Dementia in Patients Taking Alpha Blockers

Case Based Panel Discussion

Case Presentation

- A 80-year-old gentleman presented with complain of forgetfulness since last few months.

- His medical history includes
  - Hypertension since last 20 years. On ramipril 5 mg + hydrochlorothiazide 12.5 mg
  - Benign prostatic hypertrophy with Bothersome LUTS diagnosed 10 years back. On tamsulosin since 9 years. Was never ready for surgery.

- **Examination on admission:**
  - Temperature of 37 ºc
  - Heart rate of 75 beats per min
  - Blood pressure of 144/98 mm Hg lying down; and 140/94 mm Hg standing up
  - Respiratory rate of 16 breaths per min
  - Oxygen saturation of 95% with pulse oximetry without supplementary oxygen.
  - Conscious, alert, orientated, hydrated.

Case Presentation

- **DRE:** Prostate Grade III, smooth.
- **Laboratory test:** The value of serum PSA was 4.5 ng/mL.
- **Uroflowmetry:** BOO
- The values of urinalysis and blood count were within normal limits.
- Serum Creatinine – 1.3 mg/dL.

Case Presentation

- Here, based on the presenting complain, the patient was diagnosed with
  - dementia.
  - Hypertension
  - Prostatomegaly with BOO and bothersome LUTS.

Conditions that leads to dementia in this patient

- May be due to ageing process
- May be due to uncontrolled hypertension
- May be due to antihypertensive drugs
- May be due to tamsulosin ????

Discussion

➢ Age and dementia?

- Age is the most important risk factor for dementia.

- Above the **age** of 65, a person's **risk** of developing Alzheimer's disease or vascular **dementia** doubles roughly every 5 years. It is estimated that **dementia** affects one in 14 people over 65 and one in six over 80.

- This may be due to factors associated with ageing, such as: higher blood pressure, increased risk of cardiovascular diseases (eg heart disease and stroke), changes to nerve cells, DNA and cell structure, loss of sex hormones after mid-life changes, the weakening of the body's natural repair systems, changes in the immune system.

In this given case, the age of the person was 75 years – **"Very Old"** Category and the age is risk factor for development of dementia

https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_risk_factors_for_dementia.pdf

Discussion

➢ Uncontrolled Hypertension and dementia?

- According to the latest research, having elevated blood pressure as an older adult predicts an increase in one of the hallmarks of Alzheimer's disease. The study authors also saw an increased risk of brain lesions.

- Hypertension is a leading cause of vascular cognitive impairment, a term that includes all cognitive deficits attributable to vascular factors.[3] The most extreme case of vascular cognitive impairment is vascular dementia, in which multiple cognitive domains are affected, with a negative impact on the activities of daily living. Increasing evidence also suggests that hypertension is a risk factor for Alzheimer disease (AD), highlighting its participation in all major causes of cognitive impairment.

Uncontrolled high blood pressure itself is a risk factor for dementia

Hypertension. 2014;64:3-5

Discussion

➢ Can Antihypertensive Medication Reduce Dementia Risk in Older Adults?

- At baseline, 1,951 patients used antihypertensive medication. The study population's mean age was 74.4, and 46.2% of participants were men. In all, 986 patients used beta-blockers, 798 used diuretics, 623 used ACE inhibitors, 522 used calcium channel blockers, and 402 used angiotensin receptor blockers. After a median of 6.7 years of follow-up, 136 participants developed dementia.

- The use of calcium channel blockers and the use of angiotensin receptor blockers were associated with a lower incidence of dementia, compared with the use of other antihypertensive medications (hazard ratios, 0.56 and 0.60, respectively).

Neurology Reviews. 2017 December;25(12):40-41

Current Urology Reports (2018) 19:69
https://doi.org/10.1007/s11934-018-0821-0

BENIGN PROSTATIC HYPERPLASIA (K MCVARY, SECTION EDITOR)

Is Tamsulosin Linked to Dementia in the Elderly?

Jason K. Frankel[1] · Yinghui Duan[2] · Peter C. Albertsen[1]

Since tamsulosin has a strong affinity for all three neurotransmitter receptors (α_1-adrenergic, dopaminergic, and serotonergic) that regulate and modulate important central nervous system functions including mood, affection, attention, learning, and memory, Duan et al. hypothesized that tamsulosin may lead to adverse neurologic events that would not be shared by the other α_1-adrenergic receptor antagonists.

Duan et al. utilized Medicare claims data from 2006 to 2012 to conduct a cohort study among men age ≥65 years and diagnosed with BPH [40••]. They identified men taking tamsulosin ($n = 253{,}136$) and matched them 1:1 to six comparison cohorts using independent propensity-score models.

