Depression, Antidepressants and Suicidal Risks: *Has the Data Left You Hanging?*

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Disclosure

I have no financial relationships with any pharmaceutical companies

I receive honoraria for work related to rational drug use from the:

- Canadian Agency for Drugs and Technologies (CADTH); and
- Patented Medicine Price Review Board (PMPRB)

Outline

- Test your knowledge
- Background
- Literature and warnings revisited
- Impact of the warnings
- Efficacy of antidepressants and publication bias
- Questions

Learning Objectives:

1. Describe the 4 treatment options and their expected benefits in depression.
2. Describe the regulatory warnings regarding risk of suicidal behaviours associated with antidepressant use in children, adolescents and adults.
3. Discuss the evidence regarding the efficacy of antidepressant for treating MDD.
4. List 5 monitoring parameters for assessing efficacy and safety when using antidepressants for treating depression.

Circle the statements that reflect your understanding of antidepressants?

A. Depression is the most common psychiatric condition in Adults.
B. When you consider publication bias in antidepressant trials, antidepressants are **ineffective** at reducing the symptoms of depression.
C. Antidepressants are effective for treating depression in adults but NOT in children and adolescents.
D. The risk of suicidal thoughts and behaviours with SSRIs in children and adolescents is 2-3%.

Circle the statements that reflect your understanding of antidepressants?

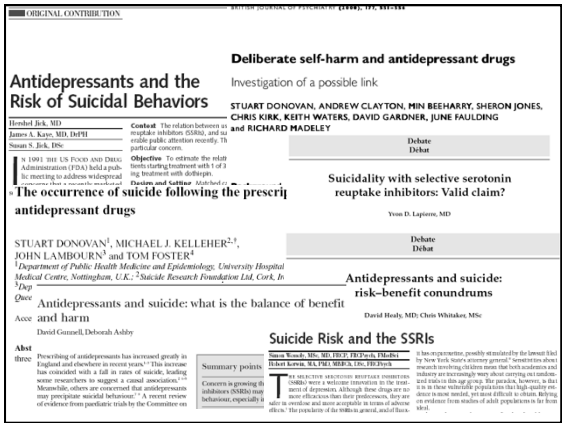
E. Antidepressants, as a class, are the 6th most common medications prescribed/dispensed in Canada
F. On average all antidepressants are equally efficacious at reducing symptoms of depression.
G. After the warnings about antidepressants, suicide rates in youth have actually gone up in Canada.
H. On average, randomized clinical trials suggest that placebo works about 20% of the time at reducing depressive symptoms.

Dr. Daniels and Jessica

- Dr. Daniels is a naturopathic physician working next door. He is concerned about his daughter Jessica
- 18 yo, wt = 55kg, with low mood x 4 mo
- Her mood has been "extremely low" since Christmas 2009
- When you inquire further, you learn that Jessica is very irritable, has been skipping classes, is excessively tired all the time and has a poor appetite

Jessica

- Sleeps 12 hrs/night & says she "can't get out of bed"
- She's about to fail 2 courses in school
- Broke up with her boyfriend 3 months ago
- NKAs; PMHx: Asthma and eczema
- Aunt and grandmother have MDD
- Dr. Daniels put her on St. John's Wort 300 mg tid a month ago with little results
- He's also done a quick search on his computer and come up with the following…



ORIGINAL CONTRIBUTION

Antidepressants and the Risk of Suicidal Behaviors

Deliberate self-harm and antidepressant drugs

Investigation of a possible link

STUART DONOVAN, ANDREW CLAYTON, MIN BEEHARRY, SHERON JONES, CHRIS KIRK, KEITH WATERS, DAVID GARDNER, JUNE FAULDING and RICHARD MADELEY

Debate / Débat

Suicidality with selective serotonin reuptake inhibitors: Valid claim?

