ESSENTIAL PSYCHOPHARMACOLOGY, 2011: TREATMENT OF DEPRESSION

Carl Salzman, M.D.
Montreal
OVERALL EFFICACY OF ANTIDEPRESSANTS

• No one antidepressant stands out as the most efficacious
  – Nortriptyline has best overall data
• Dose and duration of treatment are factors in response
• SSRIs and Dual-acting antidepressants are most popular and commonly used but TCAs may be more efficacious and safer
• MAOIs still have a role in treatment
Pooled Efficacy Rates (proportion of patients with ≥50% changes in HAMD and MADRS) for all antidepressant classes.
SSRIs vs. TCAs?

• Comparison of nortriptyline with citalopram:
  – Nortriptyline better for vegetative symptoms (i.e. melancholic depression)
  – Citalopram better for cognitive and mood symptoms

Uher, 2011
EFFICACY OF ANTIDEPRESSANTS: STAR*D
CONCLUSIONS

• Inadequate response and remission from standard treatments and treatment approaches
• No differences among antidepressants in response or remission rates
• Best results: stay on one medication for as long as possible; augmentation may be better than switching

Hansen, 2005
NO SIGNIFICANT DIFFERENCES AMONG SSRIs

Figure 1. Meta-analysis of fluoxetine compared with paroxetine.

The numbers on each side of the 95% CI are the number of responders over the total number of participants who were randomly allocated to receive that drug. The total number of responders does not always match Table 1 because of postrandomization exclusions or use of observed cases analysis.

*Trial sponsored by or authors affiliated with GlaxoSmithKline (Philadelphia, Pennsylvania) or SmithKline Beecham (Research Triangle Park, North Carolina), the manufacturer of paroxetine. †Trial sponsored by or authors affiliated with Eli Lilly (Indianapolis, Indiana), the manufacturer of fluoxetine. ‡Funding source not reported.

Hansen; Ann Int Med 2005; 143:415
“UNIQUE” QUALITIES OF SSRI’s

• Sertraline:
  – Blocks dopamine reuptake at high doses
  – May slightly improve cognition

• Paroxetine:
  – Blocks norepinephrine reuptake at high doses
  – Strong withdrawal symptoms

• Venlafaxine:
  – Elevates blood pressure even at low doses
PAROXETINE TERATOGENICITY

• Has a 2-3x increase risk of teratogenicity compared with other antidepressants
  – Mainly ventricular septal defect
  – Only at doses >25mg/d
DEPRESSION AND OSTEOPOROSIS

• 20% of depressed premenopausal women have decreased bone mineral density
  – May be due to increased pro-inflammatory cytokines (e.g. IL-6)

Eskandari; ArchInternMed
2007; 167:2329
SSRIs & BONE
DEMINERALIZATION

• SSRIs may decrease bone mineral density in postmenopausal women and in elderly men.
  – Increases risk of fractures (especially hip fx)
  – Effect is the same as with glucocorticoids

Diem; Arch InternMed 2007; 167:1240;
### Table 2. SSRI Use and Risk of Fragility Fracture

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate Adjusted Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily SSRI use</td>
<td>2.1 (1.3-3.4)</td>
</tr>
<tr>
<td>Daily dose of SSRI use</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Recurrent daily SSRI use</td>
<td>2.1 (1.1-4.0)</td>
</tr>
</tbody>
</table>

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

Fracture-free survival by selective serotonin reuptake inhibitor (SSRI) use

SSRIs AND GI BLEEDING

• SSRIs increase upper GI bleeding
  – Risk is higher when prescribed with aspirin or NSAIDs

• Proton-pump inhibitors or H$_2$ blockers decrease this risk

deAbajo 2008; Archgenpsychiat 65:795
SSRIs DURING PREGNANCY

• Discontinuation of any antidepressant increases risk of relapse

• Mixed data regarding SSRI producing fetal malformations:
  – Some data suggest increases risk of craniosynostosis, omphalocele and cardiac septal defects
  – Other data: no increase in malformations

• Persistent pulmonary hypertension with 3rd trimester use: very rare
SSRIs IN PREGNANCY

