Treat depressed teens with medication *and* psychotherapy. *J Fam Pract*. 2008;57:735-739.	
Potential PURL Review Form: Randomized controlled trials	
SECTION 1: IDENTIFYING INFORMATION	
1.0 Citation	Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*. 2008;299:901-913.
1.1 Editor's classification of nominated study	Potential PURL Review Date: 4/24/08 •
1.3 Hypertext link to PDF of full article	http://jama.ama-assn.org/cgi/reprint/299/8/901
1.4 First date published study available to readers	2/27/08
1.5 PubMed ID	18314433
1.6 Nominated By	Jim Stevermer
1.7 Institutional Affiliation of Nominator	University of Missouri
1.8 Date Nominated	3/16/08
1.9 Identified Through	InfoPOEMs Editorial Board
1.10 PURLS Editor	Bernard Ewigman
1.11 Nomination Decision Date	4/11/08
1.12 Potential PURL Review Form (PPRF) type	RCTs
1.13 Other comments, materials or discussion	
1.14 Assigned Potential PURL Reviewer	Sandy Smith
1.15 Reviewer Affiliation	University of Chicago
1.16 Date Review Due	4/24/08

1.17 Abstract	CONTEXT: Only about 60% of adolescents with depression will show an adequate clinical response to an initial treatment trial with a selective serotonin reuptake inhibitor (SSRI). There are no data to guide clinicians on subsequent treatment strategy. OBJECTIVE: To evaluate the relative efficacy of 4 treatment strategies in adolescents who continued to have depression despite adequate initial treatment with an SSRI. DESIGN, SETTING, AND PARTICIPANTS: Randomized controlled trial of a clinical sample of 334 patients aged 12 to 18 years with a primary diagnosis of major depressive disorder that had not responded to a 2-month initial treatment with an SSRI, conducted at 6 US academic and community clinics from 2000-2006. INTERVENTIONS: Twelve weeks of: (1) switch to a second, different SSRI (paroxetine, citalopram, or fluoxetine, 20-40 mg); (2) switch to a different SSRI plus cognitive behavioral therapy; (3) switch to venlafaxine (150-225 mg); or (4) switch to venlafaxine plus cognitive behavioral therapy. MAIN OUTCOME MEASURES: Clinical Global Impressions-Improvement score of 2 or less (much or very much improved) and a decrease of at least 50% in the Children's Depression Rating Scale-Revised (CDRS-R); and change in CDRS-R over time. RESULTS: Cognitive behavioral therapy plus a switch to either medication regimen showed a higher response rate (54.8%; 95% confidence interval [CI], 47%-62%) than a medication switch alone (40.5%; 95% CI, 33%-48%; *P*=.009), but there was no difference in response rate between venlafaxine and a second SSRI (48.2%; 95% CI, 41%-56% vs 47.0%; 95% CI, 40%-55%; *P*=.83). There were no differential treatment effects on change in the CDRS-R, self-rated depressive symptoms, suicidal ideation, or on the rate of harm-related or any other adverse events. There was a greater increase in diastolic blood pressure and pulse and more frequent occurrence of skin problems during venlafaxine than SSRI treatment. CONCLUSIONS: For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of cognitive behavioral therapy and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine and resulted in fewer adverse effects. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00018902.

SECTION 2: DETAILED STUDY DESCRIPTION	
2.1 Number of patients starting each arm of the study?	83 (V), 83 (V & CBT) , 85 (SSRI), 83 (SSRI & CBT)
2.2 Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	12-18 yo in active treatment for major depression with CDRS-R ≥40 & Clinical Global Impressions-Severity subscale score of ≥4 (moderate severity) & in treatment with SSRI for at least 8 weeks, the last 4 weeks with a dosage of ≥40 mg/d fluoxetine (or equivalent).
2.3 Intervention(s) being investigated?	Efficacy of switching to another SSRI (with or without CBT) , or Venlafaxine (with or without CBT)

