# Antidepressants and substance abuse – what's the story?

David Menkes

Waikato Clinical Campus

david.menkes@auckland.ac.nz

# competing interests

- background in psychology (BA 1975, UC San Diego) and pharmacology (PhD 1983, Yale)
- University of Auckland employee
- Relationships with
  - Royal Australian and NZ College of Psychiatrists
  - PTAC Mental Health Advisory Committee (PHARMAC)
  - Uppsala Monitoring Centre (WHO)
  - International Society of Drug Bulletins
  - www.healthyskepticism.org

# competing interests II

- accepted speaker's fees, support to attend conferences, and many meals from various pharmaceutical companies (1986-2004).
- received research support from and/or conducted contract research for Roche (1987), Eli Lilly (1989-90), and Douglas Pharmaceuticals (2011).
- paid member of Data Safety Monitoring Board for Dunedin-based studies of noribogaine (2014-2015) and ketamine (2016-2017).
- paid expert witness on behalf of plaintiffs in civil cases defended by Eli Lilly (fluoxetine), Roche (clonazepam), GSK (paroxetine), Pfizer (sertraline), Lundbeck (escitalopram), Wyeth (venlafaxine).
- paid expert witness on behalf of defendants in criminal cases in which prescribed medication, with or without alcohol, was a possible contributor (2003-present).

# learning objectives

by the end of this session, I hope those attending will

- where antidepressants came from, how we think they work, and why they're so popular
- their common, sometimes harmful prescription to people with liabilities to substance misuse

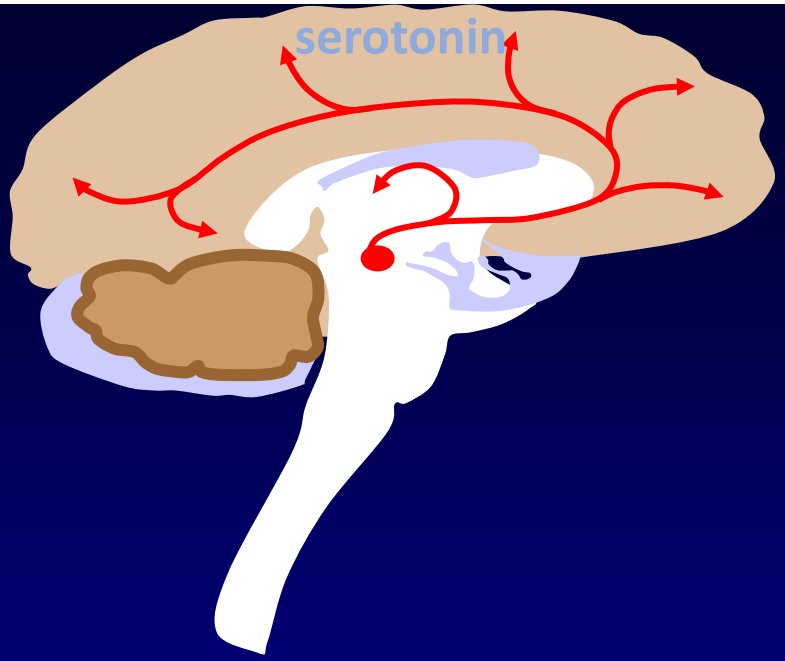
Consider

- possible mechanisms underlying the aggravation of substance misuse by antidepressants
- challenges in examining this problem, and
- obstacles in bringing it to the attention of prescribers and regulators

# Background: psychopharmacology's fertile midcentury

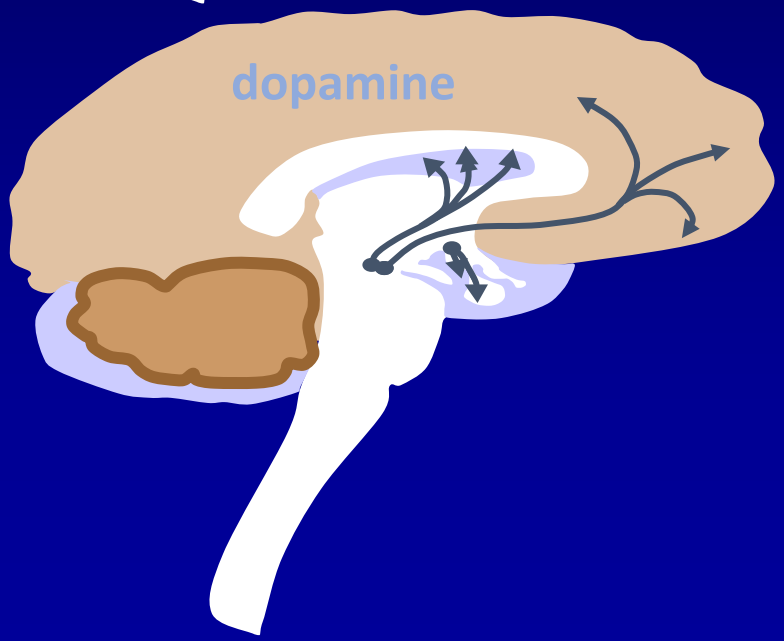
| Drugs | Measurement/Diagnosis | Scientific Advances |
|---|---|---|
| lithium (1948)<br>chlorpromazine (1952)<br>imipramine (1957)<br>phenelzine (1957)<br>meprobamate (1955)<br>chlordiazepoxide (1959)<br>carbamazepine (1962)<br>valproic acid (1962)<br>clozapine (1970) | Rating scales:<br>- HAM-D (1960); BPRS (1962)<br><br>US-UK Diagnostic Project (1972)<br><br>Operationalized diagnosis: RDC (1978); DSM-III (1980) | Julius Axelrod: neurotransmission (1950s)<br><br>MRC Depression Trial (1965)<br><br>Receptor radioligand characterization (1970s)<br><br>Imaging (PET 1983, MRI) |