• Low or standard doses do not have an effect on the fetus

• High doses:
  – Increased motor activity beginning in 2\textsuperscript{nd} trimester
  – Disrupted NREM sleep in 3\textsuperscript{rd} trimester
  – Poor inhibitory motor control during sleep near term

• Significance of these effects for post-natal development is unknown

Mulder 2011; Neuropsychohar
DUAL-ACTING ANTIDEPRESSANTS

• Dual-acting antidepressants may be superior
  – Venlafaxine; duloxetine, TCAs, mirtazepine
• Nortriptyline effective for more than 1/3 of TRD
• Venlafaxine 225-375 effective
  – Fluoxetine 20-60 combined with olanzapine 5-10 equally effective to venlafaxine
  – Response to both treatments significant at 4 weeks;
• Duloxetine likely to also be effective (especially with comorbid pain conditions)

(Arnell, 2001; Nelson, 2004; Dante, 2002; Nierenberg, 2003; Pridmore, 2004; Fava, 2003)
DESVENLAFAXINE (PRISTIQ)

- Demethylated metabolite of venlafaxine
- Inverted “U” shape response curve:
  - Effective at low dose (100mg/d)
  - Effective at high dose (400mg/d)
  - But mid dose (200mg/d) not better than placebo
- No CP 45o enzyme interactions
- Elimination half-life: 9-10 hours
- Side effects: nausea, somnolence, dry mouth, anorexia, nervousness, constipation, decreased ejaculation and orgasm
DULOXETINE VS. VENLAFAXINE FOR MAJOR DEPRESSION

Perahia; 2007; J Psychiat Res

Fig. 2. Change from baseline in HAMD_{17} total score.
“STAR-D” ANTIDEPRESSANT SWITCH STUDY

25% of SSRI (citalopram) non-responsive patients had a remission after switch to another antidepressant and treatment for 14 weeks:

- bupropion-SR (up to 400mg/d);
- sertraline (up to 200 mg/d);
- venlafaxine-XR (up to 375 mg/d)
LIMITED EFFECT OF SWITCHING ANTIDEPRESSANT CLASSES

• Metanalysis of 31 trials (8 RCTs & 23 open trials)
  – Approximately a 50% chance of response after switching to a second antidepressant; lower chance of remission
  – No particular second choice drug or class showed clinical superiority with switch

Ruhe, 2006
Table 4. Acute Outcomes of Depressed Treatment-Resistant Patients Whose Antidepressant Was Switched or Augmented

<table>
<thead>
<tr>
<th>Response</th>
<th>Augmented (N = 36)</th>
<th>Switched (N = 38)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Positive response</td>
<td>20</td>
<td>55.6</td>
<td>17</td>
</tr>
<tr>
<td>Partial response</td>
<td>5</td>
<td>13.9</td>
<td>5</td>
</tr>
<tr>
<td>Nonresponse</td>
<td>11</td>
<td>30.6</td>
<td>16</td>
</tr>
</tbody>
</table>

Postornak, 2001
HOW TO SWITCH: GENERAL PRINCIPLES

• Switch if there has been NO response after 4 weeks;
• Switch CLASSES of antidepressants
• Remember TCAs and MAOIs are useful drugs to use for a switch
• Use newer drugs to switch in treatment resistant patients
SWITCH TO MONOAMINE OXIDASE INHIBITOR

- $\text{MAO}_A$ is increased in some depressions
- MAOIs are useful for atypical depressions
- Useful for depressions with high comorbid anxiety
- Useful for depressions with comorbid personality disorders
- Add MAOI to TCA (never TCA to MAOI)

