Translating the Research on Psychotropic Medications with Children to Clinical Practice

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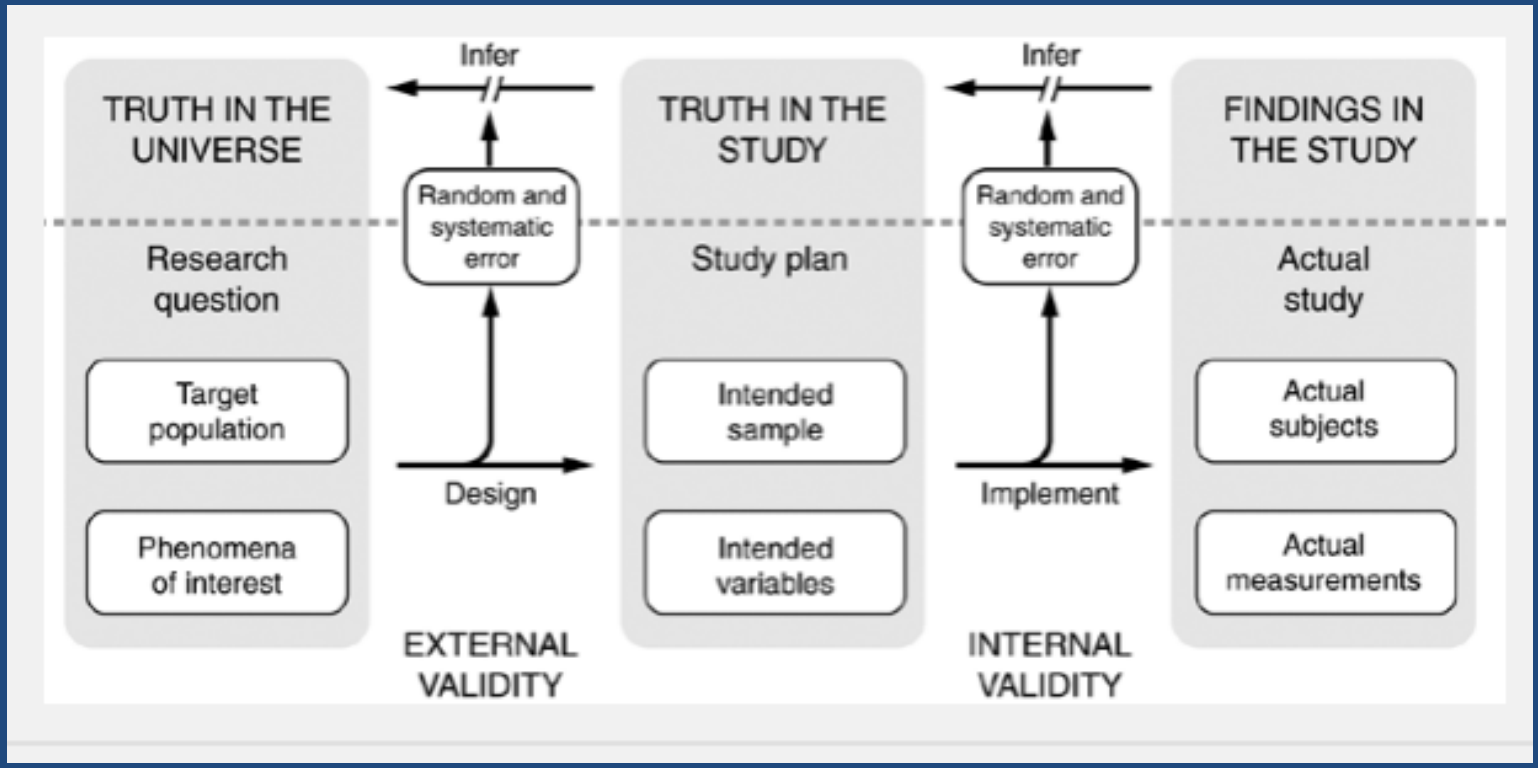

TRUTH IN THE UNIVERSE
Research question
Target population
Phenomena of interest
Infer
Random and systematic error
Design
EXTERNAL VALIDITY
TRUTH IN THE STUDY
Study plan
Intended sample
Intended variables
Infer
Random and systematic error
Implement
INTERNAL VALIDITY
FINDINGS IN THE STUDY
Actual study
Actual subjects
Actual measurements

Table 2.1 FINER Criteria for a Good Research Question

Feasible
- Adequate number of subjects
- Adequate technical expertise
- Affordable in time and money
- Manageable in scope