Yvon D. Lapierre, MD

Debate / Débat

Antidepressants and suicide: risk–benefit conundrums

David Healy, MD; Chris Whitaker, MSc

Suicide Risk and the SSRIs

Antidepressants and suicide: what is the balance of benefit and harm

David Gunnell, Deborah Ashby

The occurrence of suicide following the prescri… antidepressant drugs

STUART DONOVAN[1], MICHAEL J. KELLEHER[2,3], JOHN LAMBOURN[3] and TOM FOSTER[4]

[1]Department of Public Health Medicine and Epidemiology, University Hospital Medical Centre, Nottingham, U.K.; [2]Suicide Research Foundation Ltd, Cork, Ir… [3]Dep… Quee…

Summary points

Concern is growing th… inhibitors (SSRIs) may… behaviour, especially i…

Abst… three…

Prescribing of antidepressants has increased greatly in England and elsewhere in recent years.[1,2] This increase has coincided with a fall in rates of suicide, leading some researchers to suggest a causal association.[3–5] Meanwhile, others are concerned that antidepressants may precipitate suicidal behaviour.[1,6] A recent review of evidence from paediatric trials by the Committee on…

List the top 3 treatment options would you consider?

Please write a prescription for Jessica…

Diagnostic Criteria (DSM V): ≥ 5

1. A depressed mood.
2. Loss of interest in activities that once were pleasureful.
3. Significant **weight loss** OR decrease in appetite OR significant **weight gain**.
4. **Insomnia OR sleeping too much.**
5. Appearance of feeling **restless/agitated** OR **slowed down**.
6. **Fatigue OR loss of energy** nearly everyday.
7. Feelings of **worthlessness** OR excessive/ inappropriate **guilt**.
8. Reduced **concentration** OR **indecisiveness**.
9. Recurrent thoughts of **death or attempting suicide**.

Recalling Depressive Symptoms

- S-Sleep changes
- A-Appetite (weight change)
- D-Dysphoria (low mood)
- A-Anhedonia
- F-Fatigue
- A-Agitation/retardation
- C-Concentration
- E-Esteem/guilt
- S-Suicide

Epidemiology:

- Average age of onset is mid 20s
- Lifetime Risk
  - ~1 in 5 Women
  - ~1 in 10 Men
- ~1 in 50 children < 12
- ~1 in 15 adolescents

Overall:

At any given time, ~1 in 20 Canadians suffer from clinical depression!

Goals of Therapy

- **SHORT TERM**
  (e.g., 2-3 months)
  - –Stabilize depressive symptoms
  - –Prevent complications (e.g., suicide)
  - –Minimize side effects
  - –Induce remission (not only response)
  - –Improve quality of life
  - –Education

- *(e.g.,>3 months)*
- Prevent relapse and recurrence
- Maintain a stable mood
- Manage side effects
- Education

Depression Treatment Options

1. **Antidepressant medication(s)**
2. **Psychotherapy**
   - Cognitive behavioural therapy (CBT)
   - Intrapersonal therapy (IPT)
3. **Electroconvulsive therapy (ECT)**
4. **Light therapy**
5. **Alternative therapies**
   - St. John's wort, SAM-e, transcranial magnetic stimulation therapy, etc.

Overview of Antidepressant Classes

OPTIONS FOR 1ST OR 2ND CHOICE		
TCAs:	Tricyclic antidepressants	8 agents
SSRIs:	Selective serotonin reuptake inhibitors	6 agents
NaSSA:	Noradrenergic and serotonergic specific antidepressant	1 agent
RIMA	Reversible Inhibitor of Monoamine Oxidase	1 agent
NDRIs:	Noradrenaline dopamine reuptake inhibitors	1 agent
SNRIs:	Serotonin noradrenaline reuptake inhibitors	3 agents
RESERVED		
SARIs:	Serotonin antagonists/reuptake inhibitors	1 agent
MAOIs:	Monoamine oxidase inhibitors	2 agents
Heterocyclics:	Maprotiline	1 agent

American College of Physicians (ACP) Clinical Guidelines – Nov 2008

- Systematic Review of 5 databases (N = 80 trials)
- 4 "Strong Recommendations"
- All 2nd generation AD are equally effective
- ~ 50% respond to the first AD
- 25% of those switched will respond to second AD


ACP Clinical Guidelines

Clinical Guidelines

Using Second-Generation Antidepressants to Treat Depressive Disorders: A Clinical Practice Guideline from the American College of Physicians

