Evaluation of Appropriateness/Inappropriateness of Medication Prescribing Using the STOPP/START Criteria in Home Based Primary Care Veterans

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Edward Hines, Jr. VA Hospital
No conflict of interest to disclose

Edward Hines, Jr. VA Hospital
• 12 miles west of downtown Chicago
• Tertiary care referral center
• 483 beds
• Serves ~54,000 veterans
• Associated with Loyola University – Stritch School of Medicine

Learning Objectives
• Discuss inappropriate medication prescribing in elderly patients.
• Identify medications with a potential benefit in the elderly population.
• Discuss the use of STOPP/START criteria in elderly Home Based Primary Care Veterans.

Inappropriate Medications in Elderly Population
• Increased risk for adverse drug events
• Adverse drug events responsible for 30% of hospital admissions
• Physiologic changes can alter pharmacokinetic/pharmacodynamic properties
• Often denied potentially beneficial medications

Tools to Assess Inappropriate Prescribing
• Beers’ Criteria
• Improved Prescribing in the Elderly Tool (IPET)
• Medication Appropriateness Index (MAI)
• Assessing Care of Vulnerable Elders (ACOVE)

Screening Tool of Older People’s potentially inappropriate Prescriptions(STOPP)/Screening Tool to Alert doctors to Right Treatments (START) Criteria
• STOPP: 65 clinically significant criteria for potentially inappropriate medication use
• START: 22 evidence based prescribing indicators for commonly encountered disease states
STOPP Criteria

- 10 categories include:
  - Cardiovascular system (17)
  - Central nervous system and psychotropic drugs (13)
  - Gastrointestinal system (8)
  - Respiratory system (3)
  - Musculoskeletal system (6)
  - Urogenital system (4)
  - Endocrine system (4)
  - Drugs that adversely affect fallers (5)
  - Analgesic drugs (3)
  - Duplicate drug classes (1)
  
  Mostly related to Tricyclic Antidepressant use
  
  Aspirin > 150 mg/day
  
  Mostly related to NSAID use
  
  Systemic corticosteroids instead of inhaled corticosteroids for COPD

START Criteria

- 6 categories include:
  - Cardiovascular system (8)
  - Respiratory system (3)
  - Central nervous system (2)
  - Gastrointestinal system (2)
  - Musculoskeletal system (3)
  - Endocrine system (4)
  
  ACE-I in CHF
  
  Regular inhaled β₂ agonist or anticholinergic for asthma or COPD
  
  Antidepressant with moderate/severe depressive symptoms lasting at least 3 months
  
  PPI with severe GERD or peptic stricture requiring dilation
  
  Calcium and vitamin D in patients with known osteoporosis
  
  Antiplatelet therapy in DM with coexisting major CV risk factors

Self Assessment Question #1

The STOPP criteria identify aspirin > 150 mg/day as potentially inappropriate.

A. True
B. False

Self Assessment Question #2

Which medication class affecting the central nervous system is identified most frequently in the STOPP criteria?

A. Benzodiazepines
B. Selective Serotonin Re-uptake Inhibitors
C. Tricyclic Antidepressants
D. Neuroleptics

Previous Trials

- Gallagher et al.³
  - Objective: To compare the performance of the STOPP criteria to the Beers’ criteria
  - Methods: Prospective study of 715 acute admissions
  - Results: STOPP identified 336 potentially inappropriate medications, Beers’ criteria identified 226 potentially inappropriate medications
  - Conclusion: Significant difference in the number of potentially inappropriate medications detected by the STOPP criteria than Beers’ criteria

- Davis et al.⁴
  - Objective: To examine medication appropriateness using MAI and recommendation acceptance associated with pharmacist medication review for veterans enrolled in the home based primary care program
  - Methods: Retrospective analysis
  - Results: Statistically significant decrease in MAI score from initial review to end of study
  - Conclusion: By use of MAI for evaluation, pharmacist recommendations significantly improved appropriateness of medication use
Home Based Primary Care (HBPC) Program

- Provides primary care and outpatient monitoring to patients who are home bound
- Interdisciplinary team approach
- HBPC team reviews each patient within 14 days of admission and every 90 days thereafter
- Pharmacists conduct an evaluation of a patient's medication regimen initially and every 90 days thereafter

Study Purpose

Evaluate appropriateness/inappropriateness of medication prescribing using the STOPP/START criteria in elderly HBPC veterans and understand the potential impact of the HBPC team on the STOPP/START criteria.

Study Design

- Retrospective chart review of patients enrolled in HBPC program from 9/1/07 to 9/30/09
- Patients reviewed using Computerized Patient Record System (CPRS)
- Approved by Institutional Review Board

Study Design: Primary Outcome

- Appropriateness/inappropriateness of medication prescribing using STOPP/START criteria
  - Evaluated by comparing medication list at the initial pharmacist note for medications that met STOPP/START criteria to medication list at follow up note that occurred within 15 weeks
  - Assigning each patient STOPP score and START score
  - Identifying patients with a 2 point improvement in STOPP or START score

Study Design: Secondary Outcome

- Impact of HBPC team on STOPP/START criteria
  - Assessed by examining the number and type of pharmacist recommendations made and accepted regarding:
    - Medications discontinued
    - Medications started
    - Medications renewed
    - Dosage adjustments
    - Drug-drug interactions
    - Drug-disease interactions
    - Monitoring of lab values

STOPP and START Scoring

- "1" assigned for an active prescription
- "0" assigned in the absence of an active prescription
- STOPP: Higher score indicates more inappropriate medications
- START: Higher score indicates more appropriate medications
**Study Design**

- **Inclusion Criteria**
  - Enrolled in HBPC program
  - 65 years or older
  - Initial review and follow up review within 15 weeks

- **Exclusion Criteria**
  - Admission to hospital between initial review and follow up review
  - Admission to HBPC for palliative or hospice care
  - Death prior to completion of second medication review

**Data Collected**

- Demographic information: age, gender, race
- Medication dosages and duration of therapy
- Pharmacist recommendations:
  - Number of recommendations made and accepted
  - Medications discontinued
  - Medications started
  - Medications renewed
  - Dosage adjustments
  - Drug-drug interactions
  - Drug-disease interactions
  - Monitoring of lab values

