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Is there an increased risk of delirium among patients with overactive bladder treated with newer anticholinergic medication compared to a beta-3 agonist?

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ABSTRACT

Objective

To determine if there is an increased risk of delirium among patients with overactive bladder (OAB) started on anticholinergic medication compared to beta-3 agonist.

Methods

We conducted a population-based, retrospective, matched weight cohort study using administrative data from Ontario, Canada from January 2016 until March 2020. We matched 13865 new users of Oxybutynin to 33097 new users of newer anticholinergic medications (Solifenacin, Tolterodine, Trospium, Darifenacin and Fesoterodine), and to 56062 new users of beta-3 agonist medication (Mirabegron); all of the included medications are only used for the treatment of OAB. Matching weights (an extension of the propensity score weighting) were used to balance the three exposure groups based on 83 measured indicators of baseline health, comorbidity, medication usage and health care utilization. The primary exposure was the class of OAB medication (Oxybutynin, Newer anticholinergics, and Beta-3 agonist). The primary outcome was delirium using a validated administrative data definition. Logistic regression, and proportional hazards analysis were used to assess outcomes at 30 days, and during continuous use of the medications.

Results

The median (IQR) duration of continuous usage was 113 (30-380) days for Beta-3 agonist, 30 (28-72) days for Oxybutynin, and 62 (30-239) days for the newer anticholinergics. There was no increased risk of delirium in primary analysis among Oxybutynin and newer anticholinergics drug users compared to beta-3 agonist at the 30 days observational window (odds ratio 1.28, 95% CI 0.84-1.96, p=0.25 for Oxybutynin and OR 0.92, 95% CI 0.58-1.46, p=0.73 for newer anticholinergics). The secondary analysis accounting for the period of continuous use showed a small but significant increased risk of delirium with the use of newer anticholinergics drugs compared to beta-3 agonist (HR 1.13, 95% CI 1.02-1.26 for newer anticholinergics).

Conclusions

The use of anticholinergic medications among patients with OAB was not associated with a significantly increased risk of delirium compared to beta-3 agonist users at 30 days; however, the risk is slightly increased with continuous usage of newer anticholinergic medications.

Keywords

Overactive Bladder, Delirium, Anticholinergics, Population-based.

Summary for Lay Audience

Overactive bladder (urgency with or without incontinence, frequency and nocturia) is a common condition in 10-15% of the population with many bladder medications being used to control this condition. These medications act on the action of a brain chemical known as Acetylcholine. Recent studies suggest long term use of these medications may cause cognitive decline and dementia. Annually, 25,000 Canadians are diagnosed with dementia with an annual cost of over $12 billion spent to care for those living with dementia.

The currently approved anticholinergic medications used in Canada can be divided into two main categories: (1) Oxybutynin (the first medication approved for OAB in the 1970's); and (2) more recent medications (Tolterodine, Solifenacin, Darifenacin, Fesoterodine and Trospium).

The ODPRN (Ontario Drug Policy Research Network) final consolidation report from March 2016 recommended Oxybuytnin as the initial treatment for patients with overactive bladder syndrome while reserving the newer medications for intolerance or failure of Oxybutynin, and requiring a limited use code for coverage by the Ontario Drug Plan. Therefore Oxybutynin continues to be the sole first-line treatment option available on this plan.

This policy may be depriving people from medication that might be better tolerated, equally or more effective, and possibly safer than Oxybutynin, a very old overactive bladder agent, which has clearly been associated with dementia and cognitive impairment versus newer drugs like Fesoterodine or Mirabegron.

Older overactive bladder medications are linked to new onset of dementia and there are case reports reporting delirium associated with anticholinergic medications. We conducted this study to assess the actual risk of delirium and to see if these results might change the policy of general OAB drug use implemented by Ontario Drug Benefit. We did not demonstrate a risk of delirium associated with anticholinergics compared to the only beta-3 agonist (Mirabegron,) in the 30 days period, however during longer use we found an increased risk of delirium is associated with newer anticholinergic medications compared to mirabegron.

Our results confirm that anticholinergics should be used with caution in elderly people and those with an underlying risk of delirium.

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LIST OF ABBREVIATIONS

AA	:	Anticholinergic activity.
Abt	:	Antibiotic
Acnew	:	Anticholinergics Newer.
Acoxy	:	Anticholinergic Oxybutynin.
ADS	:	The Anticholinergic Drug Scale.
Anc	:	Anticonvulsants
Aoa	:	Angiotensin converting enzyme inhibitors or Angiotensin receptor blockers.
ARS	:	The Anticholinergics Risk Scale.
Aur	:	Acute urinary retention.
Baa	:	Beta Agonist inhaler.
Bbl	:	Beta- adrenergic antagonists.
Bez	:	Benzodiazepine.
BoNT-A	:	Intra-detrusor onabotulinumtoxinA injections.
BP	:	Blood Pressure
BPH	:	Benign prostatic hyperplasia.
CAM	:	Confusion Assessment Method.
Carcath	:	Cardiac catheterization
Ccb	:	Calcium channel blocker.
Ccs	:	Glucocorticoids.
ChIs	:	Cholinesterase inhibitors.
CHO	:	Cholinesterase inhibitors
CIHI DAD	:	Canadian Institute for Health Information Discharge Abstract Database.
CIHI SDS	:	Canadian Institute for Health Information Same Day Surgery.
DBI	:	Drug Burden Index.
Dep	:	Anti-depressants.
DSM-5	:	Diagnostic and Statistical Manual of Mental Disorders (Fifth edition).
Echo	:	Echocardiography.
Edcount	:	Number of any ER visits.
Entry	:	Year of cohort entry.
Gpcount	:	General practitioner count.
Gpmhcount	:	General Practitioner mental health visit.
Gyncount	:	Gynecology visits.

Holter	**:**	Holter monitoring.
Hospcount	**:**	Number of any hospitalizations.
HR	**:**	Heart Rate
ICD-10	**:**	International Statistical Classification of Disease and Related Health Problems, Tenth Revision from World Health Organization.
ICS	**:**	The International Continence Society.
IKN	**:**	ICES key number.
Inquint	**:**	Socioeconomic status- Neighborhood Income Quintile.
IQR	**:**	Interquartile range.
Itc	**:**	Long-term care.
KSD	**:**	Potassium sparing diuretics.
LUTS	**:**	Lower urinary tract symptoms.
Mood	**:**	Mood stabilizers.
Ms	**:**	Multiple Sclerosis.
Nab	**:**	nonspecific alpha blockers
NACRS	**:**	National Ambulatory Care Reporting System
Narc	**:**	Narcotics.
Ndins	**:**	Number of unique DINs (Drug Identification Number).
Neurocount	**:**	Neurologist visits.
Nsd	**:**	non-potassium sparing diuretics.
OAB	**:**	Overactive bladder.
Oap	**:**	other antipsychotics.
ODB	**:**	Ontario Drug Benefit database.
OHIP	**:**	Ontario Health Insurance Plan.
Otd	**:**	other antidepressants.
Pab	**:**	prostate specific alpha blocker.
Park	**:**	Parkinson's drugs.
PFMT	**:**	Pelvic floor muscle training.
Priormh	**:**	Prior non-depression mental health
PSA	**:**	Prostatic specific antigen.
Psycount	**:**	Psychiatry visits.
PTNS	**:**	Posterior tibial nerve stimulation
PVR	**:**	Post-void residual.

RPDB	**:**	Registered Person Data Base.
SAA	**:**	Serum anticholinergic activity.
Sce	**:**	smoking cessation aid.
SCI	**:**	Spinal cord injury.
SD	**:**	Standard deviation.
SNS	**:**	Sacral Neuromodulation.
Sta	**:**	statins.
Stress	**:**	Cardiac stress test.
TCA	**:**	Tricyclic antidepressant.
TURP	**:**	Transurethral resection of prostate.
Urocount	**:**	Urology visits.
UUI	**:**	Urgency Urinary Incontinence.

Introduction

Understanding Overactive Bladder

Lower urinary tract symptom (LUTS) terminology was first introduced in 1994 [1]. The International Continence Society (ICS) defines LUTS as symptoms attributed to urinary storage (increased daytime frequency, nocturia of at least one episode/night, urgency and urgency incontinence), voiding (slow or intermittent stream during micturition, splitting or spraying of the urine stream, straining, hesitation, terminal dribble) and postmicturition (feeling of incomplete emptying and postmicturition dribble) [2]. LUTS are a common health problem experienced by adults with prevalence increasing with age [3]. Overactive bladder (OAB) is a storage subset of LUTS defined by ICS as urgency with or without urgency urinary incontinence (UUI), commonly associated with frequency and nocturia [2]. The ICS also acknowledged within the definition that these symptoms are usually suggestive of urodynamically demonstrable detrusor overactivity but can be due to other forms of urethravesical dysfunction [2].

The Lower Urinary tract

Neurotransmission

Detrusor muscle contraction is achieved by acetylcholine activation of the muscarinic receptors [4-6]. The muscarinic receptor subtypes identified in the human bladder are M_1-M_3 [5]. M_1 controls the release of acetylcholine in the bladder [7]. The predominate muscarinic receptor in the human bladder appears to be M_2, however it appears that the cholinergic-induced contractions of the detrusor are mediated through M_3 receptors [6].

Overactive bladder

OAB, as previously defined, is urinary urgency, with or without urge incontinence, and is commonly associated with frequency and nocturia [2]. Urgency, the cornerstone in the diagnosis of OAB, is the compelling desire to void that is difficult to defer [2]. OAB-dry is a term used for patients who experience symptoms of OAB without urge incontinence [8]. Frequency is defined as voiding too frequently during the day and nocturia is the complaint of waking during the night to void. Both frequency and nocturia can be with or without urge incontinence [8].

OAB symptoms may be from involuntary detrusor muscle contractions [4]. Detrusor overactivity, whether neurogenic (Neurologic cause), myogenic (Muscular cause), or idiopathic (no defined cause) are characterized by involuntary contractions of the detrusor muscle during the filling phase which can be either spontaneous or provoked [2,4]. The involuntary detrusor contraction can take place at any bladder volume, but usually happens at a bladder capacity < 200 mL [4].

Age-related causes of urinary dysfunction

OAB is a common health problem affecting 10-15 % of the population [1]. In elderly, it is attributed to increased risk of falls which, in turn, can lead to hip fractures, anxiety/depression, and social withdrawal with a remarkable impact on the quality of life [9,10]. The economic burden of OAB is significant, reaching over $14 billion [11]. The elderly population has special considerations when dealing with OAB such as polypharmacy, multimorbidity, functional and cognitive impairment, frailty as well as postmenopausal estrogen status in women [12].

Polypharmacy can have an adverse impact on normal bladder function and worsen OAB symptoms, or adversely interact with OAB medications affecting their bioavailability and metabolism [13-15]. Multimorbidity is defined as the presence of two or more chronic medical conditions. Elderly patients with OAB are likely to have 3-5 concomitant diseases with diabetes, hypertension and hyperlipidemia being the most prevalent [16]. This puts them at high risk of polypharmacy and drug-drug interactions.

Poorly controlled diabetes plays a major role; the prolonged exposure to hyperglycemia results in damage to detrusor muscle and bladder innervation through oxidative stress, leading to diabetic cystopathy. Diabetic cystopathy is a triad of decreased bladder sensation, increased bladder capacity and poor bladder emptying which can exacerbate an underlying OAB symptom [17,18].

Hypertension and congestive heart failure are other conditions affecting OAB in which some treatment medications such as diuretics can counteract the effect of OAB medications. The functional limitations associated with neurologic diseases such as Parkinson's disease (PD), Multiple sclerosis and cerebrovascular accidents, can contribute to OAB symptoms such that effective treatment for OAB can be confounded.

Cholinesterase inhibitors (ChIs) are the mainstay of treatment for PD, therefore, the concomitant use of ChI with an antimuscarinic medication (majority of the OAB medications) can diminish ChI therapy and potentially exacerbate cognitive decline [19]. Hypoestrogenism contributes to worsening OAB symptoms through urogenital atrophy with subsequent urgency, frequency, nocturia, incontinence and recurrent urinary tract infections [20]. Low dose vaginal estrogen has been associated with increased bladder sensation with improved frequency, urgency, and bladder capacity [21].

Treatment of overactive bladder

First line treatment: Behavioral Therapies

Behavioral therapies, including bladder training (timed voiding and urge suppression techniques), fluid management and pelvic floor muscle training (PFMT) with increased physical activity, help to overcome functional limitations [22,23]. PFMT aims at voluntary contractions of pelvic floor muscles to suppress the detrusor overactivity, augment urethral support and overcome urine loss associated with urgency. PFMT alone has shown a reduction of incontinence ranging from 60-80% in controlled trials aiming to suppress urge through PFMT [24]. However, these methods require continued motivation and effort by the patient.

