

Childhood Depression

Graham J. Emslie, M.D.

*From the Department of Psychiatry, University of Texas Southwestern
Medical Center at Dallas and Children's Medical Center of Dallas*



happy



depressed



angry



pensive



excited



suicidal

How to recognize the moods of an Irish setter

DEPRESSIVE DISORDERS

- Major depressive disorder
- Dysthymia
- Minor depression
- Adjustment disorder with depressed mood

EPIDEMIOLOGY

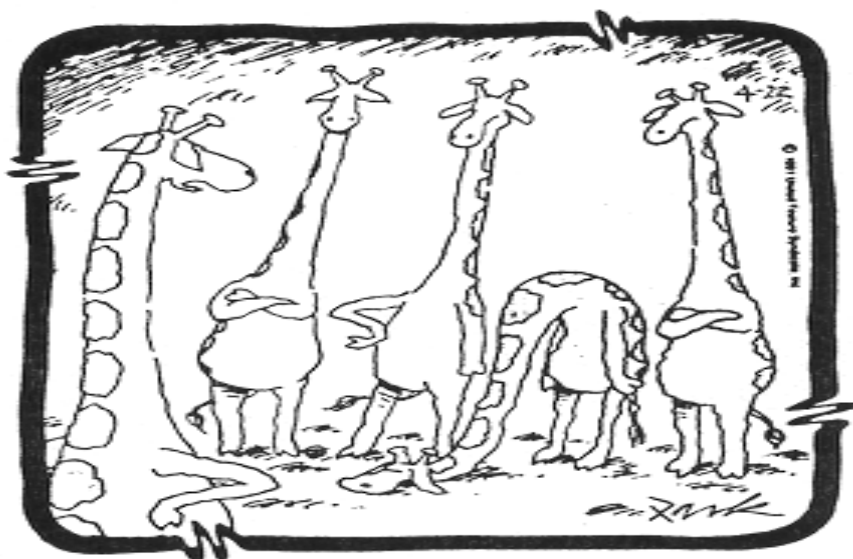
- Similar to adults
- 4.9% MDD; 6.2% any depressive disorder
- Female to male ratio becomes 2:1 beginning in adolescents
- Comorbidity is common

Early-Onset Depression

- Depression is a diagnosable condition in children and adolescents
- Diagnostic criteria are essentially the same as adults (except irritable mood)
- Multiple informants are used when diagnosing younger patients
- Diagnosis may be obscured by other comorbid disorders

OFF THE LEASH

By W R Park



"I understand one of you is depressed."

Depressive Symptoms: Hong Kong vs. Western Culture

- Secondary school students (n=996) from Hong Kong (different districts) vs. similar age students from Canada.
- Depressive symptoms based on the Chinese Beck Depression Inventory

	None	Mild	Moderate	Severe
Hong Kong	44.7%	36.4%	14.7%	4.2%
Canadian	65.5%	24%	7%	4%

Stewart, Betson, Lam, Chung, Ho, Chung, 1999

MDD Diagnosis: Hong Kong vs. Western Culture

- Following self-report questionnaires, some HK subjects (n=85) and all US (n=1,706) subjects were interviewed to assess MDD.
- HK:
 - 2.2% current diagnosis
 - 11.0% ever diagnosed
- US:
 - 2.2% current diagnosis
 - 16.1% ever diagnosed

Stewart, Lewinsohn, Lee, Ho, Kennard, Hughes, Emslie, 2002

	HK	US
Depressed mood	100%	90%
Irritability	17%	85%*
Anhedonia	75%	95%
Weight/appetite change	75%	90%
Sleep change	100%	90%
Fatigue/loss of energy	100%	70%*
Psychomotor agit/retardation	92%	85%
Worthlessness/guilt	67%	80%
Concentration/indecision	100%	90%
Suicidal ideation	75%	70%

*p=.001

Stewart, Lewinsohn, Lee, Ho, Kennard, Hughes, Emslie, 2002

COMORBID CONDITIONS

- General Medical Conditions
- Substance Use
- Psychiatric Comorbidities

COMORBID DIAGNOSES

	N (%)
Anxiety disorder	59 (46%)
Dysthymia	47 (36%)
ADHD	45 (35%)
ODD/conduct disorder	40 (31%)

