I Got You Babe!
Translating Research Into Practice

Please Logon to: ascp.com/qa and Find the Session Title to Ask your Questions

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2019 ASCP Annual Meeting & Exhibition
Aged to Perfection
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Speaker Bios

- **Amie Taggart Blaszczyk, Pharm.D., BCGP, BCPS, FASCP** is an Associate Professor and Division Head of Geriatrics at the Texas Tech University HSC School of Pharmacy on the Dallas/Fort Worth campus. She is married to the foxy Dr. Scott Blaszczyk.

- **Scott Blaszczyk, Pharm.D., BCGP** is the Director of Consultant Pharmacists with Advanced Healthcare Solutions, LLC. He thinks Amie Blaszczyk has the prettiest green eyes.
Disclosure

Dr. Amie Blaszczyk and Dr. Scott Blaszczyk have no conflicts with regard to the content of this presentation.

Learning Objectives

By the end of the session, the learner should be able to:
1. Assess the basic statistical tests and concepts for appropriateness and applicability
2. Analyze and assess current medical literature for clinical value
3. Design a recommendation for an older adult taking into account the state of the science and the realities of the senior care environment
Self-Assessment Question #1

You are reading your favorite journal and note in the current piece you are reading that the primary endpoint shows the following hazard ratio: HR 0.57 (0.44 – 0.67). Which of the following is true?

A. This HR is statistically significant
B. This HR is not statistically significant
C. This HR is clinically significant
D. This HR is not clinically significant
Types of Statistics

• Descriptive statistics – describes a sample population
  • Measures of central tendency
    • Mean, median, mode
  • Measures of spread
    • Range, interquartile range
    • Standard deviation, standard error of the mean

• Inferential statistics – using sample populations to make inferences/draw conclusions about larger populations
  • Parameter estimation
  • Hypothesis testing

Hypothesis Testing

• Null hypothesis ($H_0$)
  • No true difference exists between groups
  • Power is important here

• Alternative hypothesis ($H_1$)
  • A true difference exists between groups
Hypothesis Testing

Types of error
Type 1 error (α) – reject H₀ when it is true
Type 2 error (β) – accept H₀ when it is false

Types of error
Type 1 error (α) – to falsely reject H₀ when it is actually true
Type 2 error (β) – to accept H₀ when it is actually false

Decision
Accept H₀
Correct Decision (CI, 1-α)
Type II Error (β)

Reject H₀
Type I Error (α)
Correct Decision

Reality

H₀ True
H₀ False
Hypothesis Testing

• Power
  • Probability that a statistical test can detect a significant difference when in fact one truly exists

• p-value
  • Calculated probability of type 1 error
  • Does not indicate clinical significance

• Confidence Interval
  • Confidence that the true population value falls within the range
  • Can be used to interpret significance
    • Look for no difference
      • Mean value – not statistically significant if it contains zero
      • Odds ratio or relative risk – not statistically significant if it contains one

<table>
<thead>
<tr>
<th>Type of Data</th>
<th>Two Independent Samples</th>
<th>Related or Paired Samples</th>
<th>3 or more Independent Samples</th>
<th>3 or more Related Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal</td>
<td>1. Chi-square</td>
<td>McNemar Test</td>
<td>Chi-square for k independent samples</td>
<td>Cochran Q</td>
</tr>
<tr>
<td></td>
<td>2. Fisher’s Exact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ordinal</td>
<td>1. Mann-Whitney U</td>
<td>1. Sign test</td>
<td>Kruskal-Wallis one way ANOVA</td>
<td>Freidman 2 way ANOVA</td>
</tr>
<tr>
<td></td>
<td>2. Wilcoxon Rank Sum</td>
<td>2. Wilcoxon Signed Rank</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>1. Student’s t-test</td>
<td>Paired t-test</td>
<td>1-way ANOVA</td>
<td>2-way ANOVA</td>
</tr>
<tr>
<td></td>
<td>2. Mann-Whitney U</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-Inferiority Trials

• Determine whether one intervention is therapeutically similar to another
  • New treatment is not worse (or better) than the old treatment
  • Margin of non-inferiority
• Investigators can decide to do superiority testing if non-inferiority is met, but should be determined a priori
• Null hypothesis is different
  • New therapy is less effective than current therapy

Types of Studies

• Cross-sectional studies
• Case-control
• Cohort
  • Retrospective
  • Prospective
• Randomized, controlled clinical trial

Observational trials

Experimental trials
Bias & Validity

• Types of bias
  • Recall bias
  • Information bias
  • Selection bias
  • Sampling errors
  • Confounding

• Validity
  • Internal validity
    • Issues within the trial which make interpretation difficult
  • External validity
    • Issues with methods that make generalizability difficult

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Do anticholinergic medications cause dementia?

