



A Tale of Two Medicines and More... the antidepressants



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Disclosure Statement: Philip Hazell

Source	Consultant	Advisory Board	Stock Equity >\$10,000	Speaker's Bureau	Research Contract
Eli Lilly	Submissions to Australian drug regulatory and funding bodies	International Australia	-	Oral and poster presentations	Atomoxetine relapse prevention study, ADHD + ODD study. Switching study
Pfizer	-	-	-	Oral presentations	-
Janssen	Submissions to Australian drug regulatory and funding bodies	Australia	-	Oral presentations	-
Celltech	-	-	-	-	Trial of Metadate CD for ADHD
Novartis	-	Australia	-	-	-
Shire	-	International	-	-	-

4000 AUSTRALIAN CHILDREN AND
BABIES UNDER 10 INCLUDING
45 BABIES UNDER 12 MONTHS
HAVE BEEN PRESCRIBED AN
ANTIDEPRESSANT IN ONE SINGLE YEAR

278,000 PRESCRIPTIONS FOR
ANTIDEPRESSANTS WERE WRITTEN
FOR CHILDREN UNDER 18 YEARS

Types of antidepressant medications

- Tricyclic antidepressants (noradrenaline and serotonin reuptake inhibitors)
 - Amitriptyline, imipramine
- Reversible and non-reversible monoamine oxidase inhibitors
 - Moclobemide, phenelzine
- Selective serotonin reuptake inhibitors
 - Fluoxetine, sertraline
- Noradrenergic reuptake inhibitors
 - Venlafaxine, reboxetine
- Tetracyclic antidepressants
 - Mirtazepine, mianserin
- Noradrenaline and dopamine reuptake inhibitors
 - Bupropion

Paediatric uses for antidepressant medications

- enuresis
- attention-deficit/hyperactivity disorder
- anxiety
- obsessive-compulsive disorder
- selective mutism
- symptoms associated with autism
- symptoms associated with mental retardation
- aggression
- bulimia
- depression

TGA approvals for <18

- OCD
 - fluvoxamine, sertraline
- Enuresis
 - amitriptyline, imipramine
- *FDA approvals a little broader
- **Other meds specify caution or not for use in <18s

Antidepressant prescribing in Australian general
practice 2001-2004:
Rate per 100 encounters

<i>variable</i>	<i>< 12</i>	<i>12-17</i>	<i>20+</i>
Any AD	0.11	1.48	4.18
SSRI	0.03	1.08	2.38
fluoxetine	0.003	0.08	0.28
paroxetine	0.003	0.13	0.48
other SSRI	0.02	0.87	1.62
tricyclic	0.07	0.14	0.92
venlafaxine	0	0.17	0.47

Factors influencing prescribing

- Evolving clinical practice
- Increased awareness of psychopathology in children and adolescents
- Safety concerns
- Other societal objections to medication use

