Controversies in Treatment of Youth with Depression

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Teaching Points

- Depression in youth is a serious illness associated with morbidity
- In short term clinical studies of antidepressants in youth, 4% v 2% on placebo have risk of suicidality
- Observation data supports introduction of SSRIs associated with decreasing completed suicide rates
- Only fluoxetine is FDA-approved for depression in youth
- After consent discussion with parents, together provider and parents can consider use of antidepressants in youth

Question 1

- Which of the following ADs have FDA approval for the treatment of major depressive disorder (MDD) in youth?
- A-sertraline and fluoxetine
- B-sertraline
- C-fluoxetine and fluvoxamine
- D-fluoxetine
- E-venlafaxine

Question 2

- Which statement is true?
- A-Only fluoxetine has been associated with a small increased risk of suicidality in short term clinical trials of youth with anxiety disorders
- B-Only paroxetine has been associated with a small increased risk of suicidality in short term clinical trials of youth with anxiety disorders
- C-Only SSRIs have been associated with a small increase of suicidality only in short term clinical depression trials but not anxiety trials of youth
- D-Only fluoxetine has been associated with a small increased risk of suicidality in short term anxiety trials of youth
- E-All ADs have been associated with a small increased risk of suicidality in short term depression and anxiety clinical trials of youth

Question 3

- When published and unpublished RCTs of ADs are combined, which statement is true about the treatment of MDD in youth?
- A-only paroxetine and fluoxetine have shown statistical efficacy
- B-fluoxetine has shown no statistical efficacy
- C-fluoxetine and sertraline have shown no statistical efficacy
- D-fluoxetine has shown statistical efficacy
- E-All ADs have shown statistical efficacy

Question 4

- Which statement about pre-pubertal MDD is true?
- A-More girls than boys have depression
- B-Girls who are depressed will have later onset of menarche
- C-Both genders may have auditory hallucinations
- D-Point prevalence is 12%
- E-More girls than boys have depression

Question 5

- Which statement is true?
- A-Since 1940, suicide rate in males, 15-24 has been decreasing
- B-Since 1995, suicide rate in males 15-24 has been decreasing
- C-Since 1970, suicide rate in males 15-24 has been increasing
- D-Since 1995, suicide rate in males15-24 has been increasing
- Since1940, suicide rate in males 15-24 has been increasing

PREVIEW

- Diagnosis of Major Depressive Disorder (MDD) and Dysthymic Disorder (DD) in youth
- History of FDA and European Agency Warnings about Antidepressants in youth (AD) and the "File Drawer" problem
- Suicidal ideation v. completed suicides in youth
- Possible mechanisms for increased risk of suicidality in a subset of depressed youth
- Why has fluoxetine been the only AD to show efficacy in three clinical trials in depression in youth
- NNT and NNH
- Lessons from the Treatment for Adolescents With Depression Study (TADS)

MDD: DSMIV Criteria for all ages

- SIGECAPS for 2+ weeks

– **S**leep Disturbance
– ***I****rritability*
– **G**uilt
– **E**nergy
– **C**oncentration
– **A**ppetite
– **P**sychomotor Agitation or Retardation
– **S**uicidality

The presentation of depression in youth doesn't look the same as in adults

- Gender differences
- Clinical presentation
- Co-morbidity

MDD: Gender and Puberty

- Gender Distribution
  - 1:1 before puberty
  - 2:1 female predominance after menarche, similar to adults
  - Ratio equalizes after menopause

MDD: Children are not little adults

- Prebubes: more anxiety (especially separation anxiety disorder), somatic symptoms (headache and stomach aches), auditory hallucinations, temper tantrums and behavioral problems

- Adolescents: sleep and appetite changes (hypersomnia and hyperphagia), suicidality, irritability, explosive and conduct sxs and “acting out”, substance abuse

MDD: Co-morbidity in youth

- Dysthymia ("double trouble depression")
  - Dysthymia as "gateway" disorder
- Anxiety disorders (often precedes depression in youth)
- Disruptive disorders (attention deficit, oppositional defiant, conduct)
- Substance abuse in teens
- Somatoform disorders
- Personality disorders or traits (teenagers)

Dysthymia Diagnostic Criteria: DSM-IV

- Persistent, long-term change in mood, less intense but more chronic than MDD
- Extensive psychosocial impairment
- Depressed mood or irritability on most days for most of the day for at least 1 year for youth
- At least 2 other symptoms: appetite, sleep, self-esteem, concentration, decision-making, energy, hope (chassed)
- Person is not without symptoms for more than 2 months at a time and has not had MDD for the first year of disturbance; never had manic or hypomanic episode

Vignette: An 11 year old boy with a history of ADHD has a 6 month history of severe tantrums at home and at school. He also is described as a “velcro kid” by his mother since he will not leave mom’s side in the last 6 mos. Child complains of frequent stomach aches. He is afraid to go to sleep at night because of voices that tell him “bad things”.

