The Link Between Anticholinergics and Dementia

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Disclosures

• I have no actual or potential conflicts of interest in relation to this program/presentation.
Objectives

• At the conclusion of this activity participants should:
  1. Understand how acetylcholine is used in brain function
  2. Understand the dementia risks associated with the use of anticholinergic drugs
  3. Know what we can do to reduce risk of dementia from anticholinergic drug use
Functions of Acetylcholine

• Neurotransmitter

• Activates Muscles

• Neuromodulator
Acetylcholine

Image source: http://2.bp.blogspot.com/-w-dOA9tfB_Q/TZi4RNST2bl/AAAAAAAAABc/KkeU7tmmHL0/s1600/ca.JPG
Why is this important?

• Delirium is poorly recognized and can precipitate cognitive and functional decline.

• Medications account for 40% of delirium cases.
Medical Uses of Anticholinergics

1) GI disorders — N/V, diarrhea, ulcerative colitis, diverticulitis
2) Respiratory
3) Vertigo/motion sickness
4) Urinary retention
5) Seasonal allergies
6) Depression
Australian VA Study

- Retrospective cohort study conducted over 2 years between July 2010 and June 2012.
- Examining the effects of use of anticholinergic medications on the risk of hospitalization for confusion/dementia.
- Primary outcome of the study was hospitalization for confusion, delirium or dementia.

Australian VA Study

- Most frequently used anticholinergics in this study:
  1. Amitriptyline
  2. Oxybutynin
  3. Paroxetine

## Australian VA Study

### Table: Anticholinergic Medication Use and Hospital Admissions

<table>
<thead>
<tr>
<th># anticholinergic medications</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td># Hospital admissions</td>
<td>368</td>
<td>220</td>
<td>51</td>
<td>7</td>
</tr>
<tr>
<td>Person years</td>
<td>30,474</td>
<td>15,824</td>
<td>1,680</td>
<td>161</td>
</tr>
<tr>
<td>Rate per 10 years (95% CI)</td>
<td>.12 (0.11-0.13)</td>
<td>.14 (0.12-0.16)</td>
<td>.3 (0.23 – 0.40)</td>
<td>.43 (0.21 – 0.91)</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>1.00</td>
<td>1.15</td>
<td>2.51</td>
<td>3.58</td>
</tr>
</tbody>
</table>

## Australian VA Study

<table>
<thead>
<tr>
<th># anticholinergic medications</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3 or greater</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions</td>
<td>257</td>
<td>126</td>
<td>23</td>
<td>4</td>
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<tr>
<td>Persons</td>
<td>29,722</td>
<td>14,577</td>
<td>1,377</td>
<td>100</td>
</tr>
<tr>
<td>Rate per 10 years (95% CI)</td>
<td>.09 (.08-.10)</td>
<td>.09 (.07-.10)</td>
<td>.17 (.11-.25)</td>
<td>.40 (.15-1.06)</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (.81-1.24)</td>
<td>1.93 (1.26-2.96)</td>
<td>4.61 (1.72-12.36)</td>
</tr>
</tbody>
</table>

Cumulative Use of Strong Anticholinergic Medications and Incident Dementia

– 3,434 participants aged 65 and older
– Primary outcome was incident dementia and alzheimer’s disease using standard diagnostic criteria
– Over a 7.3 year period, 797 participants (23%) developed dementia

## Incidence of Dementia

<table>
<thead>
<tr>
<th>TSDD</th>
<th>Person-years</th>
<th># of events</th>
<th>HR</th>
<th>Unadjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5618</td>
<td>136</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>1-90</td>
<td>7704</td>
<td>203</td>
<td>0.96</td>
<td>0.77-1.20</td>
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<td>91-365</td>
<td>5051</td>
<td>172</td>
<td>1.31</td>
<td>1.04 – 1.65</td>
</tr>
<tr>
<td>366-1095</td>
<td>2626</td>
<td>102</td>
<td>1.39</td>
<td>1.07 – 1.82</td>
</tr>
<tr>
<td>&gt; 1095</td>
<td>4022</td>
<td>184</td>
<td>1.77</td>
<td>1.40 – 2.23</td>
</tr>
</tbody>
</table>

## Incidence of Alzheimer’s disease

<table>
<thead>
<tr>
<th>TSDD</th>
<th>Person-years</th>
<th># of events</th>
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<td>1.34 - 2.24</td>
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</table>

So what do we do about it?