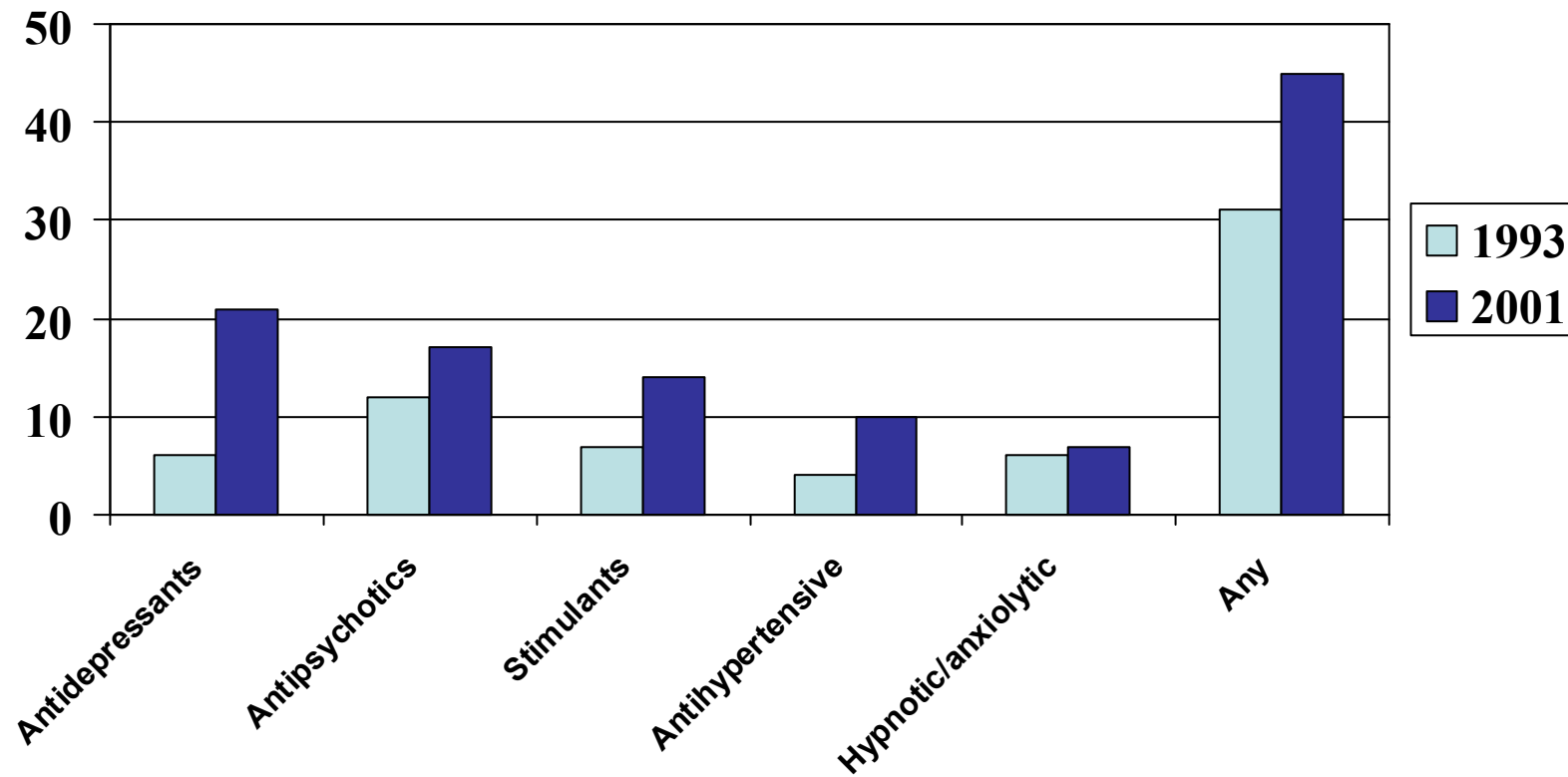
TABLE 2. Proportional Utilization of ATDs According to the 5 Leading Psychiatric Diagnoses for ATD-Treated Youths With Only Primary Care Services Compared With Those With Any Psychiatric Services in MWM Youths in 1994

Psychiatric Diagnosis	Primary Care (n = 3354)								Psychiatric Services (n = 2622)							
	Any ATD		TCAs		SSRIs		Other ATD		Any ATD		TCAs		SSRIs		Other ATD	
	n	Column %*	n	Row %*	n	Row %	n	Row %	n	Column %	n	Row %	n	Row %	n	Row %
ADHD	1448	43.2	1274	88.0	207	14.3	91	6.3	823	31.4	603	73.3	262	31.8	126	15.3
Depression	1178	35.1	541	45.9	708	60.1	176	14.9	1452	55.4	573	39.5	1021	70.3	339	23.3
Anxiety disorder	451	13.4	195	43.2	273	60.5	78	17.3	519	19.8	201	38.7	375	72.3	145	27.9
Conduct disorder	365	10.9	255	69.9	124	34.0	43	11.8	454	17.3	255	56.2	237	52.2	98	21.6
Adjustment disorder	291	8.7	160	55.0	127	43.6	58	19.9	774	29.5	359	46.4	471	60.9	171	22.1

* Column and row percentages exceed 100% because youths may have had >1 diagnosis (column) or >1 ATD subclass (row).