Qaseem A et al. ACP Clinical Guidelines

ACP Clinical Guidelines: Strong Recommendations – Nov 2008

1. Choose AD based on side effect profile, cost, and patient preference (not MoA)
2. Assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1 to 2 weeks of initiation of therapy
3. Modify treatment if response is not adequate by 6-8 wks
4. Continue treatment for 4-9 months (if first episode) and longer if recurrent episode

Overall Response Rates: Antidepressants

Meta-analysis including 262 drug-placebo comparisons from 182 clinical trials (n=36,385)

*p <0.0001

Papakostas, Fava. *Eur Neuropsychopharmacol* 2009:19:34-40

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial(s)

- NIMH Study ($35 million)
- Largest MDD trial ever conducted
- 2,876 outpatients (18-75 yrs old)
  - 76% Caucasian, 64% female
  - Mean age 40.8 yrs; Ave hx of MDD = 15 yrs (ave of 6 previous episodes);
- 41 US centres (18 primary care & 23 psychiatric settings)
- Baseline $HAMD_{17}$ score >21.8 (had to be ≥14)
- Open label (no placebo)
- (Pseudo) Randomized

Trivedi et al, Am J Psychiatry 2006; 163:28-40
(www.star-d.org)

STAR*D: Results

Level	Interventions	Remission Rate[+]	Cumulative Remission
Step 1 N=3,671	• CITALOPRAM	36.8%	36.8%
Step 2 N=1,439	• Switch: VEN / BUP / SER • Combine: BUP / BUS • Switch / Combine: CT	30.6%	56.1%
Step 3 N=390	• Switch: NOR / MIR • Augment: LI / T3	13.7%	62.1%
Step 4 N=123	• Switch: TCA / MIR+VEN	13.0%	67.0%

[+] Quick Inventory of Depressive Symptomatology-Self Report ($QIDS\text{-}SR_{16}$) ≤ 5

Rush AJ et al. Am J Psychiatry 2006;163:1905-17.

Factors to Consider When Starting Therapy

- Severity of episode
- Age
- Long term adherence
  - Risk of relapse increases if discontinued early (35%-60% vs. 10%-25%)
- Previous treatment response
- Comorbid psychiatric or medical disorders
- Drug interactions
- Accessibility
- Pharmacokinetics
- Potential side effects
- Suicide risk/impulsivity
- Patient preferences
- Clinician experience
- Effectiveness of treatment

Antidepressants: How are they similar?

- Overall benefits
- Time to see benefits
- Chance of benefiting
  - Somewhat: 70%
  - Significantly: 50-60%
  - Completely: 30%

(within 8-12 weeks)

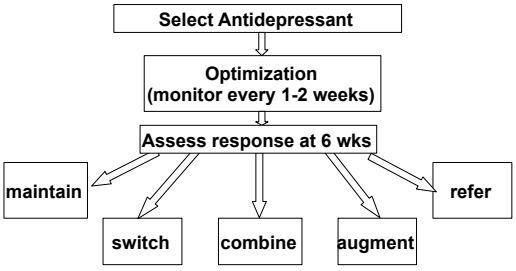
- Chance of stopping early
  - >50% within 3 months
- Duration of treatment
  - 1st or 2nd episode: 6-12 months
  - >2 episodes close together: > 1 year to indefinitely

Antidepressants: How do they differ?

- Individual response
- Side effects
- Drug interactions
- Precautions
- Experience
- Cost
- Dosing
- Need for blood tests

- Withdrawal reactions when dc treatment
- Drug-drug, drug-disease, drug-food interactions
- Specific mechanisms of action
- Patient preferences

Strategies for Reaching Remission



Kennedy et al, 2001

Clinical Issues with Antidepressants

- Intolerability
- Persistent side effect burden
- Withdrawal syndromes
- Need for multiple medications
- Suicide/self harm controversy
- Non-adherence
- Safety during pregnancy
- Safety in overdose
- Public/self perceptions

You and Dr. Daniels discussed the pros and cons of using an antidepressant. Dr. Daniels wants more information about the risk of suicide or suicidal behaviours.

