Appointments

- Research Health Scientist at Bedford VAMC
- Research Assistant Professor at BU School of Public Health
- Second Year of HSR&D CDA
Poll Question

What is your primary role in VA?

- student, trainee, or fellow
- clinician
- researcher
- Administrator, manager or policy-maker
- Other
Poll Questions

- Are you involved with any aspect of testosterone therapy?
  - Yes
  - No

- If you are involved with testosterone therapy, how are you involved?
  - I am involved in research on testosterone therapy
  - I am involved in prescribing of testosterone therapy
  - I am involved in formulating policy on testosterone therapy.
Broader HSR&D Themes

- Guideline-Concordant Prescribing

- Variation in Prescribing at Different Levels

- Mixed-methods Approach in Understanding Prescribing

- Best Practices and De-implementation of Practices
Aims of CDA

- Aim 1: To identify quantitative patient-, provider-, and site-level predictors of testosterone prescribing in the VA.

- Aim 2: To understand patient, provider, and site-leader perceptions towards testosterone prescribing in the VA.

- Aim 3: To develop and pilot test a multifaceted intervention to optimize testosterone use in the VA.
CDA-Mentoring Team

- Dan Berlowitz (Primary Mentor): Quality of Care
- Allen Gifford: Implementation Science
- Barbara Bokhour: Qualitative Methods
- Adam Rose: Medication Prescribing
- Shalender Bhasin: Hormone Therapy
Outline of Presentation

- Background: Testosterone therapy

Work Completed:

- #1: Assessment of Testosterone Prescribing Practices (Aim 0)
- #2: Patient Predictors of Testosterone Prescribing (Aim 1)
- #3: Provider and Site Predictors of Testosterone Prescribing (Aim 1)
Outline of Presentation

Work in Progress:

- #1: Qualitative: Understanding Patient, Provider, and Site Leader Perceptions towards Testosterone Prescribing (Aim 2)
- #2: QI project: Testosterone order check (Extra work)
- #3: Database: Testosterone Prescribing in Patients with HIV (Extra work)
- #4: Database: Effect of Testosterone Therapy on patients taking opioids (Extra work)
Poll Question

Do you know what low testosterone is?

- Yes
- No
Testosterone: Male hormone

- **Age-related decline:** After age 30 ~ 1% per year

- **Causes of low testosterone:** injury to testicles, genetic abnormalities, medications & illnesses.

- **Effects of low testosterone:** decreased libido, muscle mass, bone density, hemoglobin, increase in weight, cholesterol.

- **Treatment:** Testosterone Therapy (Symptoms + Low Testosterone Levels)
Testosterone Therapy

Contraindications:

- Absolute: Prostate and Breast cancer
- Relative: Untreated Obstructive Sleep Apnea
- Relative: PSA > 4 ng/ml ; Elevated hematocrit

Measurement of low T:
- Initial diagnostic test (before 10 am)
- Confirmation of diagnosis by repeat test
Testosterone Therapy

Benefits:
- Proven: Increased muscle mass, bone strength.
- Potential: Improved cognition

Risks:
- Proven: Increase in red blood cells, growth in prostate cancer, reduced sperm production
- Potential: Cardiovascular problems

FDA approval of T: Classical hypogonadism (disorders of testes, pituitary, and hypothalamus)
Testosterone Therapy

- In patients with HIV/AIDS
- In transgender populations
- Primarily for hypogonadism/androgen deficiency (low T levels)

Current VA Guidelines:

- Pharmacy Benefits Management (PBM) issued criteria for use (CFU) for testosterone therapy in adult men in 2016.
Trends in Testosterone Prescribing

- Three fold increase in the US in the last decade
- Peaked in 2013 and has been decreasing since
- Use remains many-fold higher than it was in 2000.