Second line treatment: Oral Anti-Muscarinic or Beta 3 Adrenoreceptor Agonist

The oral anti-muscarinic (anti-cholinergic) medications have been the main therapy for OAB. The use of these medications represent a challenge for elderly patients complaining of OAB symptoms arising from the polypharmacy which often exists in this vulnerable group, in conjunction with increased medication side effects together with medication noncompliance. Medications used for the treatment of other concomitant comorbidities such as digoxin, warfarin, ranitidine, and diazepam have anti-muscarinic properties which will increase the anti-muscarinic drug load and consequently, the anti-muscarinic side effects when used conjointly with OAB medications. A higher anti-muscarinic load can predispose older patients to cognitive decline, dementia, and delirium [25-27].

Oxybutynin (one of the oldest OAB medications) is associated with the highest risk of cognitive impairment. Oxybutynin is available in several preparations and doses with the transdermal preparation being most preferred to be used in older patients in order to avoid the first pass metabolism [27]. Extended-release forms of both Oxybutynin and Tolterodine are recommended due to less side effects especially dry mouth. Fesoterodine demonstrated good efficacy with similar side effect profiles in older populations when compared to younger population [28,29]. P-glycoprotein (P-gp) is the best studied transporter limiting blood brain barrier (BBB) penetration, Brain penetration is low for antimuscarinics that are P-gp substrates (Darifenacin and Trospium), and significant for those that are not P-gp substrates (Oxybutynin, Solifenacin and Tolterodine) [30]. The unique structure and hydrophilic properties of Trospium, a quaternary amine, make it the least likely to cross the BBB and therefore less likely to cause cognitive impairment. A randomized double-blind placebo-controlled trial aimed at investigating the effect of Trospium chloride on cognitive function in postmenopausal women treated for OAB showed no change in cognitive function between Trospium and placebo [31].

Mirabegron, the only approved Beta 3 adrenoreceptor agonist, stimulates the Beta 3 receptor in the bladder resulting in detrusor muscle relaxation. The bladder expresses 97% of all Beta 3 receptors; however, Beta 3 receptors are also expressed in the cardiovascular system where it mediates vasodilation by increasing atrial contractions [32,33]. The safety of Mirabegron at various doses show a minimal increase in blood pressure (BP) and heart rate (HR) [32]. Blood pressure and heart rate monitoring are recommended following the start of Mirabegron.

Anticholinergic drugs seem to have the same efficacy in managing OAB symptoms [33,34], however, because of different selectivity for muscarinic receptor subtype, they vary in their safety and tolerability profile [35-39]. The current data showed that Darifenacin has the highest M3 selectivity (which is the muscarinic receptor most abundant in bladder and responsible for the effect of anticholinergic medications on OAB symptoms) over other receptor subtypes (M1, M2 and M3) in comparison with other anticholinergics including oxybutynin [40].

Studies examining the accumulation of anticholinergic medications in the brain have been very limited but so far it appears that oxybutynin accumulates at higher

concentration levels in the brain compared to the newer anticholinergics [41,42]. Preclinical studies on muscarinic receptors with preferential selectivity for the bladder over the brain show results favoring Solifenacin and Tolterodine over Oxybutynin [43]. Evidence is emerging now that blocking the central M1 receptor has an important role in cognitive impairment and consequently, anticholinergic medications with low affinity to M3 (lowest selectivity) and high M1 affinity may yield more cognitive impairment [44].

Pharmacokinetics/drug metabolism changes attributed to aging are important considerations in older patients. Slow gastric emptying associated with aging can reduce drug bioavailability. Increased free circulating plasma level of the drug can be caused by a decrease in Albumin level which is particularly important in Tolterodine metabolism [29]. Patients with hepatic dysfunction have altered cytochrome p450 metabolism which is needed for clearance of some drugs including oxybutynin, tolterodine, darifenacin and solifenacin. Reduced renal function is another important consideration in an older population especially for renally excreted drugs such as Trospium and Tolterodine. Discussion with a medical specialist is recommended whenever there are any concerns about drug interactions [12].

Third line treatment: PTNS, Sacral Neuromodulation and Intra-Detrusor OnabotulinumtoxinA

The utilization of third line of treatments is limited in Canada. They are only considered in patients refractory to behavioral modifications and pharmacotherapy after a detailed evaluation to exclude any other causes accounting for lack of response. Third-line treatments are associated with potentially significant side effects with long term consequences.

Posterior tibial nerve stimulation (PTNS) effectiveness can be up to 60%, which is comparable to oral medication while avoiding the side effects encountered with oral medications [45]. The drawback of PTNS arises from the need of a weekly 30-minute treatment for 12 weeks then followed by monthly maintenance sessions. It is not currently easily accessible in Canada.

Sacral Neuromodulation (SNS) requires the permanent implantation of a neurostimulator device which make patients who require future magnetic resonance

imaging, or those who are unable to operate the neurostimulator, poor candidates for SNS [46]. Only a few Canadian centers offer this procedure.

Intra-detrusor onabotulinumtoxinA (BoNT-A) injections (100 U) are recommended only for selected patients after failure of the first and second-line therapies. Urinary retention requiring clean intermittent self-catheterization 2 weeks after BoNT-A injection was 6.2% among women with OAB [47]. It is important before starting the treatment that the patient must be willing to return for reassessment to measure post void residual (PVR) volume and perform clean intermittent self-catheterization if needed [48]. PVR > 150 ml increases the risk of urinary tract infection especially if acquired for a prolonged duration, and if associated with urogenital atrophy as in postmenopausal women [49]. High BMI is also associated with increased risk of BoNT-A injection failure [50].

Delirium

Definition

A state of acute brain failure marked by sudden onset of confusion, a fluctuating course, inattention, and often an abnormal level of consciousness [51-53]. Even though delirium is extremely common, the diagnosis can be challenging. Hypoactive and quiet variants of delirium are more common than purely agitated patients [51,54].

Risk factors

Multifactorial risk factors are commonly involved in delirium and often lie outside the central nervous system itself. Common risk factors are divided into predisposing factors (e.g. underlying cognitive impairment, multiple comorbidities, polypharmacy, impaired sensation, and functional abilities, etc.) and precipitating factors (e.g. severe illness, dehydration and electrolyte imbalance, urine retention, urinary catheter use, etc.). The sum of both the predisposing factors, as well as precipitating factors, are the patient's risk factors for delirium [55].

Diagnosis

The diagnosis of delirium remains a clinical diagnosis which can be easily overlooked. Most cases of delirium (55-80%) are either unrecognized or undocumented despite delirium being an extremely common illness [56-58].

The current standard diagnostic criteria are the Diagnostic and Statistical Manual of Mental Disorders (Fifth edition) (DSM-5) from the American Psychiatric Association [59] and the International Statistical Classification of Disease and Related Health Problems, Tenth Revision from the World Health Organization (ICD-10) [60]. Recognition is based on brief cognitive screening and bed side observation of the key features of delirium. The positive predictive value of retrospective administrative databases to detect delirium is 71.7% (56.3-83.5%). Negative predictive value is 90.0% (88.3-91.4%) [61].

The Confusion Assessment Method (CAM) diagnostic algorithm is the briefest screening tool for the assessment of delirium [62]. CAM examines the 4 key features of delirium: acute change in mental status and fluctuating course; inattention; disorganized thinking; and abnormal level of consciousness. The diagnosis with CAM entails the presence of the first 2 features plus either the third or fourth. CAM has a sensitivity of 82% and specificity of 99% provided that the patient has had a prior cognitive assessment [63,64]. Unfortunately, this algorithm is only used clinically, and results are not explicitly coded in administrative databases.

Neurotransmitter associated with delirium

Multiple theories are proposed to explain the pathophysiology of delirium. End products of neurochemical pathways can explain the multiple delirium subtypes (Hyperactive, Hypoactive, and mixed) [65]. The neurotransmitter hypothesis suggests a decline in cholinergic function, excess dopamine, norepinephrine, and glutamate, along with changes in serotonin and Gamma-aminobutyric acid may lead to the different clinical presentations [65].

The potential association between anticholinergics and the risk of delirium has been a concern in the recent decades. The association between acetylcholine drug intake and neuropsychiatric manifestation has been suggested based on available evidence. The most currently accepted theory for the pathogenesis of delirium is the diffuse imbalance of cerebral neurotransmission of serotonin, noradrenaline, and dopamine. Research is still inconclusive, however, and some studies consider anticholinergic drug use as a precipitating factor for delirium [66].

Anticholinergic drugs in elderly

Frail older people consume several medications that have anticholinergic side effects. According to some studies, it is estimated that more than 30 % of older residents in nursing homes take more than two anticholinergic drugs and 5% take more than five [67,68]. A relevant anticholinergic cognitive burden score is also found in about one half of community-dwelling older adults [69].

The toxic effect of these drugs in the aging brain is related to increased permeability of the blood-brain barrier with slower metabolism, drug elimination and age-related deficit in central cholinesterase transmission [70]. Furthermore, the polypharmacy frequently encountered in older populations owing to multiple diseases increase the probability of cumulative adverse effect [71]. Despite that, the side effects of anticholinergic medications are often considered to be "unavoidable" or wrongly attributed to the process of aging itself [72].

Institutionalization is an important risk factor for the prescription of anticholinergic drugs. Inappropriate drug use is common in hospitalized older adults [73,74]. Nursing care home use significantly more anticholinergic drugs than those living at home according to the data from some studies [75]. Among hospitalized patients who are 65 years and older, the prevalence of anticholinergic prescriptions significantly increase during their hospital stay even when comparing them to Geriatric Care Units who are more vigilant than other units in the scope of prescribing the anticholinergic drugs [76]. In addition, as patients advance towards death in the palliative care setting, the use of anticholinergic drugs increase [77].

Anticholinergic drug burden evaluation

Essential anticholinergic drug use, especially amongst the older population, has prompted the development of methods to estimate the overall anticholinergic drug burden an individual receives [78]. Anticholinergic scales as well as in vitro methods have been developed to predict the central and peripheral adverse events associated with anticholinergic drug burden to potentially reduce the risk of secondary negative brain effect of drug therapy and optimize polypharmacy. However, none of these methods have been standardized, nor has an exact definition of a risky drug exposure been established [79-82].

In 2008, Chew et al [83] measured the anticholinergic activity (AA) of 107

medications at doses typically administered to older adults. The aim was to help the clinician to choose between equally efficacious medications through comparing the anticholinergic activity of different drugs within the same therapeutic group. However, the in vitro method used to measure serum anticholinergic activity (SAA) faced limitations in estimating the overall anticholinergic burden on the human brain. SAA is a measure of the peripheral action of the anticholinergic medication rather than central one since it does not reflect the drug concentration in the brain [84]. Even if the AA is measured in the cerebrospinal fluid, it cannot demonstrate an individual's sensitivity to be cognitively affected by the anticholinergic medication since it does not account for the brain's distribution of the drug. There was no correlation between SAA and cholinergic function measured with electroencephalography according to one study [85]. Another consideration regarding the SAA is that it does not take into account the stress response from an acute illness or make a distinction between medications [86]. SAA levels increase during illness and decline during recovery from it [87].

The anticholinergic drug scales are expert-based score models developed to determine the anticholinergic drug burden. Such scales rank medications on a four-point scale depending on their anticholinergic potential, ranging from limited or none (0), moderate (1), strong (2), or very strong (3) potential [79,80,82]. The aim is to identify drugs with potential adverse effects and propose the withdrawal of these medications. The Anticholinergic Drug Scale (ADS) was the initial scale [85], classifying 62 medications into three levels of anticholinergic potential. SAA was shown to be significantly associated with the ADS [88]. Later, this scale had undergone modifications and been further extended [89].

ADS assesses the cognitive impact of any anticholinergic drug based on literature reviews of drugs with anticholinergic potential. The Anticholinergic Risk Scale (ARS), on the other hand, assesses the central as well as the peripheral adverse effect of anticholinergic drugs [80]. Another scale, the Drug Burden Index (DBI) includes anticholinergic drugs as well as sedatives and it differs from the other scales by the fact that it is adjusted for dose [81]. In all these scales models, the anticholinergic burden is the sum of each anticholinergic drug score assuming that different drugs respect a linear additive model. To standardize anticholinergic scales, a recent review has developed a new list containing 100 anticholinergic drugs based on previously published lists [90].

Anticholinergics and delirium

Over 600 compounds have anticholinergic properties, including not only prescription medications, but also some of the over-the-counter medications as well as some plants [91]. Antimuscarinics would be a more accurate nomenclature to describe these compounds as most of them do not inhibit nicotinic receptors. Blockage of the central M_1 receptor and consequently reducing central acetylcholine is implicated in delirium [92].

Anticholinergic delirium is a potential complication of antimuscarinic compounds. Anticholinergic medications used for the treatment of overactive bladder are among those compounds that can lead to anticholinergic delirium. Limited studies have investigated the association between anticholinergic medications and delirium with the majority being just sporadic case reports.

