

**The Myth of the Chemical Cure:
explaining the real nature of psychiatric
drugs and the consequences of their
use**

Joanna Moncrieff,
Oslo, 13th Nov 2018

Aims of talk:

- Look at assumptions that underpin the current view of drug treatment for mental health problems
- Present alternative way of understanding and using prescribed drugs for mental distress

The Myth of the Chemical Cure
A Critique of Psychiatric Drug Treatment
Joanna Moncrieff

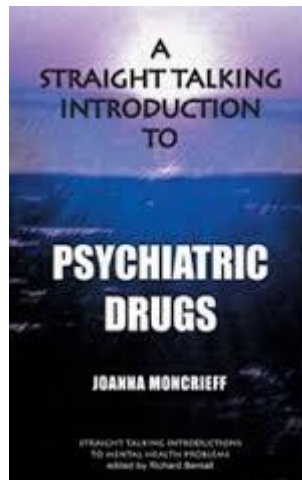


**A
STRAIGHT TALKING
INTRODUCTION
TO**

**PSYCHIATRIC
DRUGS**

JOANNA MONCRIEFF

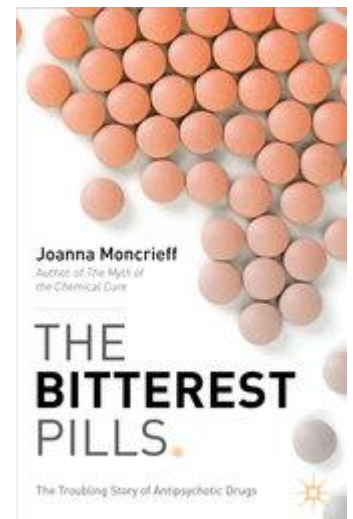
STRAIGHT TALKING INTRODUCTIONS
TO MENTAL HEALTH PROBLEMS
edited by Richard Bentall



Joanna Moncrieff
*Author of The Myth of
the Chemical Cure*

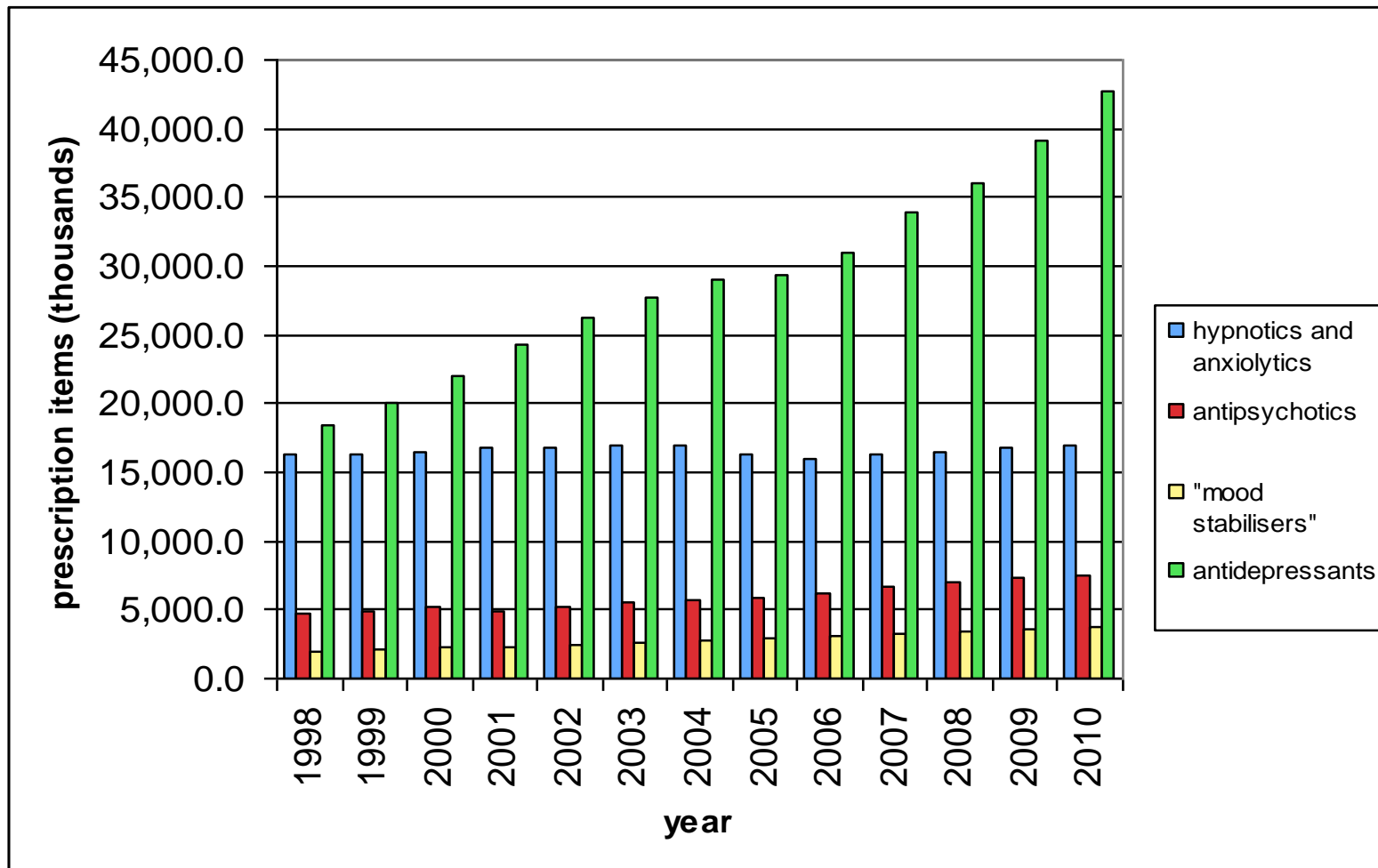
**THE
BITTEREST
PILLS**

The Troubling Story of Antipsychotic Drugs



There has been an increase in the use of prescription drugs for mental disorders:

Trends in prescriptions in England 1998-2010



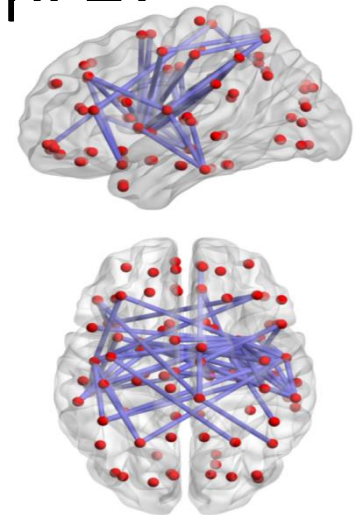
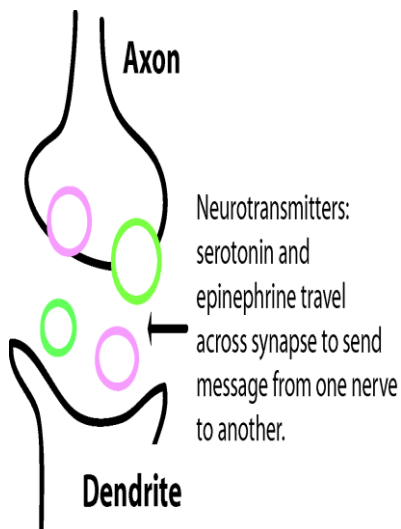
This increase is associated with a strong message that drugs work by correcting a chemical imbalance



- “Paxil CR helps balance your brain’s chemistry”
PaxilCR.com, 2009

Mechanism of drug action in psychiatry:

- Current view is that drugs target and correct an underlying biological abnormality
- Abnormality is proposed to be of neurotransmitters (chemical imbalance) circuitry or unspecified



- There is no evidence that any class of psychiatric drug works by targeting the underlying biological mechanism of the disorder or symptoms

Why?

- We don't know the mechanisms underling any disorder or even any 'symptoms'
- Placebo controlled trials do not confirm that drugs act in this way- differences from placebo can be accounted for in other ways
- Other evidence that drugs might have mechanism targeting effects is lacking
- There are other ways of explaining drug action

Models of drug action

Disease centred model	Drug centred model
Drugs correct an abnormal brain state	Drugs <i>create</i> an abnormal brain state
Drugs target specific diseases or abnormalities	Psychiatric drugs as <i>psychoactive drugs</i>
Therapeutic effects of drugs arise from their effects on disease pathology <i>or</i> the biological mechanisms that produce symptoms	Useful effects are a consequence of drug-induced changes to normal brain functioning
Example (general medicine): asthma treatments, insulin for diabetes, aspirin, paracetamol	Examples: alcohol for social anxiety, opiate anaesthetics

Psychoactive drugs

- Altered *mental* states: changes in cognition, emotion and behaviour
- Linked *physical* alterations (eg drug-induced sedation has mental and physical components)
- Can produce euphoria **or** dysphoria to different degrees
-



People have used psychoactive substances to alleviate misery for millenia



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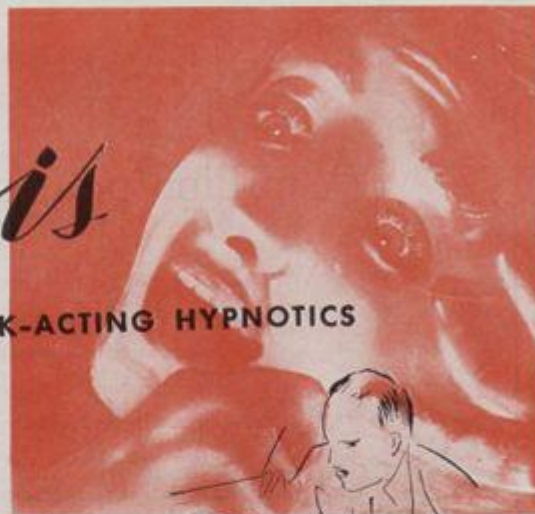
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In crises where immediate composure is imperative, Pentobarbital* and Phenobarbital*, Lakeside, have been found to be quick-acting hypnotics. And, they have the advantage of being *stable solutions, ready for instant use* . . . no measuring or mixing required.