Reasons for increase in prescribing:
- Aggressive direct-to-consumer marketing
- Establishment of low “T” clinics
- Establishment of internet pharmacies in Canada
- Availability of transdermal preparations of testosterone
- Ambiguity of guidelines to distinguish between age-related decline of testosterone and classical hypogonadism

Declining trend due to heightened FDA activity and media stories.
Proportion of Male Veterans Receiving Testosterone, FY2008-16

(Jasuja et al., Patterns of Testosterone Prescription Overuse, Curr Opin Endocrinol Diabetes Obes, 2017)
Work Completed
**Objective:** To examine whether testosterone therapy was preceded by appropriate ascertainment of androgen deficiency and potential contraindications, in accordance with practice guidelines.

*(Jasuja et al., Ascertainment of Testosterone Prescribing Practices in the VA, Medical Care, 2015).*
Methods

- Cross-sectional (FY 2009-12)
- N=111,631 male Veterans
- 1 year “look back” to check for tests & contraindications
- “Low” testosterone: total testosterone < 300 ng/dL
  free testosterone < 70 pg/mL
- Exclusions:
  - HIV positive
  - Received testosterone prescription before FY2009
  - No evidence of care in the VA in FY2008
New testosterone prescriptions increased from 20,581 in FY09 to 36,544 in FY12 (~78% increase).
## Baseline Assessment and Contraindications Before Initiation

<table>
<thead>
<tr>
<th>Baseline Assessment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement of baseline PSA level</td>
<td>76%</td>
</tr>
<tr>
<td>Measurement of baseline hematocrit level</td>
<td>84%</td>
</tr>
<tr>
<td>Measurement of baseline hematocrit and PSA levels</td>
<td>68%</td>
</tr>
<tr>
<td>Documentation of Hypogonadism by ICD-9 code</td>
<td>59%</td>
</tr>
<tr>
<td>Relative Contraindications</td>
<td></td>
</tr>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>7.5%</td>
</tr>
<tr>
<td>Elevated Hematocrit (&gt;50%)</td>
<td>3.5%</td>
</tr>
<tr>
<td>PSA level &gt; 4.0</td>
<td>2.3%</td>
</tr>
<tr>
<td>Any Relative Contraindication</td>
<td>13%</td>
</tr>
<tr>
<td>Absolute Contraindications</td>
<td></td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>1.4%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.01%</td>
</tr>
<tr>
<td>Any Absolute Contraindication</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
Baseline Evaluation

- T checked: 83.5%
- at least 1 low T: 76.8%
- 2 low T: 18.3%
- 2 low T am: 5.4%
- 2 low T am LH/FSH: 3.5%
- + 2 low T am LH/FSH no contra: 3.1%

Diagnostic and Baseline Evaluation
Sensitivity Analysis

- We used Medicare data to examine testosterone levels checked outside of the VA.

- Of the patients who had no testosterone levels in the VA at all (n=18,457), 8,237 (about half) were enrolled in fee-for-service Medicare.

- Of these, 48% had undergone testosterone testing outside VA.
Conclusions

- Only a small proportion of men receiving testosterone in VA underwent appropriate testing.
- Some received this therapy in spite of important contraindications.
- Promoting a more uniform application of clinical guidelines may facilitate appropriate use of testosterone.
Objective: To evaluate patient characteristics associated with receipt of testosterone in the VA.

Methods

- Cross-sectional (FY 2008-12)
- N=682,915 male Veterans
  (“On Testosterone”=132,764; “Not on Testosterone”=550,151)
- 1 year “look back” to check for diagnoses and medications
- Exclusions:
  - HIV positive
  - Received fills only in FY 08
  - No evidence of fills in the VA in FY 08
  - Patients with diagnosed conditions of testes, pituitary and hypothalamus (Classical hypogonadism)
  - Patients with identified gender disorder
Findings

- Only 6.3% of men on testosterone had classical hypogonadism.

- Demographics (age 40-55, White race), conditions (sleep apnea, depression, diabetes) and medications (antidepressants, corticosteroids) associated with higher testosterone receipt (AOR less than 2; \(p<0.001\)).

