6] It is predicted that 41.9 million people in the U.S. will be affected by OAB in 2020, up from 34 million in 2007.[7] It can impact people of any age and it is estimated to affect up to 50% of adults over 75.[6] The number of those suffering with OAB will rise as the aging population is increasing on a scale unparalleled in human history.

Bladder dysfunction is not only ubiquitous but can be exceedingly bothersome. It is estimated that 65% of people with OAB report their condition having an effect on their daily life.[8] Longitudinal studies of OAB suggest that it is a chronic condition and that symptom prevalence and severity tends to increase with age.[9,10] Increasing severity is also associated with decreasing health related quality of life (HRQoL) physical and mental health scores. [9,11] Bladder

dysfunction may account for population-level trends in HRQoL seen in aging adults. Those who suffer with OAB report feeling isolated and hopeless and have higher levels of fatigue, depression, anxiety, and suicidal ideation.[12-15] They are at risk for early retirement, unemployment, and comorbid conditions, threatening physical and economic public health.[16-18] The cost and impact on quality of life are comparable to that of other chronic diseases.[7,19] The effect of moderate bladder dysfunction on quality of life is similar to having diabetes, high blood pressure, or cancer; and the effect of severe bladder dysfunction is similar to having a heart attack or stroke.[20] There are also enormous societal costs associated with OAB. In 2020, annual per capita and total national costs of OAB are predicted to be $1,969 and $82.6 billion respectively, including the costs of related diagnostic tests, treatments, long-term care and sanitary products.[7] Indirect costs, including missed work due to OAB and disability also significantly impact the population. Yet despite extensive research, the etiology and natural history of OAB remain a mystery.[21]

Specific Aims

OAB has a major impact on public health, however it presents as a diverse symptomology with numerous etiologies and inconsistent treatment. This paper questions the ability of the term OAB to sufficiently capture the complexity and heterogeneity of this condition at the individual or population level from the perspective of clinical diagnosis, contributing factors and treatment. An inadequate term does not contribute to precise diagnosis, deterring thorough treatment. An inadequate term also obstructs appropriate research, specifically in the area of cognitive control. Current OAB theories revolve around the bladder organ, yet there is evidence that investing research into the relationship between the brain and the bladder could reveal pathways for intervention and ameliorating OAB symptoms.

Therefore, I suggest the following hypotheses:

Hypothesis 1: Defining OAB based on symptomology alone is an ineffective strategy for characterizing an idiopathic chronic condition.

Hypothesis 2: There is a failure of linkage between symptoms and function in the current OAB disease model. OAB etiology changes with age and overlaps with other urinary symptom complexes, suggesting an underlying age-related condition uncorrelated with symptoms.

Hypothesis 3: Overactivity of the bladder organ itself is augmented by the underactivity of cognitive control; suggesting OAB dysfunction does not originate solely from the bladder as the name implies.

A paradigm shift from bladder-centric to cognitive-inclusive brings into question the term OAB, the relative impact of neural control, the influence of aging, and proposed treatments. The results of this hypothesis paper will encourage future research into the effect of cognitive decline on attentional mechanisms affecting bladder control.

Background

Chronic Disease Perspective

Chronic diseases pose a novel threat to global health as lifestyles change and people live longer. Compared to infectious diseases, which historically represented the greatest danger to morbidity and mortality, chronic diseases tend to be a result of life-long lifestyle decisions, impacting an individual holistically on a multi-system level. Medicine has historically understood disease on the organ level, or smaller, assuming that organ systems function independently. However, the human body relies on system unison and larger networks to function. Aging physiology is affected by a broadening of the network of pathology in the body, confounded by multiple chronic conditions and decline in function.[22] Age is the greatest risk

factor for almost every major cause of morbidity and mortality in developed nations.[23] Diseases related to aging are complex, highly interrelated with other pathology, and originate on the larger system level.[24] Geriatric conditions do not adhere to the conventional organ and discipline boundaries of medicine, proving a challenge to diagnose and treat.[25]

This interrelatedness of aging conditions suggests that there are causal commonalities across the spectrum of those diseases. Geroscience is a new interdisciplinary field of research that seeks to determine the underlying mechanisms that link aging to chronic diseases to create prevention strategies for multiple diseases at once.[26] The name "overactive bladder" reflects the traditional but now antiquated medical tradition of pinpointing a specific organ as the hallmark of a condition. OAB is an oversimplified term assigned to a complex and multi-system problem. Most medicines target the bladder detrusor muscle, reducing the afferent signals it sends or paralyzing the muscle itself.[27] However, the symptoms cannot be neatly tied together and treatments are only effective for a minority of patients.[28,29] It is crucial to understand chronic conditions such as OAB on the system level, from a geroscience approach. I propose that the term OAB is still clouded by an outdated understanding of symptom linkage to function that excludes the possibility for a cognitive relationship. Thus, there is a need to examine OAB from an interprofessional perspective to comprehend the complexities of this chronic conditions.