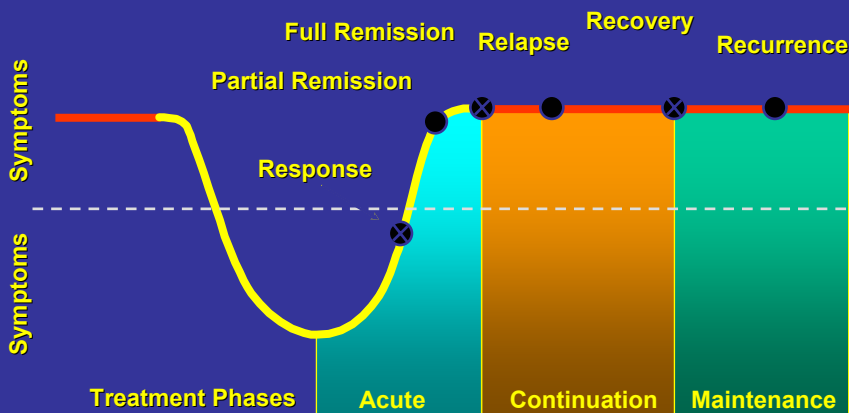
Based on 130 consecutively referred children and adolescents

OUTCOME

- Harrington et al., 1990; Lewinsohn et al., 2000
 - Increased rates of depression in adulthood
- Rao et al., 1993
 - 7 suicides (4.4%) over 10 years
- Kovacs et al., 1993
 - 9% at time of evaluation - suicide attempts
 - 24% suicide attempts by age 17
- Bardone et al., 1998
 - Increased tobacco dependence and increased medical problems

INTERVENTIONS

RESPONSE, REMISSION, RECOVERY, RELAPSE, RECURRENCE



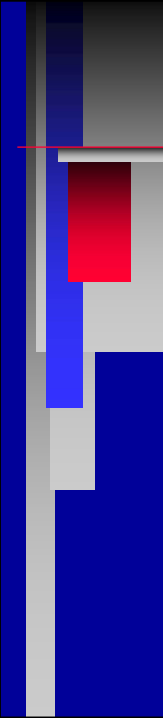
Evidence-Based Medicine

“Evidence-based medicine (EBM) is the integration of best research evidence with clinical experience and patient values.”

Sackett DL et al. Evidence-Based Medicine: How to Practice and Teach EBM (2000).

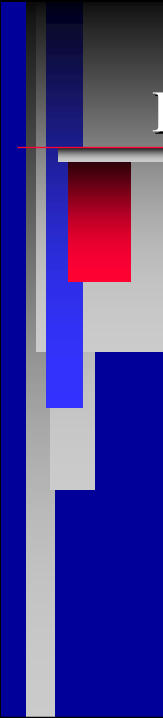
GOALS OF TREATMENT

- Shorten the acute episode
- Limit the amount of dysfunction caused by the episode
- Remission of depression
- Normalization of functioning
- Prevent recurrence



Guidelines for Primary Care: Assessment and Diagnosis

1. Evaluate depression in patients with high-risk factors for depression (previous depression, family history, etc.) using DSM-IV or ICD 10.
2. Utilize direct interview with patients and caregiver, and assess other existing psychiatric conditions.



Guidelines for Primary Care: Initial Management of Depression

1. Educate and counsel patient and caregivers about depression and treatment options.
2. Assist families in developing a treatment plan and set specific goals for functioning in home, peers, and school.
3. Assist families in seeking mental health resources in the community and collaborate with that system of care.
4. Establish a safety plan.

Guidelines for Primary Care: Treatment

1. Consider a period of active support and monitoring before starting other evidence-based treatment.
2. Consult with mental health professionals if needed.

If you plan to treat the depression...

TREATMENT INTERVENTIONS

- Medication
 - Monotherapy
 - Most effective
 - Fewest side effects
- Psychotherapy
 - Individual, group, family
 - Specific therapies (CBT, IPT)

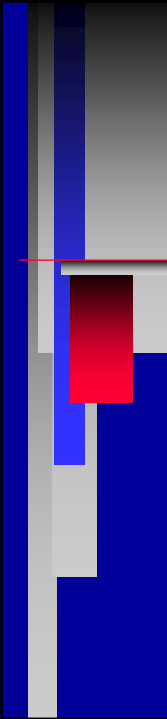
MEDICATION TREATMENT

Sorting antidepressant evidence is tough



ROBERT SULLIVAN/AFP/Getty Images

Concerns have been raised about whether antidepressants can induce suicidal thinking and behavior in youngsters.