**Statistical Analysis**

- Baseline characteristics described using counts and percentages for categorical variables and means and standard deviations for continuous variables
- Average STOPP and START score calculated at initial review and compared to follow up score
- Baseline values compared to follow up values using a paired t-test
- Average number of recommendations made and accepted compared between patients with a 2 point change in STOPP or START score
- Estimated 200 patients required to detect a small effect size of 0.2 with 80% power and alpha of 0.05

**Results: Enrollment**

- 311 Charts Reviewed
- 200 patients included
- 111 patients excluded

**Results: Baseline Characteristics**

- **Age**
  - Average age 82.4 years
- **Gender**
  - 96% male
- **Race**
  - 61.5% Caucasian
  - 23% African American
  - 2% Asian
  - 0.5% Hispanic
  - 13% unknown/unanswered

**Results: Primary Outcome**

- **Change in STOPP score and START score**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Follow-up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOPP</td>
<td>1.2</td>
<td>0.885</td>
<td>0.0014</td>
</tr>
<tr>
<td>START</td>
<td>3.3</td>
<td>3.33</td>
<td>0.5720</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th># of patients</th>
<th>Average # of Pharm.D. recommendations in patients with improved score</th>
<th>Average # of Pharm.D. recommendations in patients without 2 point improvement</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOPP</td>
<td>15</td>
<td>10.5</td>
<td>5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>START</td>
<td>8</td>
<td>5.1</td>
<td>3.2</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Results: Secondary Outcome
Average number of type of pharmacist recommendations made and accepted

Study Conclusion: Primary Outcome
• Statistically significant improvement in STOPP score
• Change in START score not found to be statistically significant
• Patients with at least a 2 point improvement in STOPP or START score had statistically significant greater number of pharmacist recommendations made; however, no difference in number of recommendations accepted

Study Conclusion: Secondary Outcome
• Greatest number of pharmacist recommendations made regarding:
  – Monitoring of lab values
  – Discontinuing medications
  – Adjusting dose

Limitations
• Retrospective chart review
• Majority of population Caucasian male
• Short duration of 15 weeks
• Some STOPP/START criteria not clearly defined

Future Direction
• Educate HBPC team to identify commonly encountered STOPP/START criteria to improve medication prescribing
• Evaluation of cost savings associated with recommendations made by HBPC pharmacists and accepted by HBPC team

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References


Establishing Pharmacist-Managed Ambulatory Care Services within a Clinical Cancer Center

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PGY2 Health-System Administrative Resident
Froedtert Hospital
Milwaukee, Wisconsin
August 2010

Objectives

• Discuss why the Breast Care Center (BCC) at Froedtert Hospital (FH) was the pilot site for implementing pharmacist-managed ambulatory care services
• Identify the role of pharmacist-managed ambulatory care services within a cancer center

Conflict of Interest

• No conflicts of interest to disclose

Overview of Presentation

• Background
• Project Purpose
• Breast Care Center Workflow
• Results
• Justification
• Conclusion
HUB model

- Specialized oncology lab
- Clinics separated by disease state
  - Courage
  - Life
  - Hope
  - Faith
  - Breast Care Center
- Day hospital infusion center
- Radiology Oncology
- Retail Oncology Pharmacy

Project Purpose

- To assess the need for pharmacist-managed ambulatory care services within a clinical cancer center

At your organization are there pharmacists within the oncology clinics that provide direct patient care?

1. Yes
2. No
3. Unknown

Breast Care Center at Froedtert Hospital

- Favorable site for piloting pharmacist-managed ambulatory care services
  - Patient need
  - Staff acceptance
  - Patient volume
  - Provides care to over 265 patients each week

Breast Care Center Staff Survey

- A pharmacist located in the BCC would improve the quality of patient care
  - 11 of 11 respondents agreed
- A pharmacist located in the BCC would save me valuable time
  - 9 of 11 respondents agreed
- A pharmacist located in the BCC would improve patient satisfaction
  - 11 of 11 respondents agreed
- Overall, a pharmacist would be a valuable addition to the BCC
  - 11 of 11 respondents agreed

Breast Care Center Work Flow

- Shadow oncology staff members
  - Physicians, mid-level practitioners, nurses, and medical assistants
  - Evaluate potential role for pharmacist interaction
- Build relationships and trust with oncology staff
  - Provide quick and accurate information to medication questions
- Develop intervention tracking tool for categorization
  - Supportive
  - Treatment
  - Financial
Intervention Tracking Tool

<table>
<thead>
<tr>
<th>Date</th>
<th>Visit type</th>
<th>Intervention</th>
<th>Intervention subtype</th>
<th>Acceptance</th>
<th>Patient Outcome</th>
<th>Time w/ intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nurse</td>
<td>treatment</td>
<td>treatment interaction identified</td>
<td>rejected</td>
<td>improved patient</td>
<td>10 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>admission</td>
<td>accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>adverse reaction</td>
<td>accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dose error</td>
<td>rejected</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>before interaction identified</td>
<td>accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>after interaction identified</td>
<td>rejected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacist Typical Day

- 0700-0830
  - Evaluate scheduled patients
- 0830-1200 (AM Oncologist)
  - Visit with select patients
- 1200-1600 (PM Oncologist)
  - Visit with select patients

Intervention Results (n=139)

- Treatment: 26%
- Financial: 12%
- Supportive: 61%

Supportive Care Intervention Results (n=86)

- Supportive: 61%

Supportive Care Intervention Results (n=86)

- Physician Interventions (n=40)
  - Antiemetic: 15%
  - Narcotic: 15%
  - Dosing: 15%
  - Interactions: 15%
  - Other: 25%
  - Side effects: 20%
Supportive Care

Patient Interventions (n=24)