Trends in psychotropic prescribing for autism 1993-2001

Aman et al. J Child Adolesc Psychopharmacol 2005;15:116-126



Idiosyncratic use

- Australian GP faced court action for prescribing sertraline to 16 yr old girl with irregular menstruation, headaches and disturbed sleep to 'take the edge of things' until OC pill 'kicked in'. Patient subsequently engaged in deliberate self harm.

Controlled trial evidence

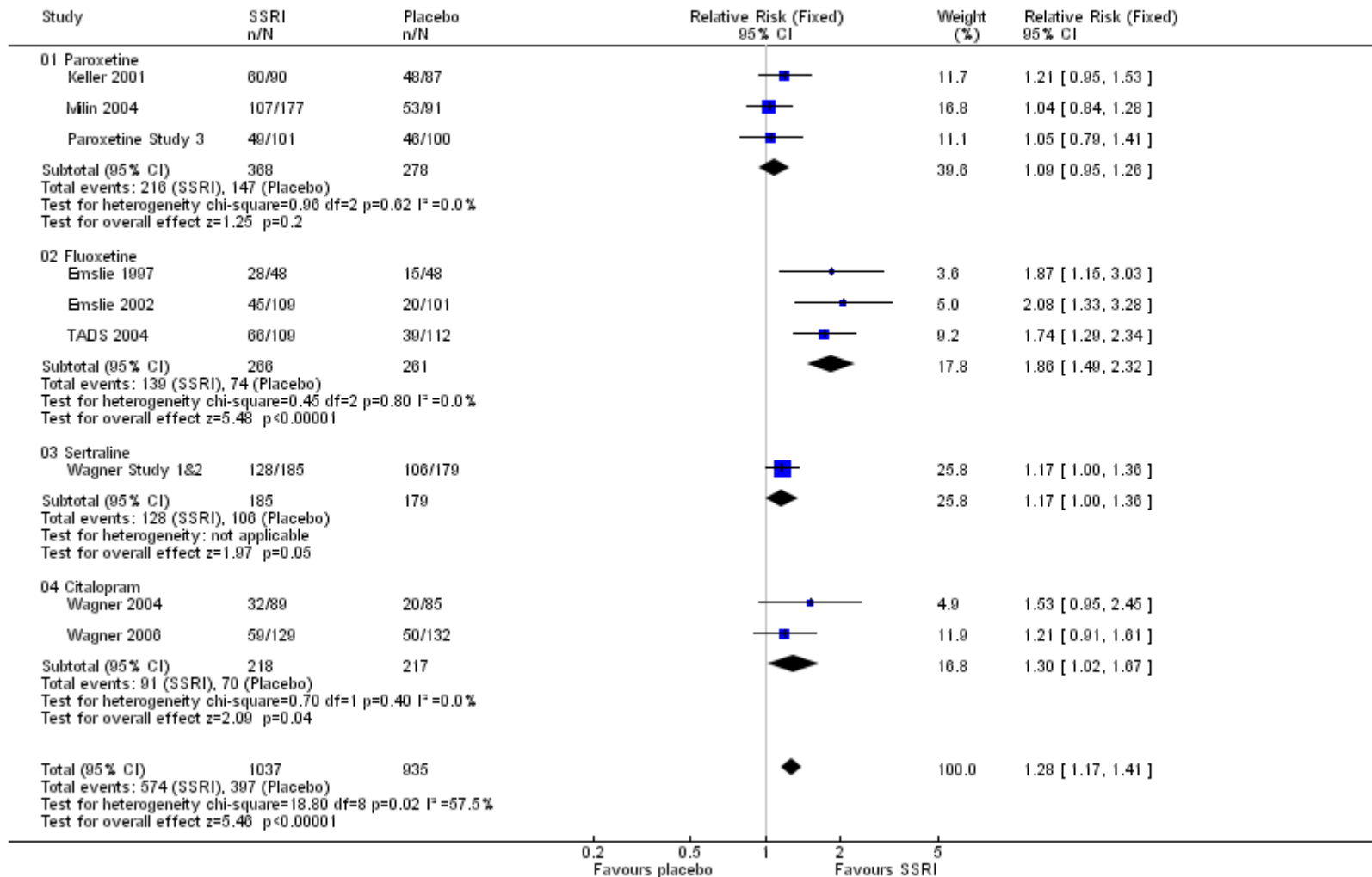
Drug class	depress	anxiety	mutism	OCD	ADHD	bulimia	autism	enuresis
MAOI	-	-	-	-	II	-	-	-
TCA	I neg	II	-	II	I	-	II	I
tetracyclic	-	-	-	-	-	-	-	-
SSRI	I	I	II	I	-	-	I neg	-
RIMA	I	-	-	-	-	-	-	-
NARI	I neg	I	-	-	-	-	-	-
bupropion	-	-	-	-	II	-	-	-