Background: Suicide facts

- Depression is a risk factor for suicide
- Suicide is the 2nd leading cause of death in Canada in those aged 10-24 years old
  - Ave. of 550 suicides in youth (age 10-24)/yr
  - 24% of all teenage deaths (Ontario MoH-1986-90)
- Ave. of 3,700 suicides/yr in Canada (2001-2005) Suicide rate = 11.6/100,000
- 35 % of depressed adolescents attempt suicide
- 2-8% of depressed youth commit suicide

Stats Canada: http://www40.statcan.gc.ca/l01/cst01/hlth66a-eng.htm July 2009
Curry Opin Psychiatry 2008; 22:1-6
www.cdc.gov/violenceprevention Summer 2009 newsletter

Test your knowledge

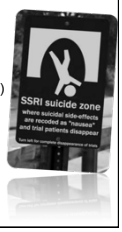
What is the ratio of suicide attempts to completed suicides for different age groups below?

- Population average
- 10 – 25 yrs old
- >65 yrs old

www.cdc.gov/violenceprevention Summer 2009 newsletter

Prior to the Regulatory Warnings

- 15 SSRI/SNRI Pediatric Depression RCTs conducted
  - ONLY 7 trials published (5 positive trials)!
  - Unaware of publication bias
- Overall results predominately neutral
  - High PLB response (~40-50%) observed (when placebo washout not utilized)
  - SSRIs were believed to be more effective (NNT 5-10) than placebo at reducing symptoms of depression
  - Improper coding for adverse effects in most trials
  - No completed suicides



Positive published trials for antidepressants in children and adolescents prior to 2006

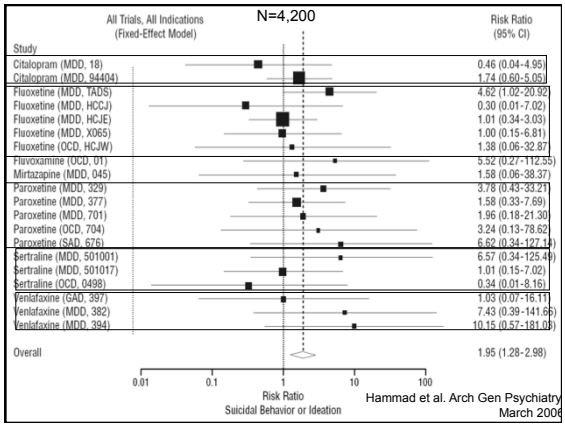
1. Emslie et al (1997): fluoxetine 58%, placebo 32%
2. Keller et al (2001): paroxetine 63%, imipramine 50%, placebo 46%, 1 of 2 primary outcome measures was significant
3. Emslie et al (2002): effects modest (fluoxetine 41%, placebo 20%) & not all outcome measures were significantly different than placebo
4. Wagner et al (2003): sertraline 69%, placebo 59%
5. Marsh et al-TADS (2004) Fluoxetine + CBT 71%; fluoxetine 61%; CBT 43%; placebo 35%

Antidepressant Warnings in Youth...

Summer 2003	**UK** – Paroxetine contraindicated in pediatric patients **FDA** – Recommends paroxetine not to be used in pediatric patients **Health Canada** - Advisory on using paroxetine and venlafaxine in pediatric patients
June '04 October 2004	**Health Canada** issues advisory for patients/doctors for ALL antidepressants **FDA - Black Box Warning** on ALL antidepressant drug labels (↑ risk of suicidality or worsening depression in children & adolescents) NOT SUICIDE!
May 2007	**FDA -** Warning expanded to included young adults (<18 - 24 years old)

What evidence are these warnings based on?

What happened after the warnings?



Hammad et al. Arch Gen Psychiatry March 2006

Overall relative & absolute risk of suicidal behavior or ideation

Relative Risk (RR):

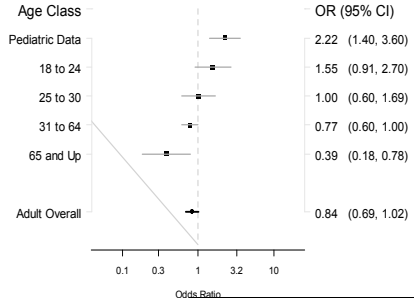
Outcomes	Overall RR all trials, all indications	Overall RR SSRI in MDD trials
Suicidal behavior or ideation	1.95 (1.28, 2.98)	1.66 (1.02, 2.68)