History of Terminology

OAB is defined as a complex of symptoms with no presumed predisposing or causative pathological conditions or infections.[5] Although multiple pathologies increase risk of OAB, the link between symptoms and pathology is not clear.[30] Urinary urgency, incontinence, frequency and nocturia tend to present simultaneously.[31] This pattern of co-occurring symptoms involved in bladder control without a reliable biomarker led to creation of the term OAB to unify them under

one diagnosis. The term OAB has only come into popular use within the last couple decades; first appearing in the literature in 1989 and reaching popularity in 1997.[32,33] In 1998 the U.S. FDA approved medication for patient-reported OAB symptoms, when previously it could only be prescribed to dysfunction confirmed by urodynamics. Patients could then report their own symptoms and receive treatment without needing medical tests.[34] In 2002 the International Continence Society defined OAB as "urinary urgency with or without urgency urinary incontinence (UUI), usually accompanied by frequency and nocturia, in the absence of urinary tract infection (UTI) or other obvious pathology". Urgency is defined as "sudden, compelling desire to pass urine that is difficult to defer".[5] This development brought incontinence care into the realm of the primary care provider and helped raise public awareness of this traditionally neglected problem. At the same time, a number of unintended consequences also followed the use of this tidy OAB definition. It quickly oversimplified a complex constellation of symptoms. Pharmaceutical companies profited from the simplification of the problem by assigning easily understood medical solutions.[34] *In an attempt to understand and treat patients suffering from OAB symptoms, the creation of the term inadvertently reduced the need to understand the etiology of individual symptoms.*

The ICS definition uses vague terminology such as "with or without" and "usually" and fails to define what might constitute "other obvious pathology".[5] Throughout the years, the definition has been interpreted differently depending on the researcher.[30] Epidemiologic research specific to OAB was inconsistent before the ICS definition in 2002. Slight differences in interpretation and use of the definition have caused broad variations in study outcome. There are some controversies in the understanding of the ICS definitions. Nocturia is defined as waking at night "one or more times to void", preceded and followed by sleep.[5] Many experts believe that

one void at night should not be considered nocturia, and many studies therefore also use a definition of at least two voids.[8,18,35] Urgency is the subjective complaint of a "sudden compelling desire to pass urine that is difficult to defer" and many patients have trouble distinguishing this clinical symptom from normal urges.[36] There have been proven difficulties of understanding OAB symptoms through questionnaires, with people misinterpreting questions and answering differently in subsequent interviews.[37] Due to different definitions of symptoms, different study objectives, and different methods of measurements, research studies often get results that cannot be compared.[38] The EPIC study used the 2002 ICS definition of nocturia as at least one nocturnal void per night and found high prevalence (49% men; 55% women).[18] When nocturia was defined as two or more void per night, the prevalence rates were reduced substantially (21% men; 24% women).[18] The EpiLUTS survey used a definition with symptoms occurring "sometimes" and subsequently "often" and found overall OAB prevalence of 36% and 25% respectively.[39] Experts disagree on the definition of the OAB condition, and subsequently on the evaluation of patients and requirements for diagnosis.[40] Although there is an agreement that OAB is a chronic condition with inconsistent symptoms and no cure; there must also be a consensus on terms so as not to confuse future research and inhibit the public health response.[40] The definitions of any disease and disease process impact all aspects of patient care. How we define a disease frames the diagnosis requirements, proposed management, scale of outcomes measured, and research potential.

Methods

Several procedures were followed for the completion of this narrative review and hypothesis paper. Hypothesis formulation was generated from an extensive literature review to examine the gaps in the literature and direction of prospective research. The literature review was conducted using UConn Health Library database searches with keywords including "overactive bladder"

"incontinence" "urgency" "prevalence" "age" "quality of life" "health care-seeking" "brain or neural*bladder". Only English language papers were reviewed. The literature was analyzed using the software TagNotate, where each article was annotated using tags related to OAB experience and physiology. In total 124 tags were created to organize themes uncovered in literature (e.g. incontinence subtypes, lower urinary tract symptoms, study designs, etc.). The tags also labeled details within those topics (e.g. SUI, MUI, UUI; urgency, frequency, nocturia; longitudinal, meta-analysis, case-control, etc.) directly in the papers to be easily pulled up with critical sections highlighted. This process created a personalized database with literature easily accessible to clearly discern overarching themes and define the shortcomings of the available information. I communicated with experts in the urology, aging, and cognition fields to confirm I had the most up to date research and receive guidance on clinical perspectives. To elucidate my hypothesis goals, I created stratifications of OAB experience by age and of OAB compared to UAB. Relevant themes to stratify by were determined by available data from my review that best represented the condition. Analysis of the review results was done by drawing together information about history, prevalence, stratification, impact, assumed pathology, and making conclusions about areas of study that have yet to be understood.

Results

Hypothesis 1: Ineffectiveness of Characterizing OAB with Bladder-Centric Symptomology

Public health should focus attention toward improving health conditions of most at-risk populations. For OAB, aging adults represent a vulnerable population due to high prevalence and severity of co-morbid diseases and conditions among older adults with OAB and other bladder dysfunctions. Prevalence and severity tends to increase over time with OAB without incontinence tending to precede OAB with incontinence.[9,10] Those with OAB report worse

HRQoL compared with those without OAB.[9] OAB is unique in that it is not life-threatening but imposes an impact on mental and physical HRQoL similar to other life-threatening conditions.[41]

The current disease model of OAB leaves a large portion of the aging population untreated and at risk of poor health. Many older adults with OAB and incontinence do not seek help despite symptom severity.[42] Often they demonstrate a lack of understanding about symptoms and treatments or consider bladder symptoms to be a normal consequence of aging.[12,43,44] This lack of understanding leads to disappointment in treatment outcome.[44] Symptom bother also tends to be higher in patients who are uncertain about their urinary symptom etiology or disease course.[45] Holding this confused perspective about OAB and other chronic diseases paints it as inevitable, and incurable in the mind of the patient, reducing their likelihood to seek help.[37,44] Presently, only 66% of women with OAB think it is a medical condition, and far fewer know that there are treatments available.[46,47] Treatment-seeking patients are only representative of a fragment of the population who suffer from OAB, but of those who are diagnosed with OAB, 76% continue to live with untreated symptoms.[48] Although they could have benefited from treatment, the majority of OAB sufferers are isolated in determining their coping strategies and experience diminished QoL.[4949] It is crucial that older adults seek help for their condition.