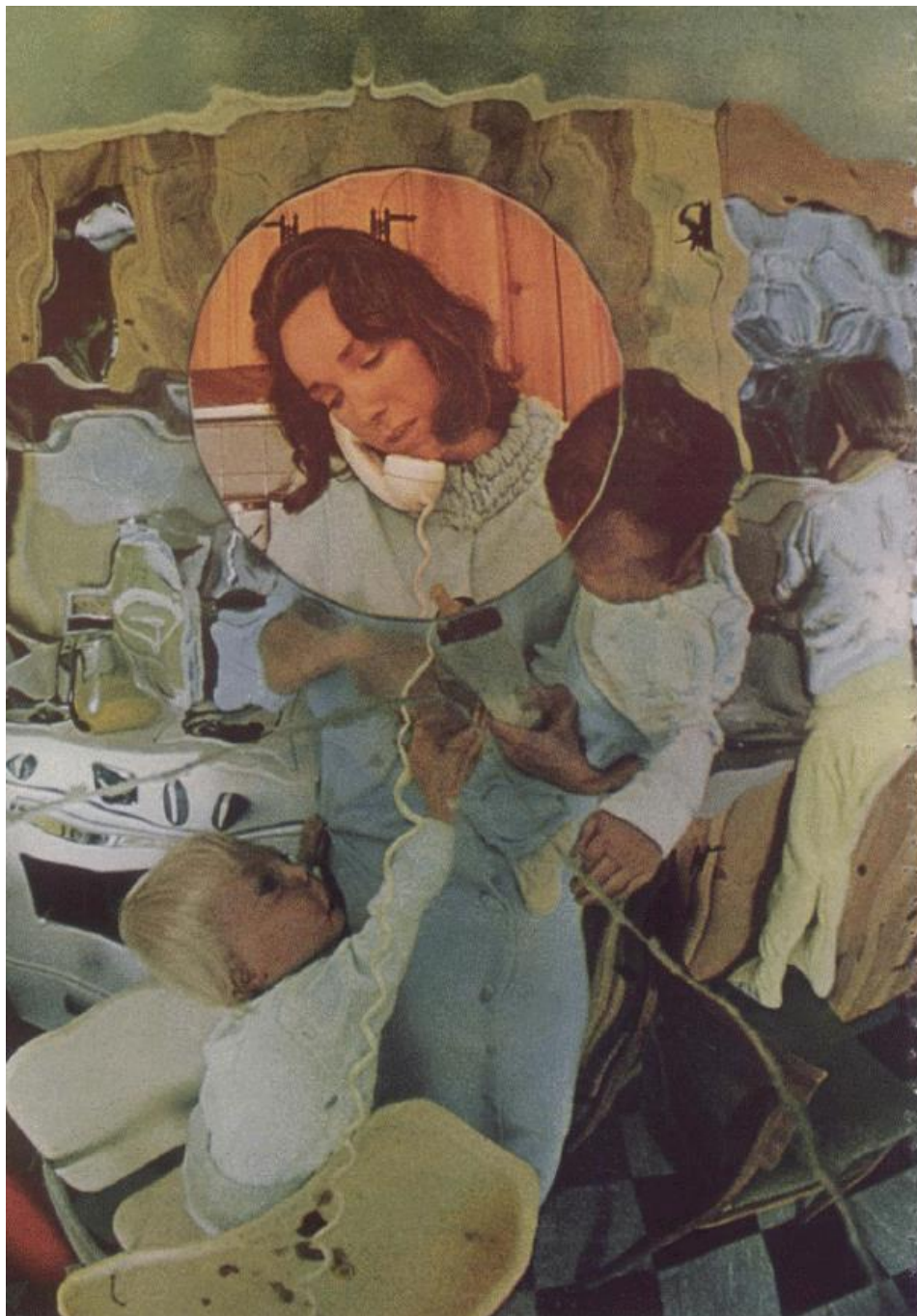
Propylene Glycol, the solvent used in these solutions, is completely miscible in water and diffuses rapidly in muscular tissue with the result that the medication acts essentially as though it were in aqueous solution. Yet these solutions remain stable, do not hydrolyze and decompose. Benzyl alcohol is added as a local anesthetic, Lakeside Laboratories, Milwaukee, Wisconsin.

***Pentobarbital**
Sodium and Benzyl Alcohol



***Phenobarbital**
Sodium and Benzyl Alcohol

LAKESIDE



Syndromes of the Sixties

The battered parent syndrome

She's the paradox of our age. Compared to her mother, she has more education, more usable income and more labor-saving devices. Yet she is physically and emotionally overworked, overwrought and—by the time you see her—probably overwhelmed.

What went wrong? Is parenthood something other than the rosy fulfillment pictured by the women's magazines? Is anxiety and tension fast becoming the occupational disease of the homemaker?

Some say it's unrealistic to educate a woman and then expect her to be content with the Cub Scouts as an intellectual outlet.

Or to grant that she is socially, politically and culturally equal, while continuing to demand domestic and biological subservience.

Or to expect her to shoulder the guilt burden of this child-centered age without unraveling around the emotional edges.

Or to compete with her husband's job for his time and involvement.

But whatever the cause, the consequences—anxiety, tension, insomnia, functional disorders—fill waiting rooms. Sometimes it helps to add 'Miltown' to her treatment—to help her relax both emotional *and* muscular tension. It's no substitute for a week in Bermuda, or for emotional readjustment. But it will often make the latter easier for her, as well as for the physician.

And 'Miltown' has been doing just that—for a dozen years now—with substantial success.

Indications: Effective in relief of anxiety and tension states; adjunctively when anxiety may be causative or disturbing factor. Fosters normal sleep through anti-anxiety and muscle-relaxant properties.

Contraindications: Previous allergic or idiosyncratic reactions to meprobamate. (Brief summary of prescribing information is continued on next page.)

 Wallace Pharmaceuticals/Cranbury, N.J.



MILTOWN[®] (MEPROBAMATE)
when reassurance is not enough

Ritalin[®]

Ritalin gently overcomes mild depression and the fatigue so often associated with it. This is one agent that really brightens mood and improves performance, helps restore alertness, enthusiasm, and drive. Patients often report that fatigue and worry seem to vanish; they are able to go all day without becoming tired.

Acts in minutes Unlike other antidepressants, Ritalin usually brings relief with the very first dose. Your patients need not wait days

or even weeks to begin feeling better. Ritalin also . . .

Offers outstanding safety

Unlike amphetamines, Ritalin rarely affects blood pressure or heart rate. It has not been associated with muscle tremors or urinary retention as have the potent MAO

inhibitors or tricyclic compounds. And toxic or adverse effects on blood, urine, liver or kidney function are not to be anticipated. For these reasons, Ritalin . . .

Proves especially valuable for the elderly

This time-tested agent is well tolerated, even by older patients. It rarely affects appetite or causes rebound depression.

Dosage Oral: Initially, two 10-mg. tablets in the morning, one at noon, and one more, if necessary, at 5:00 p.m. For maintenance, revise as needed.

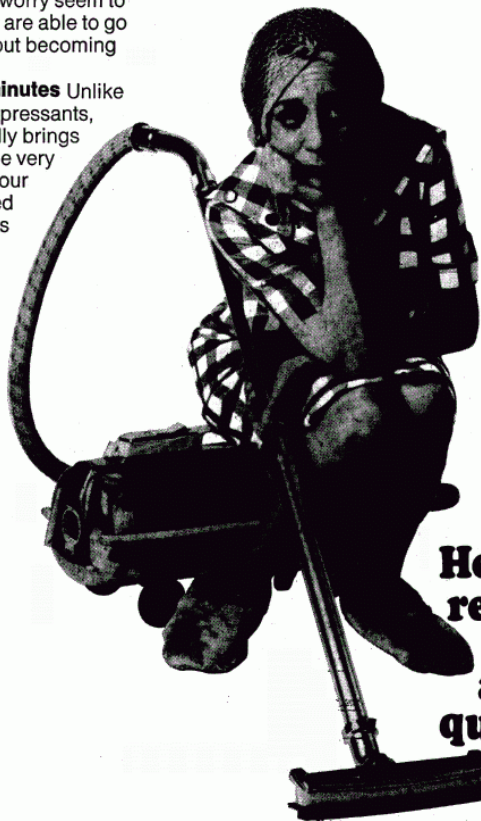
Side-effects Nervousness or insomnia, if present, can be avoided by dosage-reduction or by omitting Ritalin in the afternoon. Reports note a few cases of anorexia, dizziness, headache, palpitations, drowsiness, skin rash, overt psychotic behavior and psychic dependency.

Cautions Not recommended for severe depressions, except in hospital under close supervision. Patients with agitation may react adversely. Use cautiously in the presence of marked anxiety or tension. Ritalin may potentiate the effect of pressor agents; exercise care in use with epinephrine, levarterenol, or angiotension amide. While oral Ritalin has little or no effect on normal blood pressure, use cautiously in patients who have hypertension.

Contraindications Glaucoma, epilepsy.


Supplied

All forms contain methylphenidate hydrochloride. Tablets of 10 mg. (pale blue, scored); bottles of 100 and 500. Tablets of 20 mg. (peach, scored); bottles of 100 and 500. Ampoules of 20 mg. (lyophilized); boxes of 10 and 100.



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You can't set her free. But you can help her feel less anxious.

You know this woman.

She's anxious, tense, irritable. She's felt this way for months.

Beset by the seemingly insurmountable problems of raising a young family, and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance may have helped some, but not enough.