Current Urology Reports (2018) 19:69
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Table 1 Hazard ratio for the incidence of dementia for men taking tamsulosin compared with men taking other medications or no medications to treat lower urinary tract symptoms

Matched cohort pair	Incidence of dementia		HR (95% CI)	*p* value
	Tamsulosin	Reference group		
Tamsulosin vs no BPH medication	31.3	25.9	1.17 (1.14–1.21)	< 0.001
Tamsulosin vs doxazosin	32.7	27.5	1.20 (1.12–1.28)	< 0.001
Tamsulosin vs terazosin	37.1	32.7	1.11 (1.04–1.19)	0.002
Tamsulosin vs alfuzosin	30.4	28.4	1.12 (1.03–1.22)	0.010
Tamsulosin vs dutasteride	32.7	26.5	1.26 (1.19–1.34)	< 0.001
Tamsulosin vs finasteride	36.9	32.8	1.13 (1.07–1.19)	< 0.001

events. Convenient dosing, hov
ance the risk-benefit profile of tamsulosin regarding dementia and cognitive impairment. Gill et al. have commented that the probability of a causal relationship between tamsulosin and dementia is likely to be as high as 38% [43•]. Furthermore, they estimate that for every 186 men exposed to tamsulosin, one additional patient is at risk for dementia. We encourage other researchers to conduct additional studies to address this

These findings suggest that Duan et al.'s analysis is robust for men with both mild and moderate cases of dementia.

WILEY

ORIGINAL REPORT

Tamsulosin and the risk of dementia in older men with benign prostatic hyperplasia

Yinghui Duan[1,2] | James J. Grady[1,2] | Peter C. Albertsen[3] | Z. Helen Wu[2,4]

Results: The median follow-up period for all cohorts was 19.8 months. After propensity-score matching, the tamsulosin cohort had an incidence of dementia of 31.3/1000 person-years compared with only 25.9/1000 person-years in the no-BPH-medication cohort. The risk of dementia was significantly higher in the tamsulosin cohort, when compared with the no-BPH-medication

5 | CONCLUSION

Older men diagnosed with BPH may face an increased risk of dementia when treated with tamsulosin. More research is needed to further investigate the neurophysiological mechanisms and clinical impact of tamsulosin on patients' cognitive well-being.

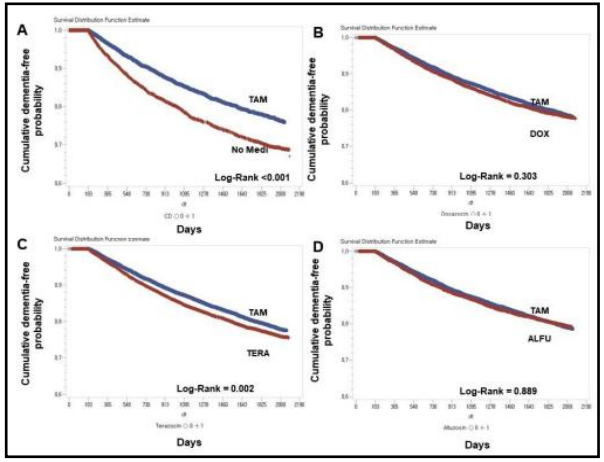
Unsurprisingly, counterarguments have been made against this study. Several studies have shown that tamsulosin has a limited ability to pass through the blood-brain barrier. Therefore, some have argued that it remains unclear how a drug with minimal penetration into the brain could promote the occurrence of dementia [4].

AUA Journals

No Access | Journal of Urology | Adult Urology | 1 Aug 2019

α-Blocker and Risk of Dementia in Patients with Benign Prostatic Hyperplasia: A Nationwide Population Based Study Using the National Health Insurance Service Database

Kaplan Meier curves of the dementia free probability in the match cohort



- Use of BPH medication is not associated with an increased risk of dementia.
- In the recent study conducted among Korean adult population with BPH, the risk of dementia did not significantly differ in the tamsulosin cohort vs the doxazosin and alfuzosin cohorts (HR 1.038, 95% CI 0.960–1.121 and HR 1.008, 95% CI 0.925–1.098), respectively. Compared to the tamsulosin cohort the terazosin cohort had a higher risk of dementia (HR 1.112, 95% CI 1.052–1.196). However, the risk of dementia was significantly lower in the terazosin cohort than in the no medication cohort.

Benign prostatic hyperplasia medication is not associated with a risk of dementia by duration of use or by type.