I = systematic review; II = at least one RCT

Response

Hetrick et al Cochrane Database 2009

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents
 Comparison: 06 SSRI versus placebo
 Outcome: 01 Response (by predefined criteria)



Combination therapy

- Increasing trend towards combined pharmacotherapy with an emergent, albeit lagging, evidence base
- Typical example would be SSRI + psychostimulant for ADHD complicated by a depressive episode
- Such clinical practice is difficult to capture in standardized data collection



CSM Dear Dr letter 10 December, 2003

- On the balance of evidence from available clinical trials CSM has advised that the risks and benefits for the treatment of major depressive disorder (MDD) in under 18s is unfavourable for sertraline, citalopram and escitalopram and unassessable for fluvoxamine.
- Only fluoxetine has been shown in clinical trials to have a favourable balance of risks and benefits for the treatment of MDD in the under 18s



FDA Public Health Advisory

March 22, 2004

WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS

- Today the Food and Drug Administration (FDA) asked manufacturers of the following antidepressant drugs to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality. The drugs that are the focus of this new Warning are: Prozac (fluoxetine); Zoloft (sertraline); Paxil (paroxetine); Luvox (fluvoxamine); Celexa (citalopram); Lexapro (escitalopram); Wellbutrin (bupropion); Effexor (venlafaxine); Serzone (nefazodone); and Remeron (mirtazapine).

FDA re-analysis

- Included trials of SSRIs, venlafaxine, nefazodone, mirtazapine and bupropion for MDD and other indications in children and adolescents
- Safety data restricted to the duration of the trial (usually weeks to months) and 30 days beyond discontinuation

FDA re-analysis

- Analysis involved data from 4256 patients (2298 active drug, 1958 placebo)
- The data set does not include the recently published “TADS” study of fluoxetine versus cognitive behaviour therapy
- No deaths were reported
- 4% of patients receiving an antidepressant drug reporting any suicide related behaviours compared with 2% of those receiving placebo
- Review identified 95 cases of ‘definitive suicide behaviour’

FDA re-analysis suicide related events

Antidepressants: Any indication

Drug	Participants	RR (CI) any	RR (CI) serious
Paroxetine	1191	2.47 (1.16-5.27)	2.65 (1.0-7.02)
Sertraline	560	1.72 (0.50-5.89)	1.48 (0.42-5.24)
Venlafaxine	681	3.03 (1.04-8.80)	4.97 (1.09-22.72)
Fluoxetine	458	0.98 (0.38-2.50)	0.92 (0.39-2.19)
Citalopram	407	1.49 (0.72-3.06)	1.37 (0.53-3.50)
Mirtazapine	258	0.52 (0.003-8.27)	1.58 (0.06-38.37)
Fluvoxamine	120	3.31 (0.14-79.67)	5.52 (0.27-112.55)