SERAX (oxazepam) cannot change her environment, of course. But it can help relieve anxiety, tension, agitation and irritability, thus strengthening her ability to cope with day-to-day problems. Eventually—as she regains confidence and composure—your counsel may be all the support she needs.

Indicated in anxiety, tension, agitation, irritability, and anxiety associated with depression.

May be used in a broad range of patients, generally with considerable dosage flexibility.

Contraindications: History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychoses.

Precautions: Hypotensive reactions are rare, but use with caution where complications could ensue from a fall in blood pressure, especially in the elderly. One patient exhibiting drug dependency by taking a chronic overdose developed upon cessation questionable withdrawal symptoms. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive prolonged use in susceptible patients (alcoholics, ex-addicts, etc.) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Caution patients against driving or operating machinery until absence of drowsiness or dizziness is ascertained. Warn patients of possible reduction in alcohol tolerance. Safety for use in pregnancy has not been established.

Not indicated in children under 6 years; absolute dosage for 6 to 12 year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever, euphoria and dysmetria.

Availability: Capsules of 10, 15 and 30 mg. oxazepam.

To help you relieve anxiety and tension

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(oxazepam)

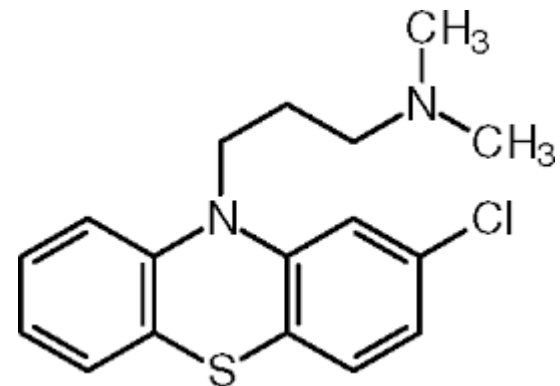


Wyeth Laboratories
Philadelphia, Pa.

Chlorpromazine was introduced into psychiatry in France in 1952

At first it was regarded as a special sort of sedative

It was referred to as a “neurological inhibitor,” then as a “neuroleptic”



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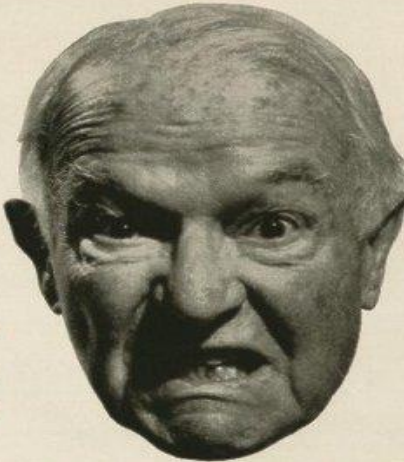


Melleril the tranquilliser pure and simple



Neuroleptics were widely advertised for agitation in the elderly and behavior problems in children up to 1970s

100



*Tyrant
in the
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'Thorazine' can control the agitated, belligerent senile
and help the patient to live a composed and useful life.

When 'Thorazine' is administered to the agitated senile, there is a marked decrease in his nerve-racking outbursts of hostility, irritability, abusiveness, incessant talking and "day-and-night" pacing or restlessness.

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Chlorpromazine, S.K.F.

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Specificity of neuroleptics

- “they appear to do more than tranquilise” (Henderson & Gillespie 1962).
- “the drugs penetrate much closer to the site of mechanism of the disease itself than any other procedure applied hitherto” (Mayer-Gross, Slater, & Roth 1960).



**in acute
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Melleril

strikes promptly at the target symptoms:
disorders of thought, affect, behaviour and perception

Melleril is a major tranquilliser with an impressive clinical record in the treatment of acute schizophrenia. Response to Melleril is rapid and predictable. Within 24 hours a tranquillising effect occurs.¹ Within 3-4 days the patient becomes calm, co-operative and sociable.² Within 7 days target symptoms begin to respond.³ An important aspect of Melleril therapy is to start with an adequate "loading" dose. Full information on Melleril, including dosage details and clinical summaries, will be supplied on request. Tablets of 25 mg., 50 mg., and 100 mg. Thioridazine Hydrochloride B.P. Also available: Syrup.

there is no anti-psychotic more effective than Melleril

¹ Canadian Medical Association Journal 84, 155, 156; ² Journal of the American Medical Society 84, 719, 1956; ³ American Journal of Psychiatry 118, 740, 1962.

Sandoz Products Limited, Sandoz House, 23 Great Castle Street, London, W1N 8AE
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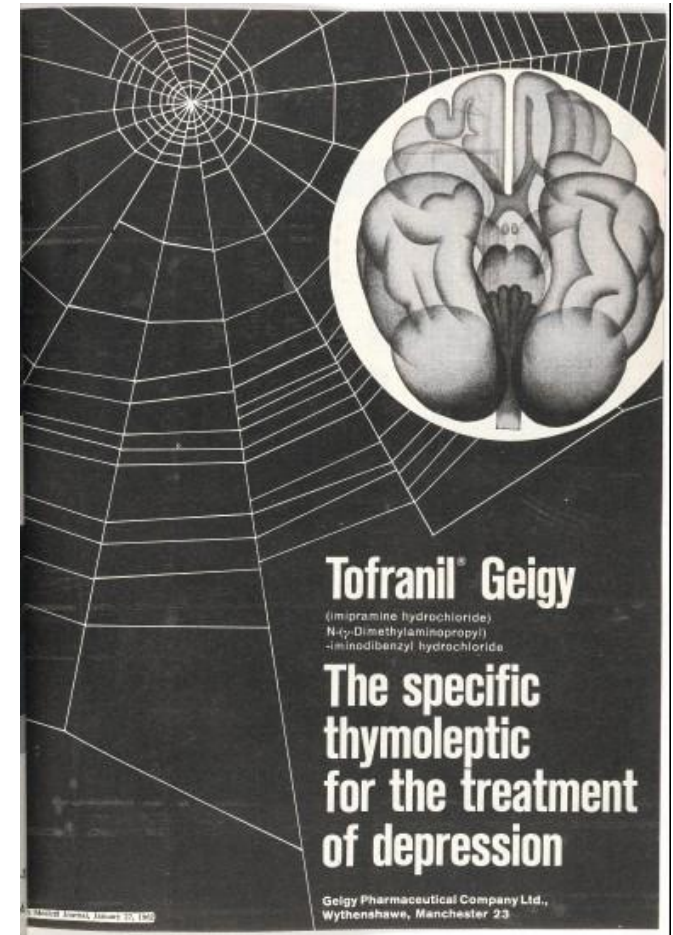


A similar process occurs with 'antidepressants'

- The first drugs commonly referred to as antidepressants were stimulant-like substances (iproniazid)
- Early papers refer to these properties, but later ones only report them as 'side effects'

Specificity of antidepressants

- antidepressants
“appear to act
specifically against
depressive symptoms”
(Dally, 1967)
- “much more specific”
than stimulants
(Psychopharmacology
conference 1962, Goldman,
(1966),



Views about how psychiatric medicines worked changed from the 1950s onwards, and the disease-centred model was adopted.

**Pre 1950s- drug
centred:**

- Sedatives
- Stimulants

**Post 1950s- disease
centred:**

- Antipsychotics
- Antidepressants
- Anxiolytics
- Mood stabilisers
- Hypnotics
- Treatment resistant psychosis

This transformation does NOT occur because of accumulating evidence for the disease-centred model

There was, and is, very little support for the disease-centred model (the idea that drugs target underlying abnormalities)

Placebo controlled trials do **not** distinguish disease-centred from drug-centred model

The drug-centred model- how do psychiatric drugs 'work'?

- Interaction of psychoactive effects and symptoms
- Placebo and 'amplified placebo' effects
- Both may produce differences from placebo in RCTs.
- But are they worthwhile?

Understanding and treating depression: is depression caused by a chemical imbalance?

- Serotonin and noradrenalin abnormalities have been proposed (monoamine theories of depression)
- Antidepressant efficacy cited as main supporting evidence (Skildkraut 1965; Mahli et al, 2005)
- Independent evidence of serotonin or noradrenalin function in depression is highly contradictory

Serotonin 1A receptor studies

- Lower levels in depressed people compared to 'normals' (Drevets et al, 1999; Sargent et al, 2000)
- Higher levels (Parsey et al, 2006; Reivich et al, 2004)
- No difference (Meyer et al, 2009; Parsey et al, 2006)
- Suicide victims: also inconsistent (Lowther et al, 1997; Matsubara et al, 1991; Stockmeier et al, 1997)

Serotonin depletion studies

- Tryptophan depletion: does not produce depression in volunteers (Murphy et al, 2002). Some studies show depression in people previously treated for depression with SSRIs (Delgado et al, 1999)
- Parachlorophenylalanine studies: reduced serotonin associated with insomnia, aggression, hypersexual behaviour, irritability, hypersensitivity to the environment, paranoia (Mendels and Frazer, 1974)

*"Groundbreaking" — By the first time
depression is not only a disorder of the mind
or the brain, it is a disorder of the whole body.
—Steven D. Dym, MD, a Psychiatrist, Harvard Medical School*

THE INFLAMED MIND

*A new way of thinking
about depression*

EDWARD BULLMORE

Depression and inflammation

- Depression is associated with deviations in some inflammatory markers
- They are also associated with social class, obesity, exercise, sleep deprivation etc
- A causal association specific to depression has not been demonstrated

So what are antidepressants and are
they helpful?