In clinical work need to assess several domains to make a diagnosis and assess improvement

- Parents can tell you about history and behaviors (with exceptions)
- Teachers give a view of youth in school setting (with exceptions)
- Child can tell you about his inner world (with exceptions)
- Clinician has to put all of these views together

In clinical work, assessment of improvement

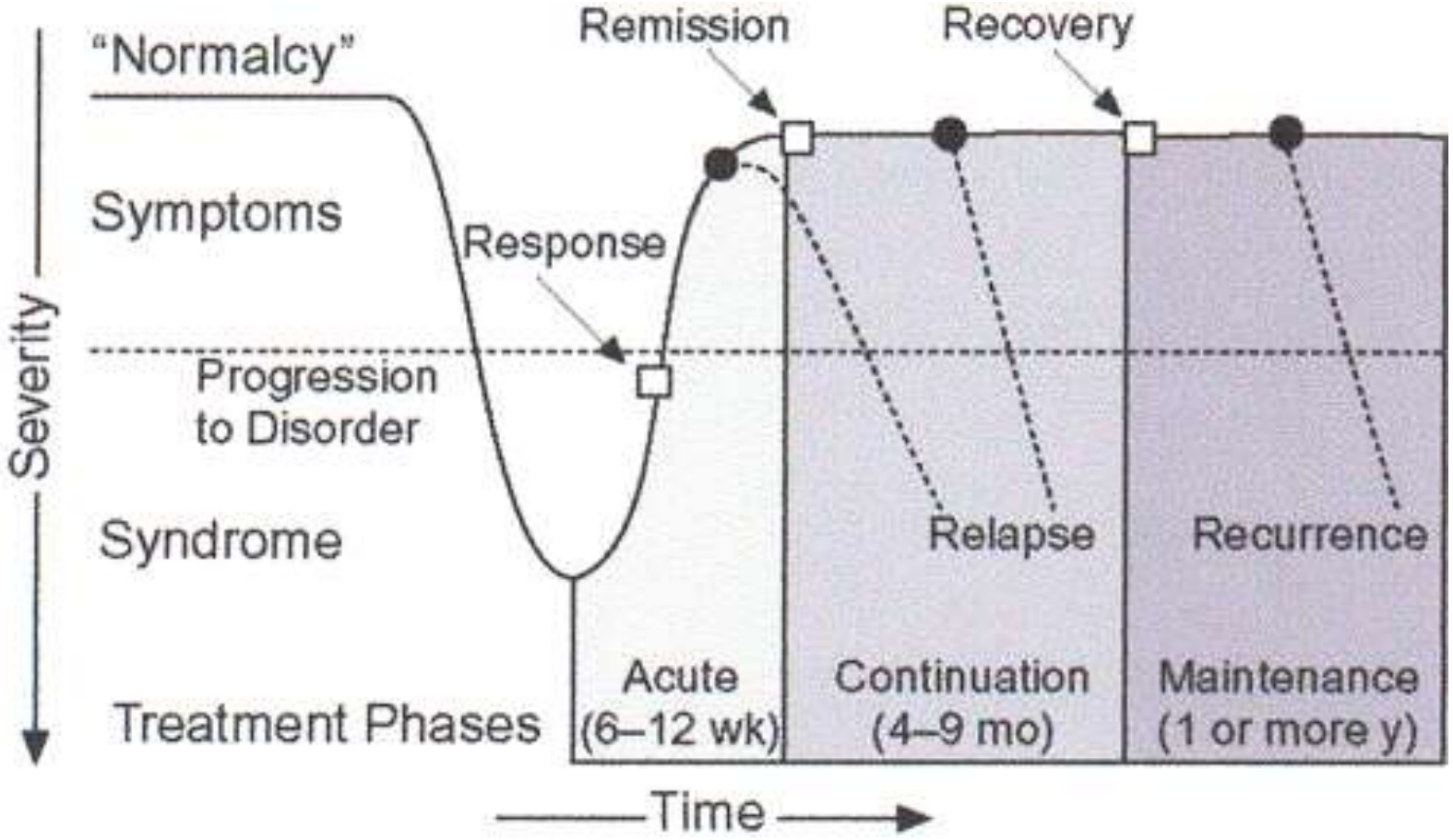
- Rely on reports from parents and youth
- Establish target symptoms prior to drug initiation and follow
- Use of screens (e.g., Children's Depression Inventory, CDI)

In research, to rate entry and improvement most common clinician rated scale-CDRS-R (Poznanski and Mokros 1996)

- Multiple sources, use behavior during interview- 40 minutes to complete
- 3 scores, parent, child and combined
- More accurate than self-report for kids (CDI)
- Clinician rated, 17 items from 1-5 or 1-7
- Minimum score is 17 and max is 113
- Depression equal or >45
- Response rate varies with the study = 30% or 40% decrease or comparative with initial
- Remission less or equal to 28

Depression is a common and serious illness in youth

- Point Prevalence: 2% of children / 4-8% of adolescents
- Lifetime Prevalence: up to 25% by end of adolescence (Kessler et al. 2001)
- 1.5 million depressed teens in US (Raz 2005)
- Dysthmia is a gateway to MDD
- Teen with MDD-> adult with MDD , but ? if childhood MDD is
- Serious impairment at crucial developmental time


"Normalcy"
Remission
Recovery
Symptoms
Response
Progression
to Disorder
Syndrome
Relapse
Recurrence
Severity
Acute
(6–12 wk)
Continuation
(4–9 mo)
Maintenance
(1 or more y)
Treatment Phases
Time

Depression is a common and serious illness in youth

- Untreated course MDD 7-8 mos, dysthymia 44 mos
- 40-60% youth with MDD have relapse after acute treatment
- 20-40% of youth develop recurrence in 1-2 yrs after remission, 70 % after 5 years
- 20-40% of youth with MDD develop BD within 5 years

1-03 FDA approval for fluoxetine in depression in youth

- 1-03-2003 ,the FDA released a “talk paper” in which fluoxetine was approved as the first antidepressant for the treatment of depression in children aged 7-17 years on basis of 2 Emslie studies. The FDA also required changes in the product insert to reflect concerns about height and weight.