Tricyclic antidepressants (TCA), including amitriptyline, are older medications historically used for the treatment of depression. However, they are no longer considered the first line of treatment with the development of selective serotonin reuptake inhibitors. The central antimuscarinic blockage activity of TCAs can result in delirium typically in the elderly [93-95]. However, a case report of a 36-year old Caucasian male diagnosed with delirium following administration of 200 mg dose of amitriptyline [96] illustrates no age preclusion.

Antihistamines are another class of medications with antimuscarinic activity, which, when taken in higher doses, can result in delirium. A case report describes anticholinergic delirium lasting for 6 days in a 14-year old after antihistamine overdose ingestion [97].

Delirium and hallucinations can be a potential side effect from anticholinergic overactive bladder medication. An 80 year-old male with no history of previous psychiatric illness was diagnosed with delirium based on ICD-10 after 1 week of daily ingestion of 5 mg of Solifenacin each morning [98]. Another case report reported on an 89 year-old man with no baseline neurological impairment who developed delirium after starting Fesoterodine 4 mg once daily for 5 days prior to the onset of delirium, when no changes had been made to his original medications [99].

Objective

Our objective is to measure the differential effects of specific overactive bladder medications on delirium. Our hypothesis is that new users of anticholinergics will have a higher risk of delirium compared to new users of beta-3 agonists. The need for this project emerges from the concern for worsening adverse effects on cognition with the use of anticholinergic medications. Limited studies have shown that adults who are users of anticholinergics are at higher risk of new onset delirium, and this risk is proportional to the cumulative dose of anticholinergic used. Beta-3 agonists provide a condition-specific comparison group that also seek medical management for their overactive bladder. There is no evidence beta-3 agonists have cognitive effects, and the efficacy of beta-3 agonists and anticholinergics are comparable.

Methods

Study Design

We conducted a retrospective, cohort study utilizing Ontario's population-based data held at ICES. The province of Ontario, Canada has a population exceeding 14 million and all Ontario residents utilize a single, universal healthcare system. Universal medication coverage is provided for those aged ≥ 65 years. Individual patient records were linked across the database using a deterministic identification number. The use of the database is authorized under the Ontario Personal Health Information Protection Act, which does not necessitate approval by the Research Ethics Board, or individual patient consent [100].

Data Sources

The following routinely collected data sources were used for the current study: the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD) for admission to acute care hospital in Ontario (provides information on patient diagnoses and procedures/interventions); the Canadian Institute for Health Information Same Day Surgery (CIHI SDS) (for single day surgeries); the National Ambulatory Care Reporting System (NACRS) (for all visits made to hospital emergency rooms and ambulatory care centers, including diagnosis, and procedures/interventions) [101,102]; the Registered Person Data Base (RPDB) (for vital statistics) [103]; the Ontario Health Insurance Plan (OHIP) (for physician billing/diagnostic codes pertaining to patient assessments or procedures) [101]; and the Ontario Drug Benefit database (ODB) (for publicly funded drug use) [104].

Patient Population

We used the Ontario Drug benefit database to identify users of either OAB anticholinergic or beta-3 agonist between 1 January 2016 until 1 March 2020. This database has >99% accuracy [104]. The anticholinergics included in this study are Oxybutynin, Solifenacin, Tolterodine, Trospium, Darifenacin and Fesoterodine. The only beta-3 agonist marketed is Mirabegron (approved for provincial coverage in June 2015, hence, our start date was set for January 2016). To identify potential differences between groups we used matching weights to make the three treatment groups comparable based on 83 baseline characteristics. We used 3 years of prior data to

ascertain medical comorbidities, 1 year of prior data for healthcare utilization variables, and 6 months of prior data to determine if the patient was a current/recent user of specific medication classes.

Inclusion Criteria

All Ontario residents 66-100 years of age with an oral prescription for one of the selected study drugs listed below. We didn't include patients aged 65-66 years of age since ODB starts at the age of 65 years of age and we would not be able to determine if a prescription represents the initial use of a medication or a continuation of a medication which was prescribed before the age of 65 years of age.

- Oxybutynin
- Newer Anticholinergic Medications: Solifenacin, Tolterodine, Trospium, Darifenacin and Fesoterodine
- Beta-3 agonist Medication: Mirabegron

Exclusion Criteria

- Missing or invalid ICES Key Number (IKN)
- Missing age or sex
- Death on or before the index date (Prescription date)
- Non-Ontario Residents
- Prescription for >1 study medication on prescription date
- A prescription of one or more of the study medications in the past 12 months prior to index date
- Prescription date is between an inpatient admission and discharge date
- $\geq$ 1 inpatient hospital discharge for any reason on or in the 2 days prior to the prescription date.
- $\geq$ 1 Emergency room registration for any reason on or in the two days prior to prescription date.

The exclusion criteria reflect that missing IKN, age and sex, death on or before

index date will result in poor data quality. We cannot track non- Ontario residents. For the prescription part, we excluded patients having more than one study medication as it won't be clear which medication the patient used. Finally, we excluded any prescription around hospitalization or emergency room visit to try and reduce confounding from any co-existing medical condition that would result from temporary use of a prescribed OAB medication.

Study Outcomes

Our primary outcome was delirium. Our hypothesis was that the risk of delirium would be significantly higher among people taking anticholinergic medications compared to our reference group of Beta-3 agonist users. There is no evidence or hypothetical mechanism through which beta-3 agonists would affect cognitive function. Delirium was defined using validated definition that uses hospital admission International Classification of Disease, 10th version (ICD-10) codes, the full list of codes related to delirium within the ICD-10 is listed in the appendix. The positive predictive value of retrospective administrative database to detect delirium is 71.7% (56.3-83.5%). Negative predictive value is 90.0% (88.3-91.4%) [61].

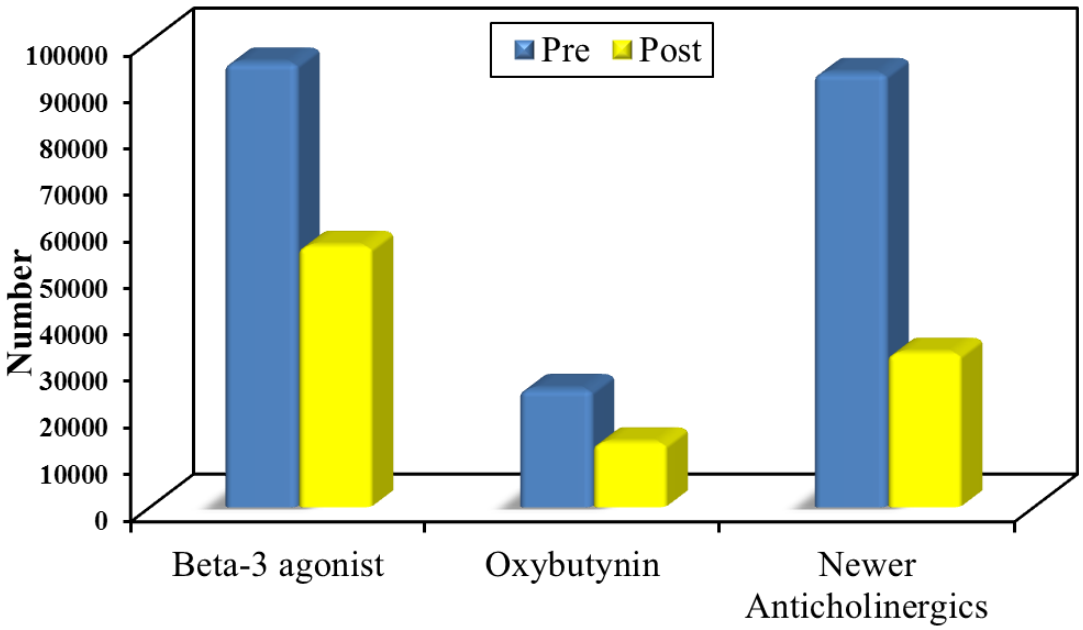
The At-risk period was the study period where we were observing for the study outcome. For our primary analysis we started that observation period from the index date (prescription date) and then added 30 days. We knew from previous research that most people used these medications for only a short period of time, and we felt delirium was most likely to occur as an acute complication of anticholinergic therapy. We did a secondary analysis considering continuous use of the medications. Continuous usage was defined as the time period during which an additional prescription of a medication from the same exposure group was filled within 1.5 times the duration of the previous prescription. Patients were censored at the end of their last prescription, death, the date of a prescription for a medication from another exposure group, or September 30, 2020. Only the period of continuous use starting with their index prescription was considered.

Statistical method

Matching weights (an extension of propensity score weighting) were used to balance the three exposure groups based on the 83 measured indicators of baseline health, comorbidity, medication usage, and healthcare utilization [105]. Matching weights were generalized to permit comparison between three groups. Propensity scores were estimated using multinomial logistic regression, where the model output contained predicted probabilities for all three exposure groups. The matching weights were then assigned as the minimum of the three predicted probabilities (propensity scores) divided by the predicted probability for the treatment they actually received. Between group differences were assessed using the average of the standardized differences obtained from the three pairwise comparisons of the two anticholinergic groups and the beta-3 agonist group (a difference of >10% is considered potentially meaningful) [106]. The primary analysis was carried out using weighted logistic regression, and odds ratios (95% confidence intervals) are reported. For the secondary analysis, a weighted Chi-squared test was used to compare the risk of the two outcomes between high-dose and low-dose users, and weighted Cox proportional hazards regression was used to analyze risk of the outcomes during continuous usage. Hazard ratios and 95% confidence intervals obtained from bootstrapping are reported. The relevant assumptions of this model were assessed using the Kolmogorov-type supremum test, a non-parametric test to confirm whether or not the data is normally distributed in the unweighted model. The analytic dataset was complete, aside from the income quintile and rural residence variable, which were missing in <0.03%. A two tailed p value <0.05 was considered significant. All analysis was conducted using SAS 9.4 statistical software (SAS Institute Inc).

Results

Figure (1) Numbers in each group pre and post implementation of exclusion criteria



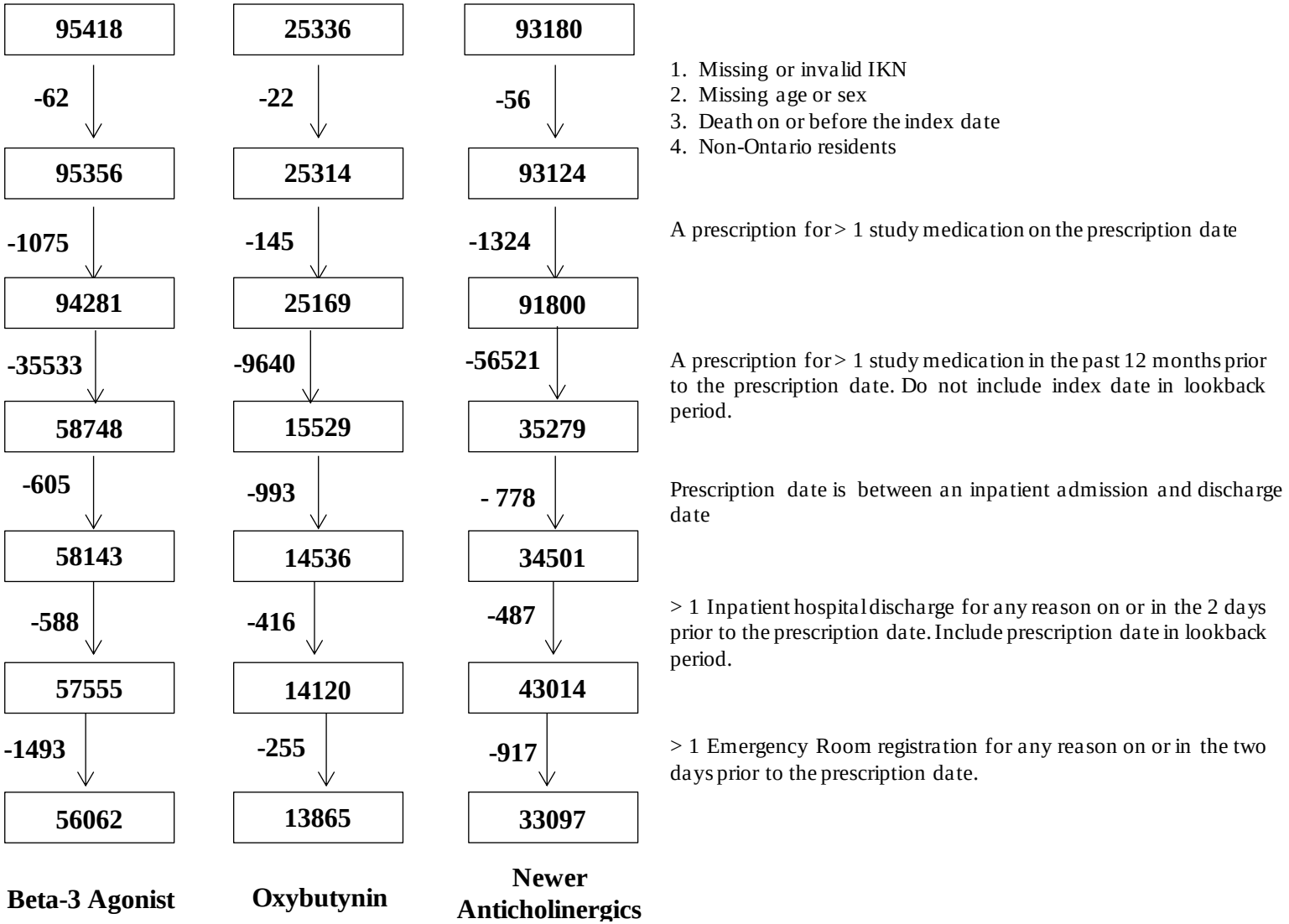


Figure (2): Flowcharts of exclusion criteria in each group

We initially identified 95418 new users of the Beta-3 agonist medications, 25336 new users of Oxybutynin, and 93180 new users of newer anticholinergics (Figures 1). After applying both the inclusion and exclusion criteria, we retained 56062 Beta-3 agonist, 13865 Oxybutynin and 33097 newer anticholinergic drug users (Figure 2).