Self-Assessment Question #2

According to the research by Coupland, et al, which of the following medication classes had no increased risk of dementia associated with it?

A. Antidepressants
B. Bladder antispasmodics
C. Antihistamines
D. Antipsychotics

Coupland, et al

• Primary aim
  • “...assess the association between cumulative anticholinergic drug use and risk of dementia...”

• Trial design
  • Nested case-control
  • Retrospective
  • Database
    • Qresearch database
      • 30 million individuals
      • 1500 general practices in the UK
Trial Design

• Inclusion
  • Cohort
    • All patients ≥ 55 years
    • No dementia at study entry
  • Cases
    • Those diagnosed with dementia during follow-up period
      • Diagnosis OR acetylcholinesterase inhibitor prescription
    • Five controls matched to cases

• Exclusion
  • Huntington’s, Parkinson’s, Creutzfeldt-Jakob, HIV, multiple sclerosis

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Trial Design

• Exposures
  • Drugs with anticholinergic properties
    • 2012/2015 American Geriatrics Society Beers’ List
    • High anticholinergic burden on Anticholinergic Cognitive Burden scale
    • Systematic review identification of “high-potency anticholinergics”
    • Additional drugs from British National Formulary
  • Exposure in year before index date not counted
  • All medications were standardized to “total standardized daily doses”
  • Primary exposure variable
    • Cumulative anticholinergic drug exposure from 1 to 11 years before the index date

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Results

• 58,769 cases – 225,574 controls
• Average age: 82.4 ± 7.0 years
• Women: 63.1%
• Prescription of anticholinergics
  • 56.6% of cases vs. 51.0% of controls
  • Median: 6 in cases vs. 4 in controls
  • Most common classes
    • Antidepressants
    • Antivertigo/antiemetic drugs
    • Bladder antimuscarinics

Cumulative Anticholinergic Burden (% of pts in group) | Adjusted Odds Ratio (Confidence Interval)
--- | ---
Nonuse (43.4%) | 1 (Ref)
1 – 90 (21.4%) | 1.06 (1.03–1.09)
91 – 365 (10.8%) | 1.17 (1.13–1.21)
366 – 1095 (7.7%) | 1.36 (1.30–1.41)
> 1095* (16.7) | 1.49 (1.44–1.54)

* 1095 ~ 3 years of daily use of the minimum effective dose of a strong anticholinergic medication

Results

<table>
<thead>
<tr>
<th>Class of Medication</th>
<th>Adjusted Odds Ratio (Confidence Interval) for &gt; 1095</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>1.70 (1.53-1.90)</td>
</tr>
<tr>
<td>Bladder antispasmodics</td>
<td>1.65 (1.56-1.75)</td>
</tr>
<tr>
<td>Antiparkinson drugs</td>
<td>1.52 (1.16-2.00)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>1.39 (1.22-1.57)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.29 (1.24-1.34)</td>
</tr>
</tbody>
</table>

No increases in risk seen with: antihistamines, skeletal muscle relaxants, antiarrhythmics, antimuscarinic bronchodilators, GI antispasmodics

Subgroup Analyses

- In > 1095 group
  - Diagnosed before 80 years: 1.81 (1.71-1.91) vs. 80 years and older: 1.35 (1.30-1.40)
  - Similar association between men and women
  - Vascular dementia: 1.68 (1.57-1.79); Alzheimer’s dementia: 1.37 (1.30-1.44)
Strengths & Limitations

• **Strengths**
  - Large study with matched controls
  - Attempts to standardize exposure to anticholinergics
  - Several confounding variables accounted for

• **Limitations**
  - Association ≠ Causality
  - Patients with undiagnosed dementia could have been controls
  - What about OTCs? PRNs?
  - Little diversity of participants

The Academic’s Conclusions

• Continues to add to the body of evidence that anticholinergics may contribute to dementia
• Little reductions might make a difference
The Practitioner’s Takeaway

• Pre-read: Anticholinergic use is relevant regardless of risk of future dementia.
• Post-read: Regardless of length of stay or current diagnosis priority should be given to anticholinergic burden.