- Bone Health: 50%
- Compliance: 29%
- Other: 21%

Staff Education Tools

Medical Management of Hot Flashes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Effectiveness</th>
<th>Time Frame</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg qAM</td>
<td>25-42% decrease in symptoms</td>
<td>1-2 weeks but may take 4-8 weeks for full effects</td>
<td>Decreased appetite, anxiety, constipation, dry mouth, and nausea</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10-12.5 mg daily</td>
<td>25-32% decrease in symptoms</td>
<td>1-2 weeks but may take 4-8 weeks for full effects</td>
<td>Headache, nausea, somnolence, insomnia, and dry mouth</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg at bedtime titrate up to 900 mg (in divided doses) as needed</td>
<td>16-30% decrease in symptoms</td>
<td>May take 2-3 weeks for full effects</td>
<td>Somnolence, fatigue, dizziness, rash</td>
</tr>
</tbody>
</table>

Treatment Intervention Results (n=36)

- Treatment: 26%
- Physician: 13%
- Other: 3%
- ADR Management: 13%
- Interactions: 41%
- Efficiency Enhancements: 33%

Treatment Intervention Results (n=36)

Financial Intervention Results (n=16)

- Financial: 12%
Financial Interventions (n=16)

New prescriptions sent to outpatient pharmacy
Completion of Prior Authorization
Education about coverage

Number of Interventions

Justification and Financial Impact

- **Customer Service (Patients and Medical Staff)**
  - Assisted medical team with dosing, side effect management/prevention, and educational updates
  - Avoided drug interactions
  - Promoted compliance and osteoporosis prevention

- **Revenue**
  - A 30% increase in the use of the outpatient pharmacy during 12 week pilot ($10,384)
  - Prescription delivered to patients while receiving chemotherapy infusion ($2,440)
  - Combined nursing-pharmacist facility charge

Future Directions

- A business plan was proposed to Froedtert Hospital management which resulted in the expansion of ambulatory pharmacy services
- Continued expansion of combined nursing and pharmacist billing
- Evaluate the need for a collaborative practice agreement to expand pharmacists role
- Explore other areas of the Clinical Cancer Center for expand pharmacy services

Conclusions

- Pharmacist-managed ambulatory care services within the BCC at Froedtert Hospital have been favorable
  - Provider/Staff satisfaction
  - Documented interventions
  - Informal patient satisfaction

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Incidence and Management of Arthralgias in Breast Cancer Patients Treated with Aromatase Inhibitors in an Outpatient Oncology Clinic

Pamela Menas, PharmD

Objectives

- Describe the role of aromatase inhibitors (AIs) in the treatment of breast cancer
- Describe the incidence and impact of AI-induced arthralgias
- Discuss the management of AI-induced arthralgias in breast cancer patients

I have no conflicts of interest to report

Study Location

- Kellogg Cancer Centers (KCC)
  - Established in 1981
  - One of the first National Cancer Institute (NCI) Community Clinical Oncology Programs (1983)
- Three locations
  - Evanston, IL
  - Glenview, IL
  - Highland Park, IL
- Average number of patients treated per month: 1100

Breast Cancer

- Most common type of cancer in women in US
  - More than 2.5 million breast cancer survivors nation-wide¹
  - 192,370 new cases per year
  - 40,170 deaths per year
  - 2nd most common cause of cancer-related deaths among women in US¹

Breast Cancer

- Approximately 75% of breast cancers are hormone receptor (+)²
- Postmenopausal women synthesize estrogen in adipose, muscle and breast tissue ²
- Aromatase enzyme converts androgens to estrogen ²
- AIs inhibit estrogen synthesis by blocking this conversion ²

Aromatase Inhibitors (AIs)

- First line adjuvant treatment in post-menopausal women with hormone receptor (+) tumors³,⁴
- Recommended length of treatment: 5 years³,⁴
AI Adverse Effects

- Hot flashes
- Insomnia
- Fatigue
- Osteoporosis
- Arthralgias

AI-Induced Arthralgias

- A common side effect of AI therapy
- Frequently cited as the primary reason for lack of compliance<br>\textsuperscript{6,9}
- Affected joints: wrists, hands, knees, back, ankles, and feet\textsuperscript{7}
- Few management strategies proposed in literature
- No standard treatment algorithm in place at Kellogg Cancer Center (KCC)

Study Purpose

- Evaluate incidence and management of AI-induced arthralgias in the outpatient oncology clinic at KCC
- Develop a treatment algorithm and electronic medical record (EMR) documentation tools

Methods

- Retrospective EMR review of 206 patients seen for follow up at KCC from 7/09 through 10/09
- IRB approved

Methods

- Inclusion Criteria:
  - Postmenopausal women with stage I-III hormone receptor positive breast cancer currently taking or have taken AI therapy
- Exclusion Criteria:
  - Pre-existing rheumatoid arthritis
  - Metastatic disease

Methods

- Definition of postmenopausal:
  - Prior bilateral oophorectomy OR
  - Amenorrhea for 1 year with intact uterus and ovaries OR
  - Serum estradiol and FSH levels commensurate with menopause for \( \geq 6\text{mos} \)
Methods

• Data Collected:
  - Age
  - Weight
  - Length of AI therapy
  - Co-morbidities
  - Medication history
  - Reports of arthralgias
  - Arthralgia management

• Primary Endpoints:
  - Assess overall incidence of AI-induced arthralgias at KCC
  - Evaluate management of AI-induced arthralgias

Methods

• Statistical Analysis:
  - Chi square and binomial two-sided exact test for descriptive statistics
  - Two-sample independent t-test for continuous variables
  - A p-value <0.05 was considered statistically significant

• Al-induced arthralgias in KCC patients occurred at a rate of 48% which was similar to those reported in literature (40%)\(^5,6,7\)

Results

• Incidence of arthralgias same among all AIs: anastrozole, exemestane and letrozole (\(p=0.729\))

• 32% documented as having arthralgias within the 1st 6 months of therapy

  - Literature suggests arthralgias occur in first year of AI therapy with 60% presenting within 1st 6 months of treatment\(^6,8,10,11\)
Results

• No difference in incidence of arthralgias in patients who received chemotherapy compared to those who did not (p=0.352)
  
  • In literature, chemotherapy sited as common cause of arthralgias, potentially making it difficult to determine cause in patients receiving both

Results

• Of patients with AI-induced arthralgias, 88% were managed without AI therapy alteration