FDA re-analysis suicide related events Antidepressants

Drug	Participants	RR (CI) any	RR (CI) serious
All MDD*	2885	-	1.71 (1.05-2.77)
SSRI MDD	1838	1.62 (1.03-2.54)	1.41 (0.84-2.37)
Non-MDD*	1365	1.93 (0.68-5.45)	2.17 (0.72-6.48)
All trials*	4250	1.81 (1.24-2.64)	1.78 (1.14-2.77)

Mosholder A, memo Aug 16, 2004

*includes nefazadone and bupropion

FDA gets tough on drugs for depression

Posted on Sat, Oct. 16, 2004

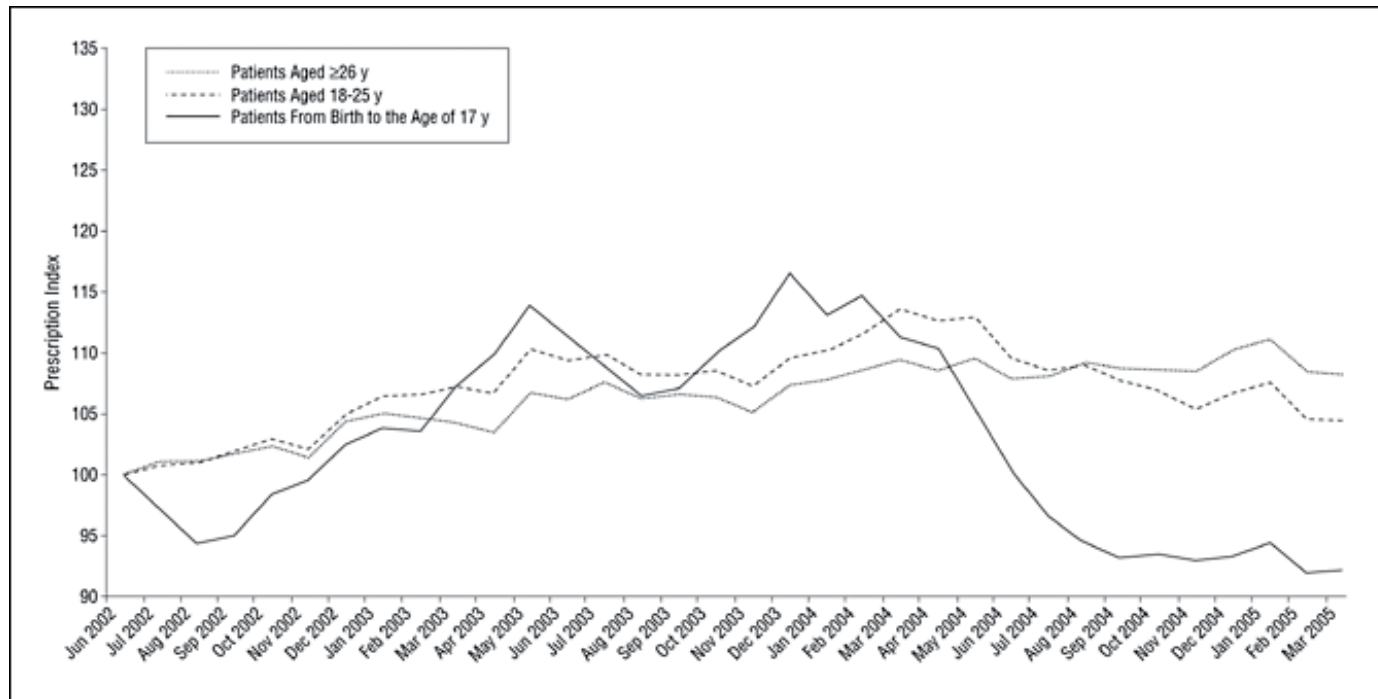
Comment

- Small but statistically significant association between antidepressant treatment and suicide related behaviours in children and adolescents in the weeks after treatment initiation
- Placed in context of prevalence of DSH the prevalence of suicide related behaviours among trial participants seems low
- Lack of data on severity of DSH in community data precludes direct comparison