Psychoactive effects of “antidepressants”

(Herrmann, W.M. & McDonald, R.J. 1978)

Tricyclic antidepressants (e.g. amitriptyline; clomipramine; lofepramine)

- Profound sedation
- Cognitive and motor impairment
- EEG slowing
- Dysphoria
- Complex effects on numerous neurotransmitter systems
- Some have dopamine blocking activity (esp. amitriptyline and clomipramine)

Psychoactive effects of SSRIs and venlafaxine (Efexor):

- “listlessness and lethargy”
- “Total loss of libido”
- “inability to care about anything”
- “general numbness/mental blankness”
- “sleepy all the time”
- “Increased anxiety.., borderline panic, mild insomnia”
- “sometimes suicidal”
- “mood swings”
- “irritability”

(Goldsmith & Moncrieff, 2011)

Are these effects useful?

Antidepressants sweeping the UK | Daily Mail Online - Windows Internet Explorer provided by NELFT Servicedesk - 03005551294

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Antidepressants sweeping the nation: Three times as many British adults prescribed the drugs as those in troubled Greece, study finds

- One in 11 British adults now take antidepressants, research shows
- UK has the fourth-most medicalised population in Europe, experts say
- 9% of adults in the country have taken them in last year
- That's three times the 3% of adults taking them in troubled Greece

By BEN SPENCER MEDICAL CORRESPONDENT FOR THE DAILY MAIL
PUBLISHED: 17:44, 10 July 2015 | UPDATED: 20:27, 10 July 2015

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At least one in 11 British adults now take antidepressants, according to research which lays bare our reliance on pills.

The UK has the fourth-most medicalised population in Europe when it comes to antidepressant drugs, academics have found.

Some 9 per cent of adults in the country have taken the pills in the last year, three times as many than the 3 per cent of adults who take antidepressants in troubled Greece.

In an EU league table of prescribing published yesterday in the British Journal of Psychiatry, the UK came fourth out of 27 nations, behind only Portugal, Lithuania and Malta.

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Drugs

Sarah Boseley
Health editor

Wed 21 Feb 2018
23.30 GMT



< 21k

The drugs do work: antidepressants are effective, study shows

Doctors hope study will put to rest doubts about the medicine, and help to address global under-treatment of depression

It's official: antidepressants are not snake oil or a conspiracy



▲ It is likely that in the UK alone 1 million more people a year should have access to either drugs or psychotherapy for depression, say experts. Photograph: Darron Cummings/AP

Antidepressants work - some more effectively than others - in treating depression, according to authors of a groundbreaking study which doctors hope will finally put to rest doubts about the controversial medicine.

Millions more people around the world should be prescribed pills or offered talking therapies, which work equally well for moderate to severe depression, say the doctors, noting that just one in six people receive proper treatment in the rich world - and one in 27 in the developing world.

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https://www.thesun.co.uk/news/5638272/gp... Mail - j.moncrieff@ud.ac.uk the sun antidepressants - Go... Selective serotonin re-uptake... GPs should prescribe anti-...

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THE DRUGS DO WORK GPs should prescribe anti-depressants to over a million more Brits, experts claim

Researchers claim the nation is not getting enough help to cope with their depression after research showed only a fraction of people are getting the help they need

By Nick McDermott, Health Editor
21st February 2018, 10:35 pm | Updated: 23rd February 2018, 4:47 am

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doi: [10.1016/S0140-6736\(17\)32802-7](https://doi.org/10.1016/S0140-6736(17)32802-7)

PMCID: PMC5889788
PMID: [29477251](https://pubmed.ncbi.nlm.nih.gov/29477251/)

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, MD,^{a,b,*} Toshi A Furukawa, Prof, MD,^{d,t} Georgia Salanti, PhD,^{e,t} Anna Chaimani, PhD,^{f,g,h} Lauren Z Atkinson, MSc,^{a,c} Yusuke Ogawa, MD,^d Stefan Leucht, Prof, MD,ⁱ Henricus G Ruhe, PhD,^{a,j} Erick H Turner, MD,^{k,l} Julian P T Higgins, Prof, PhD,^m Matthias Egger, Prof, PhD,^e Nozomi Takeshima, MD,^d Yu Hayasaka, MD,^d Hissei Imai, MD,^d Kiyomi Shinohara, MD,^d Aran Tajika, MD,^d John P A Ioannidis, Prof, MD,^{n,o} and John R Geddes, Prof, MD,^{a,b}

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See "More data, more answers: picking the optimal antidepressant" in Lancet, doi: [10.1016/S0140-6736\(18\)30421-5](https://doi.org/10.1016/S0140-6736(18)30421-5).

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Summary

Go to:

Background

Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods

We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and

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[Cochrane Database Syst Rev. 2013]

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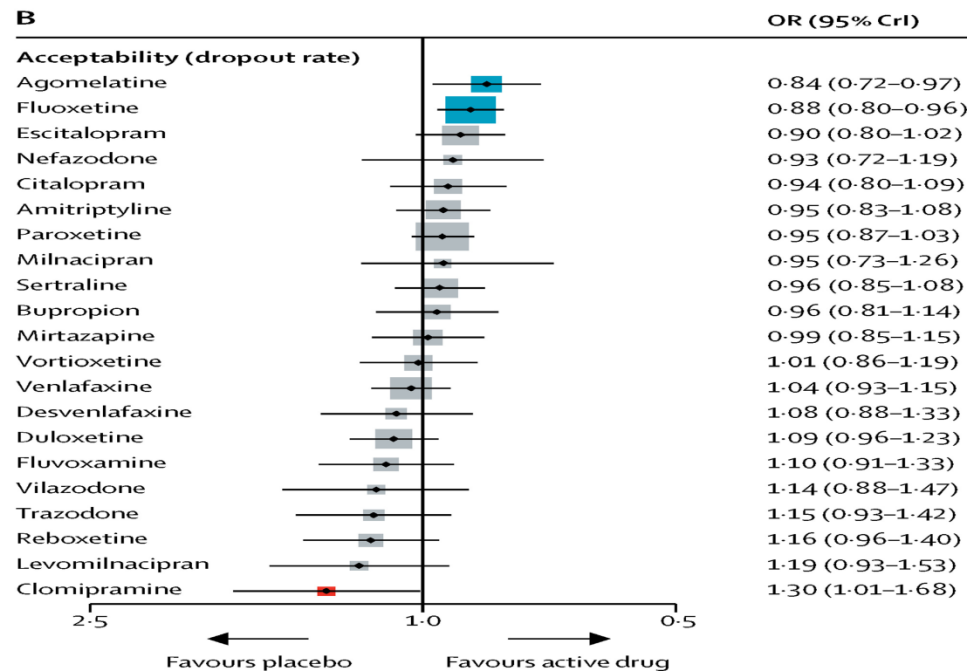
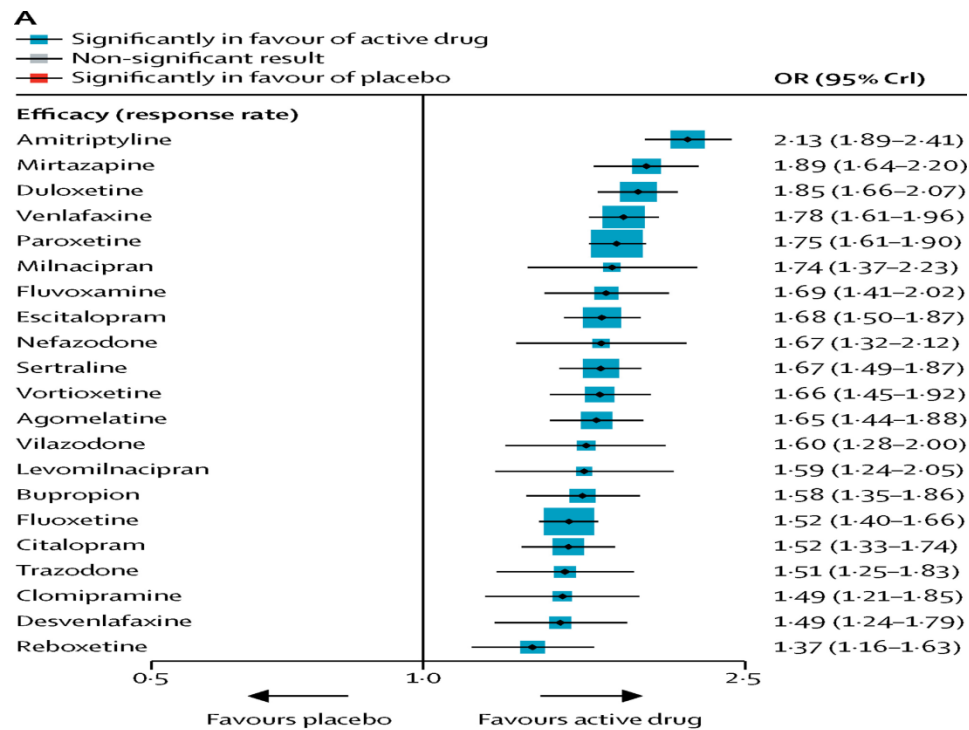
syn-Selective alkylation of terminal alkynes via the combination of photoredox and nickel [Nature Communications. 2018]

Statistically Significant Antidepressant-Placebo Differences on Subjective Symptom-Rating Scales [Frontiers in Psychiatry. 2018]