Take Home Message

- Age is the most important risk factor for dementia as well as BPH.
- Long term use of Tamsulosin may be associated with an increased risk of dementia.
- Needs more study to confirm or refute

Alpha Blockers and metabolic syndrome

Case Based Panel Discussion

Background

- Metabolic syndrome (MS) is a cluster of disorders associated with development of cardiovascular disease, increased mortality, with a common feature of insulin resistance.

- Patients with MS are twice as likely to develop cardiovascular disease and four times as likely to develop type 2 diabetes mellitus than patients without MS.

- The metabolic syndrome has known to be associated with development of benign prostatic hyperplasia (BPH) and LUTS.

1. Urology. 2016 Feb;88:135-42.
2. https://www.ics.org/Abstracts/Publish/105/000459.pdf

Background

BJU Int. 2015 Jul;116(1):124-30. doi: 10.1111/bju.12931. Epub 2014 Dec 8.

Association between metabolic syndrome and severity of lower urinary tract symptoms (LUTS): an observational study in a 4666 European men cohort.

Pashootan P[1], Ploussard G[1], Cocaul A[2], de Gouvello A[1], Desgrandchamps F[1].

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2 Endocrinology and Metabolism Department, Pitié-Salpêtrière Hospital, APHP, Paris, France.

Abstract

OBJECTIVES: To evaluate the relationship between metabolic syndrome and the frequency and severity of lower urinary tract symptoms (LUTS).

PATIENTS AND METHODS: In all, 4666 men aged 55-100 years consulting a general practitioner during a 12-day period in December 2009 have been included in this observational study. LUTS were defined according to the International Prostate Symptom Score (IPSS) and metabolic syndrome with the National Cholesterol Education Program/Adult Treatment Panel III definition. We studied the correlation between metabolic syndrome and its individual components, and the severity of LUTS (IPSS and treatment for LUTS). Analyses were adjusted for body mass index, age, and prostate-specific antigen level.

RESULTS: Metabolic syndrome was reported in 51.5% of the patients and 47% were treated for LUTS. There was a significant link between metabolic syndrome and treated LUTS ($P < 0.001$). The risk of being treated for LUTS also increased with an increasing number of metabolic syndrome components present. Metabolic syndrome was positively correlated with the severity of the LUTS ($P < 0.001$) for overall IPSS and both voiding and storage scores ($P < 0.001$). Each component of the metabolic syndrome (except high-density lipoprotein-cholesterol) appeared as an independent risk factor of high IPSS and of LUTS treatment in multivariate analysis. Metabolic syndrome was positively correlated with prostate volume.

CONCLUSIONS: Our results suggest a significant relationship between LUTS linked to benign prostatic hyperplasia and metabolic syndrome, in terms of frequency and severity. The risk of being treated for LUTS also increased with an increasing number of metabolic syndrome components present. The prevention of such modifiable factors by the promotion of dietary changes and regular physical activity practice may be of great importance for public health.

Case Presentation

- A 60 year-old gentleman presented with complain of urinary frequency, nocturia, urgency, weak urinary flow and dribbling since last few months.
- ED sine last 1 year.
- Past history:
  - Hypertension: on antihypertensives since last 8 years
  - Dyslipidemia : on Atorvastatins since last 5 years
  - Diabetes on OHA since last 7 years, poorly controlled.
  - IHD: on antiplatelets.

- **Examination on admission:**
  - Obese, weight 92 kg
  - Heart rate of 60 beats per min
  - Blood pressure of 140/96 in sitting position
  - Conscious, alert, orientated, hydrated.

Case Presentation

- **Digital rectal exam** revealed a prostate Grade II, soft and smooth consistency.
- USG KUB: 56 gms prostate, Upper tracts N, PVR 112 ml
- UFM: BOO
- **Laboratory test:**
  - Serum PSA: 4.5 ng/mL.
  - Fasting Blood sugar level : 154 mg /dl. PPBS 265 mg/dl.
  - Creatinine 1.8
  - Cholesterol 343mg/dl, Triglyceride: 350 mg/ dl, HDL 30mg/dl

- Prostatomegaly: LUTS, ED
- Metabolic syndrome:
  - DM
  - HTN
  - Dyslipidemia
  - IHD

Management issues

- Poly pharmacy: drug interactions
- CKD
- Dutasteride vs Finasteride
- Weight reduction/ Lifestyle modification
- Any preference of Alfa blocker?