Table (1): Baseline characteristics pre and post Matching Weights between the 3 groups (Beta-3 agonist, Oxybutynin and Newer anticholinergics). Full results of all the baseline characteristics are shown in Appendix 1

Variable	Value	Pre-weight							Post-weight						
		B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.	B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.
		N	SD/%	N	SD/%	N	SD/%		N	SD/%	N	SD/%	N	SD/%	
Age	Mean ± SD	77.16	7.48	76.58	7.5	76.67	7.37	0.05	76.61	3.73	76.58	7.49	76.55	4.81	0.01
	66-69	10259	18.3%	2935	21.2%	6529	19.7%	0.05	2890	21.0%	2924	21.1%	2856	20.6%	0.01
	70-74	13153	23.5%	3340	24.1%	8146	24.6%	0.02	3373	24.5%	3332	24.1%	3435	24.8%	0.01
	75-79	12105	21.6%	2978	21.5%	7206	21.8%	0.00	2843	20.7%	2973	21.5%	2948	21.3%	0.01
	80-84	10053	17.9%	2221	16.0%	5701	17.2%	0.03	2255	16.4%	2220	16.0%	2313	16.7%	0.01
	85-89	6797	12.1%	1537	11.1%	3625	11.0%	0.02	1526	11.1%	1537	11.1%	1479	10.7%	0.01
	90+	3695	6.6%	854	6.2%	1890	5.7%	0.03	866	6.3%	854	6.2%	814	5.9%	0.01
Sex	F	29171	52.0%	9812	70.8%	20338	61.4%	0.26	9653	70.2%	9789	70.7%	9841	71.1%	0.01
	M	26891	48.0%	4053	29.2%	12759	38.6%	0.26	4100	29.8%	4050	29.3%	4004	28.9%	0.01
Benign Prostatic Hyperplasia		17045	30.4%	1906	13.7%	7510	22.7%	0.27	1943	14.1%	1906	13.8%	1895	13.7%	0.01
Stroke		2015	3.6%	435	3.1%	1048	3.2%	0.02	442	3.2%	434	3.1%	421	3.0%	0.01
Congestive Heart Failure		6447	11.5%	1343	9.7%	3654	11.0%	0.04	1364	9.9%	1341	9.7%	1318	9.5%	0.01
Coronary Artery Disease		16928	30.2%	3487	25.1%	9573	28.9%	0.08	3502	25.5%	3482	25.2%	3448	24.9%	0.01
Dementia		9750	17.4%	1805	13.0%	4796	14.5%	0.08	1820	13.2%	1803	13.0%	1777	12.8%	0.01
Hypertension		26278	46.9%	6511	47.0%	16181	48.9%	0.03	6536	47.5%	6502	47.0%	6454	46.6%	0.01
Atrial Fibrillation		3947	7.0%	795	5.7%	2212	6.7%	0.03	810	5.9%	793	5.7%	769	5.6%	0.01
Prostatic cancer		6007	10.7%	877	6.3%	2983	9.0%	0.11	884	6.4%	876	6.3%	882	6.4%	0.00
Parkinson		2818	5.0%	415	3.0%	1039	3.1%	0.07	415	3.0%	415	3.0%	404	2.9%	0.01
Finasteride		6303	11.2%	615	4.4%	2539	7.7%	0.17	632	4.6%	615	4.4%	604	4.4%	0.01
Prostate specific alpha blocker		13472	24.0%	1424	10.3%	5477	16.5%	0.25	1456	10.6%	1424	10.3%	1389	10.0%	0.01
Urology clinic visit count	Mean ± SD	1.27	2.45	0.57	1.96	1.05	2.34	0.21	0.59	1.04	0.57	1.96	0.57	1.26	0.01
Trans-urethral resection of prostate		1769	3.2%	117	0.8%	720	2.2%	0.12	119	0.9%	117	0.8%	117	0.8%	0.01
Prostatic specific antigen test		9409	16.8%	1094	7.9%	4091	12.4%	0.18	1124	8.2%	1093	7.9%	1068	7.7%	0.01
Bladder scan		8978	16.0%	688	5.0%	4265	12.9%	0.24	719	5.2%	688	5.0%	688	5.0%	0.01
Post-void residual		8296	14.8%	698	5.0%	3589	10.8%	0.22	706	5.1%	698	5.0%	707	5.1%	0.00

To identify potential differences between groups, we measured 83 baseline characteristics (full base line characteristics pre- and post-matching are provided in Appendix (1-5). Pre-weight, the baseline characteristics were generally similar between the three groups (Table 1); however there were relevant differences in standardized differences in gender and multiple urological variables such as the number of urology clinics visits, Previous Benign prostatic hyperplasia (BPH), Prostatic cancer, Transurethral resection of prostate (TURP), Prostate specific antigen (PSA) tests, bladder scan and post-void residual urine volume. Some medications also showed a standard difference such as 5-alpha reductase inhibitors as well as prostate specific alpha blocker.

After matching, we retained 13752 beta-3 agonist users ,13839 oxybutynin drug users, 13845 Newer anticholinergic drug users and (Table 2). After matching, the previous difference in baseline characteristics were no longer significant.

Table (2): Delirium risk at 30 days

Outcome	Exposure	Unweighted sample		Weighted sample					
		n / N	%	n / N	%	Odds Ratio	95% CI		P-value
Delirium (30-day)	Beta-3 agonist	179 / 56062	0.32%	38/13752	0.28%	1.00 (ref)	LL	UL	
	Oxybutynin	49 / 13865	0.35%	49/ 13839	0.35%	1.28	0.84	1.96	0.25
	Newer OAB Anticholinergics	93 / 33097	0.28%	35/ 13845	0.25%	0.92	0.58	1.46	0.73

Table (3): Delirium risk during continuous usage

Outcome	Exposure	n / N	%	Person-years of follow-up	Incidence rate per 100 person-years	Rate difference	95% CI		Hazard Ratio	95% CI	
Delirium	Beta-3 agonist	299/13,752	2.2%	10,403	2.87	Reference	LL	UL	1.00 (reference)	LL	UL
	Oxybutynin	124/13,839	0.9%	3,475	3.56	+0.68 per 100 person-years	0.03	1.39	1.18	0.96	1.44
	Newer OAB Anticholinergics	263/13,845	1.9%	8.020	3.28	+0.41 per 100 person-years	0.11	0.92	1.13	1.02	1.26

The primary outcome was to assess the risk of delirium among the anticholinergic drug users (Oxybutynin, Newer anticholinergics) compared to beta-3 agonist during our observational period which was set to be 30 days from index date. There was no statistically significant difference at 30 days between Oxybutynin drug users compared to beta-3 agonist drug users (odds ratio 1.28, 95% CI 0.84-1.96 and p-value 0.25) also no statistically significant difference was found between the newer anticholinergic drug users group compared to beta-3 agonist drug users (odds ratio 0.92,95% CI 0.58-1.46 and p-value 0.73) (Table 2).

Our secondary analysis was to consider the risk of delirium during the period of continuous usage. The median interquartile range (IQR) duration of continuous usage was 113 (30-380) days for Beta-3 agonist, 30 (28-72) days for Oxybutynin, and 62 (30-239) days for the newer anticholinergics. When looking at the outcome of delirium during continuous use, the cox proportional analysis showed a slight increase in risk of delirium in the Newer Anticholinergic group compared to the Beta-3 agonist (HR 1.13, 95% CI 1.02-1.26, table 3).

Discussion

In this study we examined whether using OAB anticholinergic medications are associated with an increased risk of delirium in an elderly population. Cerebral neurotransmitter imbalance is the most accepted theory for the pathogenesis of delirium and the potential association between anticholinergics and the risk of delirium has been a concern in recent years [66].

According to Ontario Drug Benefit program which covers medications for individuals above 65 years old, a trial of Oxybutynin is still required as first line treatment of OAB [107]. This was not consistent with the findings retrieved from the data base during our study period. The Beta-3 agonist was the most prescribed medication followed by newer anticholinergics and lastly Oxybutynin. This change in prescription pattern may reflect physician knowledge that Oxybutynin has more potential cognitive risks, and the highest risk of the adverse effects as dry mouth and constipation.

The inclination of the majority of Urologist to prescribe Beta-3 agonist as an initial treatment for patients presenting with OAB was reflected in pre-weight standard difference (Table 1) in the variables specific for urology as benign prostatic hyperplasia, prostatic cancer, 5 alpha reductase inhibitors, Prostatic specific alpha blocker, bladder scan, post-void residual and the number of visits to urology clinic. On the contrary, a standard difference might have been expected to be significant between beta-3 agonist and anticholinergics especially in patients with hypertension and underlying cardiac condition since beta-3 agonist might affect blood pressure, however this was not the case. In clinical practice, even with pre-existing hypertension or cardiac condition, physicians are not hesitant to prescribe beta-3 agonist and they often just instruct patients to monitor their blood pressure after initial use. This is in keeping with recent population based cardiac safety data [107].

In contrast to previous literature on the topic of risk of dementia associated with the anticholinergic use, we expected that there would be a significant standard difference in the pre-weight group in patients with pre-existing dementia (Table 1), but this was not observed; however, there was an increased proportion of patients treated with beta-3 agonists compared to anticholinergics. The prevalence of dementia among the OAB drug users was higher than prevalence reported by public health agency of Canada, the prevalence is 5.6 % among males and 8.3 % among females. According to

our study results, 13.0% of Oxybutynin and 14.5% of newer anticholinergics drug users had underlying dementia in the pre-weight base line characteristics (Table 1). This higher percentage can be explained by the higher incidence of OAB symptoms among people with dementia [100].

Parkinson disease is another point of interest as anticholinergics play a role in improving the disease manifestation, yet no significant standard difference was evident towards prescribing anticholinergics in favor of beta-3 agonist.

We are not aware of any previous study that has investigated the risk of delirium following the usage of OAB anticholinergic medication except for some case reports. This is the first population-based study. We found that in the first 30 days after initiating oxybutynin or one of the newer OAB anticholinergics, there was no significant increased risk of delirium. This suggests that the risk of these events is low with a 30-day trial of anticholinergic medications (which is relevant to most patients given the limited long-term use of these medications [108]. When considering the period of continuous use of these medications, newer anticholinergics had a slightly increased risk of delirium (HR 1.13). These results are statistically significant; however, the relative difference is small. It is important to note that the point estimate for newer anticholinergics and delirium was OR 0.92 in the 30-day analysis, and HR 1.13 in the continuous use analysis, suggesting the risk for delirium may increase with continued use. The point estimate for oxybutynin is similar between the two analyses. This study showed no statistically significant risk of delirium between Oxybutynin and newer anticholinergics compared to the control group of beta-3 agonist users during the 30 days observational window. The differential effects of oxybutynin versus newer anticholinergics may be due to more significant central nervous system effects that specifically mediate delirium [109,110], and longer persistence with newer anticholinergic medications may have increased our statistical power for the detection of the increased risk of delirium. Our study supports the use of OAB beta-3 agonists to avoid the increased risk of delirium that is associated with OAB anticholinergic medications.

Anticholinergic drug burden might be the underlying factor that causes patients to develop delirium following administration of OAB anticholinergic medication. For example, the case report of an 89 year-old with multiple underlying co-morbid

conditions including stage 4 chronic kidney disease developed delirium following Fesoterodine; this might be the result of anticholinergic drug overload [99]. Other case reports described delirium that developed following antihistamine overdose in a 14 year old healthy female [97], or delirium following ingestion of a large dose amitriptyline in a healthy 36 year-old [96].