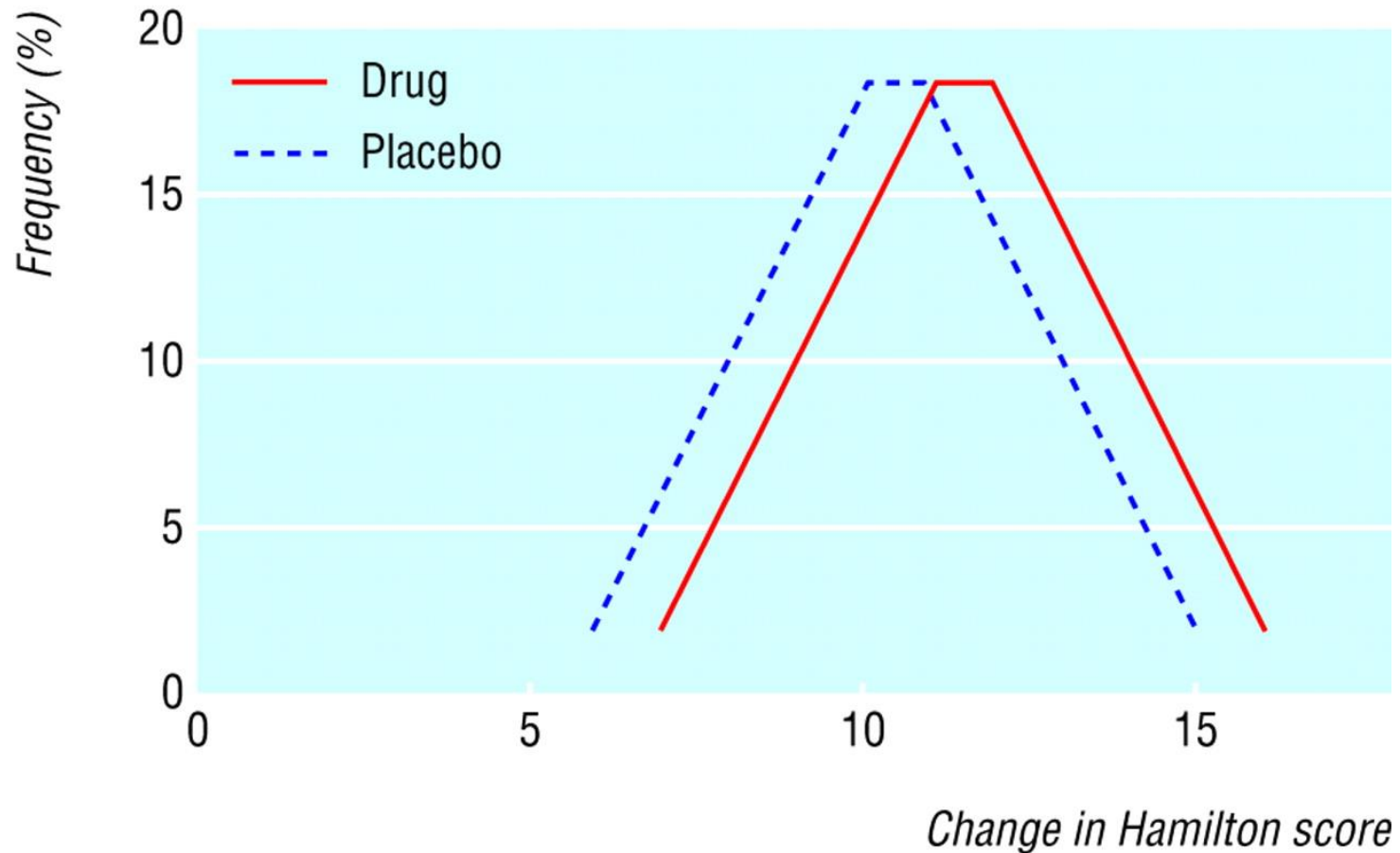
The role of inflammation in core features of depression: Insights from paradigms using exogenous [Neuroscience and biobehavioral...]

Clinical outcomes of patients with major depressive disorder treated with either duloxetine, [Neuropsychiatric Disease and T...]

Five Interpersonal Factors Are Predictive of the Response to Treatment of Major Depression With [Frontiers in Psychiatry. 2018]



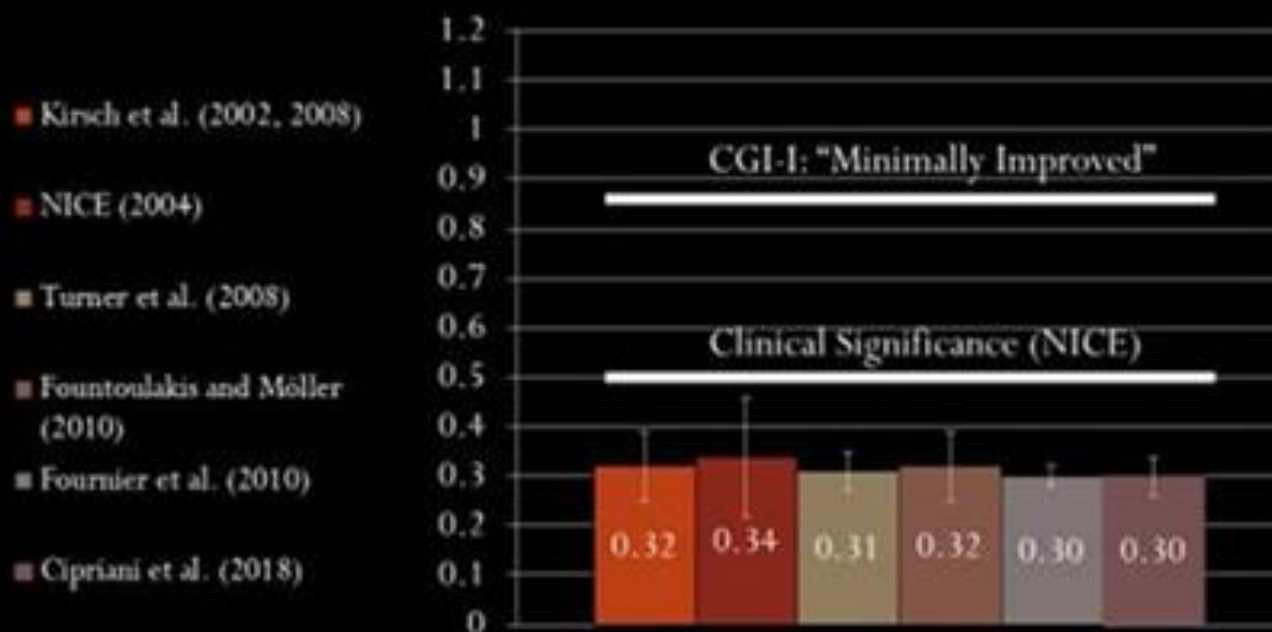
Inflation of differences through categorisation of outcome measures



- Response defined as minimum 12 point reduction in HRSD (approx 50% reduction in typical baseline depression score)
- Response on active drugs: 50%
- Response on placebo: 32%

Moncrieff & Kirsch, 2005 BMJ

Everyone gets the same results (SMD)

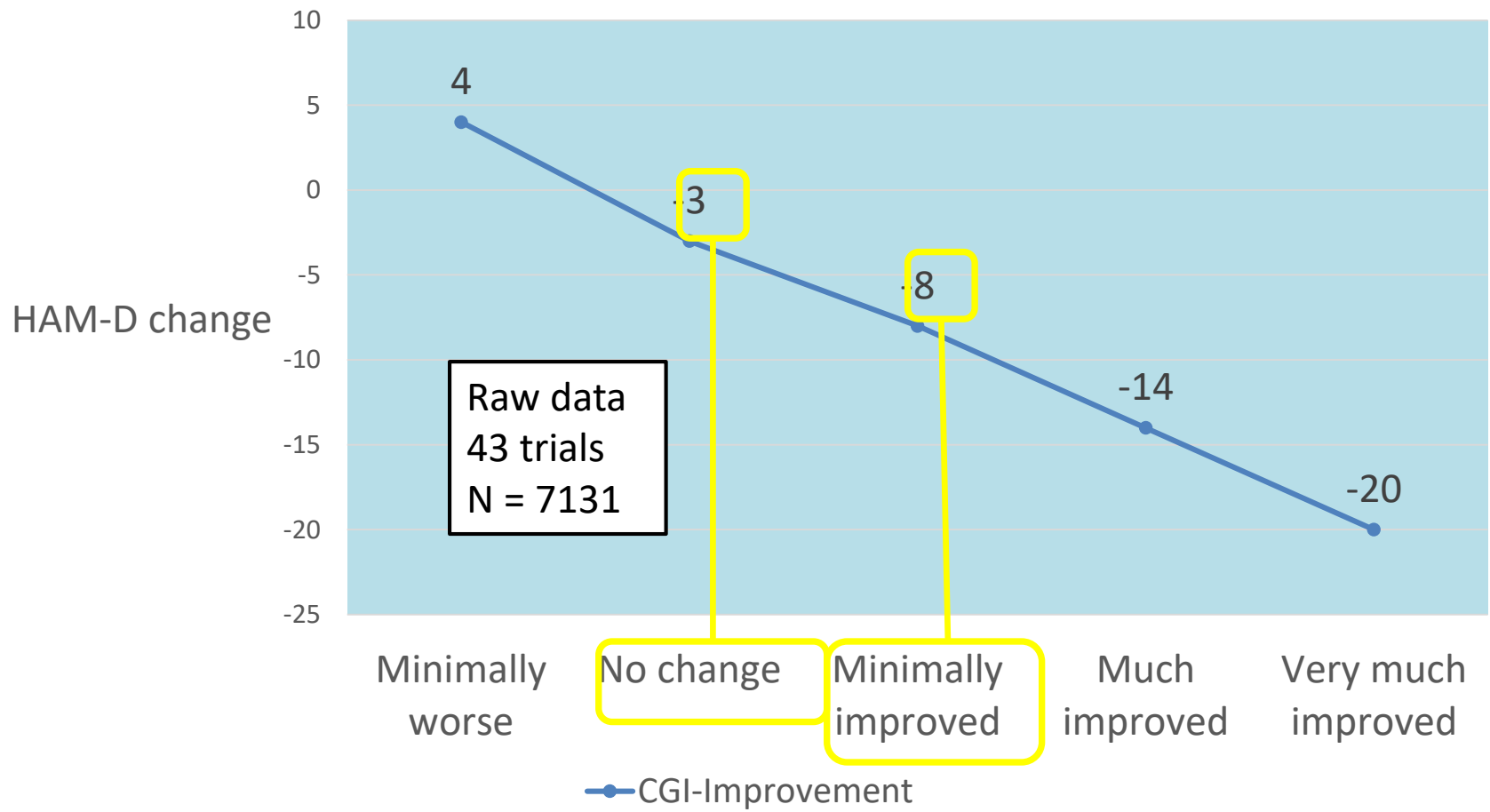


The difference between drug and placebo is
small

Are antidepressant effects useful in depression?

