RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Angermann CE, Gelbrich G, Störk S, Gunold H, Edelmann F, Wachter R, Schunkert H, Graf T, Kindermann I, Haass M, Blankenberg S, Pankuweit S, Prettin C, Gottwik M, Böhm M, Faller H, Deckert J, Ertl G; MOOD-HF Study Investigators and Committee Members. Effect of Escitalopram on All-Cause Mortality and Hospitalization in Patients With Heart Failure and Depression: The MOOD-HF Randomized Clinical Trial. JAMA. 2016 Jun 28; 315(24):2683-93. doi: 10.1001/jama.2016.7635
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/27367876
3. First date published study available to readers	6/28/2016
4. PubMed ID	27367876
5. Nominated By	Jim Stevermer Other:
6. Institutional Affiliation of Nominator	University of Missouri Other:
7. Date Nominated	7/17/2016
8. Identified Through	Other Other: JAMA
9. PURLS Editor Reviewing Nominated Potential PURL	Other Other: Corey Lyon
10. Nomination Decision Date	7/27/2016
11. Potential PURL Review Form (PPRF) Type	RCT
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Bernard Ewigman
14. Reviewer Affiliation	University of Chicago Other:
15. Date Review Due	10/27/2016
16. Abstract	IMPORTANCE: Depression is frequent in patients with heart failure and is associated with adverse clinical outcomes. Long-term efficacy and safety of selective serotonin reuptake inhibitors in these patients are unknown.

OBJECTIVE:
To determine whether 24 months of treatment with escitalopram improves mortality, morbidity, and mood in patients with chronic systolic heart failure and depression.
DESIGN, SETTING, AND PARTICIPANTS:
The Effects of Selective Serotonin Re-Uptake Inhibition on Morbidity, Mortality, and Mood in Depressed Heart Failure Patients (MOOD-HF) study was a double-blind, placebo-controlled randomized clinical trial conducted at 16 tertiary medical centers in Germany. Between March 2009 and February 2014, patients at outpatient clinics with New York Heart Association class II-IV heart failure and reduced left ventricular ejection fraction (<45%) were screened for depression using the 9-item Patient Health Questionnaire. Patients with suspected depression were then invited to undergo a Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) to establish the diagnosis.
INTERVENTIONS:
Patients were randomized 1:1 to receive escitalopram (10-20 mg) or matching placebo in addition to optimal heart failure therapy. Study duration was 24 months.
MAIN OUTCOMES AND MEASURES:
The composite primary outcome was time to all-cause death or hospitalization. Prespecified secondary outcomes included safety and depression severity at 12 weeks of treatment (including the titration period), which were determined using the 10-item Montgomery-Åsberg Depression Rating Scale (total possible score, 0 to 60; higher scores indicate more severe depression).
RESULTS:
A total of 372 patients (mean age, 62 years; 24% female) were randomized and had taken at least 1 dose of study medication when the data and safety monitoring committee recommended the trial be stopped early. During a median participation time of 18.4 months (n = 185) for the escitalopram group and 18.7 months (n = 187) for the placebo group, the primary outcome of death or hospitalization occurred in 116 (63%) patients and 119 (64%) patients, respectively (hazard ratio, 0.99 [95% CI, 0.76 to 1.27]; P = .92). The mean Montgomery-Åsberg Depression Rating Scale sum score changed from 20.2 at baseline to 11.2 at 12 weeks in the escitalopram group and from 21.4 to 12.5 in the placebo group (between-group difference, -0.9 [95% CI,-2.6 to 0.7]; P = .26). Safety parameters were comparable between groups.
CONCLUSIONS AND RELEVANCE:
In patients with chronic heart failure with reduced ejection fraction and depression, 18 months of treatment with escitalopram compared with placebo did not significantly reduce all-cause mortality or hospitalization, and there was no significant improvement in depression. These findings do not support the use of escitalopram in patients with chronic systolic heart failure and depression.