Thus, the continuous use of anticholinergics and the dosage might be the risk factor for the development of delirium, and this is consistent with our secondary findings which showed a slight increased incidence of delirium associated with continuous use of newer anticholinergic medications.

Anticholinergic medications inhibit the release of acetylcholine, and this may impair attention, sleep, and memory processes that rely on this neurotransmitter. Much of the previous study on this topic has used measures of anticholinergic load to measure the risk of delirium. Unfortunately, these scales have significant variability [111], and in a systematic review the association between delirium and anticholinergics varied based on the method used to calculate anticholinergic load [112]. This likely contributes to some of the variability in the literature, and accounts for clinical studies supporting a lack of association between anticholinergic medications and delirium [113].

The present study has some important limitations. We relied on filled prescriptions, which cannot account for the compliance of the patients. We used the ICD-10 coding for delirium to search the ICES database which has a positive predictive value of 71.7% which give us moderate confidence of the precise diagnoses of delirium [61]. However, the same definition was used for all groups, therefore we would not expect there to be differential misclassification across the 3 groups. This means that while this may have reduced the absolute rate of delirium, the relative difference (ie the hazard ratio) between the groups should still be accurate. Certain non-prescription medications have anticholinergic activity such as antihistamine use, which cannot be measured in our study, but can contribute to a patient's anticholinergic drug burden, however, we do not believe it to be a significant confounder as it would likely be similar among the 3 groups.

We did not measure some gynecological variables in the pre-weight baseline characteristics which can be a contributing factor for the higher incidence of OAB among females (61.4%) when compared to males (38.6%) (Table 1). Again, these

variables should not be differentially distributed based on the type of OAB medication initiated and are less relevant as most patients (approximately 90%) had not seen a gynecologist in the year prior to the start of OAB medications (Appendix 5).

The present study is an important addition to the literature for two main reasons. First, it reflects the change in prescription pattern that has been occurring in the last 5 years with more utilization of newer OAB medications at the expense of the older ones. Second, it shows a small but increased risk of delirium associated with newer anticholinergics during continuous use.

In conclusion, our study showed that the use of anticholinergic medications among patients with OAB was not associated with an increased risk of delirium compared to beta-3 agonist users in the 30 days duration; however, the risk is slightly increased with increased prescription duration. We believe that anticholinergics should be used with caution in elderly frail people with underlying risk factor for delirium.

References

1. Abrams P. New words for old: lower urinary tract symptoms for ‘‘prostatism’’. BMJ 1994;308:929-30.

2. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.

3. Boyle P, Robertson C, Mazzetta C, et al. The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. BJU Int 2003;92:409-14.

4. Ouslander JG. Management of overactive bladder. N Engl J Med. 2004;350:786-99.

5. Yoshimura N, Chancellor MB. Current and future pharmacological treatment for overactive bladder. J Urol. 2002;168:1897-913.

6. Fetscher C, Fleichman M, Schmidt M, Krege S, Michel MC. M(3) muscarinic receptors mediate contraction of human urinary bladder. Br J Pharmacol. 2002;136:641-3.

7. Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol. 2004;3:46-53.

8. 7. Abrams P. Describing bladder storage function: overactive bladder syndrome and detrusor overactivity. Urology. 2003;62(suppl 2):28-37.

9. Brown JS, Vittinghoff E, Wyman J, et al. Urinary incontinence: does it increase risk for fall and fracture? J Am Geriatr Soc. 2000;48:721-5. 3.

10. Coyne KS, Sexton CC, Kopp Z, et al. Assessing patients’ descriptions of lower urinary tract symptoms (LUTS) and perspectives on treatment outcomes: results of qualitative research. IJCP. 2010:1- 37.

11. Ganz ML, Smalarz AM, Krupski TL, Anger JT, Hu JC, WittrupJensen KU, et al. Economic costs of overactive bladder in the United States. Urology. 2010;75(3):526-32.

12. Pratt T S. (n.d.). Management of Overactive Bladder in Older Women. Current Urology Reports, 19(11). https://doi.org/10.1007/s11934-018-0845-5.

13. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. Clin Epidemiol. 2018;10:289-98. 28.

14. Schneidinger CS, Umek W, Böhmdorfer B. The problem of polypharmacy in female patients with overactive bladders - crosssectional study in a specialist outpatient department. Geburtshilfe Frauenheilkd. 2016;76(12): 29.

15. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227-46.

16. Ouslander JG, Shih YT, Malone-Lee J, Luber K. Overactive bladder: special considerations in the geriatric population. Am J Manag Care. 2000;6(11 Suppl):S599-606. Review.

17. Fayyad A, Hill S, Jones G. Prevalence and risk factors for bothersome lower urinary tract symptoms in women with diabetes mellitus from hospital-based diabetes clinic. Int Urogynecol J. 2009;20:1339-44. 24.

18. Yuan Z, Tang Z, Changxiao H, et al. Diabetic cystopathy: a review. J Diabetes. 2015;7:442-7.

19. Boudreau D, Yu O, Gray S, et al. Concomitant use of cholinesterase inhibitors and anticholingerics: prevalence and outcomes. J Am Geriatr Soc. 2011;59:2069–76.

20. Iosif C, Bekassy Z. Prevalence of genitourinary symptoms in the late menopause. Acta Obstet Gynaecol Scan. 1984;63:257-60

21. Tincello D, Taylor A, Spurling S, et al. Receptor isoforms that mediate estrogen and progesterone action in the female lower urinary tract. J Urol. 2009;181:1474-82.

22. Schnelle JF, MacRae PG, Ouslander JG, et al. Functional incidental training, mobility performance, and incontinence care with nursing home residents. J Am Geriatr Soc. 1995;43:1356-62.

23. Talley KC, Wyman JF, Bronas U, et al. Defeating urinary incontinence with exercise training: results of a pilot study in frail older women. J Am Geriatr Soc. 2017;65(6):1321-7.

24. Burgio KL, Goode PS, Locher JL, Umlauf MG, Roth DL, Richter HE, et al. Behavioral training with and without biofeedback in the treatment of urge incontinence in older women: a randomized controlled trial. JAMA. 2002 Nov 13;288(18):2293-9.

25. Carriere I, Fourrier-Reglat A, Dartigues J, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009;169(14):1317-24. 52.

26. Fox C, Richardson K, Maidman I, et al. Anticholinergic medication and use and cognitive impairment in the older population: the medical research council cognitive function and aging study. J Am Geriatr Soc. 2011;59(8):1477-83. 53.

27. McFerren S, Gomelsky A. Treatment of overactive bladder in the elderly female: the case for trospium, oxybutynin, fesoterodine and darifenacin. Drugs Aging. 2015;32:809-19.

28. DuBeau C, Kraus S, Griebling T, et al. Effect of fesoterodine in vulunerable elderly subjects with urgency incontinence: a doubleblind, placebo-controlled trial. J Uro. 2014;191:395-404. 57.

29. Wagg A, Khullar V, Marschall-Kehrel D, Michel MC, Oelke M, Darekar A, et al. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population. J Am Geriatr Soc. 2013;61:185-93.

30. Callegari E, Malhotra B, Bungay PJ, Webster R, Fenner KS, Kempshall S, LaPerle JL, Michel MC, Kay GG. A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. Br J Clin Pharmacol. 2011 Aug;72(2):235-46.

31. Geller EJ, Dumond JB, Bowling JM et al. Effect of trospium chloride on cognitive function in women aged 50 and older: a randomized trial. Female Pelvic Med Reconstr Surg. 2017;23(2):118-23.

32. Rosa G, Ferrero S, Nitti V, et al. Cardiovascular safety of B3- adrenoceptor agonists for the treatment of patients with overactive bladder. Eur Urol. 2016;69:311-23. 60.

33. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE,Weinstein DA The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and metaanalysis. Eur Urol (2008) 54:543-62

34. Novara G, Galfano A, Secco S et al A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol (2008) 54:740–763

35. Ikeda K, Kobayashi S, Suzuki M et al M3 receptor antagonism by the novel antimuscarinic agent solifenacin in the urinary bladder and salivary gland. Naunyn Schmiedebergs Arch Pharmacol (2002) 366:97–103

36. Napier C, Gupta P (2002) Darifenacin is selective for the human recombinant M3 receptor subtype [abstract 445]. Annual Meeting of the International Continence Society, Heidelberg, Germany. https://www.icsoffice.org/ASPNET_Membership/Membership/Abstracts/AbstractsSearch.aspx?EventID=40. Accessed 7 October 2010

37. Ohtake A, Saitoh C, Yuyama H et al Pharmacological characterization of a new antimuscarinic agent, solifenacin succinate, in comparison with other antimuscarinic agents. Biol Pharm Bull (2007) 30:54–58

38. Ney P, Pandita RK, Newgreen DT, Breidenbach A, Stohr T,Andersson KE Pharmacological characterization of a novel investigational antimuscarinic drug, fesoterodine, in vitro and in vivo. BJU Int (2008) 101:1036-42

39. Wiedemann A, Schwantes PA Antimuscarinic drugs for the tretment of overactive bladder: are they really the same?—A comparative review of data pertaining to pharmacological and physiological aspects. Euro J Geriatr (2007) 9(Suppl 1):29–42

40. Maruyama S, Tsukada H, Nishiyama S et al. In vivo quantitative autoradiographic analysis of brain muscarinic receptor occupancy by antimuscarinic agents for overactive bladder treatment. J Pharmacol Exp Ther (2008) 325:774-81

41. Yoshida A, Fujino T, Maruyama S, Ito Y, Taki Y, Yamada S The forefront for novel therapeutic agents based on the pathophysiology of lower urinary tract dysfunction: bladder selectivity based on in vivo drug–receptor binding characteristics of antimuscarinic agents for treatment of overactive bladder. J Pharmacol Sci (2010) 112:142-50

42. Yoshida A, Maruyama S, Fukumoto D, Tsukada H, Ito Y, Yamada S Noninvasive evaluation of brain muscarinic receptor occupancy of oxybutynin, darifenacin and imidafenacin in rats by positron emission tomography. Life Sci (2010) 87:175-80

43. Abrams P, Andersson KE, Buccafusco JJ et al Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. Br J Pharmacol (2006) 148:565-78

44. Yamaguchi O, Chapple CR. Beta3-adrenoceptors in urinary bladder. Neurourol Urodyn. 2007;26(6):752-6.

45. Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: a systematic review and meta-analysis. Neurourol Urodyn. 2012;31(8):1206-16.

46. Faris A, Gill B, Pizarro-Berdichevsky J. Impact of age and comorbidities on use of sacral neuromodulation. J Urol.2017;198(1):161- 6 This study challenges the existing literature regarding age and SNS outcomes, suggesting that age alone should not be considered a limiting factory in SNS and can be modestly protective against device revision.

47. Miotla P, Cartwright R, Skorupska K, Bogusiewicz M, MarkutMiotla E, Futyma K, et al. Urinary retention in female OAB after intravesical Botox injection: who

is really at risk. Int Urogynecol J. 2017;28(6):845-50.

48. Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, Das AK, Foster Jr HE, Scarpero HM, Tessier CD, Vasavada SP American Urological Association; Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline J Urol 2012;188(6 Suppl):2455-63.

49. Liao C, Kuo H. Increased risk of large post-void residual urine and decreased long-term success rate after intravesical onabotulinumtoxinA injection for refractory idiopathic detrusor overactivity. J Urol. 2013;189:1804-10.

50. Owen RK, Abrams KR, Mayne C, Slack M, Tincello DG. Patient factors associated with onabotulinum toxin A treatment outcome in women with detrusor overactivity. Neurourol Urodyn. 2017 Feb;36(2):426-31.

51. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017;377:1456-66. [PMID: 29020579]

52. Maldonado JR. Acute brain failure: pathophysiology, diagnosis, management, and sequelae of delirium. Crit Care Clin. 2017;33:461-519. [PMID: 28601132]

53. AGS/NIA Delirium Conference Writing Group, Planning Committee and Faculty. The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: research agenda on delirium in older adults. J Am Geriatr Soc. 2015;63: 843-52. [PMID: 25834932]

54. Robinson TN, Raeburn CD, Tran ZV, et al. Motor subtypes of postoperative delirium in older adults. Arch Surg. 2011;146:295- 300. [PMID: 21422360]

55. National Institute for Health and Care Excellence. Delirium: prevention, diagnosis and management. Clinical guideline CG103. Updated 14 March 2019. Accessed at www.nice .org.uk/guidance/cg103 /chapter/1-Guidance#risk -factor-assessment on 14 August 2020.

56. Zalon ML, Sandhaus S, Kovaleski M, et al. Hospitalized older adults with established delirium: recognition, documentation, and reporting. J Gerontol Nurs. 2017;43: 32-40. [PMID: 27845806].

57. Han JH, Zimmerman EE, Cutler N, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. Acad Emerg Med. 2009;16:193-200. [PMID: 19154565].