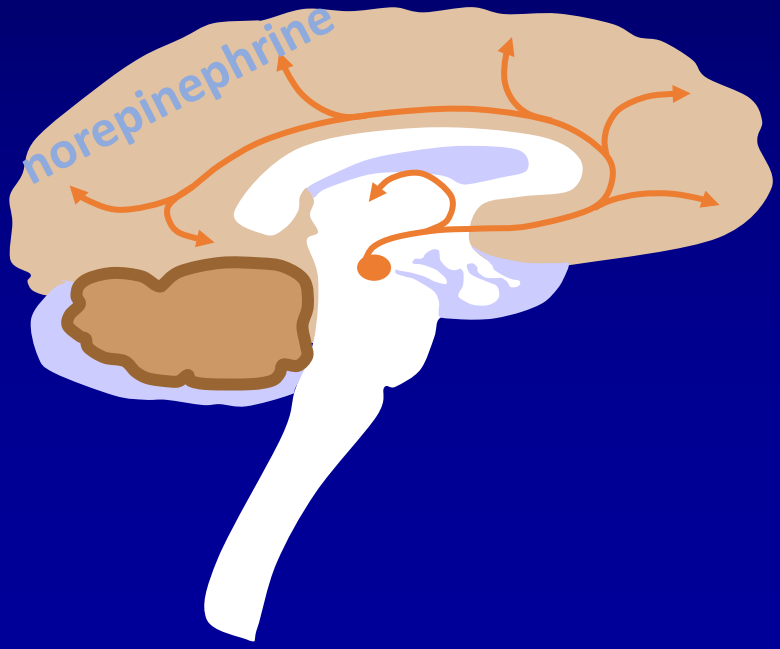
# monoamine pathways




**Common features**:

- originate from cell clusters in brainstem
- intense  dendritic arborization
- radiate to diverse cortical areas
- axons have terminal varicosities
- modulation of other transmitters



# Use of biomedical models

- Great fun, sometimes useful, but fraught with peril
- A source of endless debate and posturing across disciplines
- A major marketing tool, based in some cases on ‘biomythologies’

Moncrieff J, et al. The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular Psychiatry 2022 www.nature.com/articles/s41380-022-01661-0

Menkes DB. Putting serotonin in its place – again. BMJ 2022 https://www.bmj.com/content/379/bmj.o2357

Jauhar S, et al. A leaky umbrella has little value: evidence clearly indicates the serotonin system is implicated in depression. Molecular Psychiatry 2023 https://www.nature.com/articles/s41380-023-02095-y

# Classification conundrum

Is it more useful to classify by pharmacology or by clinical indication?

…the results are messy either way: there is a disquieting lack of specificity between drug class and usefulness in various clinical syndromes. Example: anticonvulsants and antipsychotics in severe mood disorders

also striking are the individual differences in drug response. Example: SSRI impacts on suicidality, alcohol tolerance, etc.

# Disorders and Agents

| (X) – symptomatic use | | Antidepressants | Mood Stabilizers | Anxiolytics | Antipsychotics | Others |
|---|---|---|---|---|---|---|
| Mood | depression | SSRIs, SNRIs, TCAs, MAOIs, ECT | lithium<br>valproate<br>others | | (X) | psychedelics<br>ketamine |
| | anxiety | SSRIs, SNRIs, TCAs, MAOIs | | benzos<br>buspirone | various, esp. quetiapine | clonidine<br>antihistamines |
| | bipolar disorder | SSRIs, SNRIs, TCAs, MAOIs, ECT | lithium<br>lamotrigine<br>valproate | (X) | various | |
| Schizophrenia and other psychoses | | (ECT) | (X) | (X) | various | |
| Sleep disorders | | (X) | | benzos, anti-histamines | (?X) | |
| Dependence syndromes | | nortriptyline<br>buproprion<br>varenicline (smoking) | | (X, alcohol withdrawal) | | buprenorphine<br>naltrexone<br>disulfiram<br>psychedelics |
| Dementias | | (X) | | | (X) | ChEIs |
| Personality disorders | | (X) | (X) | (?X) | (X) | |

# Antidepressants?

The term ‘antidepressant’ reflects an historical accident

consider the demonstrated efficacy of this drug class in…

- anxiety disorders*
- insomnia
- IBS
- neuropathic pain
- OCD
- Parkinsonism (including EPSE)
- PTSD
- premature ejaculation
- PMS

* Note benefit/harm better with ADs than ‘anxiolytics’

# Antidepressants

- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
  - reversible MAOI: moclobemide
- Selective serotonin reuptake inhibitors (SSRIs)
- Noradrenaline reuptake inhibitors
- Mixed and atypical agents
  - venlafaxine, duloxetine (SNRIs)
  - mianserin, mirtazapine (tetracyclics)
  - bupropion
  - trazodone