2.4 Comparison treatment(s), placebo, or nothing?	Baseline condition on SSRI: 2 x 2 factorial design, ie, (SSRI or SNRI) x (CBT or no CBT) design
2.5 Length of follow up? Note specified end points, eg, death, cure, etc.	12 weeks
2.6 What outcome measures are used? List all that assess effectiveness.	<u>Primary Outcomes</u> 1. Adequate clinical response defined as (a) Clinical Global Impressions-Severity (CGI) subscale score of 2 or less, and (b) improvement in Children's Depression Rating Scale-Revised (CDRS-R) score of at least 50% (global & symptomatic improvement). 2. Trajectory of the CDRS-R over time <u>Secondary Outcomes:</u> Beck Depression Inventory Suicide Ideation Questionnaire – Jr Childrens' Global Adjustment Scale
2.7 What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, *P*-values, etc.	Intent to Treat (ITT) (N=334) & Completer (N= 231) Analyses reported <u>ITT results for outcome Vars 1, 1(a) & 1(b)</u> Main effect for CBT (*P*=.05), but no significant main effect for medication type or the (CBT x med type) interaction across the following variables: 1. Adequate clinical response: CBT (+ SSRI/SNRI) (54.8% improved 95%CI, 47%-62%) vs SSRI/SNRI (40.5% improved; 95%CI, 33%-48%): Risk difference 14.3%, *P*=.05; NNT=7 1a) CGI score of 2 or less: Intent to treat *P* =.04, Completers *P*=.22 1b) Change in CDRS-R >=50%: Intent to treat *P*=.01, Completers *P*=.08 <u>Completer results for outcome Vars 1, 1(a) & 1(b)</u> 1. Adequate clinical response: CBT (+ SSRI/SNRI) (62.7% improved) vs SSRI/SNRI (49.6% improved) *P*=.05: Risk difference 13%, NNT=7.69 1a) CGI score of 2 or less: *P*=.22 1b) Change in CDRS-R ≥50%: *P*=.08 CDRS-R Trajectory: Significant effect for time (*P*<.001) (improvement) but not for med type, CBT, site or any interactions. <u>Secondary outcomes</u> Beck Depression Inventory: Time effect (*P*<.001) (improvement) & site effect. Suicide Ideation Questionnaire: Time effect (*P*<.001) (improvement) Childrens' Global Adjustment; Time effect (*P*<.001) (improvement) CGI: Time effect (*P*<.001) (improvement)

SECTION 3: INTERNAL VALIDITY	
3.1 Study addresses an appropriate and clearly focused question	Well addressed
3.2 Random allocation to comparison groups	Well addressed
3.3 Concealed allocation to comparison groups	Well addressed
3.4 Subjects and investigators kept "blind" to comparison group allocation	Adequately addressed Blinding failure for CBT therapy type was addressed. No problems with drug blinding.
3.5 Comparison groups are similar at the start of the trial	Adequately addressed: SSRI vs SNRI groups differed on Beck Depression Inventory scores & on PTSD, but SSRI group was higher in both cases (favors SNRI). Also, the large number of comparison variables listed in Table 1 (23) and the number of comparisons reported (SSRI vs SNRI [23] and CBT vs no CBT [23]).
3.6 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 addressed There were minor variations to the protocol, but these were rigorously monitored & tested.
3.7 Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well addressed Yes, the therapists (pharmacotherapists & psychotherapists) were trained to deliver standardized treatment and were monitored centrally by audiotape.
3.8 Are patient-oriented outcomes included? If yes, what are they?	Yes.
3.9 What percent dropped out, and were lost to follow up? Could this bias the results? How?	~31% dropped out from time of randomization until completion of protocol. Yes. The intent-to treat (ITT) results & Completer results were reported. While the absolute improvement in outcomes is better in the Completer group, the significance of the CBT vs no CBT group differences is diminished somewhat. 1. There is still a significant difference in overall clinical response (composite) for CBT effect

	for ITT (*P*=.009), but the difference was less among Completers (*P* =.05) 2. Differences in CGI subscale scores vary across the ITT & Completer analyses (CBT effect for ITT *P*=.04 vs CBT effect for Completers *P*=.22) and 3. Differences in CDRS-R subscale scores vary across the ITT & Completer analyses (CBT effect for ITT *P*=.01 vs CBT effect for Completers *P*=.08).
3.10 Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes…as reported above.
3.11 If a multi-site study, are results comparable for all sites?	Yes, sites were compared across a range of variables; small differences were noted and mostly controlled for statistically. Sensitivity analyses were performed.
3.12 Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?	NIMH funding, but significant financial disclosures were made by the researchers. The study compared a wide variety of SSRIs (from different pharmaceutical companies) with each other & the newer SNRI, and reported no significant differences among the drugs.
SECTION 4: EXTERNAL VALIDITY	
4.1 To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Severely depressed teenagers who appear unresponsive to their current SSRI or SNRI.
4.2 In what care settings might the findings apply, or not apply?	
4.3 To which clinicians or policy makers might the findings be relevant?	
SECTION 5: REVIEW OF SECONDARY LITERATURE	
5.1 DynaMed excerpts	DynaMed reviews multiple studies and concludes that multiple types of counseling (supportive therapy, cognitive therapy, behavior therapy) are effective in the short-term (4-6 months but not 1 year), that antidepressants and counseling are equally effective, that antidepressants are associated with faster recovery than counseling, and that the combination of antidepressants and counseling may be more effective than either therapy alone. DynaMed notes, however, that these findings are inconsistent, and that long-term antidepressant treatment and counseling have both been shown to reduce recurrence rate of major depressive episodes.
5.2 DynaMed citation/access date	4/16/08