58. de la Cruz M, Fan J, Yennu S, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. Support Care Cancer. 2015;23:2427- 33. [PMID: 25617070].

59. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Society; 2013.

60. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: *Diagnostic Criteria for Research*. Geneva, Switzerland:World Health Organization; 1993.

61. Katznelson R, Djaiani G, Tait G, Wasowicz M, Sutherland AM, Styra R, et al. Hospital administrative database underestimates delirium rate after cardiac surgery. Can J Anesthesia J Can D'anesthésie. 2010;57(10):898–902.

62. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med. 1990;113: 941-8. [PMID: 2240918].

63. van Velthuijsen EL, Zwakhalen SM, Warnier RM, et al. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. Int J Geriatr Psychiatry. 2016;31:974-89. [PMID: 26898375].

64. Shi Q, Warren L, Saposnik G, et al. Confusion Assessment Method: a systematic review and meta-analysis of diagnostic accuracy. Neuropsychiatr Dis Treat. 2013;9: 1359-70. [PMID: 24092976].

65. Maldonado JR. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. Crit Care Clin. 2008;24(4):789Y856. Ix.

66. Landi F, Russo A, Liperoti R et al. Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther (2007) 81:235–241.

67. Garcı´a-Gollarte F, Baleriola-Ju´lvez J, Ferrero-Lo´pez I et al. Inappropriate drug prescription at nursing home admission.J Am Med Dir Assoc (2012)13:83.e9-83.e15

68. Kolanowski A, Fick DM, Campbell J et al. A preliminary study of anticholinergic burden and relationship to a quality of life indicator, engagement in activities, in nursing home residents with dementia. J Am Med Dir Assoc (2009) 10:252-7.

69. West T, Pruchnicki MC, Porter K et al. Evaluation of anticholinergic burden of medications in older adults. J Am Pharm Assoc (2013) 53:496-504.

70. Mintzer J, Burns A Anticholinergic side-effects of drugs in elderly people. J R Soc Med (2000) 93(9):457-62.

71. Onder G, Landi F, Liperoti R et al. Impact of inappropriate drug use among hospitalized older adults. Eur J Clin Pharmacol (2005) 61:453-9.

72. Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry (2001) 62(Suppl 21):11-4.

73. Tosato M, Landi F, Martone AM et al. Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. Age Ageing(2014) 43(6):767-73. doi:10.1093/ageing/afu029

74. Onder G, Landi F, Cesari M et al. Inappropriate medication use among hospitalized older adults in Italy: results from the Italian Group of Pharmacoepidemiology in the Elderly. Eur J Clin Pharmacol (2003) 59(2):157-62

75. Tamura BK, Bell CL, Inaba M et al. Outcomes of polypharmacy in nursing home residents. Clin Geriatr Med (2012) 28:217-36.

76. Wawruch M, Macugova A, Kostkova L et al. The use of medications with anticholinergic properties and risk factors for their use in hospitalized elderly patients. Pharmacoepidemiol Drug Saf (2012) 21(2):170-6. doi:10.1002/pds.2169

77. Agar M, Currow D, Plummer J et al. Changes in anticholinergic load from regular prescribed medications in palliative care as death approaches. Palliat Med (2009) 23:257-65.

78. Kersten H, Wyller TB. Anticholinergic drug burden in older people's brain—how well is it measured? Basic Clin Pharmacol Toxicol (2014) 114(2):151-9. doi:10.1111/bcpt.12140

79. Carnahan RM, Lund BC, Perry PJ et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol (2006) 46(12):1481-6.

80. Rudolph JL, Salow MJ, Angelini MC et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med (2008) 168:508-13.

81. Hilmer SN, Mager DE, Simonsick EM et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med (2007) 167(8):781-7.

82. Boustani M, Baker MS, Campbell N et al. Impact and recognition of cognitive impairment among hospitalized elders. J Hosp Med (2010) 5(2):69–75. doi:10.1002/jhm.589

83. Chew ML, Mulsant BH, Pollock BG et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr S (2008) 56(7):1333-41. doi:10.1111/j.1532-5415.2008.01737.x

84. Scheife R, Takeda M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. Clin Ther (2005) 27:144-53.

85. Thomas C, Hestermann U, Kopitz J et al. Serum anticholinergic activity and cerebral cholinergic dysfunction: an EEG study in frail elderly with and without delirium. BMC Neurosci (2008) 15(9):86. doi:10.1186/1471-2202-9-86

86. Carnahan RM, Lund BC, Perry PJ et al. A critical appraisal of the utility of the serum anticholinergic activity assay in research and clinical practice. Psychopharmacol Bull (2002) 36(2):24-39.

87. Flacker JM, Lipsitz LA. Serum anticholinergic activity changes with acute illness in elderly medical patients. J Gerontol A Biol Sci Med Sci (1999) 54:M12-M16

88. Summers WK. A clinical method of estimating risk of drug induced delirium. Life Sci (1978) 22:1511-16.

89. Han L, McCusker J, Cole M. Use of medications with anticholinergic effects predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med (2001) 161:1099-1105.

90. Dura´n CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol (2013) 69(7):1485-96. doi:10.1007/s00228-013-1499-3

91. Su M, Goldman M. Anticholinergic poisoning. UpToDate. 2017. http://www.uptodate.com/contents/anticholinergicpoisoning. Accessed 26 Dec 2017.

92. Dawson AH, Buckley NA. Pharmacological management of anticholinergic delirium: theory, evidence and practice. Br J Clin Pharmacol. 2016;81(3):516-24.

93. Karlsson I. Drugs that induce delirium. Dement Geriatr Cognit Disord. 1999;10(5):412-5.

94. Amitriptyline: summary of product characteristics. Electronic Medicines Compendium. https://www.medicines.org.uk/emc/. Accessed Sept 2017.

95. Alagiakrishnan K. An approach to drug induced delirium in the elderly. Postgrad Med J. 2004;80(945):388-93.

96. King, M., & Ashraf, N. Tricyclic Antidepressant-Induced Anticholinergic

Delirium in a Young Healthy Male Individual. *Drug Safety - Case Reports*, (2018). *5*(1), 1-5.

97. Scott, J., Pache, D., Keane, G., Buckle, H., & O'Brien, N. Prolonged anticholinergic delirium following antihistamine overdose. *Australian and New Zealand Journal of Psychiatry*, (2007). *15*(3), 242-4.

98. Štuhec, M. Solifenacin-induced delirium and hallucinations. *General Hospital Psychiatry*, (2013)*35*(6), 682.e3–682.e4 . https://doi.org/10.1016/j.genhosppsych.2013.06.002

99. Charbonneau, J. M., Bisset, R., & Nguyen, P. V.-Q. Delirium following fesoterodine treatment for urgency incontinence in an 89-year old man. *Canadian Urological Association Journal*, (2016)*10*(7-8), E261–E263.

100. Welk B, McArthur E. Increased risk of dementia among patients with overactive bladder treated with an anticholinergic medication compared to a beta-3 agonist: a population-based cohort study. BJU Int. 2020 Jul;126(1):183-190. doi: 10.1111/bju.15040. Epub 2020 Mar 19. PMID: 32167223.

101. Raina P, Torrance-Rynard V, Wong M, Woodward C. Agreement between self-reported and routinely collected health-care utilization data among seniors. Health Serv Res 2002; 37: 751-74

102. Gibson D, Richards H, Chapman A. The national ambulatory care reporting system: factors that affect the quality of its emergency data. Int J Inform Qual 2008; 2: 97-114

103. Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. J Am Coll Cardiol 1996; 27: 1335-42

104. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003; 10: 67-71

105. Yoshida K, Hernández-Díaz S, Solomon DH, Jackson JW, Gagne JJ, Glynn RJ, et al. Matching Weights to Simultaneously Compare Three Treatment Groups. Epidemiology. 2017;28(3):387–95.

106. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. Commun Statistics - Simul Comput. 2009;38(6):1228–34.

107. Tadrous, M., Elterman, D., Khuu, W., Mamdani, M. M., Juurlink, D. N., & Gomes, T. (2018). Publicly funded overactive bladder drug treatment patterns in Ontario over 15 years: An ecological study. Canadian Urological Association Journal, 12(3), E142–5. https://doi.org/10.5489/cuaj.4541

108. Yeowell G, Smith P, Nazir J, Hakimi Z, Siddiqui E, Fatoye F. Real-world persistence, and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB): a systematic literature review. Bmj Open. 2018;8(11):e021889.

109. Kay G, Crook T, Rekeda L, Lima R, Ebinger U, Arguinzoniz M, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. European Urology. 2006 Aug;50(2):317–26.

110. Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of Tolterodine, Trospium Chloride, and Oxybutynin on the Central Nervous System. J Clin Pharmacol. 2001;41(6):636–44.

111. Lavrador M, Cabral AC, Figueiredo IV, Veríssimo MT, Castel-Branco MM, Fernandez-Llimos F. Size of the associations between anticholinergic burden tool scores and adverse outcomes in older patients. Int J Clin Pharm-net. 2021;43(1):128–36.

112. Egberts A, Moreno-Gonzalez R, Alan H, Ziere G, Mattace-Raso FUS. Anticholinergic Drug Burden and Delirium: A Systematic Review. J Am Med Dir Assoc. 2020;

113. Moorey HC, Zaidman S, Jackson TA. Delirium is not associated with anticholinergic burden or polypharmacy in older patients on admission to an acute hospital: an observational case control study. Bmc Geriatr. 2016;16(1):162.

Appendix

Appendix (1): Full results of all the baseline characteristics (1)

Variable	Value	Pre-weight							Post-weight						
		B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.	B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.
		N	%	N	%	N	%		N	%	N	%	N	%	
Year of cohort entry	2016	11639	20.8%	3590	25.9%	9568	28.9%	0.13	3516	25.6%	3581	25.9%	3628	26.2%	0.01
	2017	13142	23.4%	3688	26.6%	8249	24.9%	0.05	3637	26.4%	3683	26.6%	3737	27.0%	0.01
	2018	14456	25.8%	2848	20.5%	7847	23.7%	0.09	2833	20.6%	2847	20.6%	2846	20.6%	0.00
	2019	14533	25.9%	3276	23.6%	6509	19.7%	0.10	3293	23.9%	3267	23.6%	3198	23.1%	0.01
	2020	2292	4.1%	463	3.3%	924	2.8%	0.05	474	3.4%	462	3.3%	436	3.1%	0.01
Rural	Missing	125	0.2%	26	0.2%	81	0.2%	0.00	30	0.2%	26	0.2%	31	0.2%	0.00
	N	49837	88.9%	11625	83.8%	29206	88.2%	0.10	11496	83.6%	11619	84.0%	11626	84.0%	0.01
	Y	6100	10.9%	2214	16.0%	3810	11.5%	0.10	2227	16.2%	2194	15.9%	2189	15.8%	0.01
Incquint	Missing	137	0.2%	39	0.3%	91	0.3%	0.01	32	0.2%	39	0.3%	36	0.3%	0.01
	1	11380	20.3%	3179	22.9%	7260	21.9%	0.04	3173	23.1%	3170	22.9%	3138	22.7%	0.00
	2	11826	21.1%	3023	21.8%	7210	21.8%	0.01	3002	21.8%	3016	21.8%	3018	21.8%	0.00
	3	10855	19.4%	2726	19.7%	6587	19.9%	0.01	2711	19.7%	2722	19.7%	2723	19.7%	0.00
	4	10443	18.6%	2443	17.6%	5916	17.9%	0.02	2407	17.5%	2440	17.6%	2455	17.7%	0.00
	5	11421	20.4%	2455	17.7%	6033	18.2%	0.05	2427	17.7%	2452	17.7%	2475	17.9%	0.01
Ltc	0	54589	97.4%	13473	97.2%	32314	97.6%	0.02	13363	97.2%	13449	97.2%	13456	97.2%	0.00
	1	1473	2.6%	392	2.8%	783	2.4%	0.02	389	2.8%	390	2.8%	389	2.8%	0.00
Stroke		2015	3.6%	435	3.1%	1048	3.2%	0.02	442	3.2%	434	3.1%	421	3.0%	0.01
Chf		6447	11.5%	1343	9.7%	3654	11.0%	0.04	1364	9.9%	1341	9.7%	1318	9.5%	0.01
Cad		16928	30.2%	3487	25.1%	9573	28.9%	0.08	3502	25.5%	3482	25.2%	3448	24.9%	0.01
Depression		3669	6.5%	954	6.9%	2109	6.4%	0.01	940	6.8%	947	6.8%	952	6.9%	0.00
Cancer		5982	10.7%	1471	10.6%	3502	10.6%	0.00	1473	10.7%	1466	10.6%	1463	10.6%	0.00
Seizure		464	0.8%	103	0.7%	222	0.7%	0.01	105	0.8%	102	0.7%	98	0.7%	0.01
Charl	Mean ± SD	0.5	1.18	0.45	1.17	0.47	1.17	0.03	0.45	0.56	0.44	1.17	0.44	0.74	0.01
	Median (IQR)	0	(0-0)	0	(0-0)	0	(0-0)		0	(0-0)	0	(0-0)	0	(0-0)	
	0	43821	78.2%	11249	81.1%	26284	79.4%	0.05	11045	80.3%	11232	81.2%	11185	80.8%	0.01
	1	4372	7.8%	946	6.8%	2463	7.4%	0.03	1005	7.3%	943	6.8%	1014	7.3%	0.01
	2	4020	7.2%	842	6.1%	2186	6.6%	0.03	852	6.2%	840	6.1%	814	5.9%	0.01
	3+	3849	6.9%	828	6.0%	2164	6.5%	0.03	851	6.2%	823	5.9%	833	6.0%	0.01