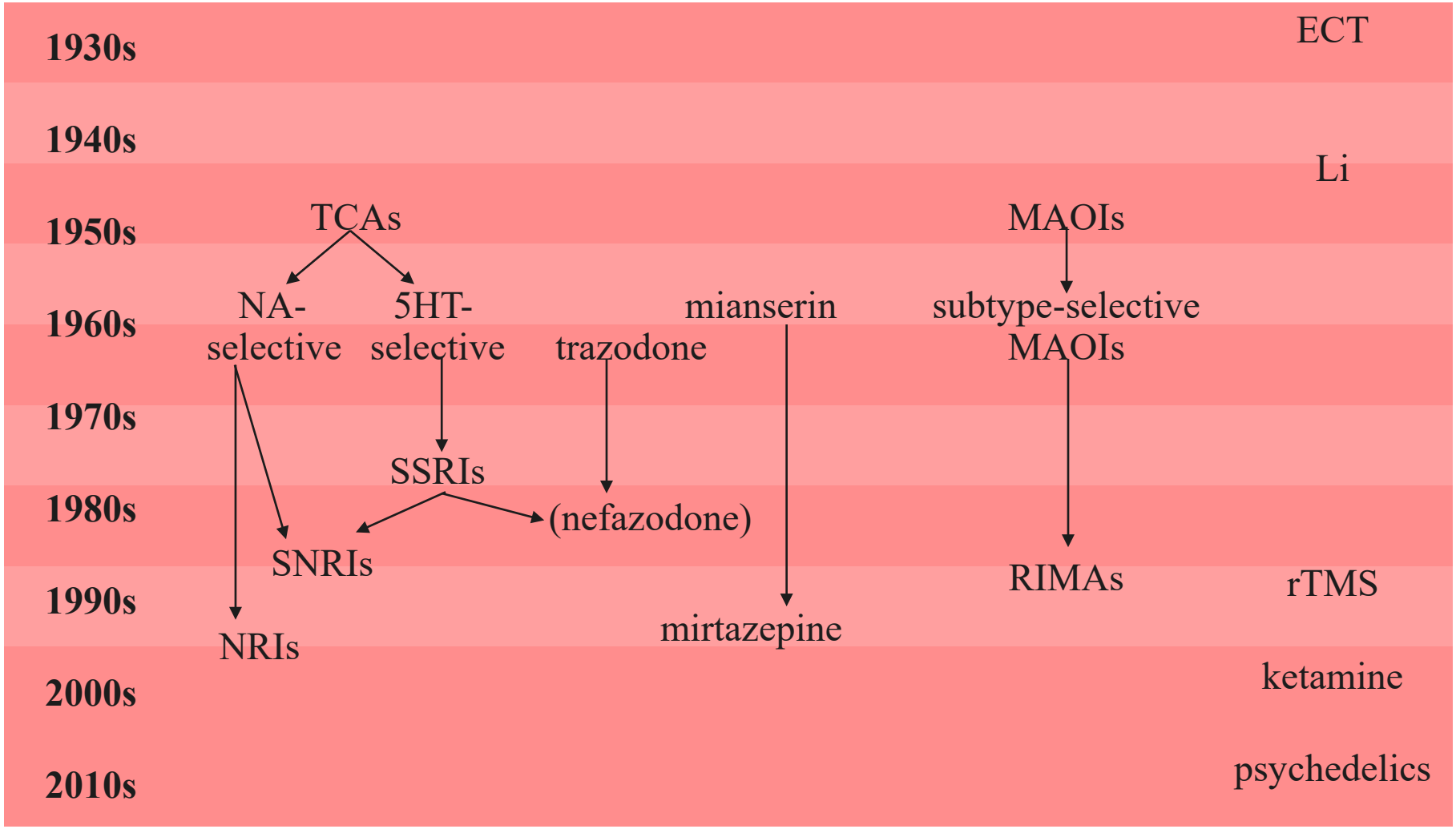
# Antidepressants are notable for…

- various acute pharmacologies
  - longer term pharmacology/adaptation is likely to be indirect, probably common to all drugs (+ ECT)
  - main initial differentiation based on tolerability, safety; daily dosing
  - generally flat dose/response profile

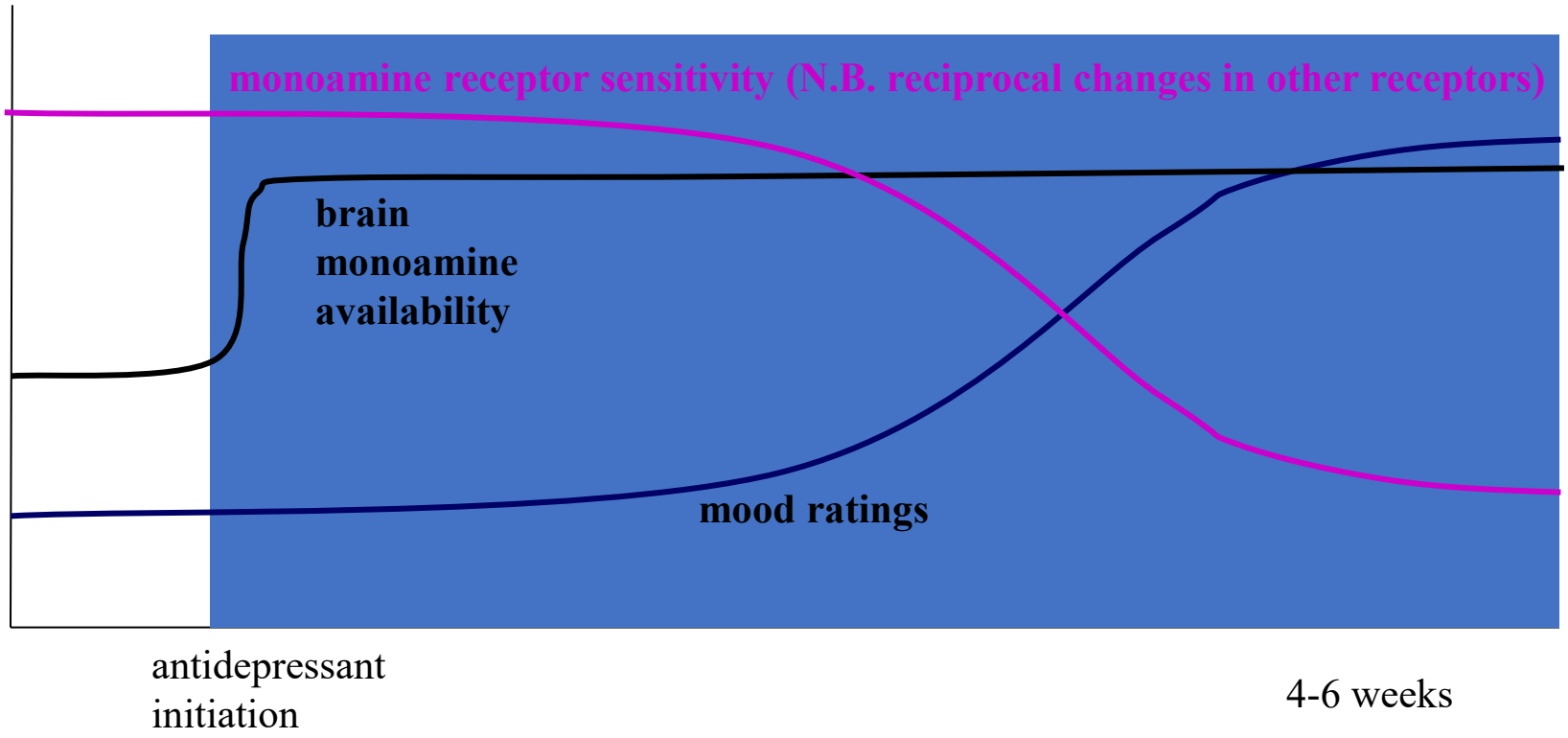
- delayed onset of action
  - more immediate effects may be seen for indications other than depression

- effectiveness in roughly 2/3 patients
  - substantial inter-individual variation in response, tolerability
  - placebo effect generally ≥ drug effect, except in severe depression

# Evolution of antidepressant treatments



# Time course of changes in AD-induced transmitter availability, receptor sensitivity and mood ratings




Theories – biogenic amine depletion (deficit predisposes to depression) – 1960s

↳ altered receptor sensitivity hypothesis (1980s)

↳ indirect action models

# Incidence

- Unipolar 15-20% lifetime prevalence, female/male (F/M) ratio approximately 2
- Bipolar 1-2% lifetime prevalence, F/M = 1

Up to half of depressed patients are unrecognised in primary care.

Depression is a major risk factor for both suicide and substance abuse.