- Difference from placebo is very small. Effect size around 0.3; translates to HRSD difference of 1.5-2.5 (max score 54)
- And **undetectable** using other measures of clinical improvement (HRSD effects of <3 points are clinically undetectable. Minimal improvement on CGI=8 points on HRSD (Leucht et al, 2013; Moncrieff & Kirsch, 2015).
- Also easily accounted for by “amplified placebo effects” or drug-induced effects like emotional flattening

HAM-D and CGI-Improvement (Leucht et al., 2013)



Unblinding

- Rabkin et al, 1986: imipramine, vs phenelzine vs placebo

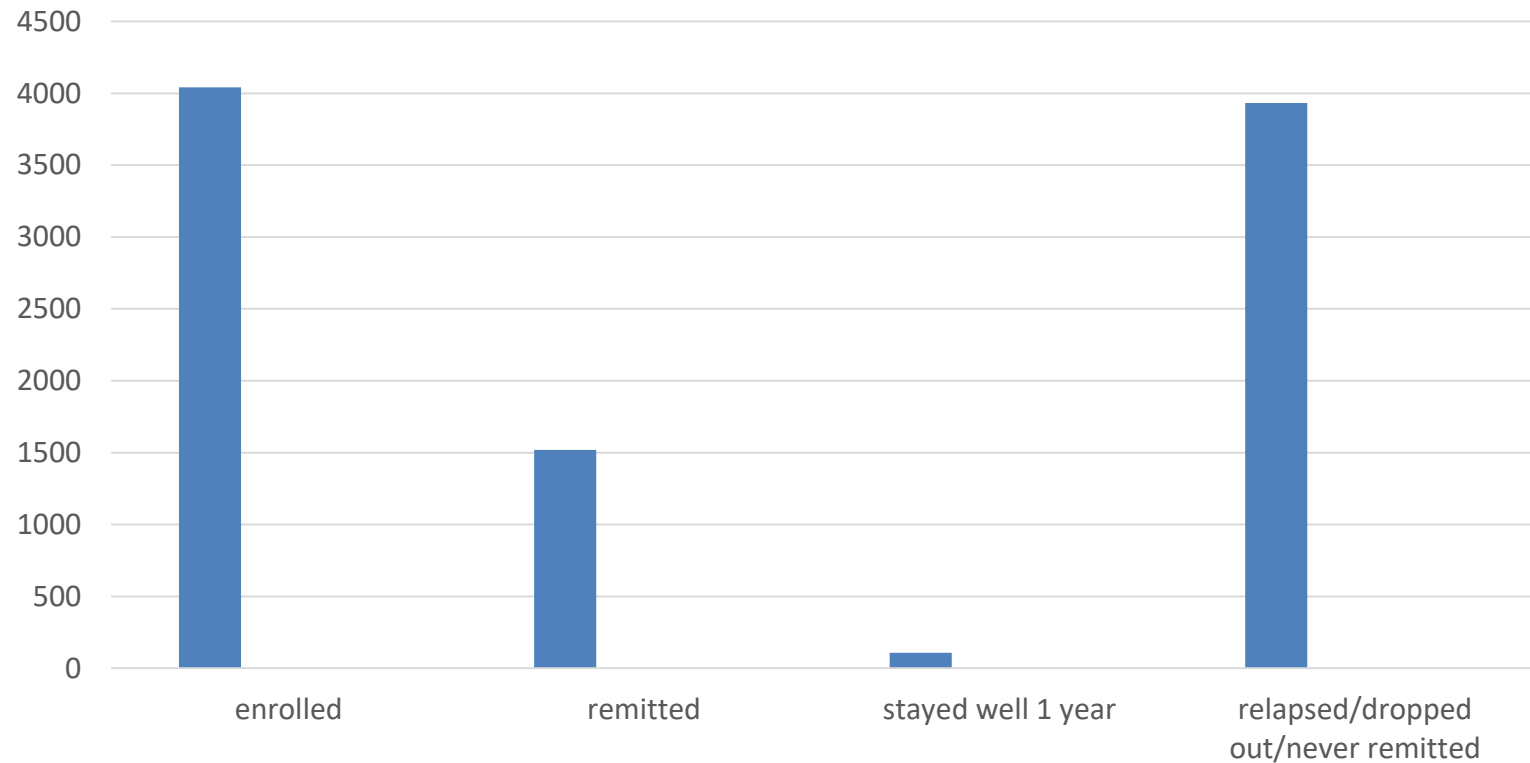
78% patients, 87% psychiatrists correctly distinguished active drug from placebo

- Marini et al, 1976: Lithium vs placebo

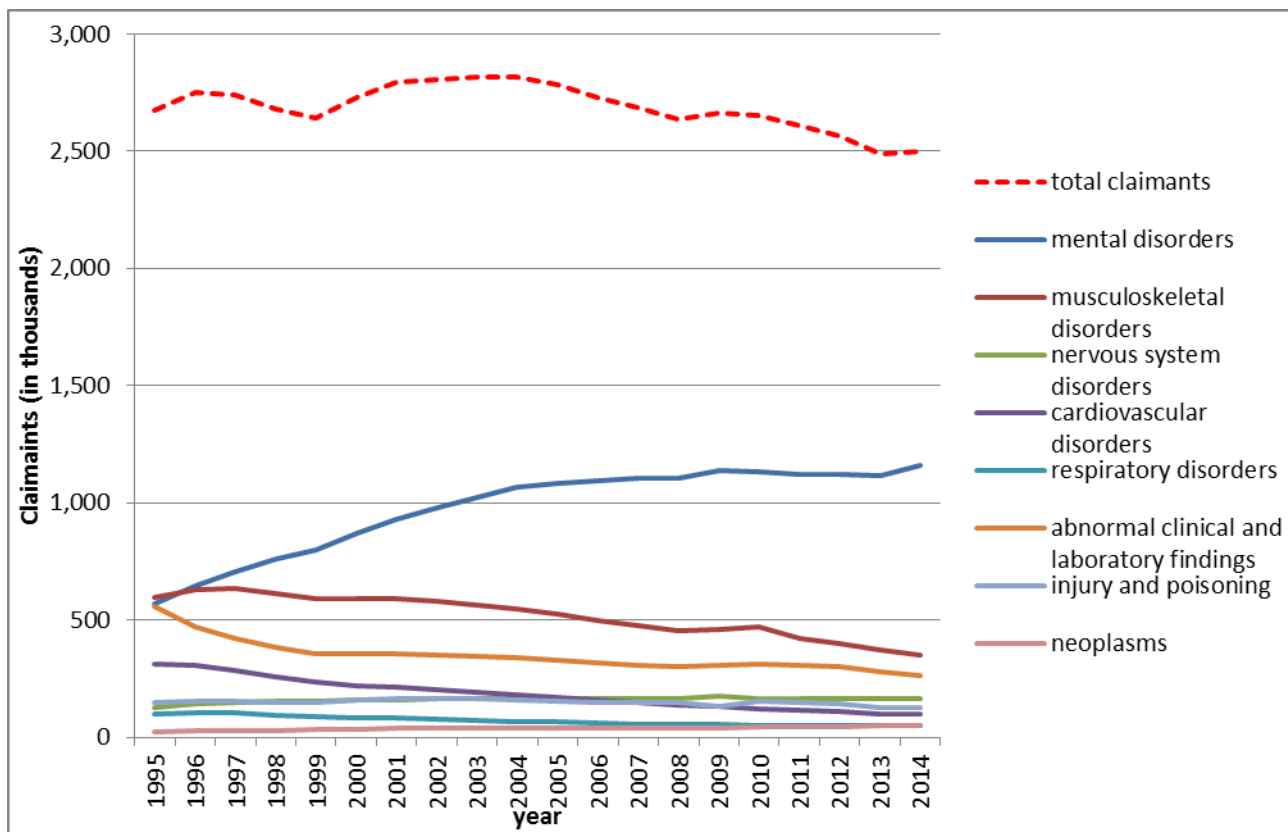
70% patients correctly identified whether they were on lithium or placebo

STAR*D trial outcomes (Pigott, E.H. 2010)