Appendix (2): Full results of all the baseline characteristics (2)

Variable	Pre-weight							Post-weight						
	B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.	B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.
	N	%	N	%	N	%		N	%	N	%	N	%	
Cranialtrauma	3115	5.6%	664	4.8%	1665	5.0%	0.03	671	4.9%	662	4.8%	644	4.7%	0.00
Encephalitis	60	0.1%	10	0.1%	34	0.1%	0.00	10	0.1%	10	0.1%	10	0.1%	0.00
Ms	263	0.5%	94	0.7%	153	0.5%	0.02	91	0.7%	92	0.7%	93	0.7%	0.00
Sci	55	0.1%	12	0.1%	48	0.1%	0.00	12	0.1%	12	0.1%	12	0.1%	0.00
Aur	4173	7.4%	652	4.7%	2020	6.1%	0.07	680	4.9%	648	4.7%	640	4.6%	0.01
Drugabuse	255	0.5%	74	0.5%	114	0.3%	0.02	71	0.5%	70	0.5%	71	0.5%	0.00
Schizo	242	0.4%	84	0.6%	149	0.5%	0.02	84	0.6%	81	0.6%	82	0.6%	0.00
Bipolar	197	0.4%	55	0.4%	138	0.4%	0.00	56	0.4%	54	0.4%	52	0.4%	0.00
Anxiety	1944	3.5%	527	3.8%	1113	3.4%	0.02	528	3.8%	520	3.8%	514	3.7%	0.01
Personality	44	0.1%	20	0.1%	33	0.1%	0.00	19	0.1%	18	0.1%	19	0.1%	0.00
Priormh	2233	4.0%	607	4.4%	1301	3.9%	0.02	607	4.4%	600	4.3%	596	4.3%	0.00
Abt	21389	38.2%	4759	34.3%	12390	37.4%	0.05	4751	34.6%	4750	34.3%	4749	34.3%	0.01
Anc	2540	4.5%	721	5.2%	1541	4.7%	0.02	728	5.3%	716	5.2%	710	5.1%	0.00
Aoa	12274	21.9%	3050	22.0%	7789	23.5%	0.03	3042	22.1%	3044	22.0%	3046	22.0%	0.00
Baa	8386	15.0%	2152	15.5%	5019	15.2%	0.01	2129	15.5%	2145	15.5%	2152	15.5%	0.00
Bbl	13670	24.4%	3214	23.2%	8383	25.3%	0.03	3240	23.6%	3208	23.2%	3165	22.9%	0.01
Bez	7863	14.0%	2089	15.1%	4783	14.5%	0.02	2070	15.1%	2080	15.0%	2095	15.1%	0.00
Ccb	13064	23.3%	3286	23.7%	8186	24.7%	0.02	3313	24.1%	3281	23.7%	3249	23.5%	0.01
Ccs	5935	10.6%	1464	10.6%	3371	10.2%	0.01	1470	10.7%	1458	10.5%	1460	10.5%	0.01
Cho	697	1.2%	81	0.6%	275	0.8%	0.04	81	0.6%	81	0.6%	80	0.6%	0.00
Dep	6076	10.8%	1661	12.0%	3451	10.4%	0.03	1635	11.9%	1651	11.9%	1661	12.0%	0.00
Ksd	1677	3.0%	456	3.3%	982	3.0%	0.01	458	3.3%	454	3.3%	455	3.3%	0.00
Mood	843	1.5%	189	1.4%	444	1.3%	0.01	195	1.4%	188	1.4%	183	1.3%	0.01
Narc	11639	20.8%	3066	22.1%	6775	20.5%	0.03	3058	22.2%	3049	22.0%	3043	22.0%	0.00
Nab	1455	2.6%	335	2.4%	826	2.5%	0.01	337	2.5%	334	2.4%	336	2.4%	0.01
Nsd	10711	19.1%	2798	20.2%	6641	20.1%	0.02	2797	20.3%	2791	20.2%	2770	20.0%	0.00
Oap	499	0.9%	175	1.3%	285	0.9%	0.03	174	1.3%	167	1.2%	166	1.2%	0.01
Otd	6835	12.2%	1824	13.2%	3913	11.8%	0.03	1819	13.2%	1816	13.1%	1812	13.1%	0.00
Pab	13472	24.0%	1424	10.3%	5477	16.5%	0.25	1456	10.6%	1424	10.3%	1389	10.0%	0.01
Park	2745	4.9%	464	3.3%	1100	3.3%	0.05	467	3.4%	463	3.3%	451	3.3%	0.01
Sce	68	0.1%	24	0.2%	42	0.1%	0.02	23	0.2%	23	0.2%	22	0.2%	0.00
Sta	15280	27.3%	3427	24.7%	9228	27.9%	0.05	3429	24.9%	3424	24.7%	3410	24.6%	0.00

Appendix (3): Full results of all the baseline characteristics (3)

Variable	Value	Pre-weight							Post-weight						
		B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.	B3 Unexposed N=56,062		ACoxy Exposed N=13,865		Acnew Exposed n=33,097		Stan. Diff.
		N	%	N	%	N	%		N	%	N	%	N	%	
Ndins	Mean ± SD	9.28	5.95	8.89	6.15	9.03	6.02	0.04	8.95	2.98	8.88	6.13	8.84	3.97	0.02
	Median (IQR)	8	(5-12)	8	(4-12)	8	(5-12)		8	(5-12)	8	(4-12)	8	(4-12)	
	0	1026	1.8%	382	2.8%	857	2.6%	0.04	328	2.4%	382	2.8%	426	3.1%	0.03
	1-4	10981	19.6%	3094	22.3%	6881	20.8%	0.05	2983	21.7%	3091	22.3%	3095	22.4%	0.01
	5-8	16984	30.3%	4253	30.7%	10008	30.2%	0.01	4199	30.5%	4249	30.7%	4148	30.0%	0.01
	9-12	13279	23.7%	2959	21.3%	7578	22.9%	0.04	3050	22.2%	2954	21.3%	3036	21.9%	0.01
	13-16	7434	13.3%	1678	12.1%	4172	12.6%	0.03	1707	12.4%	1673	12.1%	1654	11.9%	0.01
	17+	6358	11.3%	1499	10.8%	3601	10.9%	0.01	1485	10.8%	1490	10.8%	1486	10.7%	0.00
hospcount	Mean ± SD	0.3	0.71	0.26	0.69	0.28	0.69	0.04	0.26	0.34	0.26	0.69	0.26	0.43	0.00
	Median (IQR)	0	(0-0)	0	(0-0)	0	(0-0)		0	(0-0)	0	(0-0)	0	(0-0)	
	0	44435	79.3%	11451	82.6%	26594	80.4%	0.06	11265	81.9%	11433	82.6%	11356	82.0%	0.01
	1	8311	14.8%	1697	12.2%	4666	14.1%	0.05	1769	12.9%	1692	12.2%	1795	13.0%	0.01
	2	2183	3.9%	445	3.2%	1200	3.6%	0.03	467	3.4%	443	3.2%	456	3.3%	0.01
	3+	1133	2.0%	272	2.0%	637	1.9%	0.01	251	1.8%	270	2.0%	239	1.7%	0.01
edcount	Mean ± SD	0.95	1.7	0.88	1.76	0.91	1.7	0.03	0.9	0.87	0.88	1.71	0.87	1.1	0.02
	Median (IQR)	0	(0-1)	0	(0-1)	0	(0-1)		0	(0-1)	0	(0-1)	0	(0-1)	
	0	31897	56.9%	8295	59.8%	19363	58.5%	0.04	8110	59.0%	8285	59.9%	8294	59.9%	0.01
	1	11969	21.3%	2807	20.2%	7002	21.2%	0.02	2837	20.6%	2803	20.3%	2879	20.8%	0.01
	2	5666	10.1%	1298	9.4%	3118	9.4%	0.01	1327	9.6%	1295	9.4%	1248	9.0%	0.01
	3+	6530	11.6%	1465	10.6%	3614	10.9%	0.02	1478	10.7%	1456	10.5%	1424	10.3%	0.01
gpmhcount	Mean ± SD	0.32	1.18	0.32	1.44	0.32	1.26	0.00	0.32	0.58	0.32	1.44	0.32	0.79	0.00
	Median (IQR)	0	(0-0)	0	(0-0)	0	(0-0)		0	(0-0)	0	(0-0)	0	(0-0)	
	0	47592	84.9%	11833	85.3%	28157	85.1%	0.01	11674	84.9%	11812	85.4%	11771	85.0%	0.01
	1	4865	8.7%	1150	8.3%	2834	8.6%	0.01	1198	8.7%	1148	8.3%	1194	8.6%	0.01
	2	1752	3.1%	431	3.1%	976	2.9%	0.01	427	3.1%	430	3.1%	412	3.0%	0.01
	3+	1853	3.3%	451	3.3%	1130	3.4%	0.01	453	3.3%	449	3.2%	469	3.4%	0.01
gpcount	Mean ± SD	10.06	10.6	9.67	10.4	9.87	10.34	0.03	9.76	5.35	9.66	10.38	9.61	6.66	0.01
	Median (IQR)	7	(4-12)	7	(4-12)	7	(4-12)		7	(4-12)	7	(4-12)	7	(4-12)	
	0	1508	2.7%	500	3.6%	1017	3.1%	0.03	419	3.0%	499	3.6%	473	3.4%	0.02
	1-3	8993	16.0%	2543	18.3%	5630	17.0%	0.04	2400	17.4%	2540	18.4%	2535	18.3%	0.02
	4-6	13969	24.9%	3450	24.9%	8183	24.7%	0.00	3544	25.8%	3446	24.9%	3458	25.0%	0.01
	7-9	10980	19.6%	2621	18.9%	6340	19.2%	0.01	2647	19.2%	2618	18.9%	2610	18.8%	0.01
	10+	20612	36.8%	4751	34.3%	11927	36.0%	0.04	4743	34.5%	4737	34.2%	4770	34.5%	0.01

Appendix (4): Full results of all the baseline characteristics (4)

Variable	Value	Pre-weight							Post-weight						
		B3 Unexposed		ACoxy Exposed		Acnew Exposed		Stan. Diff.	B3 Unexposed		ACoxy Exposed		Acnew Exposed		Stan. Diff.
		N=56,062		N=13,865		n=33,097			N=56,062		N=13,865		n=33,097		
		N	%	N	%	N	%		N	%	N	%	N	%	
Neurcount	Mean ± SD	0.29	1.19	0.21	1.15	0.22	1.2	0.05	0.21	0.51	0.21	1.14	0.21	0.78	0.00
	Median (IQR)	0	(0-0)	0	(0-0)	0	(0-0)		0	(0-0)	0	(0-0)	0	(0-0)	
	0	49240	87.8%	12609	90.9%	29851	90.2%	0.07	12440	90.5%	12586	90.9%	12608	91.1%	0.01
	1	3120	5.6%	629	4.5%	1604	4.8%	0.03	674	4.9%	628	4.5%	626	4.5%	0.01
	2	1812	3.2%	318	2.3%	813	2.5%	0.04	332	2.4%	316	2.3%	305	2.2%	0.01
	3+	1890	3.4%	309	2.2%	829	2.5%	0.05	307	2.2%	309	2.2%	305	2.2%	0.00
Psycount	Mean ± SD	0.27	2.77	0.23	2.53	0.24	2.84	0.01	0.23	1.23	0.23	2.53	0.23	1.7	0.00
	Median (IQR)	0	(0-0)	0	(0-0)	0	(0-0)		0	(0-0)	0	(0-0)	0	(0-0)	
	0	53653	95.7%	13338	96.2%	31882	96.3%	0.02	13204	96.0%	13315	96.2%	13346	96.4%	0.01
	1	811	1.4%	152	1.1%	329	1.0%	0.03	188	1.4%	152	1.1%	137	1.0%	0.03
	2	403	0.7%	81	0.6%	212	0.6%	0.01	96	0.7%	80	0.6%	91	0.7%	0.01
	3+	1195	2.1%	294	2.1%	674	2.0%	0.01	264	1.9%	292	2.1%	271	2.0%	0.01
Urocount	Mean ± SD	1.27	2.45	0.57	1.96	1.05	2.34	0.21	0.59	1.04	0.57	1.96	0.57	1.26	0.01
	Median (IQR)	0	(0-2)	0	(0-0)	0	(0-1)		0	(0-0)	0	(0-0)	0	(0-0)	
	0	31779	56.7%	11639	83.9%	22017	66.5%	0.41	11499	83.6%	11613	83.9%	11616	83.9%	0.01
	1	9363	16.7%	690	5.0%	3974	12.0%	0.25	698	5.1%	690	5.0%	691	5.0%	0.00
	2	5762	10.3%	518	3.7%	2571	7.8%	0.18	525	3.8%	518	3.7%	515	3.7%	0.01
	3+	9158	16.3%	1018	7.3%	4535	13.7%	0.19	1030	7.5%	1018	7.4%	1023	7.4%	0.00