Confusion about the symptom etiology is one impediment to effectively reducing disease burden with the current bladder-centric paradigm and can lead to harmful cultural ideas about the disease. Bladder dysfunction and incontinence are often perceived as a "retreat to infancy" and universal symptoms of social incompetence and disgust, promulgating stigma.[12,50,51]As a result, only 46% of those with OAB consult a doctor about their symptoms.[52] Different cultural ideas about OAB stigma lead to many of the disparities seen in health seeking behaviors.[53] If they do seek treatment, women wait on average 3.1 years before consulting a physician about OAB

symptoms.[49] Undiagnosed OAB, as a result of stigma and embarrassment, leaves many without an identity as a patient or an explanation for their behaviors, often resulting in even greater psychological costs.[12] OAB patients suffer without a known etiology, often encouraging self-blame and the idea that symptoms are a result of psychological weakness.[37] Submitting to the condition as an "old people disease" leads to poor QoL and various detrimental coping strategies, including withdrawal and resignation.[12] Shame related to OAB increases the number of older adults implementing coping mechanisms such as using sanitary protection, staying home from work, and avoiding family and friends to evade leakages and embarrassment.[37] These strategies often lead to isolation and depression, and may postpone necessary health care-seeking.[12,54]

A lack of clarity about OAB etiology coupled with the resulting cultural stigma makes treatment a complicated process for patients and their physicians. Reluctance of the patient to disclose their symptoms to their physician is an initial impediment to treatment. The gap between OAB symptomatology and healthcare-seeking behaviors poses a critical public health threat. If physicians then share their perspective that OAB is normal aging and not worth investigating as many do, even fewer OAB patients find useful treatment. Lack of information and support from medical professionals leads to undertreated populations.[44] Although OAB is not curable, treatment gives people an identity as a patient that helps normalize the condition.[12]

Despite the related stigma for OAB sufferers, physicians are nine times less likely to bring up bladder concerns than patients.[55] Studies show that physicians also insufficiently address the impact of OAB on QoL when discussing the condition with patients.[56] OAB patients are often dissatisfied with their care and many believe that their doctors do not take their experience seriously.[53] Although clinical dialogue regarding OAB is physician-centered, research shows that patient-centered communication (PCC) is correlated with more effective

management of OAB.[56] In 2001, the Institute of Medicine identified PCC as a key aspect of high-quality healthcare and it has since become an increasingly important part of the research and healthcare lexicon.[57] The movement towards PCC internationally will impact the way the medical world views OAB. Despite all the research, very few initiatives directly increase physician attention to lower urinary tract symptoms (LUTS).

Without reliable healthcare seeking, population prevalence of OAB can't be estimated from medical records, adding complexity to epidemiological studies. It is essential that these studies reveal the magnitude of the population burden, yet due to inconsistent research methods and study terms, the results differ broadly. Consequently, medical centers and epidemiologists only see "the tip of the urological iceberg," which is what makes it such an interesting and complicated topic.[58] Using bladder-centric terminology, therapeutic practices, and research might leave susceptible individuals without a course of prevention or remedial action. Living with a vague diagnosis of OAB and lack of a cure is associated with significant bother that increases with age.[52]

Hypothesis 2: Failure of Linkage of Symptoms to Function

Diagnosing techniques

Appropriate diagnoses are crucial for reducing population burden, but without a firm understanding of pathology attempting accurate and precise diagnoses may be ineffective. Bladder dysfunction can be diagnosed by invasive tests called urodynamics studies (UDS), but as a symptom complex, patients can identify themselves as having OAB thus forgoing the need to invest the time into an invasive diagnosis. Clinical algorithms for treating OAB use patient report to diagnose OAB and often reserve UDS for failures in treatments.[30] OAB is considered a problem with the detrusor muscle and UDS is a method for diagnosing detrusor overactivity

(DO). However, LUTS were recognized as poor predictors for urodynamic function long before the use of the term OAB.[59] Only 54-64% of patients with OAB have urodynamic results proving DO [60,61] Inversely only 82% of patients with DO have symptoms suggestive of OAB.[61] When DO is accurately identified as the source of OAB symptoms, the DO may not persist over time despite the persistence of symptoms.[62] The incidence of persistent DO after 5 years is only 57%.[62] OAB is a chronic condition, yet often follows a pattern of incidence and remission.[38]

Despite all the clinical focus on the bladder as the source of dysfunction, it often proves an unreliable witness to underlying OAB conditions. This phenomenon highlights the disparity between symptoms and function. It explains how challenging it can be to effectively treat OAB based on symptoms or proven dysfunction. A bladder-centric model of treating OAB is insufficient for understanding the multifactorial condition.