1. Watch for symptoms of dementia

1. Decrease doses

1. Discontinue medications and switch to non-anticholinergic products
Popular anticholinergic examples

- Atropine
- Urinary – oxybutynin, tolteridine, flavoxate
- GI conditions – Loperamide, dicyclomine
- Antispasmotic - Baclofen
- Antipsychotics – Haloperidol, olanzapine
- Amitriptyline
- Doxepine
- Scopolamine
- Diphenhydramine
- Glycopyrrolate
Questions?

The Link Between Anticholinergics and Dementia

Thank You
Clinical Pearls of New HIV Medications

Cindy Lou Zoellner, PharmD, BCPS
Added Qualifications in Infectious Diseases
Senior Clinical Pharmacy Specialist in HIV
Parkland Health & Hospital System
Volunteer Clinical Associate Professor UTSA ID Division
January 16, 2016
At the end of this presentation pharmacists will be able to:

- Describe dosing, side effects, and toxicities of new HIV medications.
- Counsel patients effectively when incorporating new HIV medications into a treatment regimen.
TECHNICIAN OBJECTIVES

- At the end of this presentation pharmacy technicians will be able to:

- Describe dosing, side effects, and toxicities of new HIV medications.

- Review how patients can be effectively counseled when incorporating new HIV medications into a treatment regimen.
GLOBAL PERSPECTIVE

Adults and children estimated to be living with HIV | 2013

Total: 35.0 million [33.2 million – 37.2 million]

North America and Western and Central Europe
2.3 million
[2.0 million – 3.0 million]

Caribbean
250 000
[230 000 – 280 000]

Latin America
1.6 million
[1.4 million – 2.1 million]

Middle East & North Africa
230 000
[160 000 – 330 000]

Sub-Saharan Africa
24.7 million
[23.5 million – 26.1 million]

Eastern Europe & Central Asia
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[980 000 – 1.3 million]

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USA HIV/AIDS

CUMMULATIVE AIDS CASES REPORTED TO CDC

1) New York
2) California
3) Florida
4) Texas
5) New Jersey
6) Georgia
7) Illinois
8) Pennsylvania
9) Maryland
10) Puerto Rico
USA HIV/AIDS

- ~1.2 million persons aged ≥13 living with HIV in USA
- ~50,000 new HIV infections annually in USA
- Older patients, women, and those from racial/ethnic minorities are increasingly being impacted
  - Race – 72% from ethnic minority with 46% African American and 21% Hispanic
  - Age – 18% new infections in persons ≥50 years
- Life expectancy of an HIV patient diagnosed prior to decline in immune function is no different than a patient without HIV making HIV a treatable chronic medical condition

CDC HIV Statistics Overview 2013 www.cdc.gov
NRTI S

- Nucleoside Reverse Transcriptase Inhibitors
- 9 Drugs

Mechanism of Action:
- structurally similar to DNA bases (adenine, guanine, cytosine, and thymine) must be phosphorylated intracellularly to triphosphate, incorporates itself into the viral DNA via viral RNA dependent DNA polymerase (reverse transcriptase), producing viral DNA that is incorrect and incapable of infecting other cells
- Parent compound adefovir (Hepsera®) too nephrotoxic at doses needed for HIV treatment low dose 10mg licensed for Hepatitis B (HBV)

- Reengineered as tenofovir (Viread®) FDA approved in 2001 for HIV

- Gilead did not pursue FDA approval for tenofovir for HBV until 2008 when patent on adefovir was expiring

- Other indications Gilead pursued for tenofovir in combination with emtricitabine (Truvada®) was prevention of HIV infection or (PrEP) pre-exposure prophylaxis in HIV negative individuals
• Nucleotide analog contains 1st of 3 phosphorylations needed for antiretroviral activity creates a more metabolically active compound
• Tenofovir is renally eliminated from the body
  • glomerular filtration & active tubular secretion
• Fanconi syndrome resulting damage by tenofovir
  • acute renal failure, increased urine phosphate excretion
• Dose reduction for CrCL <50mL/min
• Decreases bone mineral density as body tries to compensate for urinary phosphate losses by breaking down bone to maintain serum phosphate levels
  • cases of osteomalacia have been reported was not FDA approved for children <18 until March 2010
TAF – NEW TENOFOVIR