Interesting
- Getting the answer intrigues the investigator and her friends

Novel
- Confirms, refutes or extends previous findings
- Provides new findings

Ethical
- Amenable to a study that institutional review board will approve

Relevant
- To scientific knowledge
- To clinical and health policy
- To future research

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name

Date of Assessment

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

_____
- **0=** Absent
- **1=** These feeling states indicated only on questioning
- **2=** These feeling states spontaneously reported verbally
- **3=** Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
- **4=** Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

_____
- **0=** Absent
- **1=** Self reproach, feels he has let people down
- **2=** Ideas of guilt or rumination over past errors or sinful deeds
- **3=** Present illness is a punishment. Delusions of guilt
- **4=** Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

_____
- **0=** Absent
- **1=** Feels life is not worth living
- **2=** Wishes he were dead or any thoughts of possible death to self
- **3=** Suicidal ideas or gesture
- **4=** Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**

_____
- **0=** No difficulty falling asleep
- **1=** Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
- **2=** Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**

_____
- **0=** No difficulty
- **1=** Patient complains of being restless and disturbed during the night
- **2=** Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. **INSOMNIA LATE**

_____
- **0=** No difficulty
- **1=** Waking in early hours of the morning but goes back to sleep
- **2=** Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**

_____
- **0=** No difficulty
- **1=** Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
- **2=** Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
- **3=** Decrease in actual time spent in activities or decrease in productivity
- **4=** Stopped working because of present illness

8. **RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____
- **0=** Normal speech and thought
- **1=** Slight retardation at interview
- **2=** Obvious retardation at interview
- **3=** Interview difficult
- **4=** Complete stupor

9. **AGITATION**

_____
- **0=** None
- **1=** Fidgetiness
- **2=** Playing with hands, hair, etc.
- **3=** Moving about, can't sit still
- **4=** Hand wringing, nail biting, hair-pulling, biting of lips

10. **ANXIETY (PSYCHOLOGICAL)**

_____
- **0=** No difficulty
- **1=** Subjective tension and irritability
- **2=** Worrying about minor matters
- **3=** Apprehensive attitude apparent in face or speech
- **4=** Fears expressed without questioning

11. **ANXIETY SOMATIC:** Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____
- **0=** Absent
- **1=** Mild
- **2=** Moderate
- **3=** Severe
- **4=** Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____
0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____
0= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____
0= Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

_____
0= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT

_____
A. When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT

_____
0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18. DIURNAL VARIATION

_____
A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No variation
1= Worse in A.M.
2= Worse in P.M.

_____
B. When present, mark the severity of the variation. Mark "None" if NO variation
0= None
1= Mild
2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

_____
0= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____
0= Absent
1= Mild
2= Severe

Total Score _____

Appendix 1: Formulas for commonly used measures of therapeutic effect

Measure of effect	Formula
Relative risk	(Event rate in intervention group) ÷ (event rate in control group)
Relative risk reduction	1 – relative risk *or* (Absolute risk reduction) ÷ (event rate in control group)
Absolute risk reduction	(Event rate in intervention group) – (event rate in control group)
Number needed to treat	1 ÷ (absolute risk reduction)

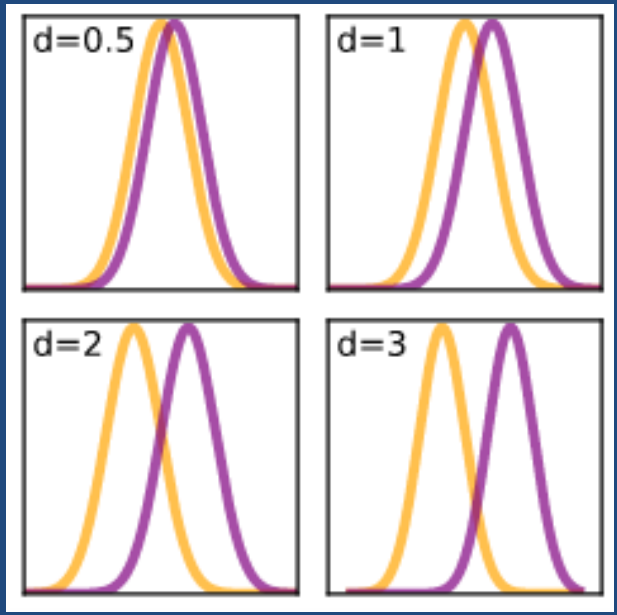
		Treatment	
		Active	**Control**
Outcome	**Success**	70	60
	Failure	30	40
	Total	100	100

NNT = 1/ Absolute Risk Reduction
= 1/ (Pa - Pc)
= 1 /(70/100 - 60/100)
= 1/ (0.7 – 0.6)
= 10