**Cheung AH, Emslie GJ, Mayes TL (2005).
Review of the efficacy and safety of
antidepressants in youth depression. *J Ch
Psychology and Psychiatry*, 46, 735-754.**

Evidence Based Decision- Making

■ Levels of evidence

Level A - Randomized, controlled clinical trials

**Level B - Epidemiologic studies, cohort
studies, retrospective analyses, etc.**

Level C - Case reports, expert opinion

PUBLISHED TRIALS

Study	N	Ages	Response	p
Fluoxetine (1997)	96	7-17	56% vs. 33%	.02
Fluoxetine (2002)	219	8-17	52% vs. 37%	.028
Paroxetine (2001)	275	12-18	66% vs. 48%	.02
Sertraline (2003)	376	6-17	63% vs. 53%	.05
Citalopram (2004)	174	7-17	47% vs. 45%	NS

OTHER TRIALS

Study	N	Ages	Response	p
Paroxetine #377 (AACAP, 1999)	275	13-18	69% vs. 57%	NS
Paroxetine #701 (AACAP, 2004)	203	7-17	49% vs. 46%	.563
Escitalopram (AACAP, 2004)	164	6-17	63% vs. 53%	NS
Citalopram (MHRA report)	233	13-18	UNK	UNK

NSRI TRIALS

Study	N	Ages	Response	p
Nefazodone (APA, 2002)	195	12-17	65% vs. 46%	.005
Nefazodone	UNK	7-17	UNK	UNK
Venlafaxine #382 (APA, 2004)	161	7-17	50% vs. 41%	.314
Venlafaxine #394 (APA, 2004)	193	7-17	67% vs. 61%	.370
Mirtazapine	126	7-17	60% vs. 57%	NS
Mirtazapine	132	7-17	54% vs. 42%	NS

VARIABILITY IN TRIALS

- Sites
 - Single vs. multi-site
 - Experience of site raters
- Recruitment
- Study design
 - Inclusion/Exclusion
 - Diagnostic process
 - Duration
- Outcome Measures

Number of Subjects Per Site and Drug-Placebo Difference

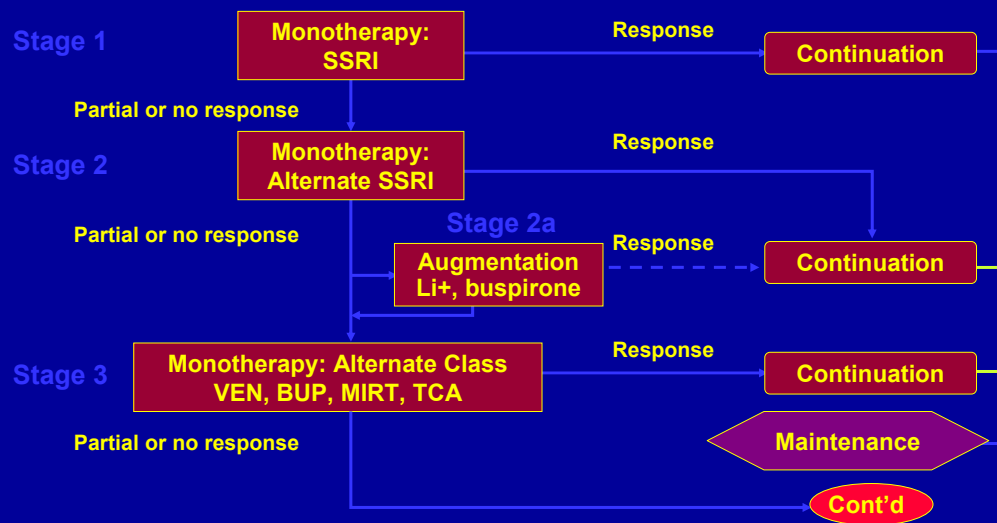
	<i># Subj. per Site</i>	<i># of Sites</i>	<i>Drug-Pbo Difference</i>
Fluoxetine (1997)	96	1	23%
Fluoxetine TADS (2004)	≈29	12	26%
Paroxetine (2001)	≈28	10	17.3%
Fluoxetine (2002)	≈15	15	16.5%
Sertraline (2003)	≈7	53	10%
Citalopram (2004)	≈8	21	2%

*Based on CGI-Improvement of 1 or 2.

REMISSION (Double-Blind Trials)

	<i>Response</i>	<i>Remission</i>
Fluoxetine	56% vs. 33%	31% vs. 23%
Fluoxetine	52% vs. 37%	41% vs. 20%
Paroxetine	66% vs. 48%	63% vs. 46%
Sertraline	63% vs. 53%	Not Available
Citalopram	47% vs. 45%	36% vs. 24%

*Guidelines for Treatment of Pediatric Depression**



*Note: Any stage(s) can be skipped depending on the clinical picture
Hughes CW, et al. *J Am Acad Child Adolesc Psychiatry*. 1999;38:1442-1454.