Impact of safety warnings 12-19 yrs

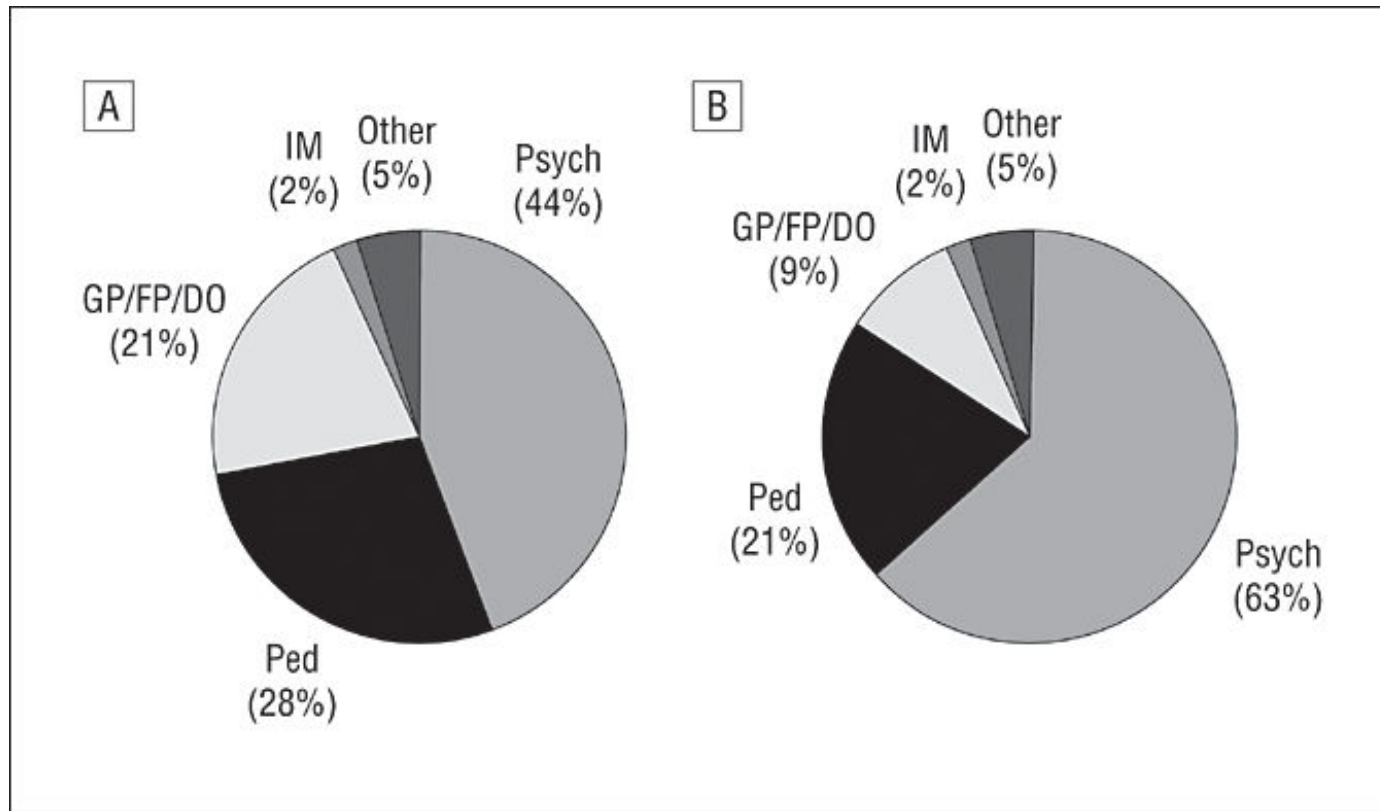
Country	Prescribing	Psychiatry Referral	Suicides
USA	↓	↑	↑
Netherlands	↓	?	↑
UK	↓ for some ADs but not SSRIs	?	No effect
Sweden	?	?	Higher than expected
Austria, Croatia, France, Germany, Norway, Singapore, Slovenia, Spain	?	?	Lower than expected
Czech Rep, Israel, Canada, Finland, Greece, Ireland, Japan, NZ, UK	?	?	Mixed

Prescription volume indexed to normalize the difference in prescription volume between the age groups



Nemeroff, C. B. et al. Arch Gen Psychiatry 2007;64:466-472.