Effect Sizes

$$Cohen's\ d = \frac{mean\ difference}{standard\ deviation}$$

$$Cohen's\ d = \frac{120 - 100}{30} = .66$$



Keller et al

(Keller MB et al, *J Am Acad Child Adolesc Psychiatry* 2001;40(7):762-772)

paroxetine vs **imipramine** vs **placebo**

outcome measure:

primary:

- "response= HAMD <=8 or >=50% reduction in HAMD score"
- change in HAMD

secondary:

- HAMD dep mood
- K-SADS-L depression item
- CGI 1 or 2
- K-SADS-L depression subscale (9 items)
- mean CGI improvement scores

Keller et al

study population: (N=275)

inclusion: M or F; age 12-18; DSM-IV current depressive episode of >8 wks (diagnosed by K-SADS-L); HAM-D of >12; CGAS of <60

exclusion: bipolar; schizoaffective; ED; ETOH/substance d/o; OCD; autism; organic brain disorder; PTSD within 12 mos; current SI; current psychotropic meds; AD within past 6 mos; pregnant or breastfeeding F

randomization: 7-14 day screening phase; computerized randomization

control group: placebo BID, up to 6 capsules per day

* All groups received supportive case management at weekly clinic visits.

Keller et al

Sample size

wanted to detect effect size of 0.4 with $\alpha = 0.05$

(power = likelihood of detecting a specific effect = $1-\beta = 0.80$)

	Null hypothesis (H_0) is true	**Null hypothesis (H_0) is false**
Reject null hypothesis	Type I error False positive α	Correct outcome True positive
Fail to reject null hypothesis	Correct outcome True negative	β Type II error False negative

Keller et al

Data analysis

- intent-to-treat (ITT)
- completers

Keller et al

Changes in outcome measures

Table 1

Outcome measures (significant results in **bold**); ordering of outcome measures is from originals

Protocol (1993, 1996) [12]	*p*	Final paper (2001) [5]	*p*
*Change in HAM-D total score	0.13	**HAM-D ⩽ 8**	**0.02**
*Responders (HAM-D ⩽ 8 or reduced by ⩾50%)	0.11	*Responders (HAM-D ⩽ 8 or reduced by ⩾50%)	0.11
Depression scale of K-SADS-L	0.07	**HAM-D depressed mood item**	**0.001**
Mean Clinical Global Improvement (CGI) score	0.09	**K-SADS-L depressed mood item**	**0.05**
Autonomous function checklist	0.15	**CGI 1 or 2**	**0.02**
Self-perception profile	0.54	Depression scale of K-SADS-L	0.07
Sickness impact scale	0.46	Mean CGI	0.09
Relapse during maintenance	0.24**	*HAM-D total score	0.13

*Protocol specified primary outcomes. **Not published, calculated by us, trend favours placebo.

(Jureidini JN et al, *Int J Risk Safety Med* 2008;20:73-81)

Keller et al

Where did the positive variables come from?

Box 1

History of the four positive 'depression related variables' unspecified in the trial protocol

HAM-D ⩽ 8	
1992 December	Part of the complex definition of 'responder' in Keller's proposal to SKB [11].
1996 October	Not specified as an outcome measure in the acute-phase protocol [14].
1997 April	First labelled as 'remission', a second "definition of 'response' during the acute phase" [16].
1999 February	Listed as an outcome variable in early drafts of the paper [15].
2001 July	By publication, 'remission' disappears altogether as a label, and 'HAM-D ⩽ 8' is conflated with 'HAM-D ⩽ 8 or reduced by ⩾50%' – see Box 2 [5].
HAM-D depression item	
1997 August	Not mentioned before the official unblinding.
CGI 1 or 2	
1997 April	Mentioned as possible outcome [16].
1998 January	Not mentioned in 'Top Line Results' [17] three months after the blind was broken. Study 329 co-author Ryan noted at the time by hand on his copy of these 'Top Line Results' the percentage of subjects fitting into each of the CGI categories but there is no indication of any decision as to how to make use of this data [18, p. 450].
K-SADS-L depressed mood item	
1998 November	First documented as an outcome variable [14, p. 44].

(Jureidini JN et al, *Int J Risk Safety Med* 2008;20:73-81)

Keller et al

Adverse events

these figures. Subsequently McCafferty's disclosures of overdose and mania were edited out, and SAEs on paroxetine were attributed to other causes. Where McCafferty's draft reads:

> worsening depression, emotional lability, headache, and hostility were considered related or possibly related to treatment [20],

the published *JAACAP* paper states:

> only headache (1 patient) was considered by the treating investigator to be related to paroxetine treatment.