- Use of opioids (>100 mg equiv. of oral morphine daily) and obesity (>40 kg/m\(^2\)) were strongest predictors of testosterone.
Findings

Opioid Dosage as a Determinant of Testosterone Receipt

- unadjusted
- fully adjusted

Odds Ratio

Oral Opioid Dosage (morphine-equivalent mg/day)

0 0.002-1 1-5 5-10 10-20 20-40 40-100 >100
Findings

cEIPT

unadjusted

fully adjusted
Conclusions

- Though obesity and opioid use is associated with unapproved, off-label use however, they may be valid reasons for receiving this therapy.

- Need for greater understanding of the context within which testosterone is prescribed.
Objective: To evaluate provider-and site-level determinants of testosterone in the VA.

(Jasuja et al., Provider and Site-Level Determinants of Testosterone Prescribing in the Veterans Healthcare System. JCEM, 2017)
Methods

- Cross-sectional (FY 2008-12)
- N=683,135 patients; N=38,659 VA providers; N=130 stations
- Associated provider who wrote index prescription
- Associated site where the patient had most encounters
## Findings: Provider Predictors (Adjusted Model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (31-40) vs. 61+</td>
<td>1.14 (1.11-1.16)</td>
</tr>
<tr>
<td>Age (41-50) vs. 61+</td>
<td>1.15 (1.13-1.17)</td>
</tr>
<tr>
<td>Age (51-60) vs. 61+</td>
<td>1.13 (1.11-1.16)</td>
</tr>
<tr>
<td>Years in VA (&lt;=1 year)</td>
<td>1.19 (1.17-1.22)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.04 (1.03-1.06)</td>
</tr>
<tr>
<td>MD, Endocrinology vs. MD, PCP</td>
<td>2.14 (2.00-2.29)</td>
</tr>
<tr>
<td>MD, Urology vs. MD, PCP</td>
<td>1.42 (1.23-1.63)</td>
</tr>
</tbody>
</table>
## Findings: Site Predictors (Adjusted Model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region: West vs. Northeast</td>
<td>1.75 (1.45-2.11)</td>
</tr>
<tr>
<td>Region: South vs. Northeast</td>
<td>1.63 (1.36-1.95)</td>
</tr>
<tr>
<td>Region: Midwest vs. Northeast</td>
<td>1.37 (1.13-1.67)</td>
</tr>
<tr>
<td>Care received at CBOC</td>
<td>1.22 (1.20-1.24)</td>
</tr>
</tbody>
</table>
Methods

- Appropriateness prescribing in new T patients FY09-12
  (N=99,102 patients; N=12,912 providers; N=129 sites)

- 3 levels of appropriate prescribing
  - Minimal: At least one low testosterone levels
  - At least two low testosterone levels
  - Maximal: At least two low AM testosterone levels
### Findings: Provider Predictors of Appropriate Prescribing

<table>
<thead>
<tr>
<th>Variable</th>
<th>2 AM Low T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider age (31-40)</td>
<td>1.30 (1.12-1.50)</td>
</tr>
<tr>
<td>Provider age (41-50)</td>
<td>1.14 (1.00-1.30)</td>
</tr>
<tr>
<td>Provider age (51-60)</td>
<td>1.12 (1.00-1.26)</td>
</tr>
<tr>
<td>Provider years in VA (&lt;=1)</td>
<td>0.82 (0.72-0.94)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.88 (0.81-0.96)</td>
</tr>
<tr>
<td>MD, Endocrinology</td>
<td>2.14 (1.54-2.97)</td>
</tr>
</tbody>
</table>
## Findings: Site Predictors of Appropriate Prescribing

<table>
<thead>
<tr>
<th>Variable</th>
<th>2 AM Low T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region: South</td>
<td>0.80 (0.72-0.90)</td>
</tr>
<tr>
<td>Care received at CBOC</td>
<td>0.83 (0.77-0.90)</td>
</tr>
<tr>
<td>Most complex sites</td>
<td>1.33 (1.18-1.49)</td>
</tr>
</tbody>
</table>
Findings highlight the opportunity to intervene both at the provider and site-level to improve testosterone prescribing.