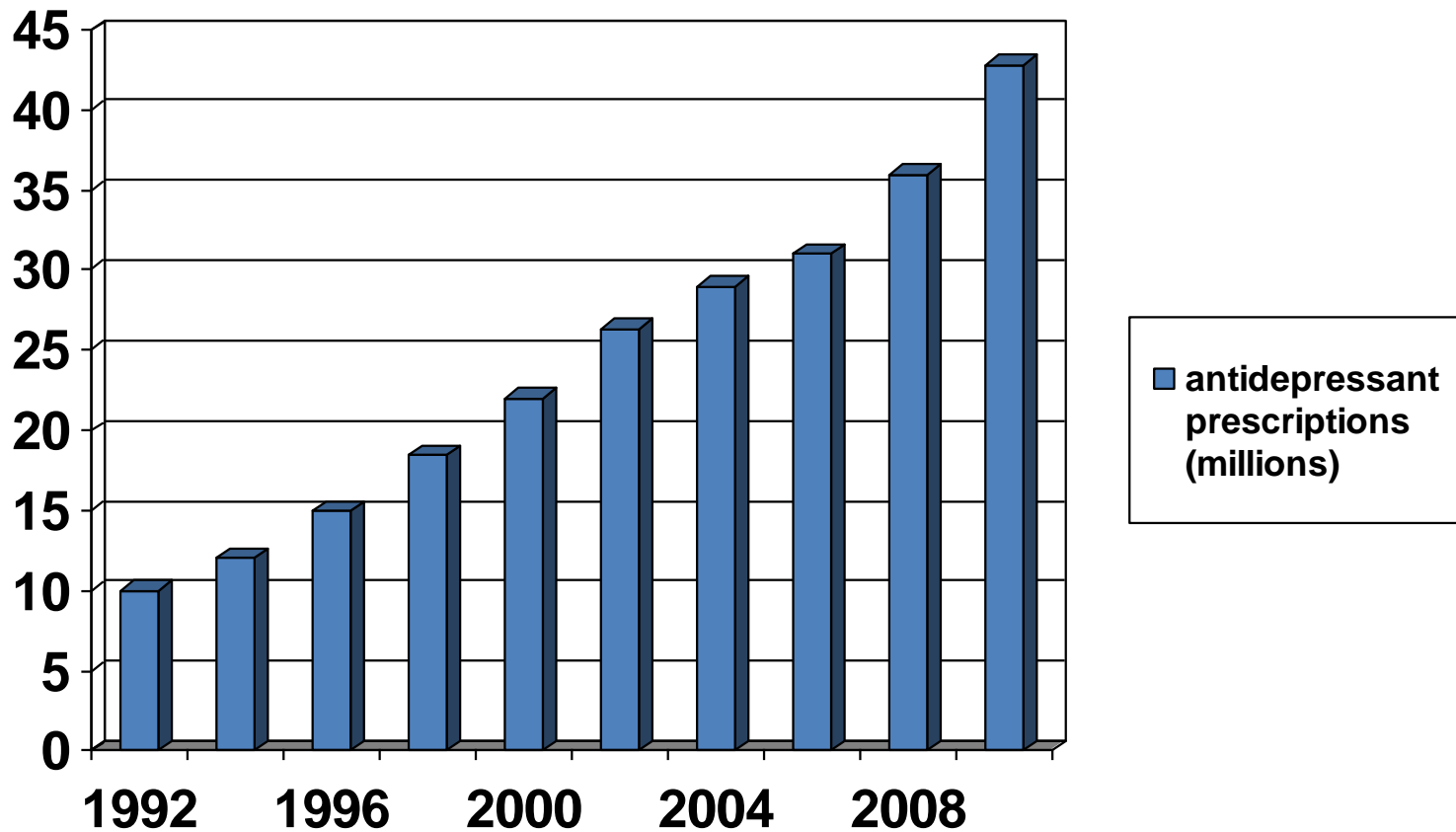
Diagramtittel



UK sickness and disability benefit claimants 1995-2014



Trends in antidepressant prescribing 1992-2010



Adverse effects of antidepressants

- Sexual impairment in humans is common (60% in some studies). Includes erectile dysfunction, genital anaesthesia, ejaculatory anhedonia and loss of libido
- **Can persist after discontinuation** (Bolton et al, 2006; Kaufmann, 2008; Farnsworth & Dinsmore, 2009; Csoka et al, 2008).
- Withdrawal effects: sometimes severe and prolonged – years (Fava et al, 2014)
- Increased suicidal thoughts and actions especially in young people
- Psychological effects: psychological dependence may increase risk of recurrence or of non-remission
- Possibly fetal malformations with some SSRIs

Long-term behavioural effects of antidepressants: animal behaviour studies of SSRIs

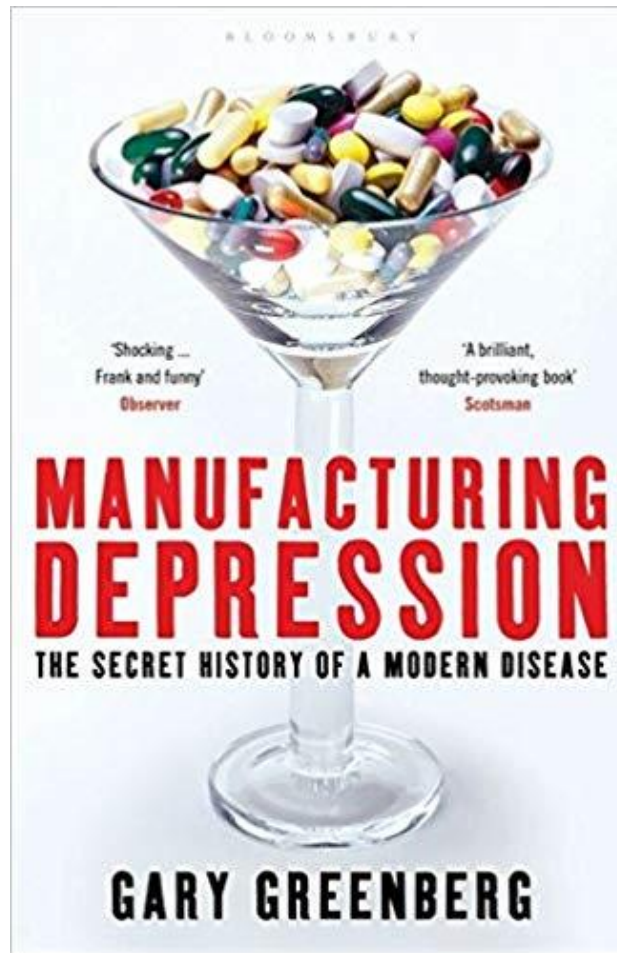
Offspring of pregnant rats given SSRIs during pregnancy show long-term behavioural effects consisting of:

- Reduced sexual behaviour
 - Decreased exploration
 - Decreased social interaction
 - Some evidence of increased anxiety/ over-activity
- (Kiryanova et al, 2013- review)

Treatment of depression from a drug-centred perspective

- Antidepressants may produce some emotional restriction or flattening
- This may or may not be perceived as helpful
- Serious adverse effects exist but are under-researched
- Sedative drugs may be useful for agitation and insomnia temporarily - but beware dependence
- Learning to be happy (Greenberg)?
- But, being in a drug-induced, altered state for a prolonged period may hinder self management and learning, and may make people more chronically ill

Manufacturing Depression, Gary Greenberg





Are antidepressant-induced alterations useful?

Patient information

The drug-centred view:

The standard view:

- The antidepressant will help normalise your serotonin levels
- The antidepressant will improve your depression

- This medicine alters the way people think and feel (not just people with depression), but we are not sure how. It may dampen down your emotions, reduce your sex drive and make you feel demotivated and lethargic.

Early accounts of antipsychotics

- Chlorpromazine first used by French psychiatrists Jean Delay and Pierre Deniker in 1950s (Hôpital St Ann, Paris)
- At first it was regarded as a special sort of sedative
- Referred to as a “neurological inhibitor,” then as a “neuroleptic”; also “major tranquilisers”



Antipsychotic drug-induced effects

- Animal/healthy volunteers studies¹⁻⁷

Antipsychotics
reduce:

- Movement
- Attention
- Reaction times
- Co-ordination
- Intellectual abilities
- Spontaneous activity

Subjective
effects:

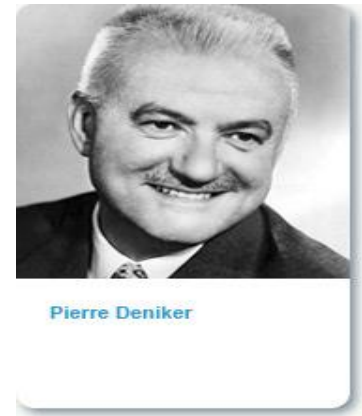
- Sedation
- Emotional flattening
- Indifference
- Reduced initiative

1. Baldessarini, 1985; 2. Gemperle et al, 2003; 3. Rosengarten et al, 2002; 4. Fagan et al, 1991; 5. McClelland et al, 1990; 6. Ramaekers et al, 1999 etc. 7. Healy & Fardipour, 1999

Memory

Healy and Farquhar, 1998

- 'A general feeling common to all subjects was some extent of **disengagement** - a feeling of uninvolvedness with the tasks at hand. Mental effort appeared to be difficult with all subjects reporting some problems with concentration'



- Deniker (and others) proposed the effects of classical neuroleptics were an attenuated form of Parkinson's disease
- They worked because the emotional suppression or indifference they produced reduced the impact of psychotic symptoms: 'patients simply lose interest in their delusions'

'Experimental neurological syndromes and the new drug therapies in psychiatry' *Comprehensive Psychiatry*, volume 1, 1960.