• 41% of patients presenting with arthralgias did not have documentation of arthralgia management in EMR

Treatment Algorithm

• A treatment algorithm based on treatments for arthralgias found in literature and KCC physician experience

  Initial AI treatment
  Assess presence of AI arthralgias
  
  YES
  NO
  
  Pain scale 0-10 to determine severity
  
  Immediate response needed?
  YES
  NO
  
  May use Omega-3 fatty acids and OTC pain reliever together if immediate response needed

  Fish oil/Omega-3 fatty acids
  1000mg BID
  Glucosamine sulfate
  500mg TID

  No relief within 2 weeks:
  OTC pain reliever
  Ibuprofen 200-400mg Q4-6h prn
  Naproxen 220mg Q8-12h prn
  Acetaminophen 500mg Q6h prn
No relief within 2 weeks:
Discontinue OTC pain relievers
Add COX-2 inhibitor
OR
Rx NSAIDs
OR
Change to another AI therapy

Documentation Tool

Documentation Tool

Documentation Tool

Documentation Tool

Documentation Tool

Documentation Tool
Documentation Tool

Based on Common Terminology Criteria for Adverse Events (CTCAE) V 3.0

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• George Carro, RPh, MS, BCOP

References


Self-Assessment Question:

Aromatase inhibitors are indicated for which types of patients with breast cancer?

A. Premenopausal women with early stage disease
B. Premenopausal women with hormone receptor positive disease
C. Postmenopausal women with hormone receptor negative disease
D. Postmenopausal women with hormone receptor positive disease
Self-Assessment Question:
Which statement regarding AI-induced arthralgias is TRUE?
A. AI-induced arthralgias never interfere with AI therapy
B. AI-induced arthralgias are highly uncommon
C. AI-induced arthralgias are the most frequently cited reason for discontinuation of AI therapy
D. There is a “gold standard” for treatment for AI-induced arthralgias
Post Test Questions

1. Aromatase inhibitors are indicated for which types of patients with breast cancer?
   A. Premenopausal women with early stage disease
   B. Premenopausal women with hormone receptor positive disease
   C. Postmenopausal women with hormone receptor negative disease
   D. Postmenopausal women with hormone receptor positive disease

2. Which statement regarding AI-induced arthralgias is TRUE?
   A. AI-induced arthralgias never interfere with AI therapy
   B. AI-induced arthralgias are highly uncommon
   C. AI-induced arthralgias are the most frequently cited reason for discontinuation of AI therapy
   D. There is a “gold standard” for treatment for AI-induced arthralgias

3. Of patients presenting with arthralgias, which percent did not have documentation of arthralgia management in EMR?
   A. 14%
   B. 34%
   C. 57%
   D. 41%
Heart Failure Exacerbation Caused by Serotonin-Norepinephrine Reuptake Inhibitors in a Veteran Population

Kelly L. Perez, Pharm.D.
Jesse Brown VA Medical Center
28 August 2010

The speaker has no conflict to disclose in relation to this program.

Learning Objectives

- Recognize modifiable risk factors that may cause heart failure (HF) exacerbation
- Define the proposed mechanism by which serotonin-norepinephrine reuptake inhibitors (SNRIs) may exacerbate HF

Outline

• Review the incidence, socioeconomic burden, and etiology of HF in the United States
• Discuss depression in patients with HF
• Discuss the proposed mechanism of SNRI-induced HF
• Introduce purpose and methods
• Review study results
• Discuss conclusions
• Address limitations and future directions

Epidemiology of Heart Failure

• Growing problem in the United States
  - Affects about 5 million individuals
  - >550,000 new cases annually
  - Incidence ~10 per 1000 individuals over age 65
  - >1.1 million hospitalizations in 2006
  - Estimated total cost of $37.2 billion for 2009
  - 1/8 deaths mention HF on the death certificate

Etiology of Heart Failure

Disease State Progression
- Hypertension (HTN)
- Coronary artery disease (CAD)
- Valvular heart disease
- Diabetes mellitus (DM)
- Cardiomyopathy

Medication-Induced
- Anthracyclines
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Thiazolidinediones
- Interferons & interleukin-2
- Glucocorticoids
- Antipsychotics
- Antimigraine drugs
- Antifungals
- Antidepressants

Depression in Heart Failure

• Common comorbidity
• Associated with poor prognosis and increased mortality
• Incidence ranges from 13.9-36.5%, possibly as high as 77%
• 2005 Cochrane review found no randomized clinical trials studying psychological interventions in HF patients
Antidepressant Use in Heart Failure

• No randomized clinical trials or practice guidelines to guide therapy

• Few studies evaluate the use of antidepressants in HF
  o Older agents limited to a short duration of therapy
  o Little information available on selective serotonin reuptake inhibitors (SSRIs) and SNRIs

• Adverse cardiac events of antidepressants: orthostatic hypotension, HTN, conduction abnormalities

• Published case reports demonstrating exacerbation or development of HF after SNRI initiation

Colucci, et al.

• Case 1: 39 yo female with stable HF prescribed venlafaxine 75 mg BID
  o Presented with increasing dyspnea, fluid retention, ejection fraction (EF) of 15%
  o Fatigued and tachycardic for 3 months post-discharge with EF of 25-30% until venlafaxine discontinued
  o 2 weeks later her symptoms fully resolved; however, mood worsened
  o Prescribed duloxetine, but cardiac symptoms resumed
  o Duloxetine was discontinued and sertraline was substituted which resulted in stabilization of all her symptoms

Drent, et al.

• Case 1: 21 yo previously healthy female
  o Presented with progressive dyspnea, cough, vomiting, 15 kg weight loss, syncope x 4 weeks
  o Reduced EF reported, but data not provided
  o Treated with corticosteroids x 10 days without improvement, then venlafaxine was discontinued
  o Full resolution of clinical condition within 2 weeks

Colucci, et al.