INTEGRATING PSYCHOTHERAPY

PSYCHOTHERAPY

- Individual, group, family
- Specific therapies (CBT, IPT)

FOCUS OF SUCCESSFUL CBT

- Increase participation in pleasant activities
- Increase and improve social interactions
- Improve conflict resolution and social problem-solving skills
- Decrease physiological tension
- Identify and modify depressive thoughts and attributions

– Kazdin and Weisz, 1998
– Kaslow and Thompson, 1998

Trials of CBT for Teen MDD

	<i>Brent CT</i>	<i>Clarke CBT</i>	<i>Wood Brief CBT</i>
N/n	107/78	123/96	53/48
Control	NST (SBFT)	WL	Relax
Length	12-16 s's/wks.	16 2-hr. s's, 8 wks.	5-8 s's in 2 mos.
Remit %	60 vs. 39 Sig.diff.	67 vs. 48 Sig.diff.	54 vs. 21 Sig.diff.

Paul Rohde / Anne Simmons: U Oregon

David Rosenberg: Wayne State

Mark Reineke: U Chicago / Northwestern

Sanjeev Pathak: Cincinnati

Norah Feeney: Case Western



Chris Kratochvil: Nebraska

Graham Emslie: UT Southwestern

Anne Marie Albano: NYU

Bruce Waslick: Columbia

Elizabeth Weller: Penn

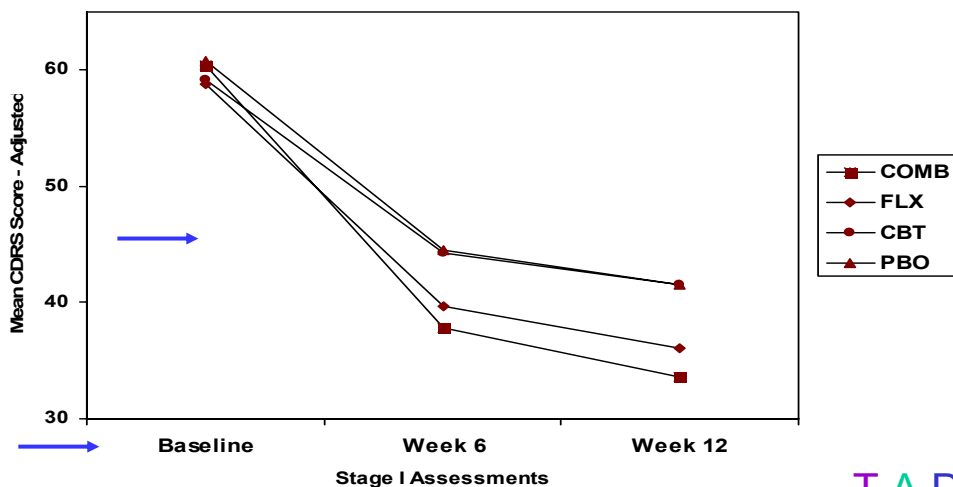
John Walkup: Hopkins

Charles Casat: Carolinas Med Ctr

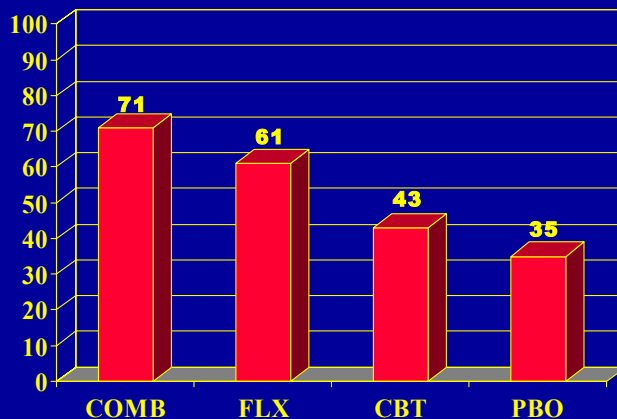
TADS Design

- 439 Adolescents (12-17) with MDD
 - COMB: 107
 - FLX: 109
 - CBT: 111
 - PBO: 112
- Acute treatment for 12 weeks
- Independent Evaluations at Weeks 6 and 12

CDRS: Adjusted Means (ITT)