Beyond testosterone, this study provides an example of how to examine contributions to prescribing variation at different levels of the healthcare system.
Work in Progress
#1: Qualitative: Aim 2 of CDA

- Aim 2: To understand patient, provider and site-leader perceptions towards testosterone prescribing in high and low testosterone prescribing sites using qualitative methods

- Completed 22 provider and local leader and 15 interviews with Veterans at 3 high and low sites

- Ongoing: Coding and data analyses
#2: Quality Improvement project

- Development and Implementation of a Testosterone order check: Dr. Eric Shirley, VISN 1 Director of Primary Care
- Alert providers about clinical recommendations in CPRS before prescribing
- Provider given the option of continuing or canceling the new order and provide justification for continuing
- **Research Aim:** To test the effectiveness of an order check in reducing new testosterone prescriptions in VISN 1.
- Rolled out in 8 VISN 1 sites in Jan. 2016
- **Next step:** Data analyses: Rate of change in new T prescriptions (Interrupted time series analyses)
#3: Testosterone Prescribing in Patients with HIV

- Use of testosterone in patients with HIV due to hypogonadism and wasting.

- **Objective:** To compare trends/rates, and guideline concordant appropriate testing in testosterone prescribing in HIV vs. non-HIV population

- **Methods:** Comparison of two cohorts (FY08-14):
  - Patients with HIV on T (N=2,484)
  - Non-HIV patients on T (N=189,369)
Trends in Testosterone Prescribing in Patients with HIV vs. Non-HIV Patients

![Graph showing trends in testosterone prescribing from FY08 to FY14 for HIV patients and Non-HIV patients.]
Trends in Testosterone Initiation in Patients with HIV vs. Non-HIV Patients

% of Patients Initiating Testosterone

Date of First Testosterone Prescription

FY09 FY10 FY11 FY12 FY13 FY14

HIV patients Non-HIV patients
Comparison of HIV and non-HIV Patients on Diagnostic and Baseline Evaluation

Diagnostic and Baseline Evaluation

- HIV patients
- Non-HIV Patients
Conclusions

- Trends of prescribing for both groups followed a similar pattern.

- Higher rates of testosterone use in patients with HIV:
  - More androgen deficiency
  - Likelihood of prescribing due to frequent provider visits
  - Greater off-label use in patients with HIV
  - Awareness of testosterone among clinicians who care for patients with HIV

- Findings suggest opportunities for improvement of testosterone treatment practices for HIV-infected men within VHA.
Suppression of hormonal production with opioid use.

Objective: To examine effect of testosterone therapy on mortality and cardiovascular outcomes in patients on long-term opioid therapy.

Methods: Comparison of 2 samples on outcomes:
- Long-term opioids + testosterone
- Only opioids

Analyses: Ongoing
Significance of Work

Important beginning to understand the unknown

- Findings will help in advising VA Operations (Pharmacy Benefits Management) in improving testosterone prescribing in the VA

- Application to other medications for optimal prescribing in the VA

- Fits in with the Medication Optimization Program of Boston/Bedford CHOIR.

- Quantitative findings: Need for improvement in provider prescribing practices for testing and documentation.

- Next step: Development and pilot testing of a multi-faceted intervention to optimize testosterone use in the VA
Acknowledgements

- **Funding**: VA HSR&D Career Development Award No. 13-265

- **Secondary Mentors**
  Joe Hanlon, Donald Miller, Angela Park

- **Operational Partners**
  Len Pogach, Anthony Morreale, Fran Cunningham

- **Project Team**
  Joel Reisman, Omid Ameli, Alex Male, Avy Skolnik, Ryann Engle
Resources

• PBM Clinical Guidance-Criteria For Use of Testosterone Therapy in Adult Men
  http://www.pbm.va.gov/PBMclinicalguidance/criteriaphore/Testosterone_Replacement_in_Adult_Males_Criteria_for_Use.pdf

• FDA Drug Safety Communication on Testosterone
  https://www.fda.gov/Drugs/DrugSafety/ucm436259.htm
Questions/Comments

Contact Information
Guneet K. Jasuja PhD (guneet.jasuja@va.gov)