6-03 First warnings

- 6-10-2003 Committee on Safety of Medicines (CSM) in Great Britain issued a “Dear Colleague” letter citing data from over 1000 children which revealed a lack of efficacy of paroxetine in the treatment of depression and an increase in the risk of “self harm and potentially suicidal behavior” of between 1.5 to 3.2 times compared to placebo: began to review unpublished studies

- **6-19-2003 This was followed by a FDA paroxetine “talk paper” in which 3 controlled studies were cited that failed to show any efficacy in youth with depression with paroxetine and also revealed a 3-fold increase in “suicide thoughts and attempts**

Incentive for drug companies to complete clinical trials

- "File drawer" problem since drug companies received a 6 month patent extension on patent (Modernization Act of 1997)
- ? of whether drug companies had any incentive to produce careful research or to publish if they were negative outcomes

Studies –published and unpublished in response to FDA Modernization Act of 1997

- 18 ADs for MDD (12 SSRIs, 3 VLF, 2 nefazodone,1 mirtazapine,) 1 citalopram, 1 escitalopram n less detail
- 3 SSRI trials for OCD
- 1 VLF for GAD
- 1 paroxetine for SAD
- 1 bupropion for ADHD

8-03

- 8-22-2003 On August 22, Wyeth issued a “Dear Health Care Professional” letter in which venlafaxine was determined to have no efficacy in the treatment of depression or generalized anxiety disorder in youth and to be associated with an increased risk of 2% for both “hostility” and “suicidal ideation” when compared with placebo.

12-03

- After review of published and unpublished clinical trials, UK Committee on the Safety of Medicines (MHRA) With exception of fluoxetine, SSRIs not effective for youth depression and can increase risk of suicide

3-04

- FDA met to consider same data
- On March 22 2004, the FDA issues a public health advisory and requested a warning label about suicidality on all antidepressants for all age groups. It contracted with Columbia to develop a classification of suicidal ideation and behaviors that would separate out non-suicidal events (Suicide Classification Project) from the raw data of 23 pediatric trials of anti-depressants that had been submitted to them.

4-04

- European Medicines Agency Scientific Committee, (EMASC) the Committee for Medicinal Products for Human Use "SSRIs/SNRIs are not authorised Europe-wide for the treatment of depression and anxiety in children and adolescents...because clinical trials have shown an increased risk of suicidal behavior (attempts and suicidal thoughts)……

10-04 FDA Black Box Warning

In September 2004, reviewed the re-analyzed Columbia data which went back to raw data and each harm-related event was evaluated and classified as suicidal or non suicidal or indeterminate and voted 15-8 in favor of a black box warning and Medguide for all antidepressants

Table 2 below compares the risk estimates derived from the two analyses, using the above-mentioned case definitions.

Table 2: Comparison of Columbia University Outcome 3 with Serious suicide-related events

Category of Trials	Total N Drug	Total N Pbo	Incidence rate ratios, serious suicide-related events (ODS analysis)*	Risk ratios, Columbia University Outcome 3, (DNDP analysis)*
Paroxetine	642	549	2.19 (0.92-5.24)	2.65 (1.00-7.02)
Sertraline	281	279	2.52 (0.49-13.01)	1.48 (0.42-5.24)
Venlafaxine	339	342	1.80 (0.52-6.20)	4.97 (1.09-22.72)
Fluoxetine	249	209	0.88 (0.32-2.44)	0.92 (0.39-2.19)
Citalopram	210	197	2.54 (0.91-7.05)	1.37 (0.53-3.50)
Mirtazapine	170	88	†	1.58 (0.06-38.37)
Nefazodone	279	189	†	**
Fluvoxamine	57	63	†	5.52 (0.27-112.55)
Bupropion	71	36	**	**
All MDD trials	1586	1299	1.95 (1.19-3.21)	1.71 (1.05-2.77)
SSRI†† MDD trials	955	843	1.87 (1.10-3.18)	1.41 (0.84-2.37)
Non-MDD trials	712	653	1.31 (0.26-6.72)	2.17 (0.72-6.48)
All trials	2298	1952	1.89 (1.18-3.04)	1.78 (1.14-2.77)

*Mantel-Haenszel method, fixed effects model
**No events in either arm
†Ratio undefined due to zero events in placebo group
††includes paroxetine, sertraline, fluoxetine, citalopram, fluvoxamine

The overall risk estimate for the primary outcome for the "all trials" analysis decreased with the Columbia University reclassification analysis from 1.89 to 1.78; the confidence intervals for both risk estimates exclude one. For the category of SSRI MDD trials, the risk estimate decreased and lost statistical significance with the Columbia University reclassification analysis. In terms of results for individual drugs, the risk estimates for paroxetine and venlafaxine increased.