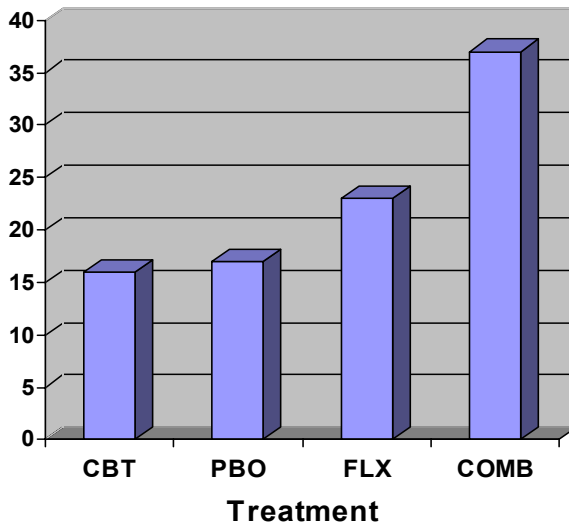
CGI-I Treatment Response: Week 12



REMISSION (TADS)

- No longer meeting criteria: 71.5%
 - COMB (85.3%), FLX (78.6%), CBT (61.1%), PBO (60.4%)
- CDRS-R ≤ 28 : 23% (102/439)
 - COMBO > FLX = CBT = PBO

Remission Rates by Treatment Group

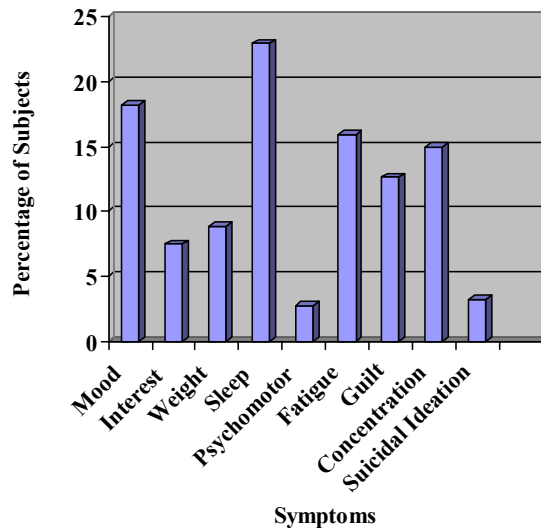


Kennard et al., submitted

Residual Symptoms in TADS

- 50% who were clinically improved (CGI 1 or 2) continued to have residual symptoms
 - Based on 1 or more symptoms on the 9 depressive items of the K-SADS at end of acute treatment

Figure 2. Frequency of Residual Major Depressive Disorder Symptoms in Responders (N = 214 ^a)



a. Of 229 responders

APA PRACTICE GUIDELINES (For Adults)

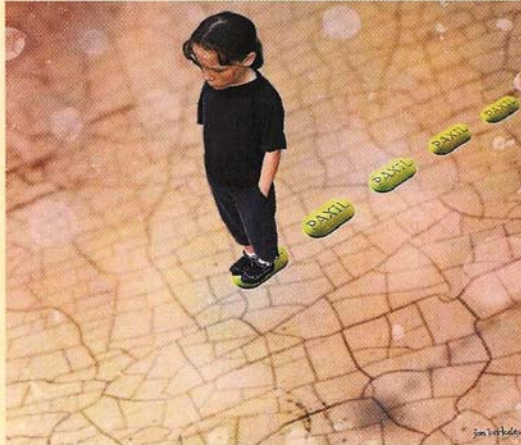
- Medication should be provided for moderate to severe depression
- Psychotherapy alone as initial treatment option for mild to moderate depression (CBT or IPT)
- Combined treatment as initial option if:
 - Significant psychosocial issues
 - History of partial response to single modality
 - Poor adherence to single modalities

MHRA and NICE

- “The balance of risks and benefits for the treatment of depressive illness in under-18s is judged to be unfavourable for paroxetine, venlafaxine, sertraline, citalopram, escitalopram, and mirtazapine.”
- Andrew Dillon, NICE chief executive said, “Psychological treatments are the most effective way to treat depression in children and young people.”
- Dr. Tim Kendall (National Collaborating Centre for Mental Health) said the evidence supporting the effectiveness of psychological therapies was “robust.”

SUMMARY

- Depression is a serious disorder in children and adolescents, with significant impairing outcomes.
- Efficacy results of antidepressants are mixed.
- Adolescents have stronger efficacy data than children.
- CBT has not been shown to be as effective in medication in 1 head-to-head trial.