**The rub: substance abuse is also a risk factor for depression**

# Risk Factors

- A past history, or family history, of depression
- Disturbed family relations in childhood
- Bereavement, separation or divorce
- Other psychosocial stress
- Early dementia
- Serious physical illness
- **Substance abuse**
- Some medications

# Antidepressant volumes are substantial and increasing

| Number of prescriptions dispensed in Canada, 2019 - 2021 | | | |
|---|---|---|---|
| | 2019 | 2020 | 2021 |
| **Antidepressants** | 57,887,625 | 61,613,142 ▲ **6.4%** | 63,984,188 ▲ **3.8%** |
| **Anxiolytics** | 25,880,432 | 25,631,644 ▼ **1%** | 25,045,074 ▼ **2.3%** |
| **Antipsychotics** | 21,804,343 | 22,388,752 ▲ **2.7%** | 23,525,041 ▲ **5.1%** |
| **Psychostimulants** | 8,352,896 | 8,854,976 ▲ **6%** | 9,952,262 ▲ **12.4%** |

Antidepressants were the largest drug category by prescription volume in Canada in 2021.
https://www.iqvia.com/-/media/iqvia/pdfs/canada/white-paper/medication-treatments-for-mental-health-disorders-in-canada.pdf

# prescription indications and outcome

- Prescribers vary!
- Guidelines are controversial/honoured in the breach
  - GP guidance* follows CANMAT 2016**
  - SSRIs predominate, followed by SNRI
  - no tricyclics or MAOIs considered first line
  - list of adverse effects ignores activation syndrome, apathy, disinhibition
  - sertraline + naltrexone recommended for alcohol abstinence
- Better data needed to estimate…
  - proportion of prescriptions that follow guidelines
  - rates of overdiagnosis and overtreatment
  - desired and adverse outcomes in practice

* Canadian Family Physician 2022;68:807-81

**Canadian Journal of Psychiatry 2016;61:540-560

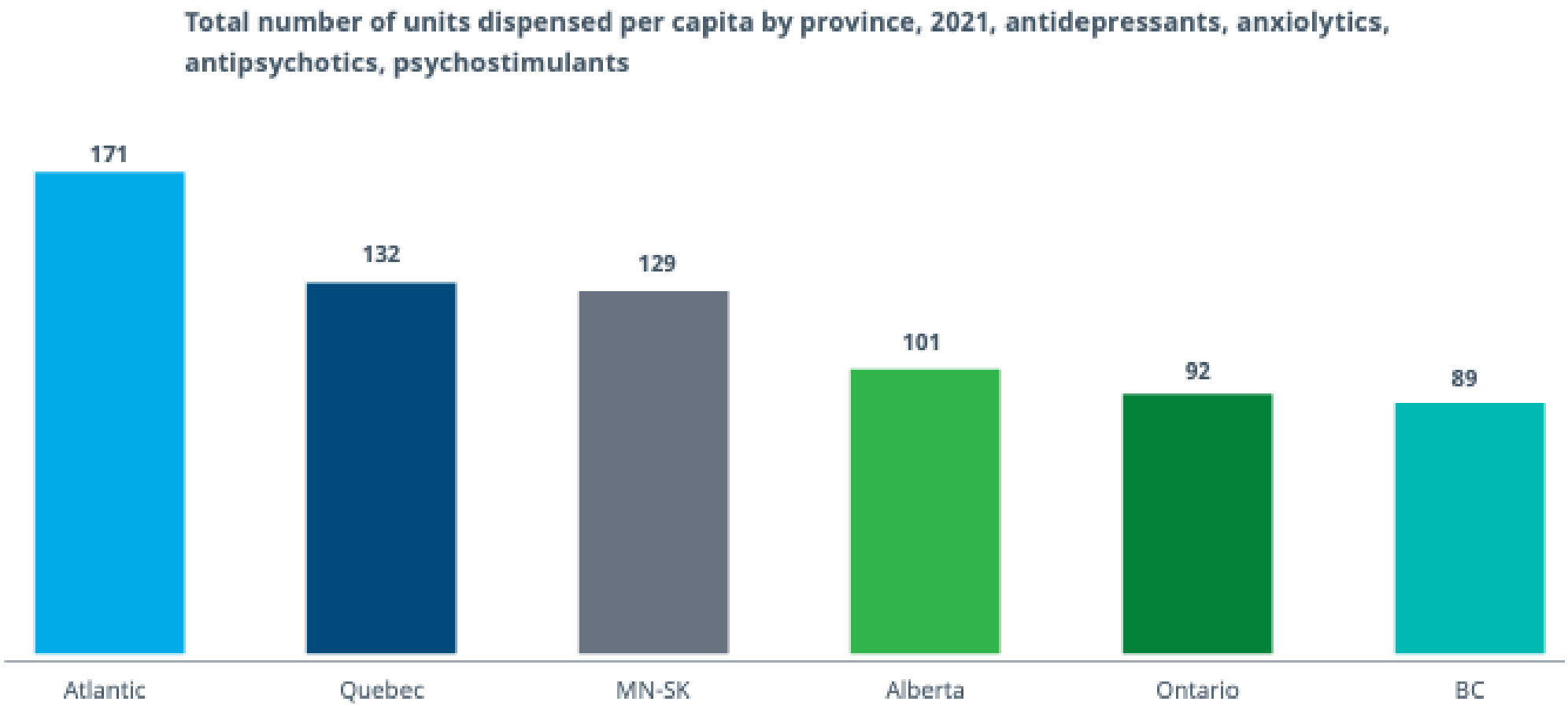
# Dartmouth overdiagnosis swim team 2013

# DSM-5 Major Depressive Disorder

- 5/9 symptoms for ≥2 weeks
- Must have either (a) depressed mood, or (b) loss of interest

- A considerable loss or gain of weight.
- Insomnia or hypersomnia
- Behaviour that is agitated or slowed down.
- Feeling fatigued/diminished energy.
- Thoughts of worthlessness or extreme guilt
- Impaired ability to think, concentrate, or make decisions
- Frequent thoughts of death or suicide (with or without a specific plan), or attempt of suicide.

# regional variation in prescription of psychotropics




https://www.iqvia.com/-/media/iqvia/pdfs/canada/white-paper/medication-treatments-for-mental-health-disorders-in-canada.pdf

paws for questions

# The dark side of antidepressants

exaggerated efficacy due to publication bias

(Turner E, et al. 2008)

drug-placebo differences significant only at severe end of spectrum

(Kirsch I, et al. 2008)

interpretation: vast, largely unnecessary investment in drug Tx; medicalisation of common symptoms

The NEW ENGLAND JOURNAL of MEDICINE

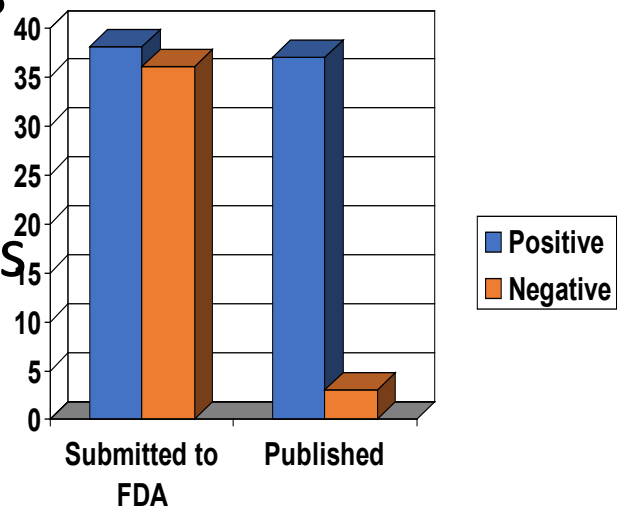
Volume 358:252-260 17 January 2008 Number 3

# Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

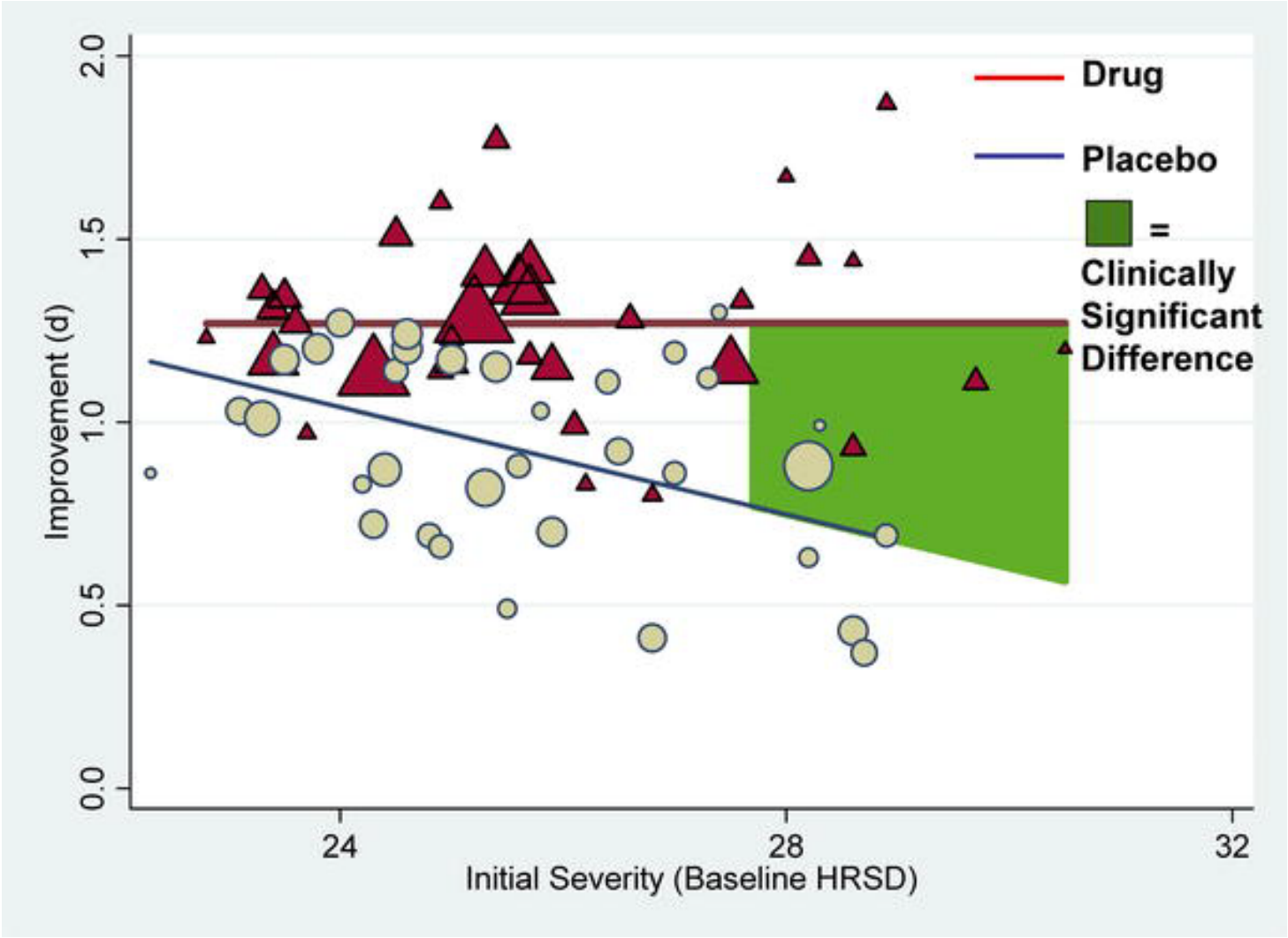
*Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.*

# All FDA trials for 12 antidepressants

- 38 trials positive results
  - 37 were published
- 36 trials negative results
  - 3 published




Turner, E., et al (2008). *Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy*. N Engl J Med; 358:252-260.




