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

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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

Hunt SA, et al. *Circulation* 2009;119:e391-e479.
Lloyd-Jones D, et al. *Circulation* 2009;119:e21-e181.

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

Slordal L, et al. *Drug Safety* 2006;29:567-586.

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

Jiang W, et al. *Arch Intern Med* 2001;161:1849-56.
Thomas SA, et al. *AACN Clin Issues* 2003;14:3-12.
Lane DA, et al. *Cochrane Database Syst Rev* 2005;1: CD003329.

Antidepressant Use in Heart Failure

- No randomized clinical trials or practice guidelines to guide therapy
- Few studies evaluate the use of antidepressants in HF
  - Older agents limited to a short duration of therapy
  - Little information available on selective serotonin reuptake inhibitors (SSRIs) and SRNIs
- Adverse cardiac events of antidepressants: orthostatic hypotension, HTN, conduction abnormalities
- Published case reports demonstrating exacerbation or development of HF after SNRI initiation

Slordal L, et al. *Drug Safety* 2006;29:567-586.
Alvarez W, et al. *Pharmacotherapy* 2003;23:754-71.

Colucci, et al.

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

Colucci VJ, et al. *Ann Pharmacother* 2008;42:882-7.

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
  - Presented with tachycardia, orthopnea, dyspnea, 3.6 kg weight gain
  - Diuresed and duloxetine was discontinued
  - 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

Colucci VJ, et al. *Ann Pharmacother* 2008;42:882-7.

Drent, et al.

- Case 1: 21 yo previously healthy female on venlafaxine 35 mg daily x 1 month, then 75 mg daily x 1 additional month
  - Presented with progressive dyspnea, cough, vomiting, 15 kg weight loss, syncope x 4 weeks
  - Reduced EF reported, but data not provided
  - Treated with corticosteroids x 10 days without improvement, then venlafaxine was discontinued
  - Full resolution of clinical condition within 2 weeks

Drent M, et al. *Am j Respir Crit Care Med* 2003;167:958-61.

Drent, et al.

- Case 2: 62 yo male with ischemic heart disease, on unspecified dose of venlafaxine x 1 month
  - Presented with exertional dyspnea, dry cough, fever
  - Venlafaxine discontinued during admission
  - Reduced EF reported, but data not provided
  - 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
  - Proposed mechanism: reduced cytochrome P450 metabolism of the drug by genetic polymorphisms causing toxic effects

Drent M, et al. *Am J Respir Crit Care Med* 2003;167:958-61.

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:
  - Sodium and water retention
  - Increases in both preload and afterload
  - Decline in left ventricular function
- Pharmacologic increase in NE, like those caused by SNRIs, has the potential to exacerbate HF

Hasking GJ, et al. *Circulation* 1986;73:615-21.
Bleske BE. *Pharmacotherapy* 2000;20:349S-58S.

Norepinephrine-Serotonin Affinity

Drug	Norepinephrine:Serotonin Affinity Ratio*
Duloxetine	7.23
Venlafaxine	116
Citalopram	3696

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

Baldessarini, RJ. *Pharmacological Basis of Therapeutics*. 11th ed, 2006.

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
Data Collection

- Demographic information
  - Age
  - Gender
  - Ethnicity
  - Baseline information
    - Blood pressure (BP) prior to SNRI initiation
    - Weight
    - Body mass index (BMI)
    - EF
- Event data
  - Weight
  - EF
- Date of HF diagnosis
  - Type of HF
  - Date(s) of exacerbation(s)
- Antidepressant information
  - Agent
  - Dose at time of exacerbation
  - Date of initiation
  - Indication

Methodology
Data Collection

- 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

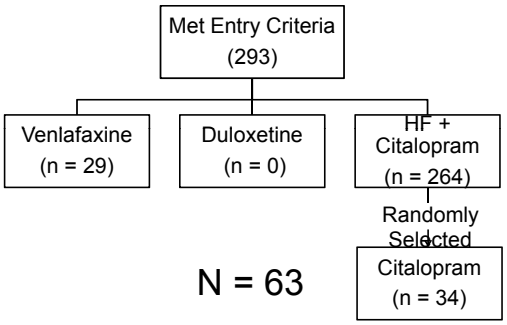
Statistical Analysis

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

Study Population



N = 63

Results: Baseline Characteristics

Characteristic	Venlafaxine (n = 29)	Citalopram (n = 34)	p-value
Mean age, years (SD)	62.7 (9.4)	68.4 (12.7)	**0.05**
Gender, n (%)			
Male	29 (100.0)	34 (100.0)	> 0.99
Female	0 (0.0)	0 (0.0)	
Race/Ethnicity, n (%)			
Caucasian	17 (58.6)	6 (17.6)	**< 0.01**
African-American	10 (34.5)	25 (73.5)	
Hispanic	2 (6.9)	3 (8.8)	
Social history, n (%)			
Tobacco	12 (41.4)	9 (26.5)	0.22
Alcohol	7 (24.1)	10 (29.4)	0.64
Cocaine or heroin	2 (6.9)	7 (20.6)	0.12
Marijuana	2 (6.9)	3 (8.8)	0.78

N = 63

Results: Baseline Characteristics

Characteristic	Venlafaxine (n = 29)	Citalopram (n = 34)	p-value
Mean SBP prior to initiation (mm Hg), n (SD)	130 (17)	131 (19)	0.94
Mean DBP prior to initiation (mm Hg), n (SD)	74 (12)	72 (13)	0.64
Weight status (BMI), n (%)			
Underweight, < 18.5	0 (0.0)	0 (0.0)	0.31
Normal, 18.5 - 24.9	6 (20.7)	11 (32.4)	
Overweight, 25.0 - 29.9	7 (24.1)	12 (35.3)	
Obesity I, 30.0 -34.9	8 (27.6)	5 (14.7)	
Obesity II, 35.0 - 39.9	5 (17.2)	3 (8.8)	
Obesity III, ≥ 40	3 (10.3)	3 (8.8)	