CONCLUSIONS

Consistent with the analysis described in the 3-19-04 consult, the DNDP meta-analysis also indicates a statistically significant association of suicidal events with antidepressant drug treatment in short-term pediatric clinical trials for all indications. In terms of subgroups of trials, the major differences were that the risk estimate for the category of SSRI MDD trials was lower and not statistically significant with the DNDP analysis, while the risk estimates for two drugs (paroxetine and venlafaxine) increased. In all three cases, however, the new point estimate falls within the confidence limits of the previous result.

RECOMMENDATIONS

Current FDA position

- The risk of suicidality for these drugs was identified in a combined analysis of short-term (up to 4 months) placebo-controlled trials of nine antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs) and others, in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders. A total of 24 trials involving over 4400 patients were included. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. Based on these data, FDA has determined that the following points are appropriate for inclusion in the boxed warning:

- * Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- * Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- * Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- * Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- * A statement regarding whether the particular drug is approved for any pediatric indication(s) and, if so, which one(s).

- Among the antidepressants, only Prozac is approved for use in treating MDD in pediatric patients. Prozac, Zoloft, Luvox, and Anafranil are approved for OCD in pediatric patients. None of the drugs is approved for other psychiatric indications in children.

Consequences of Controversy: dropoff in antidepressant usage

- Medco data on antidepressants in youth under 18 years
- 2003- increased usage up 10%
- March 2004 Black Box Warning
- 2004 – 3rd quarter fell 19%; 4th quarter fell 16%- both primary care and psychiatrists

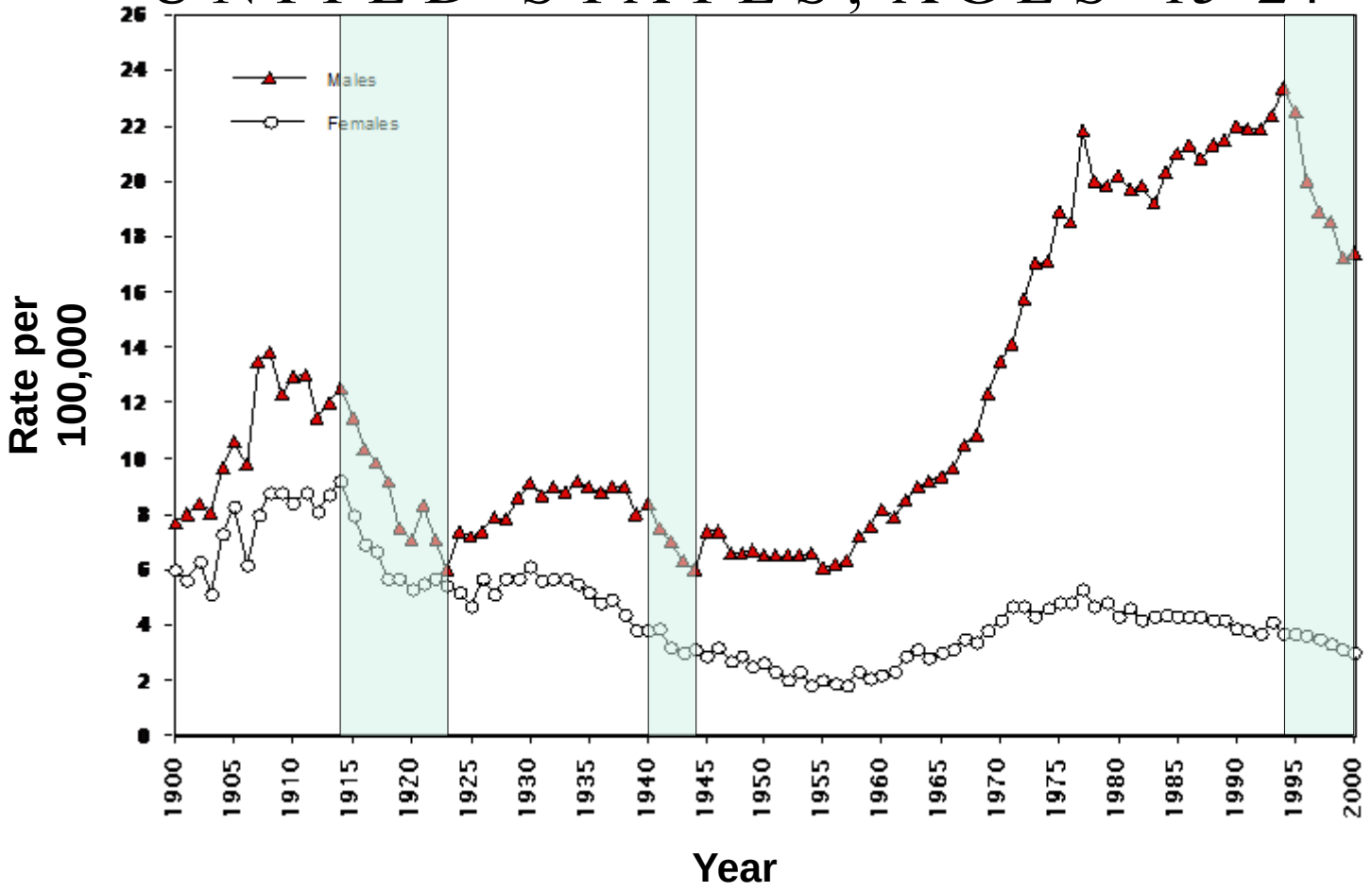
Even if one accepts there may be an early in treatment small class effect in these studies for increased suicidality,….