- Estimated 84% of US HIV patients take tenofovir in some form of ART regimen both as an individual agent and in combination products recommended preferred agent in National DHHS HIV Guidelines
- Gilead reengineered tenofovir to reduce toxicities
- Tenofovir alafenamide fumarate (TAF) (formerly GS-7340) is a novel prodrug of tenofovir
- Greater antiviral activity and better distribution into lymphoid tissues allows for reduced dosing with lower incidence of kidney and bone toxicity
- 2 doses – 25mg daily without interacting antiretrovirals (ARVs) or 10mg daily if used in combination with ritonavir or cobicistat

Gilead Press Release
TAF COMBOS

- **November 2014** – NDA submitted to FDA for new TAF version of Stribild®
- FDA approved Genvoya® 11/5/2015
- **April 2015** – NDA submitted to FDA for new TAF version of Truvada®
- **July 2015** – NDA submitted to FDA for new TAF version of Complera®
- **Anticipated 2016** – Combination of TAF, emtricitabine, darunavir, cobicistat
GENVOYA

- Genvoya® 4 drug single tablet complete HIV regimen consisting of a combination of:
  - Elvitegravir – HIV-1 integrase strand transfer inhibitor (INSTI)
  - Cobicistat – CYP3A inhibitor with no HIV activity
  - Emtricitabine – HIV-1 nucleoside analog reverse transcriptase inhibitor (NRTI)
  - Tenofovir alafenamide (TAF) – HIV-1 nucleotide analog reverse transcriptase inhibitor (NRTI)
  - treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older with renal function CrCL >30mL/min
RENAL EFFECTS

• No cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT) in clinical trials of Genvoya®

• Clinicians are encouraged to assess CrCL, urine glucose, and urine protein in all HIV patients and serum phosphorus in HIV patients with CKD before initiating Genvoya® and monitor periodically during therapy
BMD EFFECTS

• HIV treatment naïve patients

• Evaluated bone mineral density (BMD) from baseline to Week 48 by DEXA to compare the bone safety of TAF to that of tenofovir in Genvoya® vs Stribild®

• Mean BMD declines with Genvoya® vs Stribild®
  • lumbar spine -1.30% vs -2.86%
  • total hip -0.66% vs -2.95%

• Total BMD Decreases
  • ≥5% lumbar spine 10% vs 22%
  • ≥7% femoral neck 7% vs 19%

• Fractures low incidence 0.8% vs 1.4%
BMD EFFECTS

Change in Spine BMD

Change in Hip BMD

Sax, P et al. CROI 2015 Abstract 143
BMD EFFECTS

- HIV treatment experienced patients
- Evaluated BMD from baseline to Week 48 by DEXA to compare the bone safety of continuing a tenofovir based ART regimen or switching to TAF in Genvoya®
- Mean BMD increases with TAF in Genvoya® vs tenofovir
  - lumbar spine 1.86% vs -0.11%
  - total hip 1.95% vs -0.14%
- Total BMD Decreases
  - ≥5% lumbar spine 1% vs 6%
  - ≥7% femoral neck 1% vs 4%
- Fractures low incidence 1% vs 0.4%

Genvoya® Package Insert Gilead 11/2015
ASSESSMENT

• Questions:

• What are some key patient counseling points for patients changing from tenofovir to TAF regimens?