Therapies

Although available treatments for OAB patients have vastly improves over the last 50 years, none are entirely curative as underlying disease mechanisms remain mysterious. A limited understanding of OAB pathogenesis and how it uniquely presents in each patient makes prescribing treatment challenging. Drug companies stepped into this void of uncertainty and assigned drugs that aim to reduce symptom burden but fail to address the cause.[28] Effective treatment is determined through trial and error, leaving many patients dissatisfied and discouraged from continuing any treatment.[37] Only 56% of women feel their OAB medication is effective.[44] Most people only spend a few months taking OAB medication before giving up on them, and some even switch medication many times before quitting.[37]

In the absence of reliable UDS testing, OAB patients are often incorrectly assigned anticholinergics, particularly antimuscarinics. Antimuscarinics bind to receptors on the bladder

muscle in order to block the input sent to contract the muscle.[27] These drugs reduce the intensity of involuntary bladder contractions that can cause urgency and leakage. Unfortunately, muscarinic receptors exist all throughout the body and many antimuscarinic drugs are non-specific, affecting other processes and causing bothersome side effects such as dry mouth and constipation.[30] These drugs may promote more harm than good to many patients, especially among older populations. The treatment of older adults with bladder antimuscarinics is also being called into question due to a significant association with cognitive decline and an increased risk of cardiovascular disease and mortality.[63,64,65] Anticholinergics are the most common prescribed medication for OAB, but only perform modestly better than placebos.[28]

Medicinal therapy is more effective when initiated in conjunction with behavioral interventions such as fluid management, avoidance of caffeine and alcohol, bladder retraining, and double voiding and should be used as a first line of treatment.[30,66] Patients using behavioral modifications report equal or superior QoL and are less bothered by their symptoms than patients using standard care.[30] One study showed that among those using behavioral management strategies UI severity decreased by 61% after two years while the control group severity increased by 184%.[67]

Therapies which focus solely on myogenic dysfunction of the lower urinary tract can result in inadequate and unreliable outcomes since OAB symptoms do not indicate one single disease. The lack of consistent pathology, symptom presentation, and treatment for a condition under a single diagnosis for all patients may promote frustration. Frequency, urgency, urge incontinence, and nocturia are caused by numerous pathologies.[28] Rather than lumping together a group of symptoms, individual symptoms should be investigated separately to understand their individual risk factors and underlying pathophysiology. Also, encouraging the opinion that

symptoms, however mild, are part of a single medical syndrome risks overmedicalization. Approaching OAB examinations and research from different angles will provide insight into the multifactorial nature of this chronic condition. The relationships between risk factors, neural pathways and bladder outcomes are only just beginning to be understood and will reduce future OAB public health burden. Moving toward effective treatment of symptoms through recognizing individual patient history and pathologic conditions will require abandoning the antiquated concept of an OAB symptom complex or a bladder-centric condition.

Stratifications to Represent Failure of Linkage of Symptoms to Function

Numerous studies have examined the experience of OAB on the individual and population level, yet the etiology remains complex and not well understood. The suggestion of a single clinical entity for OAB symptoms implies that there is a singular etiology and a uniform treatment when in fact similar symptoms may present bother as a result of different disease processes. UI and OAB, along with other LUTS, are associated with numerous comorbidities, suggesting shared etiologies and further complicating the relationship between function and symptoms.[68] There is also agreement among experts that the pathophysiology of OAB is incompletely characterized because of the diversity of experiences across the patient spectrum.[40] Some experts suggest that OAB experiences should be phenotyped, but that does not come without its difficulties.[69] To further illustrate the failure of the term OAB to represent a singular consistent entity and question the focus on the bladder organ, we can examine the experience stratified by age (Table 1) as well as compared to similar diagnoses (Table 2).

(1) Age Stratification

The age-dependent nature of OAB suggests that bladder dysfunction and related comorbidities are determined by aging. In older patients, the condition becomes a geriatric

syndrome; having multifactorial etiology and substantially impacting quality of life.[25] An association of storage, voiding, and incontinence symptoms with conditions increasingly common in older adults, including diabetes, hypertension, depression, and constipation, further influences clinical presentation and outcomes, compounding the impact of urinary symptoms on life quality in older adults.[70] Aging is characterized by general degradation in homeostatic mechanisms in the body.[25] Homeostasis is the maintenance of numerous mechanisms with an aggregate effect of sustaining consistency in physiologic conditions regardless of external influences. As homeostatic regulation is impaired with aging, the capacity to respond appropriately to various challenges is diminished.[25] It can be a challenge to determine the relative effect of aging in older populations when considering the increasing impact of chronic conditions as both may share biological pathways.[26] In order to relate symptoms to dysfunction in an aging patient, there must be a causal understanding of how aging impacts bladder control. The term OAB makes this connection difficult, implying that the dysfunction resulting in the symptoms is DO rather than underactive control of the brain mechanisms that maintain homeostasis in healthy adults. Evidence from the age-dependent nature and neural control of OAB suggests that the current therapeutic model and terminology highlighting detrusor over activity overlooks the important function of cognitive control, conscious or unconscious. Understanding how physiological mechanisms change with age is critical to the development of appropriate diagnoses and treatments, particularly in today's rapidly aging society. The representation of OAB across the spectrum of age in Table 1 reveals the failure of the term OAB to represent the varying etiologies and symptom outcomes.