Rosenbaum, 1995; Fawcett, 1991
Feighner, 1985
<table>
<thead>
<tr>
<th>FOODS TO BE AVOIDED</th>
<th>MAOI DIET</th>
<th>FOODS ALLOWED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cheese</strong></td>
<td></td>
<td>Fresh cottage cheese, cream cheese, ricotta cheese, and processed cheese slices. All fresh milk products that have been stored properly (e.g., sour cream, yoghurt, ice cream).</td>
</tr>
<tr>
<td>All matured or aged cheese.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All casseroles made with these cheeses, e.g., lasagna.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Please note: All cheeses are considered matured or aged except those listed opposite.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meat, Fish, and Poultry</strong></td>
<td></td>
<td>All fresh packaged or processed meat (e.g., chicken loaf, hot dogs), fish, or poultry. Store in refrigerator immediately and eat as soon as possible.</td>
</tr>
<tr>
<td>Fermented/dry sausage: (salami, mortadella, summer sausage, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improperly stored meat, fish, or poultry.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improperly stored pickled herring.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fruits and Vegetables</strong></td>
<td></td>
<td>Banana pulp</td>
</tr>
<tr>
<td>Fava or broad bean pods (not beans)</td>
<td></td>
<td>All others</td>
</tr>
<tr>
<td>Banana peel</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beverages</strong></td>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td>All on-tap beer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No more than two bottled or canned beers or two 4 fl. oz. glasses of red or white wine per day. This applies to non-alcoholic beer also. Please note that red wine may produce headache unrelated to a rise in blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td>Other yeast extract (e.g., Brewer's yeast)</td>
</tr>
<tr>
<td>Marmite concentrated yeast extract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sauerkraut</td>
<td></td>
<td>Pizzas without aged cheeses added</td>
</tr>
<tr>
<td>Soy sauce and other soy bean condiments</td>
<td></td>
<td>Soy milk, tofu</td>
</tr>
</tbody>
</table>
TRANSDERMAL SELEGILINE

• Selegiline is a selective MAO-B inhibitor
• Antidepressant activity at oral doses of 30-60 mg/d effective antidepressant transdermally by 8 weeks (20 mg/20 cm$^2$)
• Side effects: rash, erythyma, pruritis, irritation at application site
• No hypertensive episodes reported

Bodkin, 2002
FIGURE 1. Kaplan Meier survival curve for time to relapse.
ECT

• Best treatment for psychotic depression;
• Excellent treatment for severe, melancholic major depression;
• Resistance to medication decreases likelihood of remission with ECT, but does not decrease response (i.e. 50% decrease in symptoms)

Pluijms, 2002; van den Broek, 2004
ANTIDEPRESSANTS AFTER ECT

- High relapse rate after ECT - higher in psychotic patients - higher in women
- Almost all relapses occur within first 5 weeks
- TCAs lower relapse rate from 84% to 60%
- Combined nortriptyline - lithium reduces relapse rate to 39%

(Sackeim, 2001)
TRANSCRANIAL MAGNETIC STIMULATION

• Effective for major and minor depression
• No data on efficacy in most severe or psychotic depression
• No significant side effects

Loo, 2003; Pascual-Leone, 1996; Kauffmann, 2004
FIGURE 2. Total Scores on the Montgomery-Åsberg Depression Rating Scale for Depressed Subjects Receiving Sham Stimulation or Active Treatment at Each Assessment for Intent-to-Treat, Last-Observation-Carried-Forward Data

Fitzgerald, 2006
TMS FOR TREATMENT RESISTANT DEPRESSION

Avery, 2006

Diagram showing HDRS scores over time with different treatments.
TRANSCRANIAL MAGNETIC STIMULATION

O’Reardon 2007, Biol Psychiat 62:1208
TMS RESPONSE AND REMISSION

Avery
VAGUS NERVE STIMULATION

• Sleep architecture severely disturbed in treatment-resistant depressed patients

• After VNS:
  – Stage 1: sleep and awake time decreased
  – Deeper stage 2 increased
  – Amplitude of all EEG rhythms significantly increased to near-normal levels

• Subjective sleep improved

• Improvement in sleep may be clinically important since persistent sleep disturbance is associated with increased risk of relapse and recurrence of depression
Vagus Nerve Stimulation in Treatment-Resistant Depression