Kirsch I, et al. PLoS Medicine 2008; 5(2):e45

# drugs work mainly for severe cases?

Fournier JC. JAMA 2010;303:47-53

placebo effects predominate in mild and moderate cases

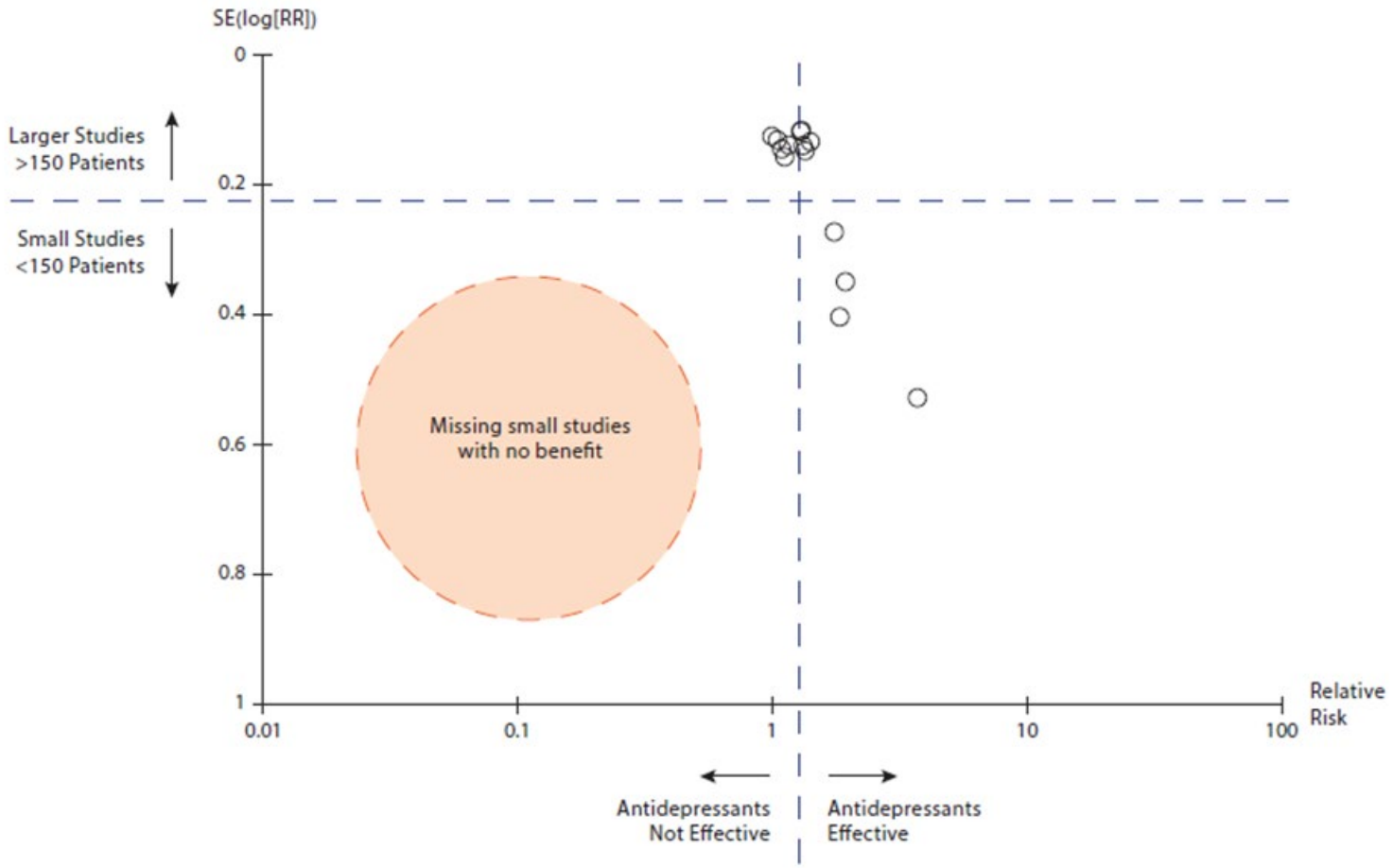
| Depression intensity | Active drug effect | Placebo effect |
|---|---|---|
| Mild moderate | 6% | 47% |
| Severe | 9% | 47% |
| Very severe | 25% | 30% |

On the other hand, there is evidence of efficacy in primary care (NNT 6-8)

Arroll B, et al. J Prim Health Care 2016;8:325-34

# evidence of publication bias

## (most studies industry funded)




Arroll B, et al.
J Prim Health Care
2016;8:325-34

# Dark side of ADs, continued

- Adverse reactions have been glossed over and wilfully misinterpreted by the pharmaceutical industry.

Examples:

- **withdrawal symptoms**, especially after paroxetine or venlafaxine, are experienced by many and may be severe in 5-10%
- apathy is common, under-recognized, may be severe
- pathological alcohol intoxication, including marked disinhibition and amnesia, occurs in a sub-group
- induction of suicidality, notably by SSRIs, is now established, subject to 'black box' warnings
- induction of violence against others also seems likely in a small, vulnerable sub-group. Healy D (2006) PLoS Medicine 3(9): e372

**Table 1**. Hostility Events in Adult and Paediatric Placebo-Controlled Trials, during Therapy and in Withdrawal Phase

| Condition | Paroxetine Events/Patients | Placebo Events/Patients | Odds Ratio (95% CI) |
|---|---|---|---|
| Overall | 60/9219 (0.65%) | 20/6,455 (0.31%) | 2.10 (1.27–3.48) |
| Depression | 20/3,799 (0.53%) | 8/2,402 (0.33%) | 1.58 (0.70–3.58) |
| OCD | 19/737 (2.58%) | 5/470 (1.06%) | 2.43 (0.91–6.45) |
| Anxiety | 16/3,823 (0.42%) | 7/3,404 (0.21%) | 2.03 (0.84–4.84) |
| PMDD | 5/760 (0.66%) | 0/379 | |

Healy D, Herxheimer A, Menkes DB. PLoS Medicine 2006; 3(9): e372

# general harms of ADs include

- inappropriate medicalisation
- placebo effect 8 to 3 times greater than drug
- patients credit drug not themselves
- risk of adverse effects, interactions
- risk of overdose
- increase suicidality, esp. in <25 years
- difficult to stop - withdrawal Sx common

  – Warner C et al. Am Fam Phys 2006;74:449

# Antidepressant toxicities

| | |
|---|---|
| TCA | anticholinergic |
| | adrenolytic |
| | sedative |
| | cardiotoxic |
| | sexual |
| SSRI | activation syndrome |
| | apathy |
| | gastrointestinal |
| | headache |
| | sexual |
| MAOI | activation |
| | cardiovascular |
| | gastrointestinal |
| | sexual |