Table 1: Stratification of OAB Prevalence, Comorbidity, Bother, and Health Care-Seeking by Age

Age	Population Prevalence of OAB from EPIC[18] (extrapolated from graphs)	Population Prevalence of OAB from EpiLUTS[6]	Population Prevalence of OAB from NOBLE[71] (extrapolated from graphs)	Population Prevalence Comorbidities[72]	Population Prevalence of Bother from Urgency (extrapolated from graphs)	Prevalence of Health Care-Seeking in OAB Population[52]
40-44	• 8% men • 11% women	Sometimes • 17% men • 37% women Usually • 8% men • 26% women	• 12-18% men 10-22% women	• 18% have multiple chronic conditions	Men 30-49[73] • Small bother: 17% • Moderate bother: 4% • Severe bother: 1% Women 40-50[74] • Any bother: 28% • Moderate-severe: 10.6%	• 24-33% men • 27-36% women
45-64	• 8-15% men • 11-16% women	Sometimes • 21-34% men • 41-47% women Usually • 10-20% men • 29-37% women	• 18-26% men • 22-23% women	• 51% have multiple chronic conditions	Men 50-69[73] • Small bother: 32% • Moderate bother: 9% • Severe bother: 3% Women 50-60[74] • Any bother: 42% • Moderate-severe:15%	• 33-46% men • 36-52% women
>65	• 16-23% men • 15-20% women	Sometimes • 34-50% men • 45-51% women Usually • 20-35% men • 36-43% women	• 30-35% men • 30-32% women	• 82% have multiple chronic conditions	Men 70-89[73] • Small bother: 40% • Moderate bother: 14% • Severe bother: 6% Women 60-80+[74] • Any bother: 46-59% • Moderate-severe:19-31%	• 58-62% men • 54-57% women

OAB=Overactive bladder, EPIC= European Prospective Investigation into Cancer and Nutrition, EpiLUTS= Epidemiology of Lower Urinary Tract Symptoms, NOBLE= The National Overactive Bladder Evaluation

Table 1 provides a description of studies that examine OAB by age. Most OAB studies do not stratify by comparable age groups, use consistent definitions, or research similar populations. Therefore, stratification is limited to a small number of studies, but trends can still be seen across the existing data. EPIC, EpiLUTS, and NOBLE studies were chosen for prevalence stratification by age for their large population size, ICS definition, and relatively comparable age groups. These studies show how prevalence increases with age in both genders. These aging populations also experience comorbidities that can impact HRQoL and influence the OAB disease experience. Related to an increasing severity, health care-seeking also increases among those with OAB with age. These stratifications represent a few elements of the OAB experience that diversify the diagnosis. Older adults experience a geriatric syndrome, related to other chronic conditions, with a potential underlying age-related cause.

There are also stratifications that aren't represented in Table 1. While symptom bother was reported by 54% of those with OAB, subgroups within the OAB population experience symptom severity and bother at widely varying degrees.[75] Those with OAB-wet (with UI) experience more bother than those with OAB-dry.[75] Further, although women are more likely to experience UI, significantly more men with UI reported bother than women with UI.[75] UI is presented differently by age as well, with older groups experiencing more urge urinary incontinence (UUI) and younger groups experiencing more stress urinary incontinence (SUI).[76] There are also race and ethnic differences in prevalence and health beliefs related to LUTS and OAB that determine burden and healthcare seeking.[44] Healthcare seeking is confounded by factors such as social influences and connectivity to others with similar symptoms that is

associated with both age and symptom severity.[77] It is also not rare that studies contradict each other in their results.

(2) Stratification by Condition

Just as age stratification demonstrates the lack of a single pathology and undermines the use of the term OAB, comparing OAB to another bladder symptom complex, UAB (underactive bladder), exposes the potential for a unifying pathology external to the bladder influencing the expression of symptoms. The similarities shown in Table 2 between OAB and UAB demonstrate how the brain-bladder axis effects bladder dysfunction. While OAB is the more widely acknowledged of the two, both have an unknown or inconsistent etiology and arise from an impairment of the micturition reflex, whether on the myogenic or neurogenic level. An impaired sensory integration and therefore compromised neural control mechanism could account for both directions of dysfunctional control (over or under). I hypothesize that overactive bladder is associated with underactive neural control of the bladder and suggest the brain might be a better witness to the source of urinary dysfunction than the bladder.

Table 2. Comparison of OAB and UAB

	OAB	Similarities	UAB

Dysfunction	• Lack of neural inhibition[78]
	• Detrusor overactivity in some cases[61]
	• May be caused by increased efferent signals from the brain to the bladder[78]
	• May be caused by increased afferent signals from the bladder to the brain[79,80]
		• Associated with aging[30,81]
		• Unknown/inconsistent/idiopathic etiology[30,82]
		• Impairment of the micturition reflex[78]
		  ○ Myogenic
		  ▪ Age-related bladder changes[83]
		  ▪ Abnormalities of the urothelium, interstitial cells, ganglia and smooth muscle cells that activate afferent nerve fibers[84,85]
		  ○ Neurogenic
		  ▪ Nervous system dysfunction[86,87]
			• Detrusor underactivity in some cases[90]
			• May be caused by decreased efferent signals from the brain to the bladder[85,91]
			• Can be due to chronic obstructive or neurologic damage[92]
			• May be cause by decreased sensitivity of the bladder[91]
			• May be caused by decreased afferent signals from the bladder to the brain[79,,]