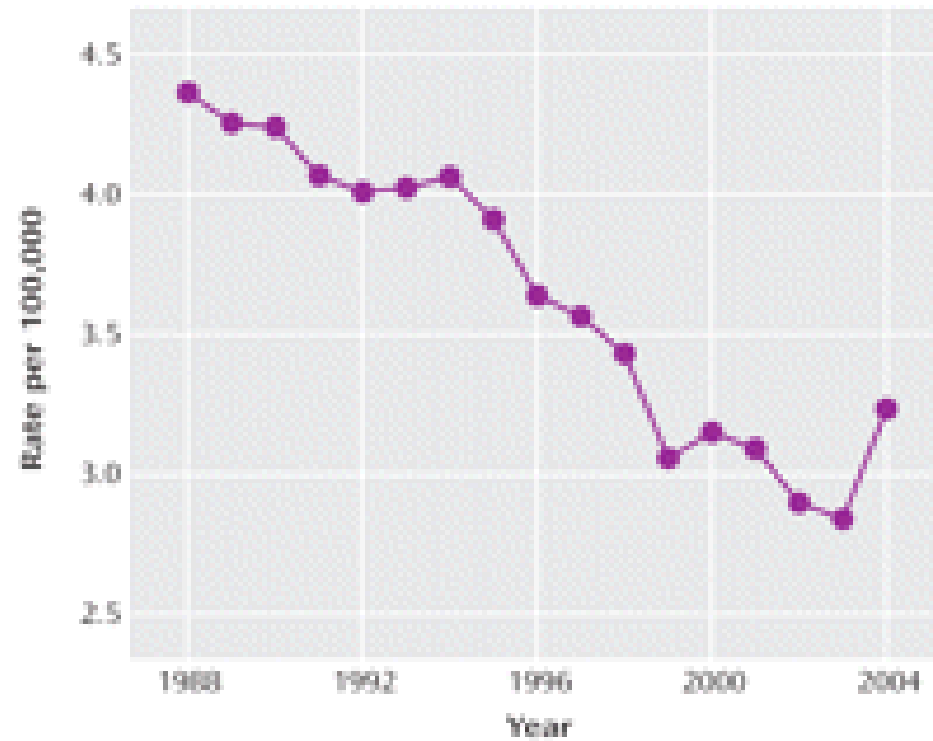
Specialty mix of antidepressant prescribers for patients younger than 18 years in quarter February 2004 (refers to December 2003 through February 2004) (A) and quarter February 2005 (refers to December 2004 through February 2005) (B)



Nemeroff, C. B. et al. Arch Gen Psychiatry 2007;64:466-472.