17. Pending PURL Review Date	10/27/2016

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?	186 escitalopram (185 actual + 1 didn't receive the med) + 190 placebo(187 actual + 3 didn't receive placebo)
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Inclusions= Adults (>/= 18 years) in heart failutre outpatient clinics w NYHA class II-IV plus LV EF<45% within last 3 months who screeend positive on PHQ9 of 12 points/then 9 points in modification had Structured Clinical Interview for Depression(SCID)with psychiatrist or psychosomatic specialist, within 2 weeks of screening. Exclusions =recent h/o MI(<3mos); acute cardiac decompensation; recent <3mo's or planned major cardiac surgery <12 mos; advanced CKD <30 mlminGFR; moderate or severe hepatic insuficiency where the TAs are >3 times normal or hepatic failure; thyrotoxicosis, other medical contraindication to treatment with SSRIs; significantly reduced life expectancy due to other comorbidity eg malignancy, use of any antidepressants, SSRIs, lithium or anticonvulsants for mood disorder in adequate dosage with at least 8 weeks of of treatment and positive clinical outcome; currently in psychotherapy; absence of response to previous trial of escitalopram; lifetime history of adverse events or side effects to escitalopram; lifetime history of early termination < 8weeks of other SSRI because of adverse events or side effects ; bipolar

; severe depresssive epsiode with psychotic features; evidence of substance abuse or dependency during last 12 months, moderate or severe dementia, imminent suicide risk, participation in another trial, inability to comply with PHQ9 or SCID tesing or telepohone monitoring for mental.linguistic or access reasons; pregnancy or nursing period, women of childbearing potential without effective contraception, expected low compliance with visit schedule or telephone monitoring, patients with long QTc >/+500 msec; current treatment with drugs inducing QT prolongation.
Demographics=Mean age 62.2/62.3, 24% female, 22/26% living alone in Treatment/Placebo groups
Settings= Heart failure outpatient clinics in 19 tertiary medical centers in Germany

3. Intervention(s) being investigated?

Escitalopram 10-20 mg vs placebo for depressed HF patients

4. Comparison treatment(s), placebo, or nothing?

placebo

5. Length of follow up? Note specified end points e.g. death, cure, etc.

Up to 24 months of drug/placebo treatment , with followup for 3-12 months after cessation of treatment.
***Note early termination occurred due to futility decision by the review committee
End points=time to first event of all cause death, or all cause hospitalization
Note FU occurred with Montgomery -Asberg Depression Rating Scale (MADRS) to assess depression and KCCQ ratings by cardiologists

6. What outcome measures are used? List all that assess effectiveness.

Primary outcome = time to a first event of the composite (all-cause death or hospitalization, excluding planned hospitalization for noncardiac).
Secondary outcomes=MADRS sum score at 12 weeks,
anxiety as assessed on the 7-item PHQ for GAD,
health related quality of life, using Kansas City Carediomyopathy Questionnaire (KCCQ) .
Other secondary outcomes= time-to-event variables, time to CV death or hospitalization for HF, escitalopram serum levels, HF phamacotherapy, HF severity scores, cardiac staus, safety. Additional subgroup analyses occurred too.
Note PHQ-9, KCCQ, PHQ 7 for GAD and MMSE .

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

Study stopped early, during median participation time of 18.4 months/18.7months
Hazard ration 0.99(95%CI, 0.76 to1.27) P-0.92)
Means MADRS changed from 20.2 baseline to 11.2 at 12 weeks in escitalopram, and 21.4 to 12.5 in placebo group
Between group differences -0.9 (95% CI, -2.6 to 0.7

8. What are the adverse effects of intervention compared with no intervention?

page 2688-safety
Escitalopram discontinuation rates after 6 weeks was 11% and 15% after 12 weeks, comparing to 5% and 7% for the placebo, P=0.04 at 6 weeks, and p=0.02 at 12 weeks.
see eTable 6 in supplement 1 for discontinuationand open label
worsening depression did occur more often in pateints in the placebo group.

9. Study addresses an appropriate and clearly focused question - ***select one***

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments: Yes, earlier studies, eg ERCHD showed some post hoc analysis of benefit with prolonged use of SSRI, but SADHART-CHF showed no benefit to sertraline

10. Random allocation to comparison groups

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments: SeeFigure 1-the placebo was a pill also-given 5mg for 3 w, then 10 mg for 3 wk, then tritrated up to 20 mg a day except seniors >65 yo were kept at max of 10 mg given drug