		▪ Failure of integration or processing in neural circuits[78] • Dysfunction of neural bladder control mechanisms[88] • Dysfunction of attentional switching mechanisms[89]	
Symptoms	• Urgency with or without urge incontinence, usually with increased frequency and nocturia[5] • May have overactive detrusor[61] • Distinguished by urgency[5]	• Symptom complexes with shared symptoms including frequency, urgency, and nocturia and can include incontinence [5,82] • Diminished sense of when the bladder is full • decreased control over bladder[87] • Both can occur together—detrusor hyperreflexia with impaired contractility (DHIC) [93] OAB may progress to UAB[87] • Symptoms and severity of UAB vary from one person to another, and the course of the disease is often unpredictable[38, 87]	• A symptom complex suggestive of detrusor underactivity which is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream [82] • Diminished sense of when the bladder is full[94] • May have high residual urine[92] • May have underactive detrusor [90] • No single distinguishing symptom[81]
Treatment	Pelvic floor exercises, delayed voiding, neuromodulation, anti-muscarinics[30]	Scheduled voiding, bladder diary, dietary changes[30,92]	Double voiding, catheterization, Surgery, muscarinic receptor agonists[92]
Experience	• Abundance of research studies[30]	• Challenging to diagnose and treat o Lack of objective tests and biomarkers[5,82] ▪ Does not correlate well with urodynamics [61,90] o Lack of consensus on terms [40,95] o Therapeutic measures are largely palliative in nature and associated with significant morbidities. [30,92] o Often remains undetected and undertreated [58] o Mechanisms not well-understood [87] • Related to stigma, embarrassment, and reduced QoL[12,96] • Age dependent [30,92] • Affects both genders[18,96] • Chronic condition [9, 87]	• Shortage of studies[82]

		• Risk factors and common comorbidities: MS, spinal cord injury, diabetes, Parkinson's disease, stroke, dementia, impaired mobility, UTIs, bladder outlet obstruction, smoking and obesity [30,97]	

OAB=Overactive Bladder, UAB=Underactive Bladder

Hypothesis 3: Overactivity of the Bladder and Underactivity of the Brain

Age-Related Changes in Bladder Tissues

Shifting away from a bladder-centric view of OAB does not mean the rejection of evidence signifying age-related bladder changes. OAB has been associated with observable alterations to tissues and responsivity as the bladder ages. These changes, including those in the urothelium, neurotransmitters and receptors, and inflammation levels have all been implicated as the source of the age-dependent distribution of OAB.[84] First, an increase in collagen content resulting in urinary fibrosis may be responsible for the decreased bladder compliance seen with aging.[97] Further, the urothelium is a complex organ that receives and transmits information about the bladder.[98] It is possible that age-related reductions in neurotransmitters released from bladder nerves, including ACh and ATP, might be responsible in part for OAB in aging adults.[99] There are also changes in muscarinic receptors in the bladder associated with normal aging that might impact bladder function.[100] Inflammation is a new field of research, and elevated inflammation biomarkers in older adults might be related to overactive bladder.[84] Innervation of the bladder decreases with age in those with OAB, however there is no evidence of declines in detrusor smooth muscle contractility or excitability as people age. [101] These alterations in the bladder tissues attributable to age might affect how appropriately the bladder responds to normal efferent signals or enhance the effect of abnormal signals.

Normal Bladder Reflex Physiology

It is helpful to move away from a bladder-centric model of OAB to fully understand the basis for disease. There are impairments to central neural processing that can amplify the age-related dysfunctions of the bladder and sensory systems. The normal physiology of the brain-bladder axis is complex and not fully understood, but existing evidence suggests that OAB may be a result of underactive control more than overactivity of the bladder. Consistent bladder control is a result of neural integration of somatic stimulation, autonomic reflexes and high-level control and decision-making mechanisms about when and where to void.[78] The normal physiology of the bladder is rooted in the neural control of the spinobulbospinal voiding reflex responsible for switching the system between storage and voiding.[102] The lower urinary tract is constantly monitored and modulated by the brain in response to afferent information from bladder wall tension.[103] As the bladder fills in the storage phase, the brainstem's periaqueductal gray (PAG) receives afferent signals.[78] The PAG sends signals to the pontine micturition center (PMC) or "Barrington's Nucleus", which relaxes the urethral sphincter and causes an involuntary void.[78]

Automatic relaxation of the urethral sphincter is speculated to be controlled by three high-level circuits that conduct sensory, motor, emotional, and cognitive processing to reserve a voiding behavior for a safe, socially acceptable, and convenient time and place.[78,104] The micturition reflex and control circuits are outlined in Figure 1. The frontal circuit (1) includes the regions includes the insula, thalamus, lateral prefrontal cortex (lPFC), and medial prefrontal cortex (mPFC) and is the target of most ascending signals from the PAG.[78] [78] Sensations from the bladder are registered in the insula, where the sensory information is put into context.[78] With the goal of maintaining homeostasis, contextualized information from the insula is then used to make the decision to void or to continue storing.[105] The midcingulate circuit (2) includes the

supplementary motor area (SMA) and dorsal anterior cingulate cortex (dACC) and serves as a secondary process in cases of failure by the frontal circuit.[78] The ACC determines how to react to visceral signals from the bladder depending on the situation.[103] The dACC triggers activation of the SMA to activate muscles of the pelvic floor and urethreal sphincter.[105] The subcortical circuit (3) involves the hippocampal and paralimbic regions and serves as a third reinforcement against incontinence. This circuit evaluates the safety of the voiding behavior and influences voiding decision-making.[103]