Most commonly used alpha blockers for BPH treatment

	Tamsulosin[1]	Silodosin[2]	Alfuzosin[3]
Metabolism Enzymes involved	**CYP3A4 and CYP2D6**	**CYP3A4**	**CYP3A4**
Clinical Trials	87	20	31
Springer Nature References	348	55	172
Pubmed studies	1085	126	379
Renal dysfunction	Safe above CLcr <10 mL/min/1.73m2	CCr 30-50 mL/min), the dose should be reduced to 4 mg, s contraindicated in patients with severe renal impairment (CCr < 30 mL/min)	Caution should be exercised in patients with severe renal insufficiency
Hepatic dysfunction	Patients with moderate hepatic dysfunction do not require an adjustment	Patients with severe hepatic impairment (Child-Pugh score > 10)	Contraindicated moderate or severe hepatic insufficiency

1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020579s016lbl.pdf

2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022206s012lbl.pdf

3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021287s013lbl.pdf

Significant drug interaction between commonly used medications in BPH and HTN/IHD

Drugs	Tamsulosin	Alfuzosin	Silodosin
Antiplatelet Therapy			
Aspirin	None	Significant	Significant
Antihypertensive Therapy			
Enalapril	None	Significant	Significant
Ramipril	None	Significant	Significant
Atenolol	None	Monitor closely	Monitor closely
Metoprolol	None	Monitor closely	Monitor closely
Amlodipine	None	Monitor closely	Monitor closely
Nifedipine	Minor	Monitor closely	Serious
Lipid Lowering Agent			
Atorvastatin	None	Monitor closely	Monitor closely

https://www.webmd.com/interaction-checker/default.htm

Hindawi
Journal of Aging Research
Volume 2018, Article ID 5728957, 6 pages
https://doi.org/10.1155/2018/5728957

Research Article

Evaluation of Potential Drug-Drug Interactions with Medications Prescribed to Geriatric Patients in a Tertiary Care Hospital

- Conclusion: A significant number of potential drug-drug interactions were seen in the prescriptions of elderly patients. Increasing age and polypharmacy were identified as the predictors of potential drug interactions.

Medication pairs involved in risk X category drug interactions (to be avoided).

Medication pairs	Number of D/Is	Effect of drug interaction
Azithromycin-silodosin	1	Increased serum concentration of silodosin
Domperidone-escitalopram	2	Enhanced QTc-prolonging effect
Domperidone-quetiapine	2	Enhanced QTc-prolonging effect
Escitalopram-quetiapine	1	Enhanced QTc-prolonging effect
Atorvastatin-silodosin	2	Increased serum concentration of silodosin
Clopidogrel-esomeprazole	4	Diminished antiplatelet effect of clopidogrel
Ciprofloxacin-domperidone	1	Enhanced QTc-prolonging effect
Domperidone-fluconazole	1	Increased serum concentration of domperidone
Nifedipine-phenytoin	1	Increased serum concentration of phenytoin
Prazosin-tamsulosin	1	Enhanced antihypertensive effect
Domperidone-granisetron	1	Enhanced QTc-prolonging effect
Escitalopram-flupentixol	1	Enhanced QTc-prolonging effect
Bambuterol-salmeterol	1	Enhanced adverse/toxic effects
Amitriptyline-salbutamol + ipratropium	1	Enhanced anticholinergic effect

Effect of Tamsulosin in Lower Urinary Tract Symptom Patients With Metabolic Syndrome

Hana Yoon, Hyun Suk Yoon, Yong Seong Lee, Sung Tae Cho, and Deok Hyun Han

CONCLUSION

In conclusion, this study suggests that MS does not alter the effect of tamsulosin on LUTS patients. After tamsulosin treatment, the quality of health, social activities, and patients' personal status showed positive changes despite the presence of MS. Furthermore, tamsulosin provided beneficial effects on the glycolipid profile of patients, such as lowering of FBG and TG levels. Further studies about the effect of tamsulosin in

Incidence of type 2 diabetes mellitus in men receiving steroid 5α-reductase inhibitors: population based cohort study

Li Wei, associate professor in epidemiology and medical statistics, Edward Chia-Cheng Lai, assistant professor, [...], and Ruth Andrew, professor of pharmaceutical endocrinology

Conclusions

The risk of developing new onset type 2 diabetes appears to be higher in men with benign prostatic hyperplasia exposed to 5α-reductase inhibitors than in men receiving tamsulosin, but did not differ between men receiving dutasteride and those receiving finasteride. Additional monitoring might be required for men starting these drugs, particularly in those with other risk factors for type 2 diabetes.

Case Presentation

- Therefore, a diagnosis of benign prostatic hyperplasia with LUTS was made on the background of diabetes and high triglyceride.

- Patient was prescribed tamsulosin 0.4 mg.

- The patient was checked up a month later, shows improvement in the symptoms of LUTS along with improvement of sugar and triglyceride level.