Table 2

Adverse events documented in SKB's final report of study 329 [14]

Type of adverse event	Paroxetine ($N = 93$)	Placebo ($N = 87$)	$p^{\wedge}$	Source table
Serious[#]	11 (12%)	2 (2.3%)	0.01	48, p. 109
Severe[##]	27 (29%)	15 (17%)	0.06	14.3.1, pp. 231–238
Hospitalisation	6[*] (6.5%)	0	0.004	48, p. 109
Nervous system				
Any	56 (60%)	29 (33%)	0.001	14.2.1, p. 227
Severe[**]	17 (18%)	4 (4.6%)	0.003	14.3.1, pp. 231–238
Requiring withdrawal	8 (8.6%)	2 (2.3%)	0.056	49, p. 111
Leading to dose reductions	8 (8.6%)	2 (2.3%)	0.056	46, p. 105

[^]Calculated by us; [#]'resulted in hospitalisation, was associated with suicidal gestures, or was described by the treating physician as serious' [5]; [##]'incapacitating and prevents normal everyday activities' [14, p. 565]; [*]stated as 7 in published paper; [**]stated as 16 for paroxetine and 3 for placebo in Table 44, p. 101.

Keller et al

5.1. Were the results for study 329 positive or negative?

There was no significant efficacy difference between paroxetine and placebo on the two primary outcomes or six secondary outcomes in the original protocol. At least 19 additional outcomes were tested. Study 329 was positive on 4 of 27 known outcomes (15%). There was a significantly higher rate of SAEs with paroxetine than with placebo. Consequently, study 329 was negative for efficacy and positive for harm.

5.3. How did selective reporting happen?

In response to criticism in *JAACAP* in 2003, Keller et al. [34] indicated that they believed that paroxetine was effective and therefore viewed the efficacy results as a false negative arising from their mistake of using the HAM-D as their depression measure. They then searched for other outcomes that matched their beliefs about efficacy. Such searching has been described as "data torturing" [35], a form of confirmation bias in which information is sought to support pre-conceived beliefs. Confirmation bias could also lead authors who were unconcerned about adverse events to look less closely at that data and to attribute adverse events in the paroxetine group to non-drug causes such as "arguments with boyfriends" [36]. Confirmation bias could be well-intentioned, so that investigators might believe that what they had done was entirely appropriate. However it does not explain the conflation of 'remission' and 'responder', the changes to the descriptions of SAEs, or flaws that were detected by peer reviewers but were not corrected.

TADS study

(March JS et al, *JAMA* 2004;292:807-820)

Fluoxetine vs **CBT** vs **fluoxetine+CBT** vs **placebo**

outcome measure:

primary:

- Change in CDRS score
- CGI 1 or 2

secondary:

- Reynolds Adolescent Depression Scale (RADS)
- Suicidal Ideation Questionnaire-Junior HS Version (SIQ-Jr)

TADS study

study population: (N=439)

inclusion: M or F; 12-17 yo; DSM-IV dx of MDD at consent and baseline; CDRS score >45, no ADs, depression in 2 of 3 contexts for 6 wks

exclusion: bipolar; conduct d/o; substance abuse/dependence; PDD; thought disorder; concurrent psychotropic meds or therapy; 2 failed SSRI trials; poor response to CBT; intolerance to fluoxetine; pregnancy

setting: 13 academic and community clinics

randomization: computerized randomization; independent evaluators

TADS study

Sample size

wanted effect size of 0.4 with $\alpha = 0.05$

(power = likelihood of detecting a specific effect = $1-\beta = 0.80$)

Data analysis

intent-to-treat (ITT)

linear random coefficient regression model (allows estimation of changes in repeated measures when data are missing)

TADS study

CDRS

fluoxetine+CBT > placebo (p=.001)

fluoxetine > placebo (p=.02)

CBT = placebo (p=0.4)

fluoxetine > CBT (p=.01)

fluoxetine+CBT = fluoxetine (p=.13)

fluoxetine+CBT > CBT (p=.001)