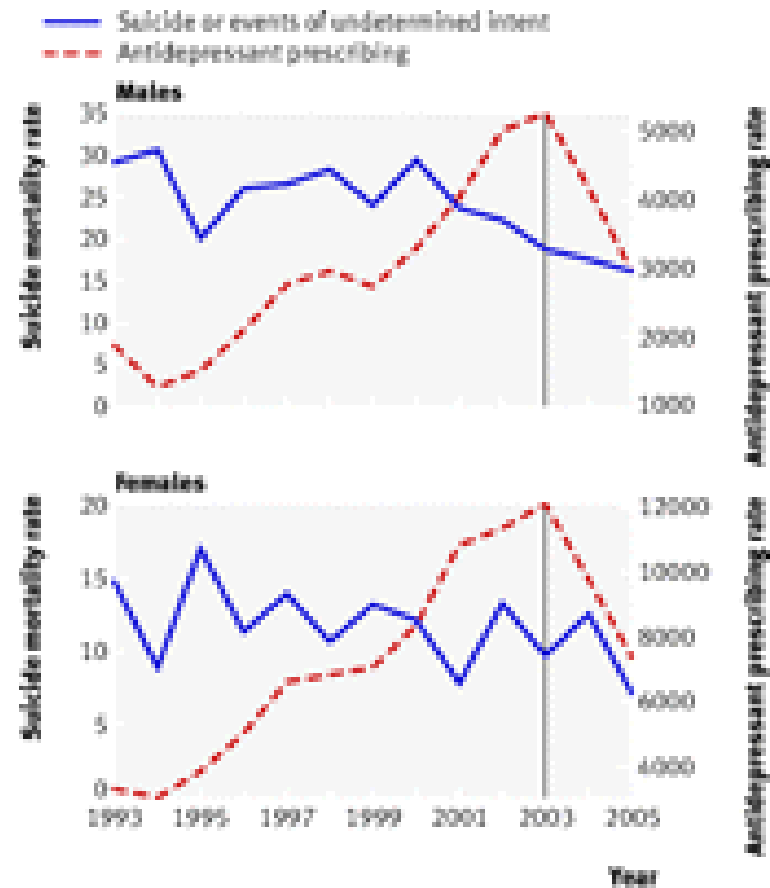
Suicide rates 5-19 yrs USA

Gibbons et al. Am J Psychiatry 2007;164: 1356-1363



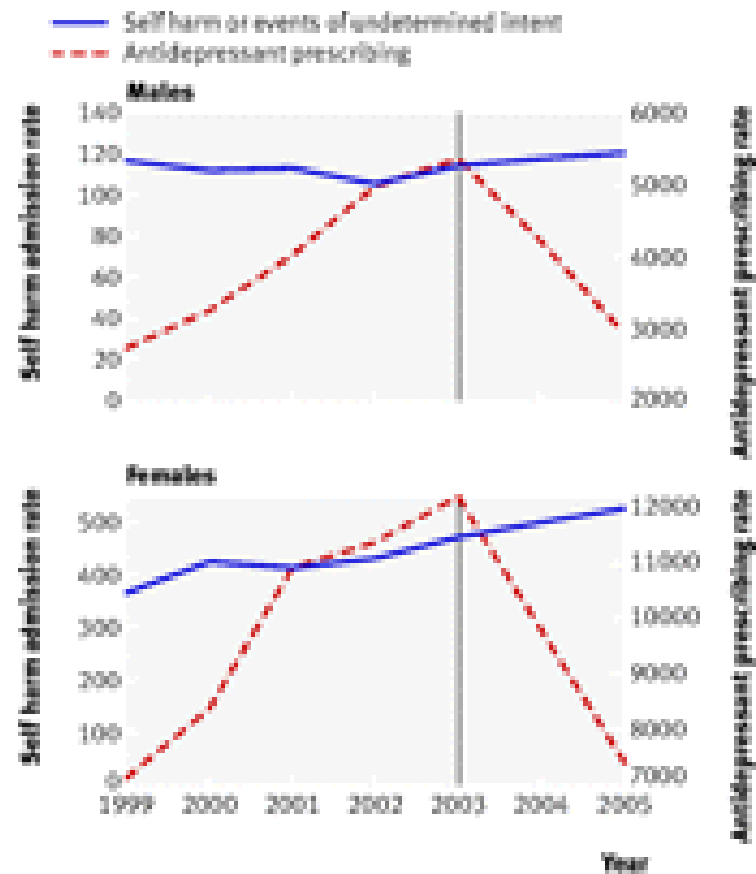
AD prescribing and suicide 12-19 yrs in UK

Wheeler et al. BMJ 2008; 336: 542



AD prescribing and presentation with self-harm 12-17 yrs in UK

Wheeler et al. BMJ 2008; 336: 542



Summary

- Antidepressants are a heterogeneous group of drugs directed to a heterogeneous group of paediatric conditions
- Evidence lags behind practice, but most important bases are covered
- Contrary to media reports, prescribing of antidepressants to young children in Australia is uncommon
- Based on available evidence, SSRI prescribing for autism may be unjustified. There are insufficient data concerning aggression, mental retardation
- Recommended resources: *Clinical Evidence*, *Cochrane Database*, *Journal of Pediatric Child and Adolescent Psychopharmacology*