The Practitioner’s Takeaway

• Main Offenders: 1st generation antihistamines, Urinary incontinence agents, Antidepressants (TCAs), Antiemetics, Antipsychotics
• Tool to evaluate anticholinergic load
  • Beers List
  • Anticholinergic burden scales:
    Anticholinergic Drug Scale (ADS)
    Anticholinergic Cognitive Burden Scale (ACB)
    Anticholinergic Risk Scale (ARS)
The Practitioner’s Takeaway

• Is delaying dementia still necessary for long stay residents?
• Should we still reduce anticholinergic load for those already diagnosed with dementia?
• What about bed bound residents? No risk of falls. Should we still try and minimize anticholinergic medications?
• Antihistamines not identified as risk of dementia in article, but the class is one of our main offenders for anticholinergic load contributing to falls and confusion.

• Verify diagnosis for anticholinergic drugs
  • Benadryl for sleep? Better options
• Polypharmacy
  • Is the Lasix the reason for the Oxybutynin? Adjust dosing times
  • Is decreasing urgency still necessary?
• Monitor for unused PRNs for low hanging fruit DC.
Self-Assessment Question #2

According to the research by Coupland, et al, which of the following medication classes had no increased risk of dementia associated with it?

A. Antidepressants
B. Bladder antispasmodics
C. Antihistamines
D. Antipsychotics

33
Is trazodone a better option?


Self-Assessment Question #3

True or False. Trazodone is a safer option than quetiapine when it comes to falls and major osteoporotic fractures.

A. True  
B. False
Watt, et al.

- **Primary aim**
  - To compare the risk of several outcomes between trazodone and atypical antipsychotics in older adults with dementia
    - Composite: falls and major osteoporotic fractures
    - Individually: falls, major osteoporotic fractures, hip fractures and all-cause mortality

- **Trial design**
  - Retrospective cohort study

### Trial Design

- **Data Sources**
  - Databases from Ontario, Canada
    - Individuals 65 years and older
    - Several different patient-level databases were used
      - Medications, Physicians, Mental Health, Ambulatory Care, etc.

- **Inclusion**
  - Patients newly prescribed trazodone or an atypical antipsychotic medication between 12/1/09 – 12/31/15
  - Full interRAI assessment within 30 days of entry into cohort
  - Aged 66 or older with dementia
  - Living in long-term care facilities
Trial Design

• Exclusion
  • Incomplete interRAI
  • Receipt of any antipsychotic or trazodone within 1 year
  • Prescribed two or more target medications on the index date
  • Palliative care within 180 days of cohort entry
  • Study drugs in question were given above a maximum dose
    • > 300 mg trazodone, > 3 mg risperidone, > 300 mg quetiapine, > 10 mg olanzapine
    • > 105 years

interRAI – international resident assessment instrument

Results

• Cohort of 9463 patients
  • Average age: 85.3 ± 7.2 years
  • Female: 68.7%
  • Medications used
    • Trazodone: 6588
    • Atypical antipsychotic: 2875
      • Quetiapine – 52.6%
      • Risperidone – 37.9%
      • Olanzapine – 9.6%
Results

• Primary
  • Rates of falls and fractures similar between two groups
    • HR 0.89 (95% CI 0.73 - 1.07)

• Secondary
  • Falls (HR 0.91 [95% CI 0.75-1.11])
  • Major osteoporotic fracture (HR 1.03 [95% CI 0.73-1.47])
  • Hip fracture (HR 0.92 [95% CI 0.59-1.43])
  • All-cause mortality (HR 0.75 [95% CI 0.66-0.85])


Strengths & Limitations

• Strengths
  • Large sample
  • Looked at appropriate time window
  • Accounted for appropriate confounders in propensity score analysis

• Limitations
  • Cohort study
  • Power?
  • External validity
  • Scheduled vs. PRN use – could this have had an impact

The Academic’s Conclusions

• When it comes to outcomes we care about, low-dose trazodone may not be the safer alternative we had hoped
• Potential safety from a mortality standpoint of trazodone is not new news

The Practitioner’s Takeaway

• Pre-read: I’m sticking with trazodone
• Post-read: Continue with trazodone, but share the risks that it is not as harmless as previously thought.
The Practitioner’s Takeaway

• Doses cited in the article seem excessive.
  • Zero trazodone 300mg in dementia in my caseload.
• Study is Canadian.
  • Risperidone is approved for symptomatic management of aggression or psychosis restricted to severe dementia of the Alzheimer’s type.