Teen Suicide Pills?

An FDA panel calls for tough labels on antidepressants. What it means for you

Suicidal Behavior

- **General population:**
 - 9% of teens make an actual suicide attempt.
 - 19% of teens have suicidal ideation.
- **Suicidal behavior is a symptom of depression.**
 - 35-50% of depressed teens make a suicide attempt.
- **Suicide rates have decreased over the past decade, as antidepressant prescriptions have increased.**
- **6 completed suicides per 100,000 (.006%)**

** Olfson et al. 2003; World Health Organization 2003

Examples of Difficulties in Adverse Event Labeling

<u>Original Label</u>	<u>Narratives</u>
Personality Disorder	10 y.o. male exhibited sx's of PD of moderate severity and was discontinued, one day later pt. attempted to hang himself w/ a rope after dispute w/ his father. Investigator did not consider this an SAE but rather part of the PD.
Accidental Overdose AND Neurosis	The overdose of 6 capsules of study medication was in fact intentional and in response to an argument with the subject's mother.
Medication Error	Age 14: The patient took 11 tablets impulsively and then went to school...the patient denied that it was a suicide attempt.
Hostility	Age 10: Before his mother's call to the site and again after arguing with his stepfather, he wrapped a cord from the miniblinds around his neck, threatening to kill himself.

More Examples of Difficulties in Adverse Event Labeling

<u>Original Label</u>	<u>Narratives</u>
Emotional Lab./ Suicide Attempt	Age 14: The patient is reported to have engaged in an episode of "automutilation" where she slapped herself in the face.
Suicide Attempt	Pt. had thoughts of killing self but had no intention of acting on them
Suicide Attempt	Suicidal thoughts
Suicide Attempt	Self-destructive impulses
	**Note severity goes both ways- labels more severe than they should be as well as less severe than warranted

Suicide Attempt Definition

- A self-injurious act committed with at least some intent to die, **as a result of the act.**
- Any non-zero intent - does not have to be 100%.
- Intent can sometimes be inferred clinically from the behavior or circumstances. For example, if someone denies intent to die, but they thought that what they did could be lethal, intent can be inferred.
- There does not have to be any injury or harm, just the **potential** for injury or harm.

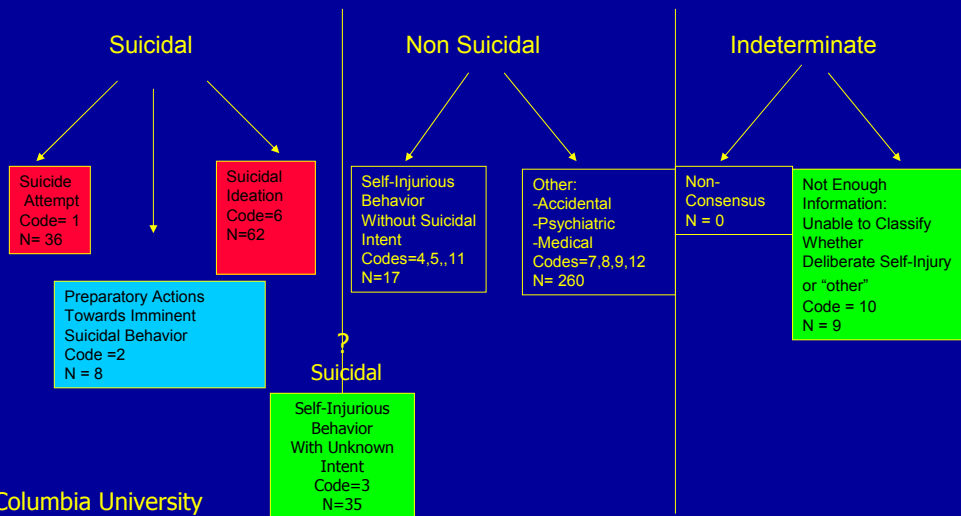
Preparatory Behaviors Towards Imminent Suicidal Behavior: Suicidal Behavior w/o Potential Injury

Person takes steps to injure self but is stopped by self or other before the threshold of potential for harm has been reached. Intent to die is either stated or inferred. Anything beyond a verbalization including:

Interrupted Attempt: individual is stopped by an outside circumstance from starting the self-injurious act

Aborted Attempt: individual takes steps towards making a suicide attempt, but stops himself before engaging in any potentially self-destructive behavior

What is the Classification Scheme?