5.3 UpToDate excerpts	UpToDate does not have a definitive recommendation and notes that TADS and TORDIA will provide evidence for how to best initiate treatment for adolescents with depression and how to respond if the first intervention is not effective.
5.4 UpToDate citation/access date	4/16/08
5.5 PEPID PCP excerpts	**Therapeutics** 1. Acute treatment ○ Suicidal ideation: ▪ Identify if present, hospitalize and referral to mental health professional ○ Safety plan: ▪ Requires discussion with patient and family how to anticipate increased suicidal urges, how to communicate about these, and steps to take to help alleviate these urges ▪ Plan should include an agreement with patient to contact a responsible adult if these urges become overwhelming 2. Further management (24 hrs) ○ Suicidal ideation: ▪ Safety plan in place, have a practitioner available 24 hrs a day to address any concerns for safety /suicidality 3. Long-term care ○ Education: ▪ Discuss disease with patient and family ▪ Discuss signs and symptoms of suicidality with family ○ Cognitive behavioral therapy (CBT) ▪ Helps patients recognize and counteract distorted patterns of thinking that relate to depression. ▪ Most studied form of psychotherapy for depression. ▪ Efficacious for adolescents but less than pharmacotherapy ○ Interpersonal therapy (IPT) ▪ Addresses depression in terms of dysfunctional relationships and teaches patient awareness and skills to change these patterns ○ Pharmacotherapy ▪ Fluoxetine ▪ Initial dose 5-10 mg/day, may increase q7days to target dose 10-20 mg/day (max 20 mg/day)

	▪ Only SSRI with FDA approval for Tx of depression in patients 8-18 yo ▪ Risk vs benefit: efficacy in treating depression (fluoxetine NNT = 6) vs suicidality risk (fluoxetine NNH = 48) + side effects ▪ Monitoring: Close follow up in the office, especially in first 3 months (see Follow Up) ▪ Black box warning (2004): ▪ FDA mandated warning on all antidepressants: increased suicidality, small, but real increase shown in meta analysis ▪ Treatment of pediatric depression with SSRI ▪ Number needed to treat (NNT) = 8 ▪ Number needed to harm (NNH) = 59 ▪ SSRIs appropriate only in context of education, ongoing clinical monitoring, and safety plan ▪ Follow Up ▪ Low risk for suicide: ▪ Weekly follow up during first 30 days on medication, then biweekly for 60 days ▪ Higher risk patients (severe depression, possibility of bipolar illness, personal/family hx of suicide attempts/suicide): ▪ Follow more closely ▪ Types, FDA approval: ▪ Fluoxetine only SSRI currently to have FDA approval for Tx of depression in patients under age 18 (approved ages 8-18) ▪ Sertraline: double blinded placebo controlled trials, no difference with placebo ▪ Citalopram: published/unpublished poorly designed trials showed uncertain efficacy ▪ Paroxetine: published/unpublished trials showed no benefit in primary outcome measure ▪ TCAs: not first line therapy for pediatric population given side effect profile and uncertain efficacy
5.6 PEPID citation/access data	4/16/08

SECTION 6: CONCLUSIONS	
6.1 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)	**2**
6.2 If 6.1 was coded as 4 or greater, 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?	
6.3 Are the results of this study relevant to the health care needs of patients cared for by "full scope" family physicians, general internists, general pediatricians, or general OB/GYNs? Are they applicable without significant change in programs or policies such as the organization or financing of practice? Give one number on a scale of 1 to 7 (1=absolutely relevant; 4=neutral; 7=not at all relevant)	**1**
6.4 Please explain your response to item 6.3.	This is a serious problem in a small number of adolescents & this option provides physicians with an alternative form of treatment should the current SSRI or SNRI not be effective.
6.5 What is the main recommendation for change in practice, if any? Include a description of the change in practice, the indications, and the target population.	In adolescent suffering from severe depression whose current SSRI or SNRI is not efficacious physicians should consider switching to another SSRI in conjunction with a 12 week course of CBT from a trained therapist.
SECTION 7: EDITORIAL DECISIONS	
7.1 FPIN PURLs editorial decision (select one)	PURL—Forward to JFP Editor for interest in JFP publication
7.2 FPIN PURLS Editor	Bernard Ewigman

7.3 Date of decision	September 22, 2008