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The Practitioner’s Takeaway

• Trazodone does not carry the Black Box Warning of antipsychotics
  • Not on surveyor’s radar
• GDR to DC of trazodone may be easier to achieve than GDR of antipsychotic.
• As stated in the article, trazodone is not without it’s own risks.
  • Orthostatic Hypotension
    • Dose-related
  • QTc prolongation

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The Practitioner’s Takeaway

• Actively trying to DC low dose antipsychotics (<Seroquel 50mg) and offer trazodone as alternative.
  • Regulatory rationale

Self-Assessment Question #3

True or False. Trazodone is a safer option than quetiapine when it comes to falls and major osteoporotic fractures.
  A. True
  B. False
Self-Assessment Question #3

True or False. Trazodone is a safer option than quetiapine when it comes to falls and major osteoporotic fractures.

A. True
B. False

Bisphosphonates in the frail elderly: is it really a good idea?

Self-Assessment Question #4

Which of the following is an appropriate medication for prevention of hip fracture in a frail elderly patient residing in LTC?

A. Alendronate  
B. Calcitonin  
C. Calcium citrate  
D. No treatment is appropriate in a frail elderly patient residing in LTC

Zullo, et al.

• Primary Aim
  • To compare effectiveness of bisphosphonates for the treatment of hip and non-vertebral fracture and safety in causing hospitalization secondary to esophagitis

• Trial Design
  • Retrospective cohort  
  • Utilized MDS, OSCAR data and Medicare claims

Trial Design

• Inclusion
  • Long-stay resident 65 years of age and older
  • New users of a bisphosphonate (PO or IV) or calcitonin after admission to nursing home

• Exclusion
  • Less than 365 days of continuous enrollment in Medicare A, B and D
  • Medicare Advantage enrollment at any time
  • Dispensed bisphosphonate and calcitonin on the same day
  • Hospice or very severe cognitive impairment
  • Paralyzed or quadriplegic
  • MDS completed > 100 days before drug started

Results

• Final cohort
  • 5209 bisphosphonate users and 5209 calcitonin users
  • Average age: 85 ± 8 years
  • 87.1% women
  • Average follow-up: 2.4 ± 1.7 years
Results

• Primary outcomes
  • Rate of hip fracture: HR 0.83 (95% CI 0.71-0.98)
    • NNT over 3 years: 239
    • NNT over 6 years: 154
  • Rate of non-vertebral fracture: HR 0.91 (95% CI 0.80-1.03)
  • Esophagitis: HR 1.11 (0.84-1.47)

Strengths & Limitations

• Strengths
  • External validity
  • Follow-up timeframe appropriate
  • Active comparator rather than placebo

• Limitations
  • Cohort study
  • Unknown confounders could influence
  • No ability to look at IV separately
  • Outcome of hospitalized esophagitis isn’t the same as a patient experiencing issues
The Academic’s Conclusions

• Meh...
• NNT not super stellar
• Residents in LTC are undertreated for osteoporosis, and every fracture is one that potentially can be avoided
• Can feel a bit better that there was no increased risk of hospitalization for esophagitis when recommending a bisphosphonate
• Not every article is a winner...


The Practitioner’s Takeaway

• Pre-read: Many residents could probably benefit from addition of bisphosphonate
• Post-read: Number needed to treat seems high, but a more targeted approach to bisphosphonate initiation may be worthwhile
The Practitioner’s Takeaway

• No DEXA scans
• Target males and females?
• Once weekly dosing administration errors
• Restrictive administration; perhaps leading to GERD and H2 or PPI use.
• Typically adding Calcium + Vitamin D at the same time. Need to balance prescriber concerns regarding deprescribing.
• Continue indefinitely or engage drug holidays?

Self-Assessment Question #4

Which of the following is an appropriate medication for prevention of hip fracture in a frail elderly patient residing in LTC?

A. Alendronate
B. Calcitonin
C. Calcium citrate
D. No treatment is appropriate in a frail elderly patient residing in LTC
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A. Alendronate  
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D. No treatment is appropriate in a frail elderly patient residing in LTC

Wrapping it up

• Amie  
  • Don’t just read the abstract  
  • Don’t be afraid to put references in your recommendations  
• Scott  
  • What can I put into practice on Monday?  
  • Looking at the whole resident. There is a tie that binds between the articles. Perhaps the high anticholinergic and trazodone/antipsychotic population is a good candidate for initiating bisphosphonates  
  • Even as practicing consultant pharmacists, we need to understand biostats to get past the abstract and understand the journal articles that can improve our practice  
  • I’m ready to do journal club with my wife!
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Resources for further study

• Biostatistics
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• Biostatistics

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