• Case 2: 68 yo male with NYHA Class IV HF (stable EF ~25%) on duloxetine 30 mg QD x 1 week, then 60 mg QD x 1 additional week for DM neuropathy
  o Presented with tachycardia, orthopnea, dyspnea, 3.6 kg weight gain
  o Diuresed and duloxetine was discontinued
  o Lost 3.2 kg, HR normalized, and symptom resolution within 2 days

• Authors attributed increased serum norepinephrine (NE), which may negate the effects of sympatholytics, to both patients’ worsening HF

Proposed Mechanism of SNRI-Induced HF and Exacerbation

• Mediated by increasing NE, secondary to inhibition of reuptake in the neuronal synapse

• Causes an increase in sympathetic nervous system activity

• Based on the neurohormonal model of HF, sympathetic activation causes:
  o Sodium and water retention
  o Increases in both preload and afterload
  o Decline in left ventricular function

• Pharmacologic increase in NE, like those caused by SNRIs, has the potential to exacerbate HF

Drent, et al.

• Case 2: 62 yo male with ischemic heart disease, on unspecified dose of venlafaxine x 1 month
  o Presented with exertional dyspnea, dry cough, fever
  o Venlafaxine discontinued during admission
  o Reduced EF reported, but data not provided
  o Patient’s condition complicated by lung cancer and worsened until he expired

• Authors believe both patients suffered from SNRI-induced noneosinophilic interstitial pneumonia and cardiac failure
  o Proposed mechanism: reduced cytochrome P450 metabolism of the drug by genetic polymorphisms causing toxic effects

Drent et al.

• Mediated by increasing NE, secondary to inhibition of reuptake in the neuronal synapse

• Causes an increase in sympathetic nervous system activity

• Based on the neurohormonal model of HF, sympathetic activation causes:
  o Sodium and water retention
  o Increases in both preload and afterload
  o Decline in left ventricular function

• Pharmacologic increase in NE, like those caused by SNRIs, has the potential to exacerbate HF
Norepinephrine-Serotonin Affinity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Norepinephrine:Serotonin Affinity Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>7.23</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>116</td>
</tr>
<tr>
<td>Citalopram</td>
<td>3696</td>
</tr>
</tbody>
</table>

* Based on K_i (inhibitory constant); the smaller the ratio the greater the affinity/inhibition

Purpose

- To evaluate the incidence of HF exacerbations in patients receiving a SNRI, either venlafaxine or duloxetine, compared to the SSRI citalopram

Methodology

- Retrospective, electronic chart review of HF exacerbations at Jesse Brown VA Medical Center (JBVAMC)
- IRB and VA Research and Development Committee approved
- List generated from available databases
- All indications for SNRI use were included in the study
- Exacerbation of HF includes any documentation by the patient’s provider in the electronic chart using terminology suggesting worsening HF

Methodology

- Inclusion criteria
  - ≥ 18 years of age
  - From 1 Oct 06 to 15 Sept 09:
    - ICD-9 diagnosis of HF
    - Prescription for venlafaxine, duloxetine, or citalopram
- Exclusion criteria
  - None

Methodology

- Co-morbidities
  - A fib/a flutter
  - HTN
  - CKD
  - Anemia
  - Hyper-/hypo-thyroidism
  - DM
- Social history
- Recommended HF therapies
  - ACE inhibitors/ARBs
  - Beta adrenergic antagonists
  - Diuretics
  - Aldosterone antagonists
  - Hydralazine + nitrates
  - Digoxin
- Medications that may worsen HF
Statistical Analysis

- Student’s t-test for continuous data
- Chi-square test for nominal data
- Alpha was set at 0.05 for a power of 80%

Endpoints

- Primary
  - Incidence of HF exacerbation in patients receiving a SNRI versus patients receiving citalopram
- Secondary
  - Time to HF event post-SNRI initiation
  - To determine if a difference exists in severity of HF exacerbation (either treated as an outpatient or requiring hospitalization) between treatment groups

Study Population

Met Entry Criteria

Venlafaxine (n = 29)

Duloxetine (n = 0)

HF + Citalopram (n = 264)

Randomly Selected

Citalopram (n = 34)

N = 63

Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venlafaxine n = 29</th>
<th>Citalopram n = 34</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>62.7 (8.4)</td>
<td>68.4 (12.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male 29 (100.0)</td>
<td>34 (100.0)</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>Female 0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Caucasian 17 (58.6)</td>
<td>6 (17.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American 10 (34.5)</td>
<td>25 (73.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic 2 (6.9)</td>
<td>3 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social history, n (%)</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Tobacco 12 (41.4)</td>
<td>9 (26.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol 7 (24.1)</td>
<td>10 (29.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine or heroin 2 (6.9)</td>
<td>7 (20.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana 2 (6.9)</td>
<td>3 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP prior to initiation (mm Hg), n SD</td>
<td>130 (17)</td>
<td>131 (19)</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean DBP prior to initiation (mm Hg), n SD</td>
<td>74 (12)</td>
<td>72 (13)</td>
<td>0.64</td>
</tr>
<tr>
<td>Weight status (BMI), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight, &lt; 18.5</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Normal, 18.5 - 24.9</td>
<td>6 (20.7)</td>
<td>11 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Overweight, 25.0 - 29.5</td>
<td>7 (24.1)</td>
<td>12 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Obesity I, 30.0 - 34.5</td>
<td>8 (27.6)</td>
<td>5 (14.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Obesity II, 35.0 - 39.5</td>
<td>5 (17.2)</td>
<td>3 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Obesity III, ≥ 40</td>
<td>3 (10.3)</td>
<td>3 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>6 (20.7)</td>
<td>7 (20.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>29 (100.0)</td>
<td>33 (97.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>1 (3.4)</td>
<td>15 (44.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>2 (6.9)</td>
<td>6 (17.6)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (51.7)</td>
<td>19 (55.9)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypothyroidism, n (%)</td>
<td>2 (6.9)</td>
<td>4 (11.8)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
### Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venlafaxine (n = 29)</th>
<th>Citalopram (n = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HF, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>6 (20.7)</td>
<td>10 (29.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>Systolic</td>
<td>6 (20.7)</td>
<td>15 (44.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>No diagnosis of HF at baseline</td>
<td>17 (58.6)</td>
<td>9 (26.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Indication for use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>22 (75.9)</td>
<td>24 (70.6)</td>
<td></td>
</tr>
<tr>
<td>Post traumatic stress disorder</td>
<td>5 (17.2)</td>
<td>2 (5.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1 (3.4)</td>
<td>4 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>1 (3.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 indication</td>
<td>0 (0.0)</td>
<td>4 (11.8)</td>
<td></td>
</tr>
</tbody>
</table>