	guidelines for elderly. All groups were maximized in their heart failure treatment also Randomized around age, sex, depression severity, time since last hospitalization Followup with MADRS and KCCQ each time which was: Weekly monitoring of depressive symptoms status until 12 weeks Bimonthly monitoring after 12 weeks, with specialized nurses assessing patients PHQ and drug adherence during phone calls If worsening or suicidal ideastion, the nurse referred to psychiatrist, at which point Open label prescription of an antidepressant might occur. .
11. Concealed allocation to comparison groups	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: See Figure 1
12. Subjects and investigators kept "blind" to comparison group allocation	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: Primary Outcome of study-to-event times were adjucated by blinded assessors
12. Comparison groups are similar at the start of the trial	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: See table 1
14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: See table 1- no differences
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: Cardiologists administered the MADRS every FU visit
16. Are patient oriented outcomes included? If yes, what are they?	if Depression severity on MADRS is patient oriented, then yes. and KCCQ is QOL oriented, so yes
17. What percent dropped out, and were lost to follow up? Could this bias the results? How?	See ETable 6- SSRI group: 11% drop out by week 6, 15% by week 12 Placebo group: 5% drop out by week 6, 7% by 12 weeks This was a difference showing statistical of p=0.04 at 6 wk and p=0.02 at 12 wk
18. Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes, there was a modified Intention to Treat, based on those that took the medicien-see the arms described above. Note, the primary end point event occurred in 116 (63%) in escitalopram group, 119(64%) in placebo group

19. If a multi-site study, are results comparable for all sites?	yes
20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	Note, 11/19 researchers receive other funding grants etc from several drug companies.Lundbeck AS which supplied the meds, and the German Ministry were not involved in the protocoals etc but 2 of the19 researchers have had funding before from Lundbeck AS, which makes escitalopram
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Patients with HF class NYHA II-IV so symptoms, plus HFrEF who HAVE NOT previously had major depression Those with major depression who had ever been treated successfully with SSRIs---these were excluded
22. In what care settings might the findings apply, or not apply?	Can apply in primary care and tertiary care outpatient care
23. To which clinicians or policy makers might the findings be relevant?	PCPs, Cardiologists and HF centers, Psychiatrists

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions	For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year. EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.} For DynaMed, use the following style: Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}
1. DynaMed excerpts	*** 1 *** 2
2. DynaMed citation/access date	Title. Heart Failure with reduced ejection fraction Author. Oettgen, In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: 8/16/2016. Accessed 10/10/2016
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Dynamed bottom line" Escitaolpram may not reduce risk of death or hospitalization or improve depression symptoms in patients with chronic systolic heart failure and depression JAMA 2016 June 28"
4. UpToDate excerpts	1 self care 2 dep
5. UpToDate citation/access date	Always use Basow DS as editor & current year as publication year. Title. (1)Heart Failure Self Management (2) Predictors of survival in heart failure due to systolic dysfunction (2) ColuccinAuthor. (1)Horowitz, Krumholz (2) In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: oct 15 2015 but current through Sep 2016. Accessed10/10/2016

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	Bottom line UTD (1)"Patients with depression and HF have higher rates of medication nonadherence, hospitalization and mortality" (2) "depression appears to be both relatively common and associated with a worse prognosis in patients with HF"
7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor pw: pepidpcp	No fpin found
8. PEPID citation/access data	Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? ☐ Yes, there is important evidence or recommendations that are missing ☐ No, this topic is current, accurate and up to date. If yes, which PEPID Topic, Title(s): 2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon ( ) that should be updated on the basis of the review? ☐ Yes, there is important evidence or recommendations that are missing ☒ No, this topic is current, accurate and up to date. If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s): none found
10. Other excerpts (USPSTF; other guidelines; etc.)	Cochrane
11. Citations for other excerpts	***
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	***

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	Blinded time to event primary outcome assessment was adjudicated by a blinded, separate committee
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.	Yes, this is a common problem in practice but a negative study of benefit of SSRI

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

Stop prescribing escitalopram and SSRIs in general to HF patients with depression they will get a bit better over 3-6 months without the SSRI, if severely depressed, may be a bit worse however. Also any patients that have previously responded to SSRIs are excluded from the study, so do not apply these results to those patients.

7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

Give one number on a scale of 1 to 7
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

the KCCQ has patient oriented outcomes, and functional status of NYHA is also patient oriented, as a functional assessment, and rehospitalization rates are also patient oriented

13. In your opinion, is this a Pending PURL? Criteria for a Pending PURL: • Valid: Strong internal scientific validity; the findings appears to be true. • Relevant: Relevant to the practice of family medicine • Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice. • Applicability in medical setting: • Immediacy of implementation	Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
14. Comments on your response in 4.13	Stop prescribing SSRIs for depressed HF patients who have not been depressed previously (as these were excluded.)