Appendix (5): Full results of all the baseline characteristics (5)

Variable	Value	Pre-weight							Post-weight						
		B3 Unexposed		ACoxy Exposed		Acnew Exposed		Stan. Diff.	B3 Unexposed		ACoxy Exposed		Acnew Exposed		Stan. Diff.
		N=56,062		N=13,865		n=33,097			N=56,062		N=13,865		n=33,097		
		N	%	N	%	N	%		N	%	N	%	N	%	
Gyncount	Mean ± SD	0.23	0.98	0.21	1.02	0.28	1.08	0.05	0.22	0.41	0.21	1.02	0.21	0.54	0.01
	Median (IQR)	0	(0-0)	0	(0-0)	0	(0-0)		0	(0-0)	0	(0-0)	0	(0-0)	
	0	50752	90.5%	12711	91.7%	29358	88.7%	0.07	12339	89.7%	12685	91.7%	12429	89.8%	0.05
	1	2421	4.3%	514	3.7%	1740	5.3%	0.05	718	5.2%	513	3.7%	747	5.4%	0.05
	2	1147	2.0%	253	1.8%	778	2.4%	0.03	322	2.3%	253	1.8%	300	2.2%	0.03
	3+	1742	3.1%	387	2.8%	1221	3.7%	0.03	373	2.7%	387	2.8%	370	2.7%	0.01
Carcath		940	1.7%	198	1.4%	563	1.7%	0.01	197	1.4%	198	1.4%	202	1.5%	0.01
Echo		12513	22.3%	2622	18.9%	6878	20.8%	0.06	2633	19.1%	2617	18.9%	2580	18.6%	0.01
Holter		5805	10.4%	1124	8.1%	3122	9.4%	0.05	1135	8.3%	1123	8.1%	1106	8.0%	0.01
Stress		7789	13.9%	1610	11.6%	4301	13.0%	0.05	1626	11.8%	1609	11.6%	1598	11.5%	0.01
Cthead		8021	14.3%	1750	12.6%	4313	13.0%	0.03	1753	12.7%	1745	12.6%	1738	12.6%	0.00
Mrihead		3019	5.4%	546	3.9%	1439	4.3%	0.05	550	4.0%	545	3.9%	534	3.9%	0.01
Chestxray		20966	37.4%	4816	34.7%	11969	36.2%	0.04	4832	35.1%	4803	34.7%	4761	34.4%	0.01
Urineculture		28419	50.7%	6163	44.5%	15965	48.2%	0.08	6182	45.0%	6156	44.5%	6116	44.2%	0.01
Turp		1769	3.2%	117	0.8%	720	2.2%	0.12	119	0.9%	117	0.8%	117	0.8%	0.01
Psatest		9409	16.8%	1094	7.9%	4091	12.4%	0.18	1124	8.2%	1093	7.9%	1068	7.7%	0.01
Trusbiopsy		744	1.3%	160	1.2%	475	1.4%	0.01	159	1.2%	160	1.2%	163	1.2%	0.00
Bladderscan		8978	16.0%	688	5.0%	4265	12.9%	0.24	719	5.2%	688	5.0%	688	5.0%	0.01
Postvoid		8296	14.8%	698	5.0%	3589	10.8%	0.22	706	5.1%	698	5.0%	707	5.1%	0.00
Stressincontsurg		277	0.5%	28	0.2%	154	0.5%	0.03	28	0.2%	28	0.2%	28	0.2%	0.00

Appendix (6) Delirium Codes

ICD-10 version	
F05	Delirium due to known physiological condition
F10121	Alcohol abuse with intoxication delirium
F10221	Alcohol dependence with intoxication delirium
F10231	Alcohol dependence with withdrawal delirium
F10921	Alcohol use, unspecified with intoxication delirium
F11121	Opioid abuse with intoxication delirium
F11221	Opioid dependence with intoxication delirium
F11921	Opioid use, unspecified with intoxication delirium
F12121	Cannabis abuse with intoxication delirium
F12221	Cannabis dependence with intoxication delirium
F12921	Cannabis use, unspecified with intoxication delirium
F13121	Sedative, hypnotic or anxiolytic abuse with intoxication delirium
F13221	Sedative, hypnotic or anxiolytic dependence with intoxication delirium
F13231	Sedative, hypnotic or anxiolytic dependence with withdrawal delirium
F13921	Sedative, hypnotic or anxiolytic use, unspecified with intoxication delirium
F13931	Sedative, hypnotic or anxiolytic use, unspecified with withdrawal delirium
F14121	Cocaine abuse with intoxication with delirium
F14221	Cocaine dependence with intoxication delirium
F14921	Cocaine use, unspecified with intoxication delirium
F15121	Other stimulant abuse with intoxication delirium
F15221	Other stimulant dependence with intoxication delirium
F15921	Other stimulant use, unspecified with intoxication delirium
F16121	Hallucinogen abuse with intoxication with delirium
F16221	Hallucinogen dependence with intoxication with delirium
F16921	Hallucinogen use, unspecified with intoxication with delirium
F18121	Inhalant abuse with intoxication delirium
F18221	Inhalant dependence with intoxication delirium
F18921	Inhalant use, unspecified with intoxication with delirium
F19121	Other psychoactive substance abuse with intoxication delirium
F19221	Other psychoactive substance dependence with intoxication delirium
F19231	Other psychoactive substance dependence with withdrawal delirium
F19921	Other psychoactive substance use, unspecified with intoxication with delirium
F19931	Other psychoactive substance use, unspecified with withdrawal delirium
A812	Progressive multifocal leukoencephalopathy
E512	Wernicke's encephalopathy
G0430	Acute necrotizing hemorrhagic encephalopathy, unspecified
G0431	Post-infectious acute necrotizing hemorrhagic encephalopathy
G0432	Post-immunization acute necrotizing hemorrhagic encephalopathy
G0439	Other acute necrotizing hemorrhagic encephalopathy
G92	Toxic encephalopathy
G9340	Encephalopathy, unspecified
G9341	Metabolic encephalopathy
G9349	Other encephalopathy
I673	Progressive vascular leukoencephalopathy
I674	Hypertensive encephalopathy
I6783	Posterior reversible encephalopathy syndrome
J1081	Influenza due to other identified influenza virus with encephalopathy
J1181	Influenza due to unidentified influenza virus with encephalopathy
P9160	Hypoxic ischemic encephalopathy, unspecified
P9161	Mild hypoxic ischemic encephalopathy
P9162	Moderate hypoxic ischemic encephalopathy
P9163	Severe hypoxic ischemic encephalopathy

Khaled Etaby

My career aim is to work as a Uro-gynecologist in a Canadian academic center that provides access to a wide range of clinical work, research, and teaching activities. I am very passionate about providing the best care for my patients through up-to-date clinical knowledge, working closely in a multi-disciplinary team and communicating with different referring departments. Performing good patient communication and offering all option of care so my patients can select what suits them. I love the interaction with patients and with my colleagues.

EXPERIENCE

September 2020 – PRESENT

Master of Surgery

Western University, London, ON, Canada

Urology/ Uro-gynecology departments, Victoria Hospital My duties include:

- Attending lectures required for fulfilling the Master degree
- Preparing the thesis for defence
- Reviewing up to date guidelines and literature review about current recommended treatment

Thesis Defence Scheduled for August 2021

September 2016- PRESENT

Ph.D. Obstetrics and Gynecology/ Assistant Lecturer

Alexandria University Faculty of Medicine

Obstetrics and Gynecology Department, El Shatby Maternity Hospital

My duties include:

- On Call specialist managing complicated Obstetrics and Gynecology cases.
- Independent specialist at University Hospital
- Independent specialist at private hospitals and outpatient clinic
- Supervising and teaching residents
- Grand rounds supervision and presentation
- Teaching undergraduate medical students
- Attending exams required for fulfilling the Ph.D. requirement
- Thesis defence (thesis is Co-supervision between Urogynecology department at Western University and Alexandria University hospital).

  Currently pending on thesis defence to obtain the degree (Delay is due to travel restrictions implemented by COVID-19)

JULY 2018 – JUNE 2020

CLINICAL FELLOW IN Urogynecology

Department of Obstetrics and Gynecology, Schulich School of Medicine and Dentistry
Western University, London, ON, Canada My duties included:

- Primary Surgeon/ Primary assistant in Urogynecology operative list 3 days/week.
- Outpatient Urogynecology clinic 2 days/ week.
- Rotation with Urology, Colorectal and minimally invasive gynecological surgery.
- Review and discuss challenging cases with consultants and residents
- Participate in Journal club and present in urogynecology Journal club days.
- Resident and Medical student teaching.
- Participate in urogynecology grand rounds.

JAN 2018 – April 2018

OBSERVER IN Urogynecology

Department of Obstetrics and Gynecology, Schulich School of Medicine and Dentistry
Western University, London, ON, Canada

August 2014 – September 2016

Demonstrator/ Obstetrics and Gynecology Specialist

Alexandria University Faculty of Medicine
Obstetrics and Gynecology Department, El Shatby Maternity Hospital
Department of Obstetrics and Gynecology, Alexandria University, Egypt My duties included:

- On Call specialist managing complicated Obstetrics and Gynecology cases.
- Independent specialist at University Hospital
- Supervising and teaching residents
- Grand rounds supervision and presentation
- Teaching undergraduate medical students

June 2011-August 2014

Obstetrics and Gynecology resident

MAR 2011 – JUN 2011

GENERAL PRACTITIONER

Directorate of Health Affairs, Alexandria, Egypt

MAR 2010 – FEB 2011

HOUSE OFFICER

Faculty of Medicine, Alexandria University Hospital, Egypt

EDUCATION

July 2016: ECFMG Certified (USMLE Step 1,2 and CS)

May 2015: Master Degree in Obstetrics and Gynecology

JULY 2003 – JUNE 2010
BACHELOR OF MEDICINE AND SURGERY: MBBCH
University of Alexandria, Faculty of Medicine, Alexandria, Egypt

May 2010 - June 2010 Clinical Elective
Department of Gynaecological Oncology, Northwestern Memorial Hospital, Northwestern University, Chicago, IL

August 2007 Clinical Elective
General Surgery Department, Clinical Centre Skopje, Macedonia

July 2006 Clinical Elective
Pulmonary Diseases/ Clinical Epidemiology, Utrecht Medical Summer School, Holland

LANGUAGE SKILLS

- Arabic Fluent, written and spoken
- English Fluent, written and spoken
- French Conversational

TEACHING

- Teaching and mentoring of junior colleagues during Obstetrics and Gynecology Residency and Clinical Fellowships
- Presentations at weekly Department rounds in Alexandria University and in London Health Sciences Centre.
- Teaching undergraduate medical students in Alexandria University

PRESENTATIONS

1. **Etaby k, Karkour T** Road traffic injuries during pregnancy. Safety of different imaging modalities. 33rd annual conference [Egypt], June 2015.

2. **Etaby k, Elsayed B** Ultrasound Guided hysteroscopic resection of submucous myoma. 33rd annual conference [Egypt], June 2015.

3. **Etaby K, Abdelnabi M** Ultrasound in assessment of female infertility. 23rd Scientific conference [Egypt]. July 2014

PUBLICATIONS / RESEARCH

Primary Interest: My urogynecology Fellowship has built my knowledge to utilize noninvasive management to improve general quality of health. My long-term research interest is to explore non mesh treatment in female patient presenting with stress urinary incontinence
Current:

Safety and clinical efficacy of retropubic tension-free vaginal tape versus anti-incontinence pessary for treating women with stress urinary incontinence: a randomized clinical trial.

Additional research: Current:

Is there an increased risk of delirium among patients with overactive bladder treated with newer anticholinergic medication compared to a beta-3 agonist?

Ultrasound-Guided Hysteroscopic resection of submucous myoma: Thesis submitted as a partial fulfilment of Master Degree, Alexandria University, Faculty of Medicine, May 2015