N = 63

### Definitions

- **New HF diagnosis**
  - First occurrence of HF during the study period in patients without pre-existing HF

- **HF exacerbation**
  - Any occurrence of HF during the study period in patients with a prior diagnosis of HF

- **HF event**
  - Both new HF diagnoses and HF exacerbations

### Results: Venlafaxine Arm

HF + Venlafaxine (n = 29)

- HF diagnosis prior to SNRI initiation (n = 12)
  - 1 HF exacerbation
  - 17 new HF diagnoses
- HF diagnosis post SNRI initiation (n = 17)
  - 21 HF events
  - 4 HF exacerbations

### Results: Citalopram Arm

HF + Citalopram (n = 34)

- HF diagnosis prior to SSRI initiation (n = 25)
  - 17 HF exacerbations
- HF diagnosis post SSRI initiation (n = 9)
  - 10 HF events
  - 9 new HF diagnoses
  - 1 HF exacerbation

### Results: HF Events

- Venlafaxine: 17 (p = 0.01)
- Citalopram: 9 (p = 0.54)

- Exacerbations in Patients with Baseline HF: 1 (p = 0.54)
- New HF Diagnoses in Newly Diagnosed Patients: 17 (p = 0.18)
Results: Event Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Venlafaxine (n = 22)</th>
<th>Citalopram (n = 27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median dose at event, mg (IQR)</td>
<td>150 (75 – 225)</td>
<td>20 (20 – 27.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean change in weight from baseline, n (SD)</td>
<td>4.1 (12.2)</td>
<td>0.7 (7.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Mean change in EF from baseline, % (SD)</td>
<td>6.9 (16.2)</td>
<td>2.6 (15.2)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* Baseline data not available for all events

Results: HF Therapy

<table>
<thead>
<tr>
<th>Agent, n (%)</th>
<th>Venlafaxine (n = 22)</th>
<th>Citalopram (n = 27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor/ARB</td>
<td>17 (77)</td>
<td>24 (89)</td>
<td>0.32</td>
</tr>
<tr>
<td>β adrenergic antagonists</td>
<td>16 (73)</td>
<td>22 (81)</td>
<td>0.46</td>
</tr>
<tr>
<td>Diuretic(s)</td>
<td>9 (41)</td>
<td>24 (89)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2 (9)</td>
<td>6 (22)</td>
<td>0.22</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>2 (9)</td>
<td>0 (0.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hydralazine + nitrate</td>
<td>1 (5)</td>
<td>2 (7)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

n = 49

Results: Confounding Medications

<table>
<thead>
<tr>
<th>Detrimental Agent, n (%)</th>
<th>Venlafaxine (n = 22)</th>
<th>Citalopram (n = 27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics*</td>
<td>6 (27)</td>
<td>0 (0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>NSAIDs/COX-2 inhibitors</td>
<td>3 (14)</td>
<td>0 (0)</td>
<td>0.14</td>
</tr>
<tr>
<td>TCAs</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cytotoxic agents</td>
<td>1 (5)</td>
<td>2 (7)</td>
<td>0.68</td>
</tr>
<tr>
<td>IMM/antibodies</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Non-DHP CCBs</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Androgens</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

* Antipsychotics, n = 6: risperidone, 5; olanzapine, 1

n = 49

Results: Time to Event

<table>
<thead>
<tr>
<th></th>
<th>Venlafaxine (n = 18)</th>
<th>Citalopram (n = 16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first event, months (IQR)</td>
<td>27.5 (20.3 – 39)</td>
<td>14.5 (4.8 – 43.3)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

n = 49

Results: Severity of HF Events

- All HF events were treated in the inpatient setting
  - Venlafaxine (n=22) .................................. 22 (100%)
  - Citalopram (n=27) .................................. 27 (100%)

n = 49

Results: HF Events

- Exacerbations in Patients with Baseline HF
  - Venlafaxine: 17
  - Citalopram: 17
  - p = 0.16

- New HF Diagnoses
  - Venlafaxine: 9
  - Citalopram: 4
  - p = 0.01

- HF Exacerbations in Newly Diagnosed Patients
  - Venlafaxine: 1
  - Citalopram: 1
  - p = 0.54

n = 49
**Results: New HF Diagnoses**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venlafaxine (n = 17)</th>
<th>Citalopram (n = 9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to diagnosis, months (range)</td>
<td>24 (20 – 39)</td>
<td>28 (11 – 50)</td>
<td>0.50</td>
</tr>
<tr>
<td>Median dose at diagnosis, mg (range)</td>
<td>150 (75 – 225)</td>
<td>20 (20 – 20)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

n = 26

**Discussion**

- No significant difference in HF events between groups
  - Median venlafaxine dose at exacerbation (150 mg) is at the approximation where NE reuptake inhibition begins
  - Duloxetine exhibits equal reuptake inhibition of serotonin (5-HT) and NE across the dosing spectrum
    - No duloxetine arm was established for this study

**Discussion**

- Baseline differences in SNRI vs. SSRI treatment arms
  - Patients in citalopram arm were older, had more severe HF, and a higher incidence of African Americans and CKD
  - More patients on diuretics in citalopram arm
  - 1 patient in the citalopram arm had 8 exacerbations

- Significant difference in concomitant antipsychotic therapy in venlafaxine arm
  - 5 patients on risperidone; may increase risk of HF
  - This finding may be a confounding variable

**Discussion**

- Lack of association between initiation of SNRI and time to HF exacerbation
  - Large distribution in data
  - Most exacerbations occurred > 6 months post-initiation

- All exacerbations in the SNRI and SSRI groups were similar in severity, requiring inpatient treatment

**Discussion**

- Based on the patients reviewed, a significant difference was found for new diagnoses in the venlafaxine arm vs. citalopram arm
  - No difference in time to diagnosis between agents
  - Median dose of venlafaxine at threshold of NE reuptake
  - Confounders were not fully assessed