• When patients change to TAF do they no longer need any renal monitoring labs?
PATIENT COUNSELING

- Key points to patient counseling for patients changing from tenofovir to TAF regimens
  - less impact on kidneys
  - less impact on bones
  - important to keep follow up appointments with your doctor and get labs because all HIV medications need to be monitored for safety and efficacy
CONCLUSION

• HIV is a treatable chronic medical condition
• Tenofovir is a central component of the majority of HIV medication prevention and treatment regimens
• Concerns over long term bone safety and nephrotoxicity led Gilead to develop TAF
• Anticipate 4 TAF containing HIV combination products to be FDA approved and available to HIV patients within the next year
Use of calcium channel blockers to slow the progression of diabetic nephropathy

COURTNEY DUVAL, PHARM.D.
ASSISTANT PROFESSOR
DEPARTMENT OF PHARMACY PRACTICE - AMBULATORY CARE DIVISION
TEXAS TECH SCHOOL OF PHARMACY – DFW CAMPUS
Objectives

- **Pharmacist objectives:**
  - Describe the mechanisms in which calcium channel blockers are proposed to prevent the progression of diabetic nephropathy.
  - Evaluate the utility of calcium channel blockers for prevention/treatment of diabetic nephropathy alone or as an adjunct to renin-angiotensin-aldosterone system blockade based on current evidence.

- **Pharmacy technician objectives:**
  - Describe the mechanisms in which calcium channel blockers are proposed to prevent the progression of diabetic nephropathy.
  - Understand the place in therapy of calcium channel blockers for the prevention/treatment of diabetic nephropathy.
Abbreviations

- **ACE-inhibitor** = angiotensin converting enzyme inhibitor
- **ARB** = angiotensin receptor blocker
- **SCr** = serum creatinine
- **NE** = norepinephrine
- **CCB** = calcium channel blocker
- **Non-DHP** = non-dihydropyridine
- **DHP** = dihydropyridine
- **T2DM** = type 2 diabetes mellitus
- **UACR** = urine albumin: creatinine ratio
Diabetes and Nephropathy

- Now termed “diabetic kidney disease”
- Multiple mechanisms that lead to tissue damage at play
- Standard of care:
  - Control blood glucose
  - Control blood pressure
  - Renin-angiotensin-aldosterone system blockade
    - ACE-inhibitors or ARBs
    - For those with albuminuria

Soldatos G. Diabetes Res Clin Pr. 2008; 82S: s75-s79.
Clinical Case Scenarios

- You have a patient in your clinic with type 2 diabetes mellitus who has confirmed albuminuria. This patient is unable to tolerate ACE-inhibitors or ARBs due to hyperkalemia and increased SCr (doubled) with prior use.

- You have a patient in your clinic with type 2 diabetes mellitus, already on an ACE-inhibitor, with noted progression of diabetic kidney disease.
Calcium channels and the Kidney

- Types of calcium channels that impact kidney function
  - L-type:
    - Present in the afferent arteriole
  - T-type
    - Present in the afferent and efferent arteriole
  - N-type
    - Present on sympathetic nerve endings
    - Activation $\rightarrow$ NE release $\rightarrow$ renin secretion and decreased renal blood flow
    - Affects both afferent and efferent arterioles

Adapted from www.pulmcrit.org
Can CCB’s provide additional nephroprotection independent of blood pressure lowering?
Not all calcium channel blockers are created equal

- Non-dihydropyridine calcium channel blockers
  - Verapamil, Diltiazem
  - More cardioselective

- Dihydropyridine calcium channel blockers
  - “Traditional” DHP CCB
    - Block L-type calcium channels on vascular smooth muscle → BP lowering
    - Examples: amlodipine, nifedipine, felodipine
  - “Novel” DHP CCB
    - Block N-type or T-type calcium channels in addition to L-type
    - Examples: cilnidipine (L-/N-types), benidipine (L-/T-types), efonidipine (L-/T-types)
    - Not yet available in the U.S.

Non-DHP CCB and Diabetic Kidney Disease

- Appear to reduce albuminuria more so than “traditional” DHP CCB
  - Thought to reduce glomerular membrane permeability
- Conflicting evidence:
  - Comparing Non-DHP CCB to DHP CCB
    - Non-DHP CCB reduce albuminuria > DHP CCB
    - Independent of blood pressure lowering
  - Non-DHP added to ACE-inhibitor
    - No added benefit of non-DHP when added to ACE-inhibitor for prevention of microalbuminuria (BENEDICT-A, BENEDICT-B)
    - No difference in decrease in albuminuria with non-DHP CCB vs DHP CCB added to ACE-inhibitor (Toto et al 2008)