- There were no suicides in the 4400 subjects
- If ADs “pose a significant risk of suicide, then one would expect an increase in suicide rates to correspond with use in a pediatric population”(Bridge et al 2006)
- But observational data shows a decrease in completed youth suicides with introduction of SSRIs in many countries (Sweden, Denmark, Finland and Norway)
- And US, rate has decreased since 1995 in US in association with availability of SSRIs

FDA presentation Schaffer 2004

20TH-CENTURY - CHANGES IN YOUTH SUICIDE RATES

—UNITED STATES, AGES 15–24—



Anderson 2002, CDC Wonder 2003, USDHEW 1956, Vital Statistics U.S. 1954–1978

Recent Database studies inyouth

Olfson 2003	Prescription data from 1 mo 1989 and 2001 on 10-19 yr olds and completed suicides from CDC by county	1% increase in ADs exc TCAs dispensed associated with decrease of 0.23 suicides /100,000 esp for male 15-19 and lower income areas
Valuck 2004	12-18 yr olds large managed care database prescription data and suicide attempts	No increased suicide attempts with SSRIs or other AD v no AD Rx with AD for 24 wks fewer suicide attempts those with less than 8 weeks
Jick 2004`	UK, GBRD 1 script for Ami, FLU, parox ,dothepine and nonfatal suicide behavior or ideation 1993-99	4x more in first 9 days and equal b/w 4: ?more paroxetine; no increase in 10-19 yr olds Completed suicides=17 and only 1 had meds in prior 90 dys
Martinez 2005	UK, GPRD new diagnosis of depression 1995-2001	< 18y, higher rate of self harm with SSRIs v TCAs, no suicides ? Highest paroxetine

Two issues have emerged

- “Some individuals have an increase in suicidality which may or may not result in in an increased risk for completed suicide. Other individuals may have a decreased risk” (Ryan 2005)
- Why does only fluoxetine show efficacy in 3 RCTs in youth??

Vitello and Sweedo 2004

- “suicidal ideation is not an accurate predictor of suicide since most persons with such ideation do not attempt or die by suicide”

FREQUENCY OF SUICIDAL IDEATION AND ATTEMPTS

— U.S. HIGH-SCHOOL STUDENTS, AGE 15–19, YRBS ——

(2001, N=13,601)

	RATE	N
Ideation	**19.0%**	**3.8 million**
Attempt	**8.8%**	**1.8 million**
Attempt received medical attention	**2.6%**	**520,000**
SUICIDE (age 15–19)*	**.008%**	**1,611**

- **Anderson 2002; Grunbaum et al. 2002 (YRBS), U.S. Census 2000, FDA presentation**
- **Schaffer 2004**

TEEN ATTEMPTERS
ATTEMPTS PER YEAR

(2001, YRBS, N=13,601)

1	**53%**
2 or 3	**30%**
4 or More	**17%**

- ***Similar findings in patient studies***
- ***1 attempt increases risk of another 15-fold***

Barter et al. 1968, Brent 1993, CDC 2002 (YRBS 2001 Codebook), Goldacre & Hawton 1985, Goldston et al. 1999, Hawton et al. 1982, Hulten 2001, Kotila 1992, Lewinsohn et al. 1994, McIntire et al. 1977, Spirito 1992, Spirito et al. 2003, Wichstrom 2000 FDA presentation Shaffer 2004

TEEN IDEATORS

EPISODES OF IDEATION* PER YEAR

(N=981)

1	**45%**
2	**24%**
3 or More	**31%**

Reifman & Windle 1995; *"How often have you thought about killing yourself?"; past year, N=698; last 6 months, N=283)FDA presentation Schaffer 2004

August, 2004 the Treatment for Adolescents With Depression Study (TADS) in youth aged 12-17 published

- 4 arms: fluoxetine, fluoxetine and CBT, CBT alone and placebo (March 2004). It is unique among the published medication trials since admission criteria permitted teens with suicidal ideation (but not those at high risk for suicidality) to enter (29% by question 13 of CDRS).
- 13 sites
- CBT arms were not blinded
- There was an independent evaluator

Whats unique about TADS

- Not industry sponsored
- Similar to real-life clinical samples in terms of co-morbidity
- Separate assessment tool for suicidal ideation (SIQ)
- Depression in 2/3 contexts over 6 wks;(moderate-severe)
- AEs separated: Harm-Related AE (e.g. cutting, worsening ideation without self-harm or any attempt or harm to others, aggression or violent ideation) Suicide-Related AE (worsening of suicide ideation or attempt, but not cutting without suicidal intent)
- Carefully executed

HOW ARE SUICIDAL ADOLESCENTS EXCLUDED FROM PSYCHOPHARM STUDIES?