- Premature to assign clinical significance
  - Warrants future prospective studies

**Limitations**

- Retrospective study
- Potential for Type II error due to small sample size
- Large distribution may account for lack of significance in data
- Possible treatment of exacerbations at outside medical centers
- No duloxetine arm
- Medication adherence was not assessed
Conclusion

• No difference in rate, onset, or severity of HF exacerbations was found between patients receiving venlafaxine and citalopram
• Trend toward increased risk for new HF diagnosis with venlafaxine

Future Directions

• Prospective evaluation of HF patients on SNRIs vs. SSRIs comparing:
  o Incidence of HF exacerbation
  o New-onset HF
• These prospective studies should include duloxetine due to its different dosing spectrum than venlafaxine

Self Assessment Question 1

True or False

Self Assessment Question 2

Which of the following medications may potentiate heart failure?

a) Naproxen
b) Acetaminophen
c) Rosiglitazone
d) All of the above
e) A & C

Acknowledgements

• Jesse Brown VA Medical Center Clinical Pharmacy Service
  o Donna M. Givone, Pharm.D., BCPP
  o Judith A. Toth, Pharm.D., CGP, CDE, FASCP

• University of Illinois at Chicago Center for Clinical and Translational Services

Heart Failure Exacerbation Caused by Serotonin-Norepinephrine Reuptake Inhibitors in a Veteran Population

Kelly L. Perez, Pharm.D.
PGY-1 Pharmacy Resident
Jesse Brown VA Medical Center
Chicago, Illinois
28 August 2010
References


References, continued


Post Test Question


2. Which of the following medications may potentiate heart failure?
   a) Naproxen
   b) Acetaminophen
   c) Rosiglitazone
   d) All of the above
   e) A and C
PSYCHIATRIC ADVERSE EVENTS AND USE OF PSYCHOTROPIC MEDICATIONS BEFORE & DURING INTERFERON TREATMENT FOR HEPATITIS C (HCV)
Sheri VanOsdol Pharm.D.
PGY-2 in Drug Information
University of Illinois, Chicago, Drug Information Group
August 28, 2010
The speaker has no conflict to disclose.

Objectives
- List potential complications of untreated Hepatitis C virus (HCV)
- Describe the complications of psychiatric adverse effects that occur during HCV therapy
- Identify patients at higher risk for developing psychiatric adverse effects during HCV therapy

Natural History of HCV

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CDC Division of Viral Hepatitis, 2009

HCV Treatment
- Goal: Achieve Sustained Virologic Response (SVR)
  - Undetectable viral load 24 weeks after treatment discontinuation
- Factors associated with a decreased likelihood of sustaining SVR
  - Genotype 1
  - High baseline viral load
  - African American ethnicity
  - Liver transplant recipient
  - Previous treatment failures
  - Uncontrolled diabetes
Muir et al., 2004
Ghany et al., 2009

HCV Treatment
- Pegylated Interferon (PegIFN) & Ribavirin
  - PegIFN alfa-2a or 2b administered SC weekly
  - Ribavirin twice daily dose depends on PegIFN & HCV genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 4</td>
<td>48 weeks recommended (up to 72 weeks)</td>
</tr>
<tr>
<td>2, 3</td>
<td>24 weeks recommended (up to 48 weeks)</td>
</tr>
<tr>
<td>5, 6</td>
<td>No specific guidelines for the U.S.</td>
</tr>
</tbody>
</table>

Ghany et al., 2009

Adverse Effects of Treatment

PegIFN
- Flu-like symptoms
- Injection site reactions
- Neutropenia
- Thrombocytopenia
- Thyroid dysfunction
- Insomnia
- Rash and pruritus
- Anorexia
- Diabetes
- Hyperlipidemia
- Psychiatric disorders
  - Depression, irritability

Ribavirin
- Hemolytic anemia
- Dyspnea
- Chest pains
- Pruritus
- Rash
- Cough
- Anorexia
- Teratogenicity
Depression & HCV Treatment

- In psychiatric patients, HCV prevalence is 6.8 - 8.5%.
- Registration trials of PegIFN alfa-2a & 2b + Ribavirin:
  - 10-14% dropout due to AEs
    - >50% flu-like symptoms
    - 22-31% psychiatric AEs
- Interferon-specific depression:
  - Mood, anxiety, cognitive complaints
  - Fatigue, anorexia, pain, psychomotor slowing
- Psychiatric AEs correlate to poor treatment adherence
  - Impact on SVR is unclear

Self Assessment Question

Which of the following factors make a patient a better candidate for achieving sustained virological response to HCV therapy?

a. Genotype 1 disease
b. African American ethnicity
c. Uncontrolled diabetes
d. HCV RNA level less than 300,000 IU/mL

Self Assessment Question

True or False:

The incidence of psychiatric adverse effects associated with interferon or pegylated interferon therapy ranges between 5% to 20%.

Study Objectives

- **Aim 1**: To assess the incidence of new onset psychiatric adverse events and new or increased psychotropic medication use after the initiation of interferon therapy.
- **Aim 2**: To identify risk factors associated with psychotropic medication use and/or psychiatric adverse events in subjects receiving treatment for HCV.