ANTIDEPRESSANT PROPERTIES OF CRF$_1$ ANTAGONISTS

- CRF$_1$ antagonists have antidepressant properties
- SSRI therapeutic effect correlates with reduction of CRF levels
- ECT decreases CRF levels
- Lithium and valproic acid decrease activity of CRF neurons in hypothalamus and corticolimbic structures
AUGMENTING ANTIDEPRESSANTS

- Add lithium (not helpful for patients resistant to 2 or more antidepressants)
- Using a second antidepressant
  - Bupropion, tricyclic MAO inhibitor
- Using a stimulant
  - Methylphenidate, amphetamines, modafinil
- Using an atypical antipsychotic
  - Olanzapine, risperidone
- Using a mood stabilizer
  - Lamotrigine, oxcarbazepine
- Omega-3 fatty acids; folic acid; SAMe; TMS; VNS; Deep-brain stimulation

Nierenberg, 2003; DeBattista, 2003; Fava, 2003; Bauer, 2003
Figure 1: Response rates in 9 placebo-controlled trials on the efficacy of lithium augmentation of antidepressant medication in patients with major depression.
Addition of TCA or
Bupropion to Fluoxetine

Clinical studies and open clinical trial suggest more
receptor downregulation and response

Addition in fluoxetine nonresponders indicates 65%
more responders (Weilberg et al., 1991)

Controls but used low TCA doses 25-50mg of
(Iac et al., study 1994)
Desipramine Alone vs Desipramine Plus Fluoxetine in Depressed Patients

Retrospective Comparison

% Change in HAM-D score

- Desipramine alone
- Desipramine + fluoxetine

Weeks of treatment

ADD BUPROPION

• Very common augmentation of SSRIs
• Combination may be better than monotherapy with either drug

Lam, 2004
COMBINING 5HT UPTAKE BLOCKADE WITH 5HT$_{2C}$ BLOCKADE

- Both increase corticolimbic noradrenergic and serotonergic transmission
- Both increase frontocortical DA transmission
- Both have antidepressant effects

**SSRI:**
- Decreases anxiety
- Decreases impulsive behavior

**5HT$_{2C}$ antagonist:**
- Decreases SSRI nervousness
- Improves sleep
- Improves sexual function
When to Use $T_4$ vs. $T_3$

- $T_3$ (50 mg)  Euthyroid treatment resistant depression
  - Sick euthyroid syndrome
    - Beware $T_3 \rightarrow$ TSH $\rightarrow$ $T_4 \rightarrow$ $T_3$

- $T_4$  Depressed, hypothyroid
  - May need to try out various "euthyroid" levels
  - Rapid cycling bipolar women
T₃ AUGMENTATION OF SERTRALINE

Figure 2. Adjusted (from analysis of covariance) mean Hamilton Rating Scale for Depression scores (last observation carried forward) of patients treated with sertraline hydrochloride plus liothyronine sodium (SERT-T₃) or sertraline plus placebo (SERT-PLB) for 8 weeks.

Cooper-Kazaz; Arch Gen Psychiat 2007; 64:679
COMBINING 5HT UPTAKE BLOCKADE (SSRI) WITH 5HT\textsubscript{2C} BLOCKADE

- Both increase corticolimbic noradrenergic and serotonergic transmission
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**5HT\textsubscript{2C} antagonist:**
- Decreases SSRI nervousness
- Improves sleep
- Improves sexual function
AUGMENTATION WITH ANTICONVULSANTS

• Lamotrigine given to unipolar depressed patients who failed on 2 previous AD trials
  – Mean dose 112 mg/d for 6 weeks
  – Nearly 50% response

• Topiramate added to standard AD

  » Barbee, 2002; Barbosa, 2003
  » Schmidt, 2002
Stimulant Augmentation of SSRIs

• Stimulants reported to combat anergic side effects

• Stoll and Pillay (1996) - methylphenidate (10-40mg/day) produces robust effect in 5 consecutive cases of SSRI non or partial response

Stoll, 1996; Chiarello, 1987
AUGMENTATION WITH ESTROGEN

• Estrogen interacts with monoamine pathways
• Enhances NE and 5HT transmission:
  – Acts directly on nucleus and on membrane located monoamine receptors
  – Inhibits 5-HT and NE transporter proteins
  – Reduces $\alpha_2$ autoreceptors
  – Desensitizes presynaptic 5-HT$_{1A}$ autoreceptors
• Enhances SSRIs and NARIs
AUGMENTATION WITH ATYPICAL ANTIPSYCHOTICS