Absolute Risk Increase (ARI):

- Overall ARI for SSRIs in MDD trials = 2-3%
- For every 100 pediatric patients treated, 2 to 3 patients have some increase in suicidality during short-term treatment

Note that TADS data was added to analyses
Ref: Tarek A. Hammad, MD, FDA Sept.04

Suicidal Behavior and Ideation
Psychiatric Indications
Odds Ratio



Levenson, M et al. FDA Dec 2006

Relative Risk of Suicidal Behavior or Ideation by Drug

Drug	Relative Risk (95% CI), MDD trials	Relative Risk (95% CI), all trials, all indications
Citalopram	1.37 (0.53, 3.50)	1.37 (0.53, 3.50)
Fluvoxamine	No MDD trials	5.52 (0.27, 112.55)
Paroxetine	2.15 (0.71, 6.52)	2.65 (1.00, 7.02)
Fluoxetine*	1.53 (0.74, 3.16)	1.52 (0.75, 3.09)
Sertraline	2.16 (0.48, 9.62)	1.48 (0.42, 5.24)
Venlafaxine	8.84 (1.12, 69.51)	4.97 (1.09, 22.72)
Mirtazapine	1.58 (0.06, 38.37)	1.58 (0.06, 38.37)
Bupropion	No MDD trials	No events

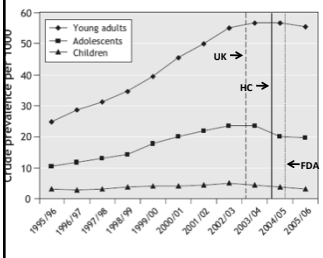
*Note that TADS data are added to Fluoxetine
Ref: Tarek A. Hammad, MD, FDA Sept.04

FDA

Canadian Prescribing of Antidepressants pre and post warnings

Annual prevalence of antidepressant prescriptions per 1000 (in Manitoba)

N= 2, 920, 890



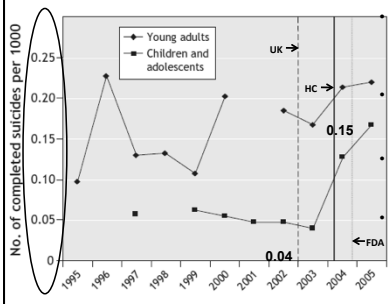
Antidepressant prescription rates ↓ after HC warnings:

- Children and Adolescents: RR = 0.86 [0.81-0.91]
- Young adults: RR = 0.90 [0.86 – 0.93]

Slight increase in prescribing of fluoxetine and decrease in all other antidepressants

Katz et al, CMAJ 2008; 178 (8): 1005-11

Annual Suicide Rates/1000 Pre and Post Warnings



↑ post advisory suicide rate in those aged 5-17 RR = **1.25 [1.08-1.44]**

No change in those aged 19-24): RR = **1.01 [0.93-1.10]**

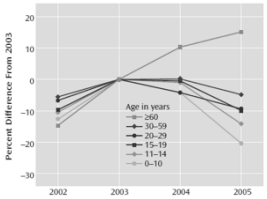
10% of C&A completing suicide received an antidepressant

Hanging was the most common method

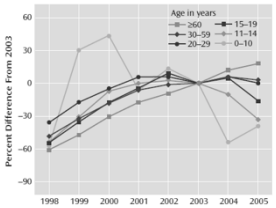
Katz et al, CMAJ 2008; 178 (8): 1005-11

US and Netherlands Prescribing of Antidepressants pre and post 2003

SSRI prescriptions in the USA (2002-2005)



SSRI prescriptions in the Netherlands (1998-2005)

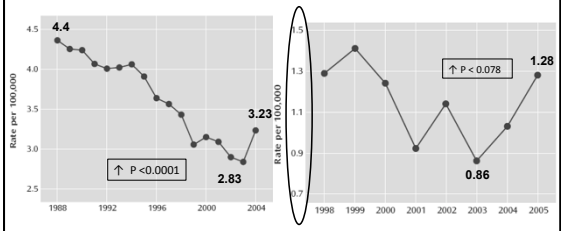


Gibsons et al, Am J Psychiatry 2007; 164 (6): 884-891

US and Netherlands Suicide rates in youth pre and post 2003

Suicide rate in C&A (5-19 years old) US (1988-2004)