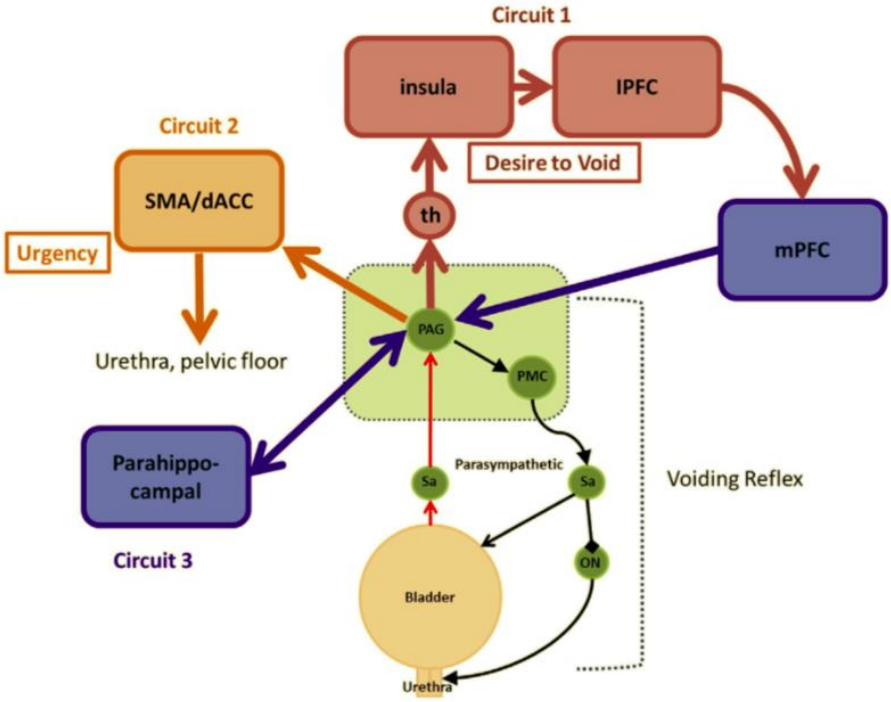

Figure 1. Model of brain-bladder control. PAG= Periaqueductal Grey, dACC= dorsal anterior cingulate cortex, lPFC=lateral prefrontal cortex, mPFC=medial prefrontal cortex, ON=Onuf nucleus, Sa= sacral cord, SMA= supplementary motor area, th=thalamus. From de Groat WC, Griffiths D, Yoshimura N. Neural control of the lower urinary tract. Compr Physiol 2015;5(1):327–96 [78]

Age-Related Changes in Neural Control

Adults without OAB can maintain continence through these inhibitory controls and make calm decisions about when to void. The dysfunction of these inhibitions, or the underactivity of control is what this paper proposes to influence the cause of OAB symptoms. OAB patients exhibit abnormal connections between inhibitory circuits, recruiting accessory circuits involving the parieto-temporal lobes, parahippocampal gyrus, and cerebellum.[106] Irrespective of the bladder, there are differences in motor and sensory regions (precentral and postcentral gyrus) as well as attention (inferior parietal) and decision-making regions (inferior and superior frontal gyrus) between those with and without OAB.[107]

The overall influence of age on the brain is a general decrease of response in all areas, potentially responsible for the reduced sensory feedback required for bladder control.[108] Brain responses differ in old and young individuals with OAB despite similar symptoms, reiterating the earlier point of inconsistent etiology under the same term and exemplifying the potential for inhibition interruption in older adults.[108] When younger adults experience urgency, there are reduced responses at smaller bladder volumes and exaggerated responses at high volumes. In older adults, small volumes elicit stronger responses and more modest responses at large volumes.[108] Also, white matter hyperintensities (WMH) are associated with aging, cognitive impairments and incontinence and might be responsible for decreasing neural connectivity hindering inhibition circuits.[108]

The brain normally has the ability to switch attention to address the most immediate concern or threat to safety. Until an alert from the bladder that it is getting full, attention may not be focused on the bladder, instead fixing on more pressing matters. There is existing evidence that suggests that attention is a crucial element of age-related decline in cognitive control of the bladder. In normal physiology, PMC innervates the bladder neurons as well as the locus

coeruleus (LC), which in turn activates the cortex increasing arousal to stimuli and shifting attention.[89] Functional MRI studies have demonstrated that the orbitofrontal cortex, involved in cognitive processing and decision making, is increasingly activated in those with normal bladder control, but weak among those with OAB regardless of detrusor activity.[109] Additionally, emotional interference in the limbic system might also be implicated in attentional switching. The insula, ACC, and mPFC become less activated and signals in the frontal and midcingulate circuits less substantial as people age, reducing the ability to maintain continence regardless of OAB diagnosis.[110] In subjects with OAB, fMRI studies show there is increased activation in the limbic cortex including the ACC and insula associated with urgency suggesting that urgency promotes an increased emotional response in those with OAB.[109,111] The overwhelming emotional conflict of potential social embarrassment due to leakage can impair inhibition processes in those with OAB.[112] Increased emotional response might reduce the ability to switch focus away from the troubling sensation of a filling bladder, promoting urgency.