DHP-CCB and Diabetic Kidney Disease

- **“Traditional” DHP-CCB**
  - Dilate afferent arterioles only
  - Studied: Nifedipine, Amlodipine, Nicardipine, Felodipine, Isradipine, Nisoldipine
  - Overall, no benefit seen for reducing proteinuria with or without ACE-inhibition

- **“Novel” DHP-CCB**
  - Dilate afferent and efferent arterioles
  - Appear more effective in reducing albuminuria compared to L-type only calcium channel blockers

References:
## Evidence with “novel” DHP-CCB: Cilnidipine vs L-type CCB

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Duration</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLEARED</strong></td>
<td>Fukumoto S, et al. 2011.</td>
<td>T2DM UACR &lt;300mg/g</td>
<td>Crossover 6 months each</td>
<td>Cilnidipine vs L-type CCB</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Decreased UACR with cilnidipine</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Prolonged effect of cilnidipine on UACR</td>
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<tr>
<td>Masuda T, et al. 2011</td>
<td>HTN T2DM group</td>
<td>Crossover 8-9 months each</td>
<td>Cilnidipine vs Amlodipine</td>
<td>UACR lower with cilnidipine use</td>
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<tr>
<td><strong>SAKURA</strong></td>
<td>Ando K, et al. 2012.</td>
<td>T2DM UACR 30-300mg/d RAS inhibition</td>
<td>12 months</td>
<td>Cilnidipine vs amlodipine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UACR decreased more with cilnidipine initially (3 to 6 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant difference seen after 12 months</td>
</tr>
</tbody>
</table>

T2DM: Type 2 Diabetes Mellitus  
UACR: Urinary Albumin Creatinine Ratio  
RAS: Renin-Angiotensin System
Evidence with “novel” DHP-CCB:

Cilnidipine + RAS inhibitor vs RAS inhibitor alone

<table>
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<tr>
<td>Katayama K, et al. 2006.</td>
<td>T2DM UACR &lt;300mg/g</td>
<td>12 months</td>
<td>Valsartan vs valsartan + cilnidipine</td>
<td>Greater UACR reduction in combination group vs valsartan alone</td>
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</table>
Evidence with “novel” DHP-CCB: T-type CCB

<table>
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<td>Sasaki H, et al. 2009</td>
<td>T2DM HTN Nephropathy (UACR &gt;300mg/g) On candesartan</td>
<td>12 months</td>
<td>Efonidipine vs amlodipine</td>
<td>Decrease in eGFR and increase in UACR with amlodipine No change in renal function with efonidipine</td>
</tr>
<tr>
<td>Abe M, et al. 2010</td>
<td>CKD stages 3-5 UACR ≥ 300mg/g HTN ~50% diabetic nephropathy On max dose ARB</td>
<td>12 months</td>
<td>Benidipine vs Cilnidipine</td>
<td>Decrease in UACR in both groups (no significant difference between groups)</td>
</tr>
</tbody>
</table>
Clinical Case Scenarios – What are your recommendations?

- You have a patient in your clinic with type 2 diabetes mellitus who has confirmed albuminuria. This patient is unable to tolerate ACE-inhibitors or ARBs due to hyperkalemia and increased SCr (doubled) with prior use.

- You have a patient in your clinic with type 2 diabetes mellitus, already on an ACE-inhibitor, with noted progression of diabetic kidney disease.
Conclusions

- Limited evidence to support use of specific CCBs available in the US for prevention of progression of diabetic kidney disease
- Evidence that blocking N-type and T-type calcium channels provide benefit to prevent or delay progression of diabetic kidney disease
- Novel CCB will hopefully become available in the US that can be utilized for prevention of progression diabetic kidney disease in addition to RAAS inhibition and in those unable to tolerate ACE-inhibitors or ARBs
Assessment Question #1

Blockade of which calcium channels will lead to dilation of both afferent and efferent glomerular arterioles?

A. L-type and C-type
B. C-type and T-type
C. N-type and T-type
D. N-type and C-type
Which of the following calcium channel blockers has shown to decrease urine albumin: creatinine ratio in patients with diabetic kidney disease or at risk for developing diabetic kidney disease?

- A. Amlodipine
- B. Cilnidipine
- C. Nifedipine
- D. Felodipine


References