Suicide rate in C&A (<19 years old) Netherlands 1998-2005



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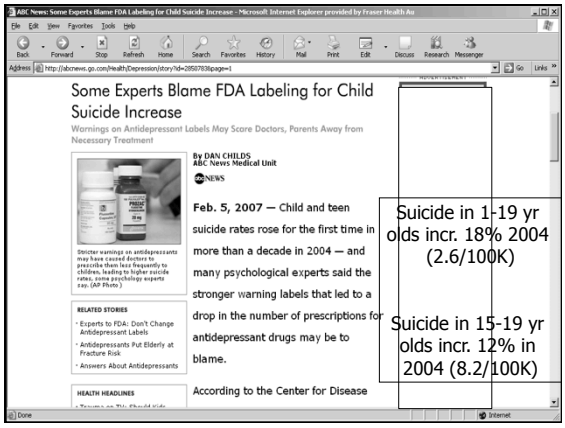

Suicide in 1-19 yr olds incr. 18% 2004 (2.6/100K)

Suicide in 15-19 yr olds incr. 12% in 2004 (8.2/100K)

Limitations of Database Trials

- Retrospective and observational → can not draw causal conclusions
- Confounders not accounted for
- Inaccuracies
  - Prescription data may not represent use
  - Improper coding of data (e.g., diagnosis, suicide)
  - Missing data

Key Messages: Pediatric Trials

- 27 RCTs: MDD (15), OCD (6), other anx. d o's (6)
- Efficacy based on trial defined "response"
- NNT =10 for MDD, 6 for OCD & 3 for other anx. d/o's
- Suicidal ideation 0.7% (0.1 – 1.3%) *underestimate?*
- No suicides


JAMA, April 18, 2007—Vol 297, No. 15

Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment

A Meta-analysis of Randomized Controlled Trials

Key Messages 1: What Does the Evidence Support in the Youth?

- Warnings impacted prescribing behaviour
- Antidepressants slightly increase suicidality (2-3%)
- Monitoring for efficacy & worsening depression is essential

Depression:

- Fluoxetine first line ± CBT
- Others can be used with suitable precautions and vigilance
- Weekly monitoring in the first month then monthly for 3 months
- Avoid venlafaxine and paroxetine

Anxiety:

- OCD
  - CBT ± sertraline, fluvoxamine or fluoxetine
- Panic disorder
  - Short-term: benzodiazepine (e.g., clonazepam)
  - Long-term: fluoxetine

Factors to consider

- In those with untreated depression, is the risk for suicide greater or less than those prescribed an antidepressant?
  - Depression scores decline with placebo in RCTs
  - Monitoring patients on a weekly basis taking placebo does not equal "no treatment"
- Suicidal behaviours have not been divided into low or high lethality
  - low lethality events do not accurately predict the likelihood of suicide
-
  - Not all with depressive symptoms have MDD
  - Support and counseling suffice for many with mild symptomatology

Key Messages #2

- Cumulative data from published & unpublished trials suggests that antidepressants are marginally EFFECTIVE (vs. placebo) at reducing the symptoms of depression
- Selective reporting of antidepressant trial data resulted in an over-estimation of treatment effects
- Antidepressants help reduce symptoms of (moderate to severe) depression in 50-60% of adults and decrease the risk of relapse by approximately 50% (at 1 yr)

Monitoring Parameter	Timeline
1. Target Symptoms for depression, (SAD-A-FACES; severity of symptoms and functioning (efficacy of antidepressant – aim for remission)	q7-14 days for 4-6 wks then q 1-3 months (to watch for relapse
2. Antidepressant adverse effects (depends on the medication selected – you should be able to identify 3-4 adverse effects you'd be concerned with)	q7-14 days for 4 wks then q 3 months
3. Increase in obsessive, obtrusive suicidal thoughts/behaviours (especially in children, adolescents and young adults)	q7-14 days for 4-8 wks
4. Serotonin syndrome	First 2 wks of AD or new medication
5. Discontinuation syndrome	At discontinuation of therapy