Beyond the visceral substantiation, the hypothesis that overactive bladder is primarily modulated by underactive cognitive control is exemplified by empirical evidence. Older adults have a harder time multitasking, disengaging from distractions, and switching between focuses which may be potentially related to the neural integration dysfunctions we see in those with OAB.[113] Urgency can be influenced by circumstances, and often plays tricks on OAB sufferers, determined by the immediacy of finding a bathroom or having limited competing distractions, not necessarily signaling a full bladder.[12] Those with OAB and incontinence cite common triggers such as putting the house key in the door and undoing pants in preparation for using the bathroom that often prompt urgency and leakages.[37]

These triggers highlight the influence of inappropriate attentional switching, lack of conscious control and indicate the influence of what can be called the "forgetful bladder". The "forgetful bladder" is part of a complex interaction of aging bladder tissues, sensory networks, neural integrations and cognitive attentional abilities that may account for a lack or excess of attention as a result of bladder filling. The cognitive ability to forget a sensation is evolutionarily beneficial to maintain homeostasis and can allocate appropriate attention to the most pressing concern, but any imbalance could result in the abnormal storage and voiding symptoms categorized as OAB.

Discussion

This thesis is an attempt to comprehensively summarize the current literature describing the condition of OAB and how the sole focus on the bladder is a detriment to public health. OAB is defined as a condition with no known underlying condition so attempting to understand a potential cause is part of the effort to decrease disease burden. There is neither established natural history nor causal understanding of OAB, both of which are vital for effective public health prevention and control.[114] Recent years have seen the major increase in available therapies for OAB, but none are entirely curative. This situation could be because most research has focused on the bladder organ as the source of dysfunction. With appropriate causal understanding and more accurate diagnoses, more focused treatments may be assigned.

The proposal to invest research into the cognitive control of the bladder is a result of a literature review and the determination of gaps in current knowledge. Piecing together literature that approaches OAB from many different angles brought me to the synthesis of my hypothesis that the urgency sensation that is a hallmark of OAB may be a product of the brain's diminished ability to administer appropriate attentional focus to physiological changes as a result of aging.

These attentional errors related to both aging and OAB may be compounded by age-related changes at the bladder level. There may be heightened amount of sensory information being sent to the brain encouraging the higher processes to immediately seek a place to void at lower volumes or the decreased sensitivity to the sensory information being sent from the bladder producing an insufficient reaction to the filling bladder until urgency is the only option (cite both). The underactivity of cognitive control of the bladder may also prove to be the dysfunction influencing idiopathic OAB, UAB, or other urinary control symptoms.

The available literature is written from a variety of professional perspectives including epidemiological, clinical, and experimental. Examining all of it together highlights the need for future research to merge disciplinary silos. Chronic diseases like OAB affect the individual across the spectrum of the social-ecological model: genetic and lifestyle risk factors can generate numerous dysfunctions that may interact to present a variety of symptoms, interpersonal relationships with health care providers may determine treatments, and societal norms may influence stigma and care-seeking behaviors. This hypothesis paper attempts to emphasize how interprofessional research may reveal OAB dysfunction and an effort was made to include research taking diverse approaches. However, this broad goal of understanding all angles may also be a limitation, as the review could not be systematically focused around a single element of OAB literature.

Conclusion

Today's aging population is continually increasing the number at risk for chronic conditions. OAB is a common condition that poses a considerable threat to quality of life, but few effective therapeutic measures are available. Advancing age is implicated as the greatest risk factor for incidence and severity of OAB, and special attention should be paid to the bladder

symptoms of the aging population. This thesis summarizes how OAB is a symptom complex with vague terminology representing a variety of co-occurring LUTS. By synthesizing the literature, this paper aims to illuminate how the bladder-centric nature of OAB terms is misleading. The first hypothesis was that this classification of OAB negatively impacts public health. Secondly, this review hypothesized that there is a potential for underlying age-related conditions separate from the bladder. Remarking on the failure of linkage from symptoms to function, this hypothesis is expressed by stratifying prevalence and experience by age and displaying similarities across bladder control conditions. When OAB is compared to UAB, sensory integration and control malfunction arises as a commonality between the two conditions, accounting for the unique symptoms of each complex. The bladder is part of a complex network involving neural control systems that are affected by age. The analysis of existing research leads to the third hypothesis that the cognitive and attentional deficits of sensory integration in an aging brain directly impact the overactive bladder. Information synthesized in this thesis suggests that a more thorough understanding of the attentional mechanisms could encourage new management strategies.

Investment into research on cognition and bladder control would require a paradigm switch from a bladder-centric view of OAB to include the possibility for neural integration dysfunction. The fact that at least half of urgency and leakage episodes vanish when using mindful urge suppression strategies alone is convincing evidence for the power of the brain over the bladder and suggests that cognitive circuits are a useful target for OAB therapies.[115] Future research should describe the relative contributions of motor, sensory, biomechanical, and cognitive dysfunctions to bladder function associated with aging. To understand the effect of emotional or cognitive function on urgency and bladder dysfunction researchers should combine

brain-scanning and urodynamic practices while performing distracting or emotional tasks. If cognitive function is found to be substantially linked to urgency in older adults, researchers can assume that bladder sensations might be sufficiently distracting to hinder performance of previously achievable tasks such as driving.

Public health professionals can advocate for this perspective change as it might result in more helpful diagnosing techniques when patient history suggests age-related cognitive decline, thus reducing the population suffering without a cure for OAB. Recognizing the failure of the term OAB to represent dysfunction and improve health, and subsequently investigating the role of cognition in bladder control could reduce chronic disease burden in the older adult population, improving health-years as life-years are continuously extended.

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