# alcohol/antidepressant interaction

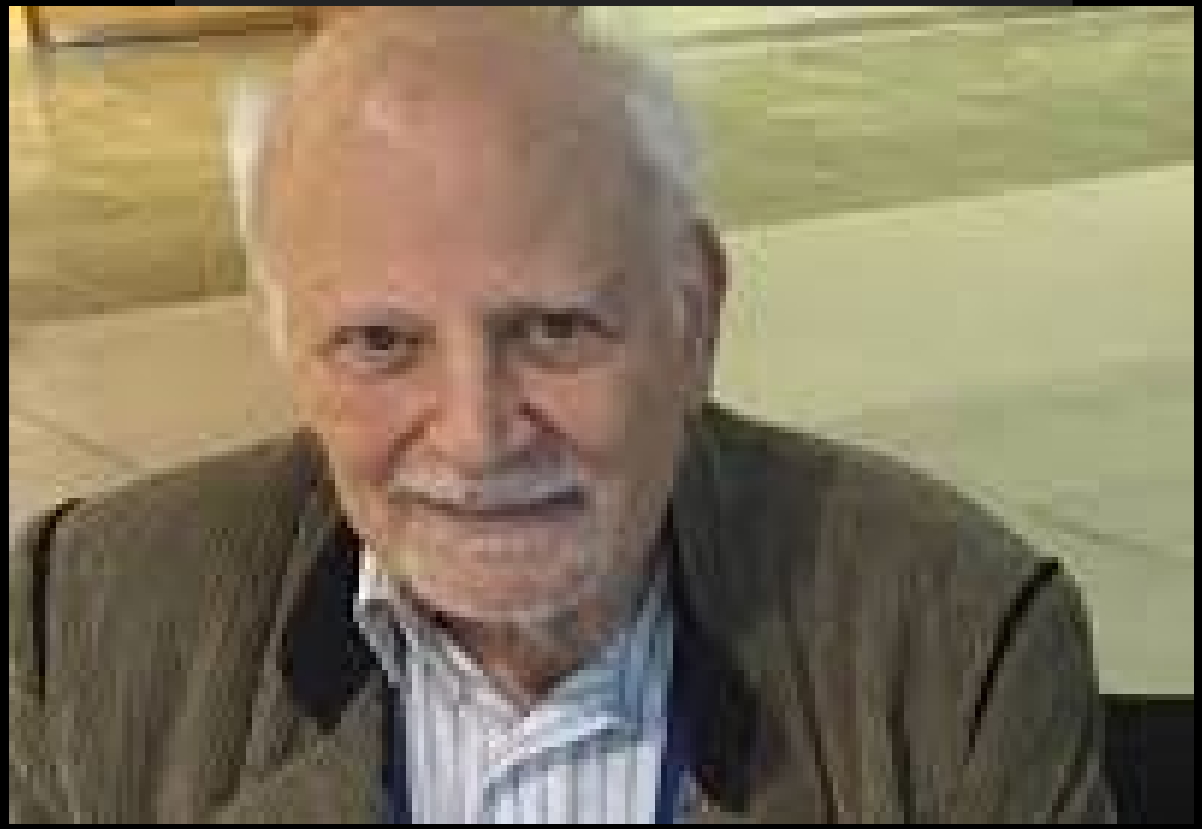
- both commonly used in many countries

- clinical trial evidence that antidepressant treatment may worsen drinking outcomes in alcohol use disorder, especially Type 2
  - Journal of Psychopharmacology 2004;18:293-335
  - Drug and Alcohol Dependence 2004;74:61-70

- having been struck by patients in whom SSRI treatment dramatically affected responses to usual amounts of alcohol, Andrew Herxheimer and I started to collect a case series

- detailed literature searches prior to 2014 failed to identify reports of such effects

Andrew Herxheimer,
1925-2016



# case collection

- significant psychological or behavioural disturbance associated with alcohol consumption during antidepressant treatment
  - our and a colleague's clinical practice in the UK (n=40)
  - pharmacovigilance reports from FDA and MHRA (n=40)
  - screened case histories from The Antidepressant Web (n=121/5000)
  - a detailed case description "Extroverted like me" in Slate https://slate.com/human-interest/2018/01/how-a-month-and-a-half-on-paxil-taught-me-to-love-being-shy.html

- standard WHO causality assessment criteria applied to 201 cases
- several cases excluded for likely bias (forensic, political, personal)

# interaction categories

'caseness' required probable or definite causality of either

- exaggerated intoxication (left shift in dose-response curve), or
- pathological intoxication (uncharacteristic disinhibition or violence)

additional features included

- increased use of alcohol
- changed pattern of alcohol use
- memory impairment
- increased hangover

# outcomes were often extreme

- homicide: 8 cases, including two double and one triple (n=12 deaths)
- attempted murder
- attempted and completed suicide
- many cases of
  - serious assault
  - unintended intercourse
  - other damaging or painfully embarrassing social behaviour
- memory impairment lacking, often completely, in half of cases (n=53)
- comparable patterns observed in our 3 main sources of case reports

Table 1

Typology of cases with sufficient detail to be analyzed

| Drug & approximate year of UK introduction | Reports | Cases | Memory loss | Increased alcohol use | Serious violence | Males |
|---|---|---|---|---|---|---|
| Bupropion (1999) | 1 | 1 | 1 | 0 | 1 | 1 |
| Citalopram (1997) | 16 | 4 | 2 | 0 | 0 | 0 |
| Desvenlafaxine* | 1 | 1 | 1 | 0 | 0 | 0 |
| Escitalopram (2002) | 4 | 0 | 0 | 0 | 0 | 0 |
| Fluoxetine (1984) | 54 | 28 | 17 | 8 | 16 | 10 |
| Fluvoxamine (1980) | 1 | 1 | 0 | 0 | 1 | 1 |
| Paroxetine (1990) | 97 | 51 | 23 | 19 | 26 | 22 |
| Sertraline (1990) | 5 | 4 | 3 | 3 | 4 | 2 |
| Venlafaxine (1991) | 22 | 10 | 6 | 2 | 8 | 6 |
| All | 201 | 100 | 53 | 32 | 56 | 42 |

Cases are reports with probable or definite pathological intoxication, as described in Method. The last four columns indicate frequencies among defined cases for each drug. Serious violence includes homicide, attempted murder, suicide, significant self-harm, and assault leading to hospitalization of the victim or a criminal charge. * not registered in the UK.

International Journal of Risk & Safety in Medicine 2014;26:163-170

# cases from The Antidepressant Web

| | | | |
|---|---|---|---|
| F | 35 | paroxetine | Uncharacteristic verbal and physical aggression after 2–3 drinks, remitted when discontinued and recurred when resumed paroxetine challenge-dechallenge-rechallenge. Seriously injured, lost teeth during one episode; relationships jeopardized; lost boyfriend |
| F | ? | fluoxetine | No problem until started drinking; craved alcohol "all the time" and became disinhibited with impaired judgment, regretted loss of virginity. Experienced blackouts, told of further "stupidity" by friends; very embarrassed. Clear history of remission of pathological alcohol effect and recurrence when stopped and later re-started drug challenge-dechallenge-rechallenge |
| F | ? | paroxetine | Treatment effective for mood and bulimia symptoms, but noted exaggerated effect, "passing out" on previously well tolerated amounts of alcohol. Increased dose (20 mg/d) resulted in craving, blackouts, and "crazy" behaviour. Arrested twice. Clear history of dose dependence, and of challenge-dechallenge-rechallenge when stopped and resumed paroxetine |

# cases from our own practice

| | | | |
|---|---|---|---|
| F | 35 | fluoxetine | Woman treated for anxiety and depression with fluoxetine; she found a recurrent, extremely distressing pattern of uncharacteristic disinhibition with usual modest amounts of alcohol, including multiple episodes of unintended sexual intercourse. The problem completely ceased when she stopped fluoxetine |
| M | 40 | fluoxetine | Upset at relationship loss, this sleep-deprived man took an initial 40–60 mg dose of fluoxetine and over 5 hours drank 200–300 mL of whisky before driving across town and shooting his ex-partner and two others to death. He had no prior history of violence and now faces life imprisonment |
| M | 28 | paroxetine | Treated for depression, this man noted emotional detachment more than a lift in mood. Previously a weekend drinker, on paroxetine he developed a craving for alcohol, and began drinking 4–5 cans of beer daily, which made him irritable and sullen. He fatally stabbed a neighbour with a pocketknife during a public altercation; has scant memory of the event |