Response rates (CGI = 1 or 2)

fluoxetine+CBT = 71.0%

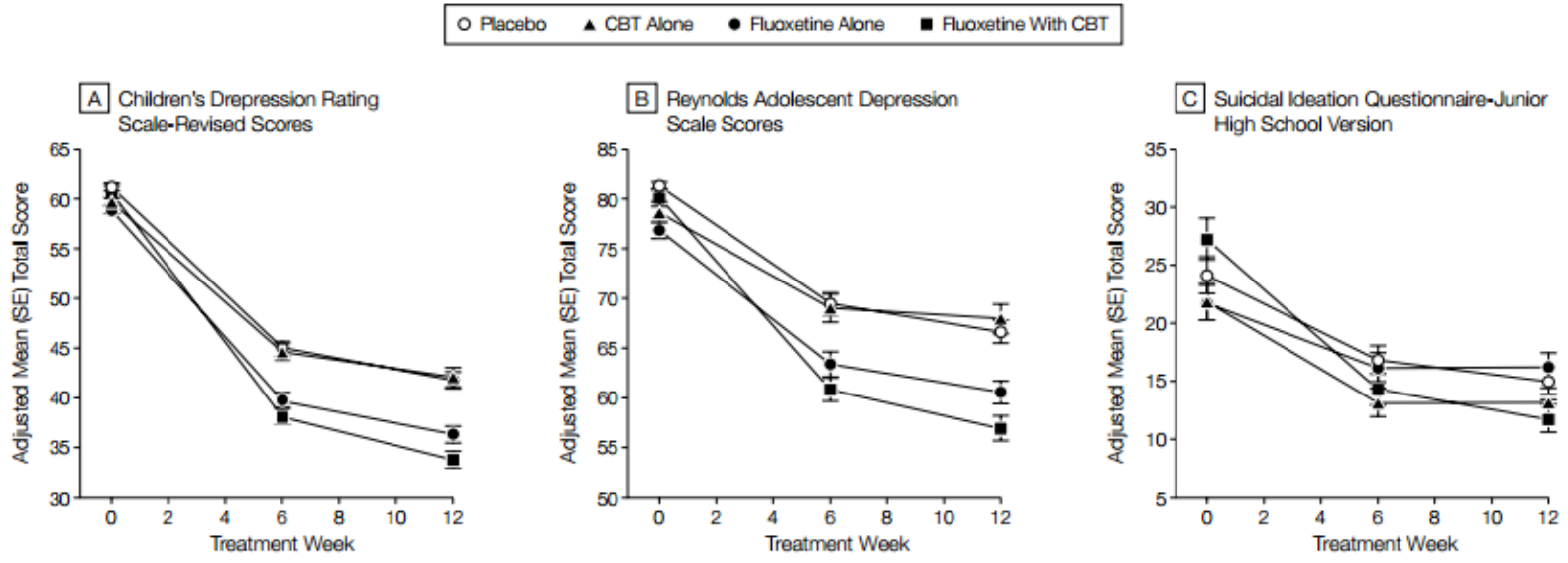
fluoxetine = 60.6%

CBT = 43.2%

placebo = 34.8%

TADS study

Figure 2. Adjusted Mean (SE) Scale Scores for Participants in the Treatment for Adolescents With Depression Study



TADS study

Table 3. Harm- and Suicide-Related Adverse Events

	Total No. of Patients	Intent-to-Treat Cases	
		Harm-Related	Suicide-Related
Active Treatment vs Placebo			
CBT with fluoxetine			
No. (%) of patients	107	9 (8.41)	6 (5.61)
OR (95% CI)		1.62 (0.56-4.72)	1.60 (0.44-5.85)
Fluoxetine alone			
No. (%) of patients	109	13 (11.93)	9 (8.26)
OR (95% CI)		2.39 (0.87-6.54)	2.43 (0.73-8.14)
CBT alone			
No. (%) of patients	111	5 (4.50)	5 (4.50)
OR (95% CI)		0.83 (0.25-2.81)	1.27 (0.33-4.87)
Placebo			
No. (%) of patients	112	6 (5.36)	4 (3.57)
SSRI vs No SSRI			
SSRI			
No. (%) of patients	216	22 (10.19)	15 (6.94)
OR (95% CI)		2.19 (1.03-4.62)	1.77 (0.76-4.15)
No SSRI			
No. (%) of patients	223	11 (4.93)	9 (4.04)
CBT vs No CBT			
CBT			
No. (%) of patients	218	14 (6.42)	11 (5.05)
OR (95% CI)		0.73 (0.36-1.49)	0.85 (0.37-1.94)
No CBT			
No. (%) of patients	221	19 (8.60)	13 (5.88)

Abbreviations: CBT, cognitive-behavioral therapy; CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

Other resources

www.criticalthinkrx.org

(online curriculum about psychotropic meds and children [includes CE credit])

www.1boringoldman.com

(blog devoted to psychiatric issues, including critical analysis of research, etc)

www.alltrials.net

www.healthyskepticism.org

www.rxisk.org

www.rxbalance.org

Thank You

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