• Numerous studies suggest efficacy of adding olanzapine, ziprasidone or risperidone to an antidepressant;
• Quetiapine is less effective;
• Recent study showing effectiveness of aripiprazole

Barbee, 2004; Kennedy, 2003
Papakostas, 2004; Shelton, 2003
Mahmoud, 2007
OLANZAPINE/FLUOXETINE EFFICACY FOR TREATMENT RESISTANT DEPRESSION

Figure 1. Mean Change From Baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score Over Time for Patients Treated With Olanzapine/Fluoxetine Combination

All post-baseline scores were statistically significantly better than baseline at \( p = 0.0001 \) using a mixed-effects model repeated-measures method. The mean baseline total score was 31.6 for patients with a baseline and post-baseline observation \( (N = 552) \).
Figure 1. Percentage of Patients Considered Responders (≥ 50% Improvement) to Olanzapine-Fluoxetine Combination Treatment According to HAM-D Scores.

Reprinted with permission from Dubé et al. Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
Figure 3  Kaplan–Meier estimates of the time to relapse in the total patient group.
ARIPIPRAZOLE AS AN ADJUNCT FOR ANTIDEPRESSANTS

**Figure 1.** Fasting mean changes (SE) in metabolic measures* from the end of the prospective phase to the end of randomized treatment.
Buspirone has been reported to be an effective "Augmentor" of SSRIs.

- 3 Open trials, n=36, 3 wks Rx, 20-50 mg
  - 75% response rate

- 1 Double-blind, placebo-controlled, n=117, 4 wks Rx
  - Buspirone (n=54):
    - 60% improved
    - 52% "very much or much improved"
  - Buspirone vs. placebo: no statistical difference 2° to high placebo rate

## Pindolol Augmentation of Treatment-Resistant Depression

<table>
<thead>
<tr>
<th>Current Treatment</th>
<th>HAM-D Before Pindolol</th>
<th>Treatment Period (Days)</th>
<th>HAM-D After Pindolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine 40 mg (6 weeks)</td>
<td>36</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Paroxetine 40 mg (4 months)</td>
<td>30</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Paroxetine 20 mg (6 weeks)</td>
<td>32</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Paroxetine 20 mg (6 weeks)</td>
<td>14</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Fluvoxamine 200 mg (8 weeks)</td>
<td>18</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Imipramine 200 mg (8 weeks)</td>
<td>17</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Phenelzine 60 mg (6 weeks)</td>
<td>27</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

Artigas et al. Arch Gen Psychiatry. 1994;51:248
DOPAMINERGIC AUGMENTATION

• Pramipexole (Mirapex) is a D2-D3 dopamine agonist
  – Added to TCA or SSRIs (mean dose 0.99 mg/d)
  – Effective augmentation in treatment-resistant depression
  – Effective over 30 weeks

• Bromocriptine, piribedil also used

Bouras, 1982; Lattanzi, 2002
FOLIC ACID FOR ANTIDEPRESSANT AUGMENTATION

• Folic acid 500 mg added to SSRI
• Better augmentation response in women (73% improvement)
• Mechanism: enhances synthesis of tetrahydrobiopterin, a cofactor in the synthesis of monoamines
• Vitamin B12 (decreases homocysteine)

(Coppen, 2000; Papakostas, 2004)
ADDITIONAL AUGMENTATION STRATEGIES

- SAMe (s-adenosylmethionine)
  - Modestly augments SSRIs
- Omega-3
  - Modest mood stabilization with mild antidepressant properties
- St. John’s Wort (not helpful)
- Inositol
- Estrogen; DHEA
- Opiates

Papakostas, 2004; Gelenberg, 2004; Echols, 2000; Salzman, 1998; Fava, 2001
2 NEW ANTIDEPRESSANTS
AGOMELATINE