N = 63

Results: Baseline Characteristics

Characteristic	Venlafaxine (n = 29)	Citalopram (n = 34)	p-value
Atrial fibrillation, n (%)	6 (20.7)	7 (20.6)	0.55
Hypertension, n (%)	29 (100.0)	33 (97.1)	0.35
Chronic kidney disease, n (%)	1 (3.4)	15 (44.1)	**< 0.01**
Anemia, n (%)	2 (6.9)	6 (17.6)	0.20
Diabetes mellitus, n (%)	15 (51.7)	19 (55.9)	0.74
Hypothyroidism, n (%)	2 (6.9)	4 (11.8)	0.51

N = 63

Results: Baseline Characteristics

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

N = 63

Results: Baseline Characteristics

- Baseline EF not available for all subjects
- Of the subjects with baseline EF:

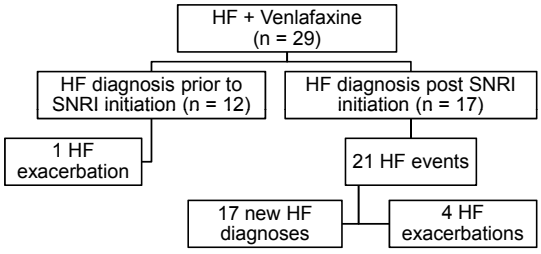
EF	Venlafaxine (n = 17)	Citalopram (n = 26)	p-value
≥ 40	16 (96.6)	16 (70.6)	**0.04**
< 40	1 (3.4)	10 (29.4)	

n = 43

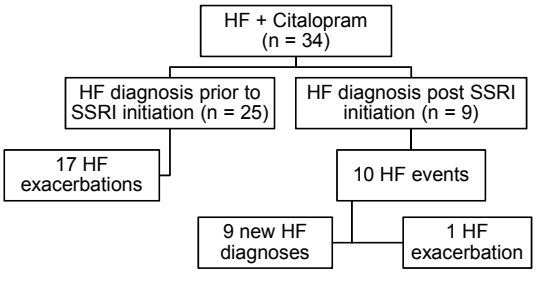
Definitions

- 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

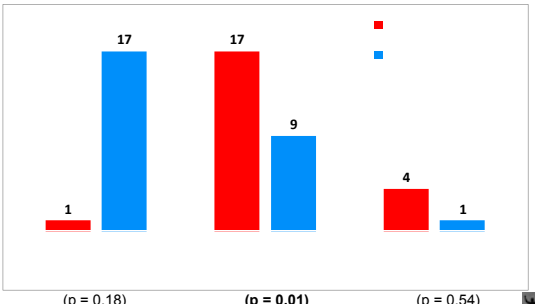
Results: Venlafaxine Arm



Results: Citalopram Arm



Results: HF Events



n = 49

Results: Event Clinical Data

	Venlafaxine (n = 22)	Citalopram (n = 27)	p-value
Median dose at event, mg (IQR)	150 (75 – 225)	20 (20 – 27.5)	N/A
Mean change in weight from baseline, n (SD)	4.1 (12.2)	0.7 (7.3)	0.53

	Venlafaxine (n = 8)*	Citalopram (n = 19)*	p-value
Mean change in EF from baseline, % (SD)	-6.9 (16.2)	2.6 (15.2)	0.16

* Baseline data not available for all events

Results: HF Therapy

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

n = 49

Results: Confounding Medications

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

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

n = 49

Results: Time to Event

FIRST EVENT			
	Venlafaxine (n = 18)	Citalopram (n = 16)	p-value
Median time to first event, months (IQR)	27.5 (20.3 – 39)	14.5 (4.8 – 43.3)	0.33

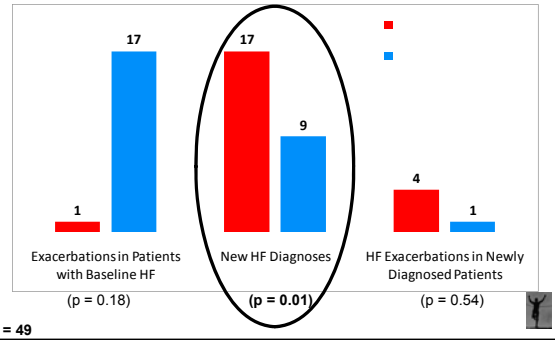
SUBSEQUENT EVENTS		
	Venlafaxine (n = 3)	Citalopram (n = 4)
Total number of exacerbations	4	11
Number of patients		
1 exacerbation	2	2
2 exacerbations	1	1
≥ 3 exacerbations	0	1
Mean time between exacerbations, months (SD)	44.3 (35.9)	3.5 (4.0)

Results: Severity of HF Events

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

n = 49

Results: HF Events



n = 49

Results: New HF Diagnoses

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

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 antipyschotic 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:
  - Incidence of HF exacerbation
  - New-onset HF
- These prospective studies should include duloxetine due to its different dosing spectrum than venlafaxine

Self Assessment Question 1

True or False

Guidelines exist for the treatment of depression in patients with heart failure.

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

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Post Test Question

1. True or False: Guidelines exist for the treatment of depression in patients with heart failure.

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