STUDY	EXCLUSION CRITERIA
Sertraline ***(Wagner et al. 2003)***	**"previous attempt or posing significant suicidal risk"**
Fluoxetine ***(Emslie et al. 2002)***	**"serious suicidal risk"**
Fluoxetine ***(Emslie et al. 1997)***	**not specified**
Paroxetine ***(Keller et al. 2001)***	**"current ideation with intent or specific plan OR history of attempts by drug overdose"**
Citalopram ***(Wagner et al. 2001)***	**not specified**

FDA presentation 2/04
Shaffer

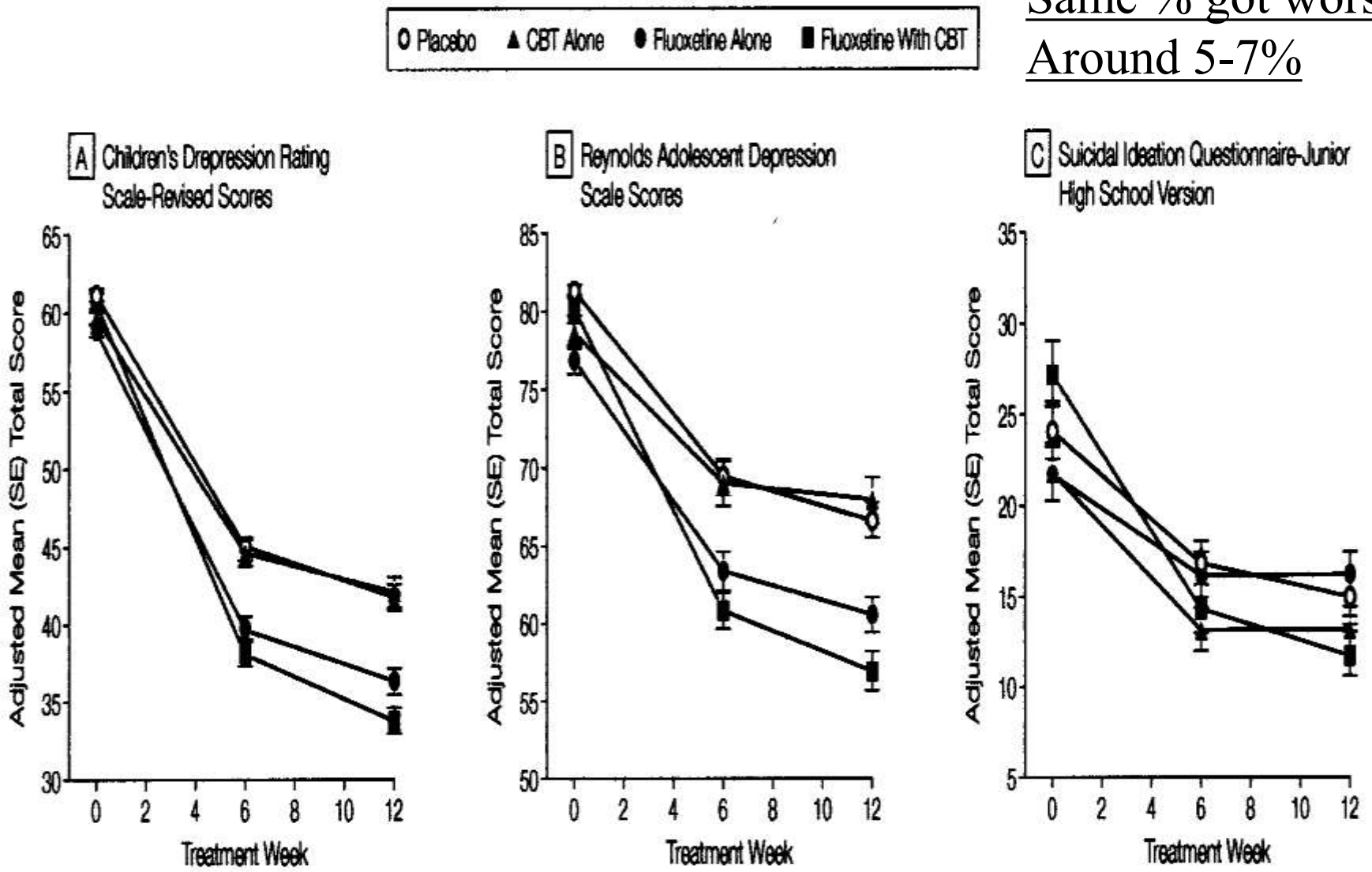
Why was CBT included?

- CBT most frequently investigated treatment for depression in youth- effective in about 50- 60%
  - Depressed children and CBT: 4 of 5 child CBT studies demonstrate short-term efficacy; 1 study demonstrated efficacy maintained 9 months later
  - Depressed adolescents and CBT: 7 of 9 adolescent CBT studies demonstrate short-term efficacy (Curry 2001)
  - Works better with longer interventions and less well when youth has difficult parents

  Before TADS, researchers believed CBT would equal fluoxetine in efficacy

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

Same % got worse
Around 5-7%



CBT indicates cognitive-behavioral therapy. Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random coefficient model.

Suicidality –CDRS, SIQ, AEs

- All interventions improved suicidal ideation according to SIQ
- Fluoxetine did not increase suicidal ideation, but did increase AEs-harm-related and suicide AEs mean (mean fluoxetine dose 30mg)
- CBT protective of harm-related AEs and suicide AEs but small ES (mean fluoxetine dose 27 mg)
- Or was it the difference in dosing?

Fluoxetine 30mg but fluox+CBT=27 mg or is CBT protective

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.