Examples of Self-Injurious Behavior, Intent Unknown

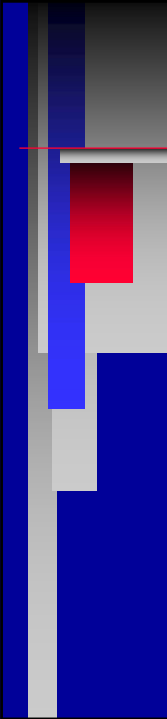
- CASE 1: The patient, age 10, had superficial scratches, left arm, scratched self with scissors
- CASE 2: The patient, age 14, ingested or simulated ingestion of 2-3 cigarettes. The patient was reported as feeling tired and playing a theatrical role
- CASE 3: Subject, age 9, reported he had ingested four of his brother's tablets "on a dare"

**Fixed Effect Results on Suicidal Behavior/Ideation (1,2,6) and on Possible Suicidal Behavior/Ideation (1,2,3,6,10)
For All Trials and SSRI/MDD Trials
(23 drug program trials + TADS)**

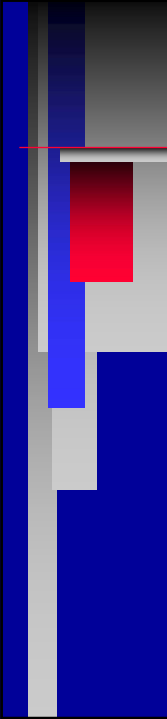
<i>Trial Group</i>	<i>RR (95% CI) for 1,2,6 (Suicidal Behavior/Ideation)</i>	<i>RR (95% CI) for 1,2,3,6,10 (Possible Suicidal Behavior/Ideation)</i>
<i>All Trials & Indications (23 + 1)</i>	<i>1.95 (1.28,2.98)*</i>	<i>2.19 (1.50,3.19)*</i>
<i>SSRI/MDD Trials (10 + 1)</i>	<i>1.66 (1.02,2.68)*</i>	<i>1.91 (1.27,2.89)*</i>

**Fixed Effect Results on Suicidal Behavior/Ideation (1,2,6), Suicidal Behavior (1,2), and Suicidal Ideation (6)
By Drug in MDD Trials (Seven Programs)**

<i>Drug Program (# of trials)</i>	<i>RR (95% CI) for 1,2,6 (Sui Behav/Ideation)</i>	<i>RR (95% CI) for 1,2 (Sui Behav)</i>	<i>RR (95% CI) for 6 (Sui Ideation)</i>
<i>Celexa (2)</i>	<i>1.37 (0.53,3.50)</i>	<i>2.23 (0.59,8.46)</i>	<i>0.75 (0.19,2.95)</i>
<i>Effexor (2)</i>	<i>8.84 (1.12,69.51)*</i>	<i>2.77 (0.11,67.10)</i>	<i>7.89 (0.99,62.59)</i>
<i>Paxil (3)</i>	<i>2.15 (0.71,6.52)</i>	<i>2.30 (0.67,7.93)</i>	<i>1.09 (0.24,5.01)</i>
<i>Prozac (3 + 1)</i>	<i>1.53 (0.74,3.16)</i>	<i>2.15 (0.50,9.26)</i>	<i>1.30 (0.59,2.87)</i>
<i>Remeron (1)</i>	<i>1.58 (0.06,38.37)</i>	<i>No Events</i>	<i>1.58 (0.06,38.37)</i>
<i>Serzone (2)</i>	<i>No Events</i>	<i>No Events</i>	<i>No Events</i>
<i>Zoloft (2)</i>	<i>2.16 (0.48,9.62)</i>	<i>0.98 (0.17,5.68)</i>	<i>3.88 (0.44,34.54)</i>



*97 cases of definitive suicidal
behavior in 4,250 youth studied.*

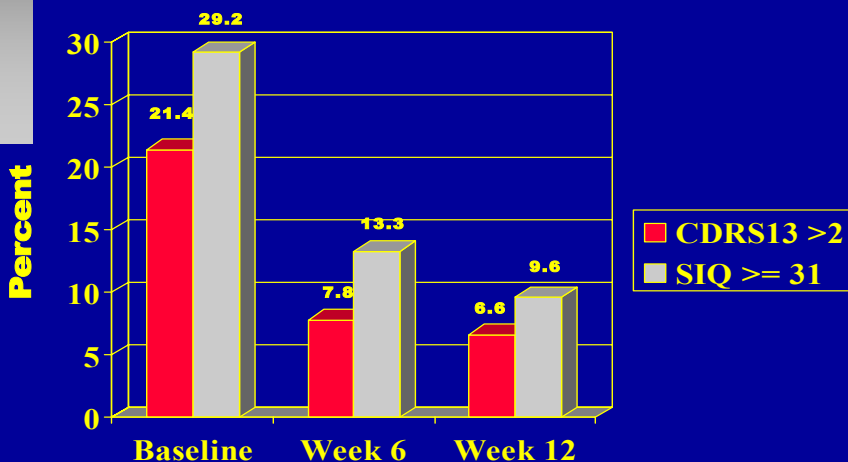


*NO completed suicides in more
than 2,800 depressed children
and adolescents studied.*