Syncope in Patients Taking Alpha Blockers

Case Based Panel Discussion

Case Presentation

- A 76-year-old gentleman presented with fracture neck femur following a fall at night while trying to go to the washroom.
- He gives history of rapid onset asthenia and weakness and a sense of reeling of head while trying to sit from lying down position.
- The patient refers these symptoms from the day he started to take **Terazosin** orally
- His medical history includes:
  - hypertension on medication since last 8 years.
  - Recently diagnosed to have BOO secondary to prostatomegaly.
- Examination on admission:
  - Temperature of 37 ºc
  - Heart rate of 60 beats per min
  - Blood pressure of 104/68 mm Hg lying down; and 82/58 mm Hg standing up
  - Respiratory rate of 16 breaths per min
  - Oxygen saturation of 91% with pulse oximetry without supplementary oxygen.
  - Conscious, alert, orientated, hydrated.
  - Fracture right neck femur.

Case Presentation

- **DRE:** Grade III benign prostate clinically.

- **Labs:** CBC, CRP normal

  - Serum PSA 2.5 ng/mL.
  - RFT WNL

- What went wrong?

Case Presentation

- Orthostatic hypotension as an adverse drug reaction to Terazosin.
- The patient was hospitalized.
- He was checked up by the urology service that stopped Terazosin and started Tamsulosin and Dutasteride.
- Warned about orthostatic hypotension and syncopal attack.
- Counseled about ways to prevent it.
- Reviewed up a month later, without new orthostatic hypotension episodes.

Discussion

- Treatment of benign prostatic hyperplasia (BPH) can be medical or surgical.
- The pharmacological treatment options:
  - alpha- adrenergic antagonists
  - 5-alpha reductase inhibitors
  - PDE5 inhibitors.

1. BMJ, 336, 7637 (2008).
2. Eur. Urol., 64, 2 (2013).
3. Maturitas, 73, 3 (2012).

Discussion

- Three types of alfa adrenergic receptor:
  - Alfa 1a, 1b and 1c, the first one being predominant in the prostate, bladder neck and urethra.
- Two specific alpha 1a receptor blockers:
  - Tamsulosin and silodosin, having much lower affinity for alpha 1b and alpha 1c receptors, responsible for maintaining vascular tone induced by adrenergic ligands
- Non-selective alpha receptor blockers:
  - Doxazosin, terazosin, prazosin, alfuzosin.
  - Non-selective molecules, they generate significant vasodilation
  - Can be used in the treatment of benign prostatic hyperplasia accompanied by hypertension or as a second line treatment for HTN
  - Caution should be there on orthostatic hypotension the treatment of hypertension as second line drugs

1. BMJ, 336, 7637 (2008).
2. Eur. Urol., 64, 2 (2013).

Discussion

- However, its use in non-hypertensive patients like this, with BPH as only condition, can lead to severe postural hypotension as an adverse reaction to the drug.

- In fact, three alpha 1-adrenergic non-selective antagonists (doxazosin, prazosin, terazosin) have the black box warning issued by the FDA of severe hypotension and syncope, especially after the first dose.

1. J. Am. Osteopath. Assoc., 108, 7 (2008).
2. BMJ, 347 (2013).

Is Tamsulosin and Silodosin safe?

- Tamsulosin also carries a risk of generating low blood pressure, although this is lower than that generated by non-selective alpha adrenergic antagonists.
  - A systematic review that included 26 randomized trials of alpha-1 adrenergic antagonists found that vascular adverse events defined as dizziness, syncope or hypotension had the following comparative OR: 3.71 (95% CI 2.48 - 5.53) with terazosin, 3.32 (95% CI 2.1 - 5.23) with doxazosin, 1.66 (95% CI 1.17 - 2.36) with alfuzosin and 1.42 (95% CI 0.99 - 2.05) with tamsulosin (8).
  - Incidence of severe hypotension (requiring hospital admission) with tamsulosin was extremely low (42.4 events per 10,000 person years) .
  - The risk of severe hypotension is higher in the first 8 weeks of treatment.

- This is also the case for silodosin. It can produce orthostatic hypotension, dizziness, or syncope.

1.BMJ, 347 (2013).
2. Rapaflo® (silodosin) capsules prescribing information. Corona, CA, 2008, Oct.

Discussion

- In conclusion, it is considered that two medication errors could happened in this patient;
  - The first regarding with the selection of the drug for BPH treatment
  - Secondly for not taken care to warn the patient about a possible first-dose hypotension, which in fact occurred, and was severe enough to warrant admission to the hospital.