• Antidepressant:
  – Agonist at melatonin receptors 1 & 2
  – Antagonist at 5HT$_{2C}$ receptors
• Equal antidepressant efficacy to sertraline
• Superior sleep efficiency and daytime functioning

AGOMELATINE FOR DEPRESSION

Zajęcka, 2010

![Graph showing the mean HAM-D17 total score over weeks for different groups. The graph compares Placebo (N=167), Agomelatine 25 mg (N=156), and Agomelatine 50 mg (N=161). Significant p-values are indicated for each group comparison.](image-url)
AGOMELATINE FOR SLEEP

Zajecka 2010
VILAZODONE (VIIBRYD)

- SSRI + $5HT_{1A}$ partial agonist
  - (Buspar is also a $5HT_{1A}$ partial agonist)
- More effective than placebo
  - approved by FDA
  - Daily dose: 40 mg
- Significant residual symptoms
- No sexual side effects
- Primary side effects: Headache, nausea, diarrhea

Rickels 2009; J Clin Psychiatry 70:326
GLUTAMATE-BASED TREATMENT OF DEPRESSION

- Glutamate antagonists may have antidepressant properties
- I.V. Ketamine produced significant, lasting antidepressant effects in a controlled trial

Zarate, 2006
NMDA ANTAGONISTS HAVE ANTIDEPRESSANT ACTIVITY

Zarate, 2007
DO ANTIDEPRESSANTS CAUSE SUICIDE?

• Definition of suicidality:
  – Completed suicide
  – Acts of suicide
  – Preparation for suicide
  – Suicide ideation
SUMMARY OF 207 CLINICAL TRIALS IN ADULTS

- Completed suicide in depressed patients: 21/40,028 0.05 (no increase)
- Completed suicide in anxious patients: 2/10,972 0.02% (no increase)
- Ratio of completed suicides in antidepressant recipients compared with placebo recipients: 1.07 (no difference)
- No significant differences in rates of suicidality between drug and placebo for any individual medication except for venlafaxine for suicidal ideation.

ANTIDEPRESSANT RISK OF SUICIDE
DO ANTIDEPRESSANTS CAUSE SUICIDE?

• Children and adolescents:
  – No completed suicides in 4400 cases reviewed
  – Increased suicidality (4%) with antidepressants compared with placebo or no treatment (2%)
  – Most cases with paroxetine or venlafaxine
  – Most cases prescribed by non-psychiatrists
“ACTIVATION SYNDROME”?

• Occurs in 4% of newly treated patients
• Most common in patients with personality disorder
• Symptoms develop within 3 months of starting an antidepressant: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, or mania
• Symptoms often relieved by adding a benzodiazepine

Harada 2008; Depress & Anx
SUICIDE IN SEVERELY DEPRESSED CHILDREN (and adults)

- Medicaid data: suicide attempt $n=263$
  - Significant increased risk (OR=1.52) but no total numbers of treated cases given

- Medicaid data: completed suicide $n=8$ cases
  - Significant increased risk (OR=15.62) but no total numbers of treated cases given

Olfson M. Arch Gen Psychiatry 2006;63:865
CRITIQUE OF FDA SUICIDALITY ANALYSIS IN CHILDREN

• Increase in suicidal thoughts rather than completed suicide was used to conclude that antidepressants presented an increased risk;

• **No significant differences in rates of suicidality between drug and placebo for any individual medication except for venlafaxine for suicidal ideation.**

• No increase in non-depressed patients

• Inadequate statistical power (i.e. sample is too small to detect a rare event

Klein DF. Neuropsychopharmacology 2006; 31: 689
ACNP TASK FORCE REPORT ON SSRIs AND SUICIDAL BEHAVIOR IN YOUTH

• Data from randomized clinical trials indicate that “SSRIs and other new generation antidepressants drugs, in aggregate, are associated with a small increase in the risk of increased suicidal thinking or suicide attempts”.

Mann JJ. Neuropsychopharmacology 2006; 31:473
Kaplan-Meier failure curve for emergence of suicidality among males with depression treated with citalopram by genotype (rs4675690)