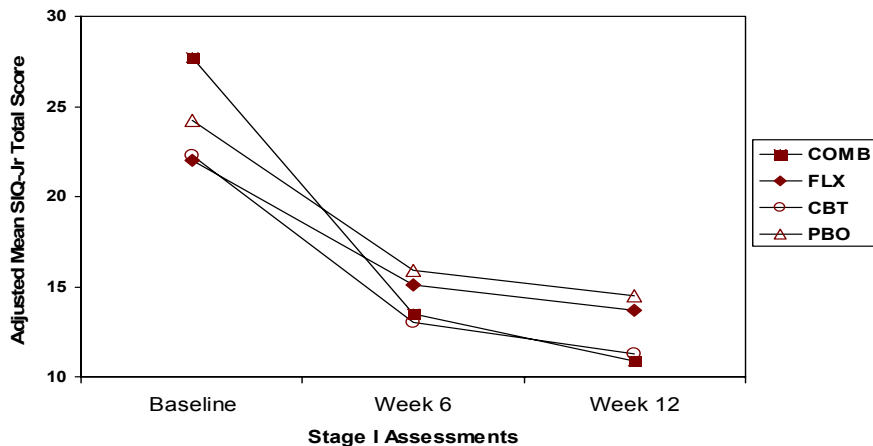
TOXICOLOGY STUDIES

- 80% of adults depressed patients were not on antidepressants at the time of the suicide
- Gray et al., 2003
 - 49 adolescent suicides
 - 24% had been prescribed antidepressants
 - None tested positive for antidepressants
- Leon et al., 2004
 - Post mortem study of 66 suicides in youth
 - 54 (82%) had serum toxicology for antidepressants within 3 days of death
 - 2 had imipramine and 2 had fluoxetine detected.

TADS: Suicidality Improves Overall (OC)



TADS: Improvement in Suicidal Ideation



SUMMARY

- Suicidal ideation is common in adolescents in the general population, and even more frequent in depressed teens.
- Overall, suicidality (suicidal ideation and behavior) improves with treatment.
- In a few subjects, suicidality worsens, and is more common on active medication than with placebo (pooled data).
- Epidemiologic data shows a decrease in suicides.



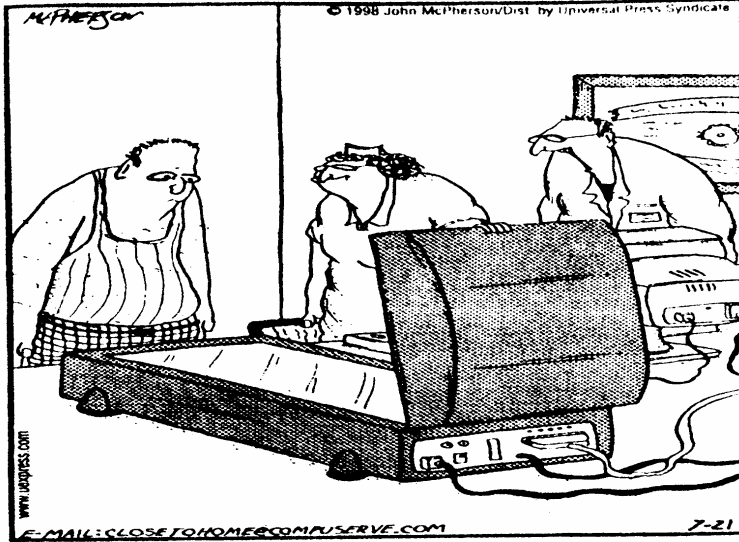
So, Where are we exactly?

FUTURE DIRECTIONS

- Better models for understanding the illness.
- Right interventions for the right people.
- Better monitoring of risk for treatment and for non-treatment.

CLOSE TO HOME

By John McPherson



"Nearly all of our diagnoses are done by computer these days. Please open your mouth and say 'Aaah' while pressing your face into the scanner."