Mechanisms proposed of Increased suicidal behaviors

1-"rollback"-energizing depressed patients to act on pre-existing suicidal ideation

2-paradoxically worsening depression- <not TADS>

3- inducing akathisia with associated self-destructive or aggressive impulses <FDA metastudy supports association with hostility and agitation, but no support from TADS, however, no study with week by week analysis since can arise at any time. What is relationship betweens activation,behaviorial disinhibition, akathisia, agitation, aggression see diagram>

4- inducing panic attacks-<not TADS>

5- switching patients into manic or mixed states <Martin et al 2004, 5.4% more in peripubertal children, only 1 in TADS>

6-producing severe insomnia or interfering with sleep architecture <not TADS>

7- inducing an organic obsessional state

8- producing an organic personality disorder with borderline features

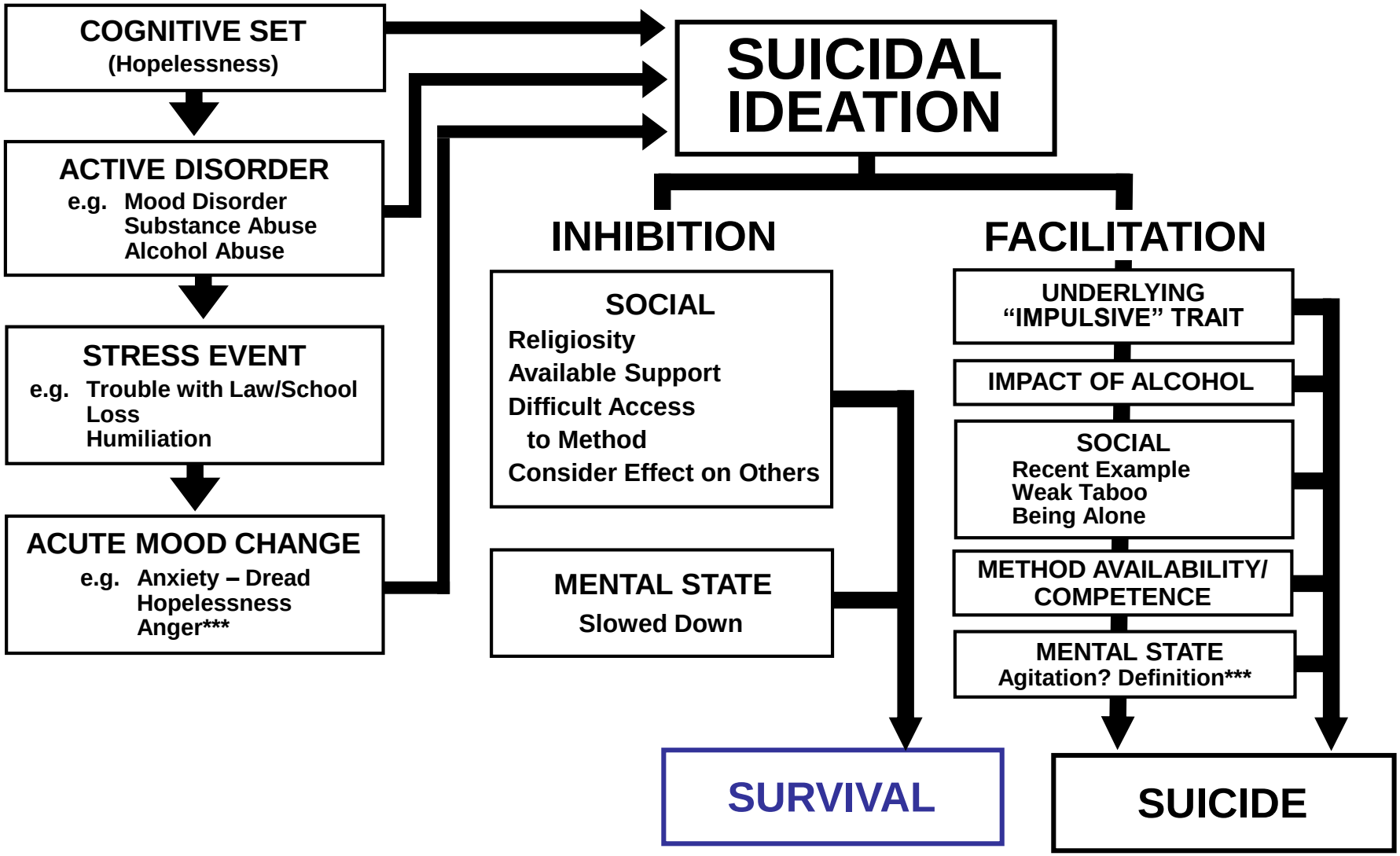
9-exacerbating or inducing electroencephalogram (EEG) or other neurological difficulty

(TEICHER ET AL 1993)

FDA presentation, Shaffer 2004

HOW SUICIDES OCCUR

—PATHWAYS TO AND FROM IDEATION—



C.MO1.XX

AEs, from TADS physical symptom checklist

- Rate of mania-1 case only; dx with of 9 items: 68% racing thoughts, cant concentrate etc at baseline---- 15% worsening of manic symptoms but no different than other arms
- Irritability, agitation etc not significantly different in fluoxetine arm v rest of arms, but not continuous observation

Why only fluoxetine shown to be effective in MDD in youth?

- Not true in adult studies of MDD
- Not true in anxiety studies in youth

Why does only fluoxetine show efficacy in youth? Methodology (Cheung 2006)

High placebo response of 33-59% in studies: placebo run in and depression dx across domains help reduce placebo response

Increased number of sites and less subjects per site increased research conduct variability as well as no interrater reliability in sertraline study

Experience of investigators varied

Patient selection ?severity of illness- severe cases may have better response, <but similar CDRS, Wagner 58, TADS 58.9>

Non-adherence favors fluoxetine because of long half-life <90% pills taken in TAD>,

Why only fluoxetine?