Study Design

- Retrospective chart review
- Reviewed all subjects evaluated for HCV therapy at UIMC outpatient liver clinic from July 1999 through August 2009
- Utilized objective reporting of psychotropic medication use as surrogate marker for depressive or other psychiatric symptoms
- This study was IRB approved by our institution on 10/22/2009 prior to data collection
Subject Selection

• Inclusion criteria
  – All patients ≥ 18 years old
  – Receiving PegIFN + Ribavirin
  – First round of HCV therapy at UIMC

• Exclusion criteria
  – HIV
  – Hepatitis B
  – HCV therapy from outside provider
  – Therapy taking place outside the pre-specified date range

Data Collection

Baseline
• Sex
• Age
• Race
• Height & Weight
• HCV Genotype
• Past Medical History
• Risk Factors for HCV

All Visits
• Viral Load
• Psychotropic Medications
• Hemoglobin
• Weight

Statistical Analysis

• Student’s T-test was used to correlate new or worsened psychiatric effects with
  – Age
  – BMI

• Chi-squared test was used to correlate new or worsened psychiatric effects with
  – Sex
  – Race
  – Baseline psychotropic medication use
  – Treatment response

Definitions

• Psychotropic medications: antidepressants, antipsychotics, mood stabilizers, anxiolytics, sedative hypnotics

• Psychotropic medication history: use of psychotropic medications prior to initiation of HCV therapy

• New/worsened psychiatric adverse events during therapy: addition of new medication, increased dose of current medication, or change of drug as surrogate maker for new/worsened psychiatric symptoms at any time during HCV treatment

• Treatment response: achievement of undetectable viral load before discontinuation of therapy

• Non-response: undesirable change in viral load leading to discontinuation of therapy; change from treatment to maintenance dosing for PegIFN

• Lost to follow-up: patients who self-discontinued therapy for financial reasons or unknown reasons

• Side effects: therapy discontinued by patient or provider due to side effects (e.g. uncontrolled anemia, psychiatric hospitalization, hallucinations, anhedonia, severe anorexia, etc.)

RESULTS
409 charts screened

Excluded patients (238):
- 169 never treated
- 15 HIV +
- 6 HBV +
- 2 on maintenance therapy
- 32 treated by outside provider

14 treated outside of study period

54 patients experienced psychiatric AEs on HCV therapy (31.6%)

117 patients had no psychiatric AEs while on HCV therapy (68.4%)

Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>61%</td>
</tr>
<tr>
<td>Mean Age (yr)</td>
<td>49</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>29</td>
</tr>
<tr>
<td>Initial Drug (%)</td>
<td>33.9%</td>
</tr>
<tr>
<td>Genotype (n=168)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>87.3% (113)</td>
</tr>
<tr>
<td>2</td>
<td>19.6% (33)</td>
</tr>
<tr>
<td>3</td>
<td>11.9% (20)</td>
</tr>
<tr>
<td>4</td>
<td>1.2% (2)</td>
</tr>
<tr>
<td>Stage (n=117)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11.1% (11)</td>
</tr>
<tr>
<td>2</td>
<td>38% (45)</td>
</tr>
<tr>
<td>3</td>
<td>24% (28)</td>
</tr>
<tr>
<td>4</td>
<td>26% (31)</td>
</tr>
<tr>
<td>Treatment naïve (n=182)</td>
<td>63.4% (161)</td>
</tr>
</tbody>
</table>

Baseline Characteristics: Race

- Caucasian: 38%
- African American: 38%
- Hispanic: 21%
- Other: 5.3%
- Asian: 1.8%

n=171

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=171)</th>
<th>New/ Worsened Psychiatric AEs (n=54)</th>
<th>No Psychiatric AEs (n=117)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric AEs (%)</td>
<td></td>
<td>31.6</td>
<td>68.4</td>
<td>--</td>
</tr>
<tr>
<td>Male (%)</td>
<td>61%</td>
<td>64.8</td>
<td>59</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Age (yr)</td>
<td>49</td>
<td>48.9 +/- 8.8</td>
<td>48.7 +/- 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>29</td>
<td>29 +/- 6.4</td>
<td>29.2 +/- 7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Initial Drug (%)</td>
<td>33.9%</td>
<td>46.3</td>
<td>28.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Bipolar (%)</td>
<td>2.3%</td>
<td>3.7</td>
<td>1.7</td>
<td>--</td>
</tr>
<tr>
<td>Anxiety (%)</td>
<td>2.3%</td>
<td>5.6</td>
<td>0.9</td>
<td>--</td>
</tr>
<tr>
<td>Schizophrenia (%)</td>
<td>1.8%</td>
<td>5.6</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

Distribution by Race

<table>
<thead>
<tr>
<th></th>
<th>Total (n=171)</th>
<th>New/ Worsened Psychiatric AEs (n=54)</th>
<th>No Psychiatric AEs (n=117)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric AEs (%)</td>
<td></td>
<td>31.6</td>
<td>68.4</td>
<td>--</td>
</tr>
<tr>
<td>African American (%)</td>
<td></td>
<td>38</td>
<td>29.6</td>
<td>41.2</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td></td>
<td>21</td>
<td>20.4</td>
<td>21.4</td>
</tr>
<tr>
<td>Other (%)</td>
<td></td>
<td>7</td>
<td>5.6</td>
<td>7.7</td>
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</table>

Discontinuation of Therapy

<table>
<thead>
<tr>
<th></th>
<th>Total Population (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation (%)</td>
<td></td>
</tr>
<tr>
<td>Total Population</td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>40.9</td>
</tr>
<tr>
<td>Non-responders</td>
<td>29.2</td>
</tr>
<tr>
<td>Lost-to-follow-up</td>
<td>13.5</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>16.4</td>
</tr>
</tbody>
</table>
Discontinuation of Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>No Psychiatric AEs (n=117)</th>
<th>Psychiatric AEs (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>15.1%</td>
<td>35.9%</td>
</tr>
<tr>
<td>Non-responder</td>
<td>27.8%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Lost-to-follow-up</td>
<td>9.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>18.8%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

Conclusion

- Subjects using psychotropic medications prior to initiation of HCV therapy were statistically more likely to develop depression or other psychiatric symptoms while on HCV therapy.
- No correlations were made between response to therapy or treatment discontinuation.
- No correlation was made with new/worsened psychiatric AEs.
  - Sex, age, race, BMI, reason for discontinuation of HCV therapy.

Discussion

Study Limitations
- Inconsistency of documentation.
- Medication use as surrogate marker.
- Depression vs other psychiatric AEs.
- Referral center.
- Inability to obtain SVR.
- Exclusion of HIV+, Hepatitis B+ patients.


Impact on Clinical Practice

- Proposed use of validated depression screening tools at baseline and follow-up visits for patients undergoing HCV therapy.
  - Beck Depression Inventory.
  - Zung Self-Rating Depression Scale.

References

CDC Division of Viral Hepatitis - Statistics and Surveillance 2009.

8/10/2010