# cases from FDA pharmacovigilance

| | | |
|---|---|---|
| ? | fluoxetine | Report of woman taking fluoxetine who consumed 3 drinks and shot and paralyzed her boyfriend before attempting suicide. She had no prior history of violence, and was convicted of attempted murder |
| 24 | paroxetine | Woman treated with paroxetine got uncharacteristically and repeatedly drunk, arrested for speeding, running red lights and killing another driver; convicted of manslaughter. On another occasion hit a policeman |
| 16 | paroxetine | Never before aggressive or violent, this boy was prescribed paroxetine, but didn't like it because he felt "jittery and weird". Parents noted he became increasingly aggressive. After 3 weeks of treatment, he robbed his step-grandmother and stabbed her 61 times after drinking alcohol; convicted of homicide |

# conclusions

- we identified a syndrome of pathological alcohol intoxication during treatment with SSRI and related drugs
- prominent memory impairment occurred in just over half of cases
- in contrast to evaluation of efficacy, for which RCTs are essential, the evidential hierarchy is reversed for evaluating harms

(Vandenbroucke JP. PLoS Medicine 2008;5:e67)

# limitations

- opportunistic collection of cases
- many cross-sectional or with incomplete detail
- biased reporting could not be completely excluded
- frequency estimates will require prospective studies with careful collection of alcohol use data before, during, and after treatment

# other literature

- a Welsh/Canadian team described cases of alcohol dependence after SSRIs
  - 35 spontaneous reports to RxISK.org, together with
  - 80 responses to a blog post posted on RxISK.org and DavidHealy.org
  - yielded 93 episodes of alcohol dependence reported by 79 individuals
  - evidence of serious consequences (relationship or job loss, death)
  - evidence of return to baseline after SSRI stopped (dechallenge)

  (International Journal of Risk & Safety in Medicine 2014;26:99-107)

- warnings to avoid alcohol with ADs are inconsistent, non-specific, and ignored

  (Pharmaceutical Journal 2011;287:732-733)

- antidepressant treatment in alcohol use disorder remains controversial

  (Australian & NZ Journal of Psychiatry 2016;50:199-200)

# it's not just alcohol…

- RCT of venlafaxine for depression with cannabis use disorder (n=103)
  - mood improvement comparable with venlafaxine and placebo
  - abstinence rates markedly worse with venlafaxine (11.8%) v placebo (36.5%)
  - mood improvement related to cannabis reduction in placebo group only

  (Addiction 2013;108:1084-94)

- RCT of sertraline for depression in methamphetamine dependence
  - 12 weeks of treatment completed for sertraline (n=61) v placebo (n=68)
  - more sertraline (n=13) than placebo subjects (n=5) *increased* meth use (p=.03)
  - meth use predicted by increased craving during treatment

  (Drug and Alcohol Dependence 2011;118:500-503)

- inconsistent effects of antidepressant treatment in opiate dependence

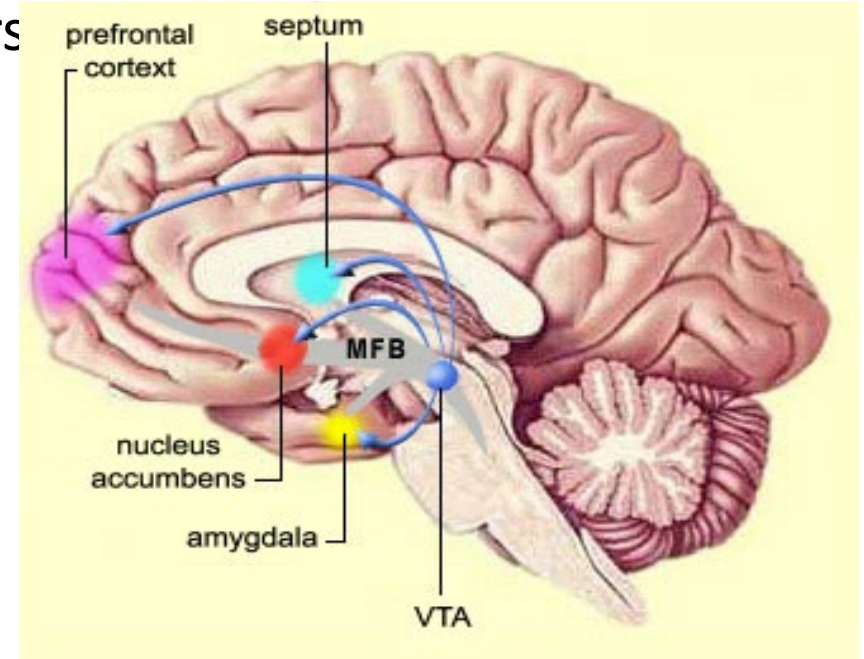
  (Biological Psychiatry 2004;56:793-802)

# Drug/alcohol dependence

- Dependence-inducing drugs have many different pharmacologies, e.g.,
  - alcohol, BZDs, zopiclone - $GABA_A$
  - opioids – μ-opioid receptors
  - nicotine – $\alpha_4\beta_2$-nicotinic receptors
  - amphetamines, methylphenidate – DA release
  - cocaine – DA uptake blockade
  - THC, synthetics – $CB_1$ receptors
  - et cetera…

…but all increase DA release

in the nucleus accumbens



# Treatment of drug/alcohol dependence

| Substitution treatment: | Anti-craving medication: | Antagonist/aversive medication | Insight-oriented treatment |
| --- | --- | --- | --- |
| •methadone, buprenorphine for opioid dependence<br>•NRT, varenicline for smoking | •naltrexone/acamprosate for alcohol dependence<br>•buproprion, nortriptyline for smoking | •naltrexone for opioid dependence<br>•disulfiram for alcohol dependence | •psychotherapy ± psychedelics |

# unanswered questions

- given that antidepressant treatment can
  - worsen substance use disorder outcomes (alcohol, cannabis, stimulants)
  - produce episodes of pathological intoxication in ‘normal’ drinkers
  - produce new-onset alcohol use disorders

- how common are these problems?
- how specific to serotonergic antidepressants?

- how can at-risk individuals or groups be identified?

- how to bring this issue to the attention of prescribers and regulators?

# the way forward

- confront the obstacles
  - regarding alcohol as a drug
  - recording alcohol use/effects before, during, and after prescription drug trials
- constructively engage with pharmacovigilance agencies
  - Uppsala Monitoring Centre
  - National centres: FDA, MHRA, TGA, Health Canada, Medsafe
- explore genetic testing of cohorts
  - serotonin polymorphisms, etc.
- link to animal research
  (Alen F, et al. International J Neuropsychopharmacology 2013;16:1809-1818)

# comments, suggestions, ideas

please get in touch

david.menkes@auckland.ac.nz