Disease state- is depression different in children than teens <both teens and kids in 2 Emslie studies, but in 2 other studies, efficacy only for teens, similar to TCA meta-analysis, Hazell 2002>

Drug- Is fluoxetine unique either in pharmacokinetics (stable blood levels because of nor-fluoxetine's long half-life) or pharmacodynamics or unique non-SRI profile.

Do other drugs have increased rate of withdrawal reactions or lack of efficacy associated with imperfect adherence

TADS Lesson 1-Importance of documenting AEs pre-treatment

- Depression is associated with physical symptoms
- In TADS: AE that caused dysfunction on physical symptoms pre-treatment (physical symptom checklist)
  - 12-17% dizziness
  - 13 % easy bruising
  - 30% headache------. Improves with treatment
  - 56% sleep disturbance--→ 41%
  - 30 % nightmares→ improves with treatment

TADS Lesson 2-Importance of keeping teens on medicine

- 83% completed fluoxetine arm compared to about 70% (quoted in the literature) as tolerating fluoxetine
- 90% adherence

Benefit of Prescribing:NNT (Bridge et al 2006)

- Number of patients that would need to be treated with a drug/therapy to achieve one favorable outcome
- Calculated by taking the inverse of the drug-placebo response difference
- Fuoxetine drug-placebo difference is 19.6%, so NNT =1/0.196=6

NNH (Bridge et al 2006)

- Number of patients needed to treat to cause one additional person to have an adverse event
- Suicidality in fluoxetine trials is 5.9 and placebo 3.8 NNH=1/0.021= 48
- Eight times more patients will experience improvement than worsen

For other ADs (Bridge et al 2006)

- Sertraline: NNT =69-59%= 1/0.10= 10

and NNH=2.7-1.1==1/0.15= 63

- Six times more patients will benefit from treatment with sertraline
- Citalopram: NNT=9 NNH 77
- Not positive for VLF or paroxetine

Nat Inst for Health/Clin Excellence (NICE) Guidelines for Dep in Youth

- Youth with mild depression should not initially receive medication
- Youth with mod/severe depression should be initially offered CBT/IPT or family therapy and medication only in combination with these
- Fluoxetine is only antidepressant for which trials show benefits outweigh risks
- Careful monitoring of AEs esp early in treatment
- Importance of treating co-morbid conditions
- Do not use paroxetine, venlafaxine, St John's wort

NICE (cont)

- Fluoxetine-start 10 mg: less with smaller kids
- Little evidence for higher doses than 20 mg exc in heavier older
- Careful monitoring
- After response, continue for 6 mos with very slow taper

Summary

- MDD is a severe and potential life threatening illness in youth
- Educate family and youth about depression and AEs, suicidal rescue plan
- Start with fluoxetine
- Overall SSRIs appear to be associated with decreased completed suicides
- There may be a small subgroup of youth who have increased suicidal ideation or behaviors with ADs
- Need to be vigilant in assessing ALL youth on ADs especially early in treatment and with additional dosing
- Adherence is crucial
- If fluoxetine fails or there are AEs, try another SSRI with favorable NNT to NNH ratio
- When non-fluoxetine meds are used, keep an eagle eye on adherence
- Venlafaxine, paroxetine should be lower on list

Question 1

- Which of the following ADs have FDA approval for the treatment of MDD in youth?
- A-sertraline and fluoxetine
- B-sertraline
- C-fluoxetine and fluvoxamine
- D-fluoxetine
- E-venlafaxine

Question 2

- Which statement is true?
- A-Only fluoxetine has been associated with a small increased risk of suicidality in short term clinical trials of youth with anxiety disorders
- B-Only paroxetine has been associated with a small increased risk of suicidality in short term clinical trials of youth with anxiety disorders
- C-Only SSRIs have been associated with a small increase of suicidality only in short term clinical depression trials but not anxiety trials of youth
- D-Only fluoxetine has been associated with a small increased risk of suicidality in short term anxiety trials of youth
- E-All ADs have been associated with a small increased risk of suicidality in short term depression and anxiety clinical trials of youth

Question 3

- When published and unpublished RCTs of ADs are combined, which statement is true about the treatment of MDD in youth?
- A-only paroxetine and fluoxetine have shown statistical efficacy
- B-fluoxetine has shown no statistical efficacy
- C-fluoxetine and sertraline have shown no statistical efficacy
- D-fluoxetine has shown statistical efficacy
- E-All ADs have shown statistical efficacy

Question 4

- Which statement about pre-pubertal MDD is true?
- A-More girls than boys have depression
- B-Girls who are depressed will have later onset of menarche
- C-Both genders may have auditory hallucinations
- D-Point prevalence is 12%
- E-More girls than boys have depression

Question 5

- Which statement is true?
- A-Since 1940, suicide rate in males 15-24 has been decreasing
- B-Since 1995, suicide rate in males 15-24 has been decreasing
- C-Since 1970, suicide rate in males 15-24has been increasing
- D-Since 1995, suicide rate in males 15-24 has been increasing
- Since1940, suicide rate in males15-24 has been increasing

Answers

- 1-D
- 2-E
- 3-D
- 4-C
- 5-B