Patient accounts of the alterations produced by typical 'antipsychotics' and risperidone

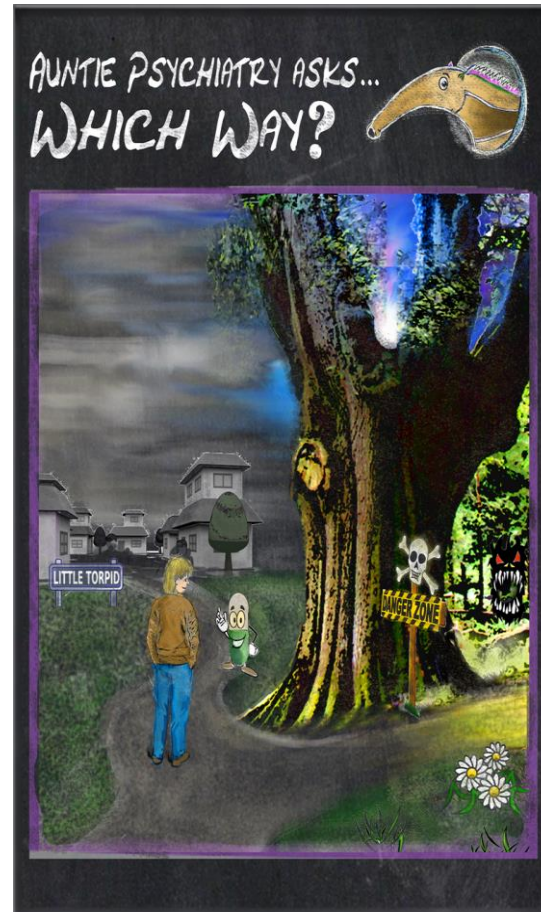
Comments from 'askapatient.com'

- *Mental and physical stagnance*
- *Emotionally empty, dead inside*
- *A weird spacey empty feeling*
- *Lethargy and indifference*

(Moncrieff et al, 2008)

“Although I felt very well, I felt as if I had absolutely nothing to talk about. I kept wondering about whatever [it] was that had been so interesting during most of my life that I had suddenly lost... But I was very much in contact with reality and for that I was thankful” (haloperidol)

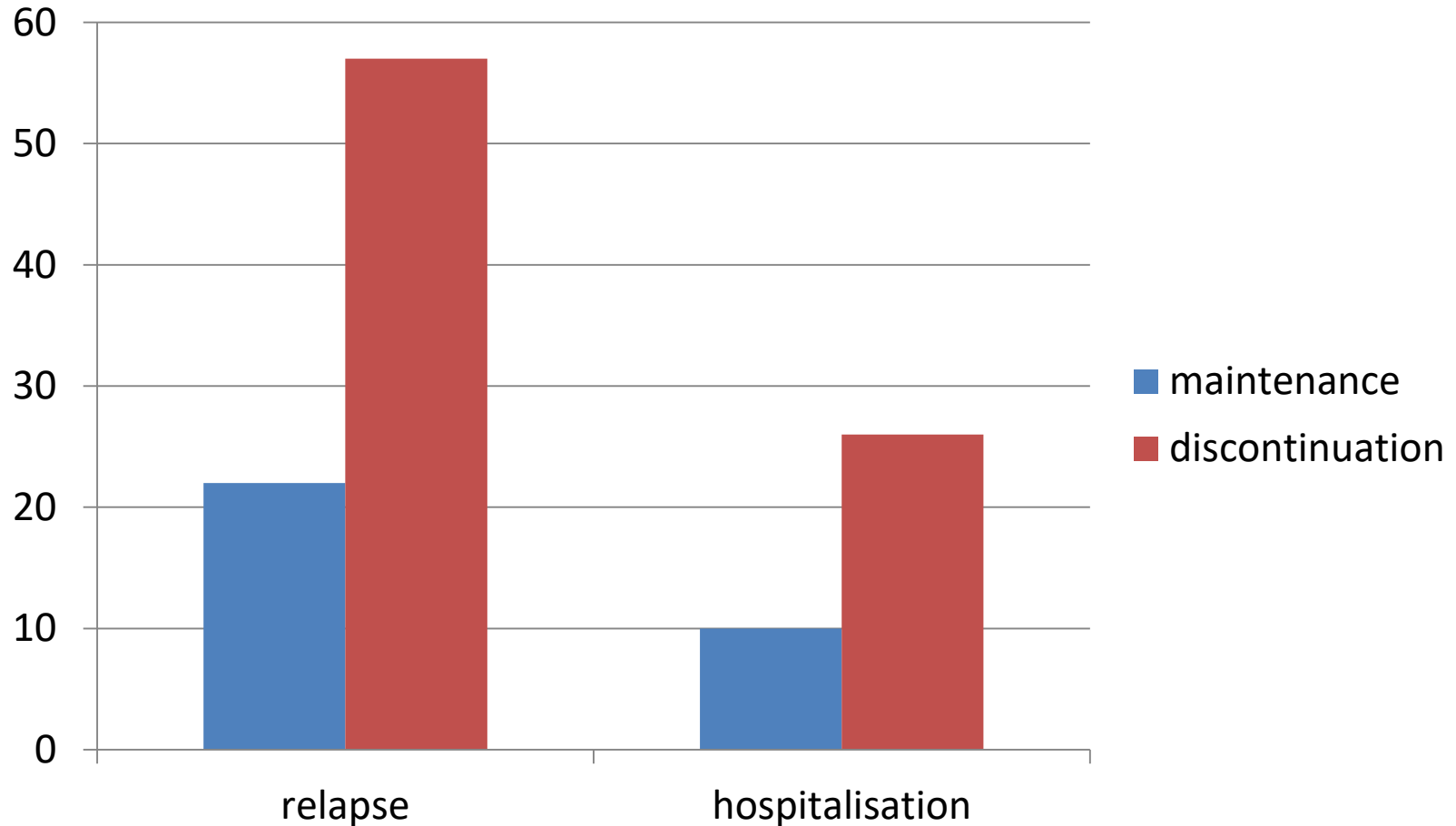
“Rottenly normal” (Oliver Sack’s brother)



A drug centred approach to the treatment of psychosis

- Effects of antipsychotics may be useful to suppress acute symptoms
- Long-term the impairment and adverse physical effects may outweigh possible advantages for some, maybe many

Antipsychotic discontinuation trials, Leucht et al, 2012



Limitations of antipsychotic maintenance studies

- Evidence consists of antipsychotic *discontinuation* studies, which are confounded by adverse effects of discontinuation
- Most studies less than 6 months – only 6/65 trials in Leucht et al lasted > 1 year
- Little data on outcomes other than relapse

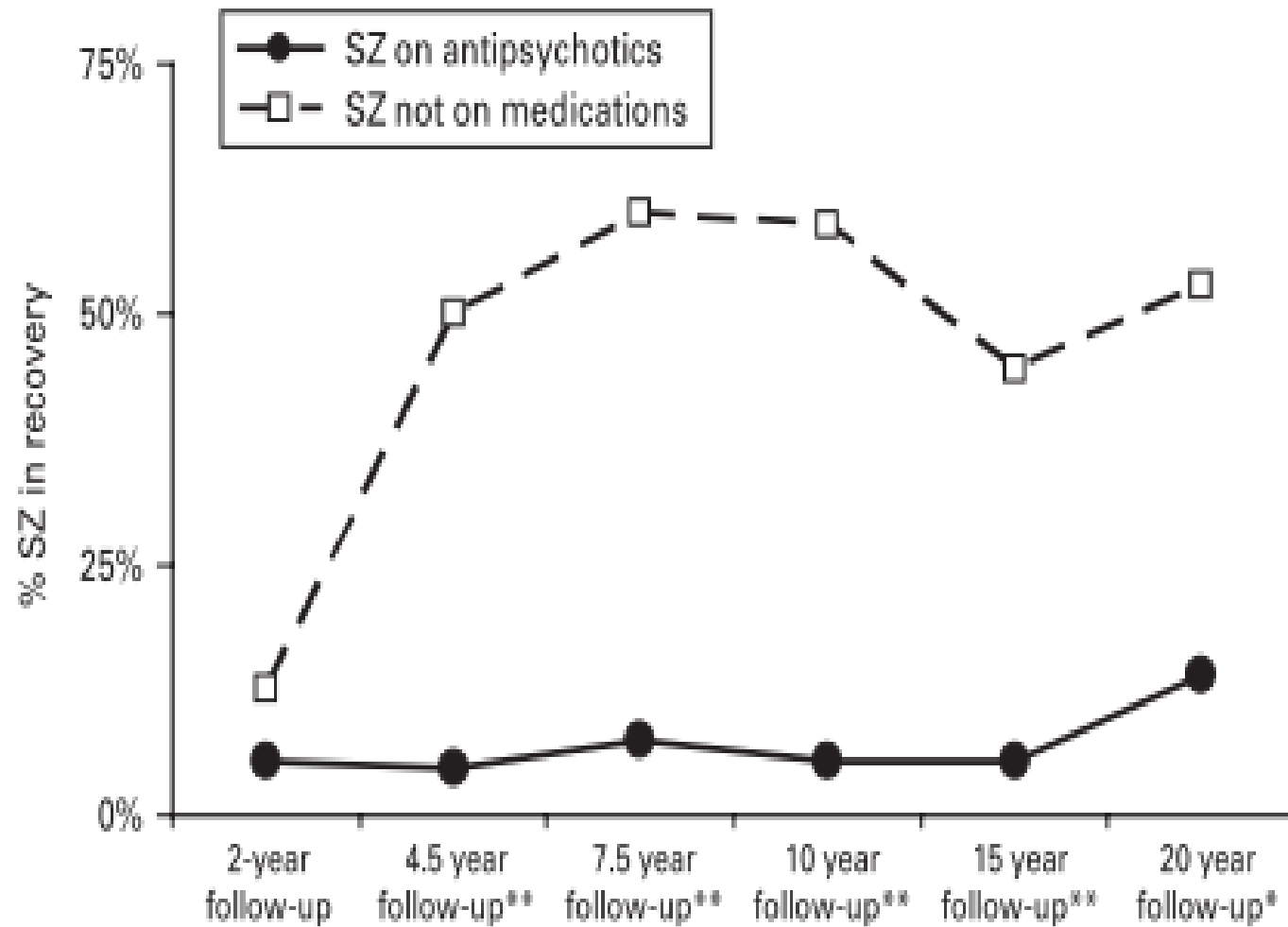


Figure 1. Relationship between recovery and use of antipsychotics in schizophrenia (SZ). * $p < 0.01$, ** $p < 0.001$

7 year follow-up

From: **Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial**

JAMA Psychiatry. 2013;70(9):913-920. doi:10.1001/jamapsychiatry.2013.19

Table 2. Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

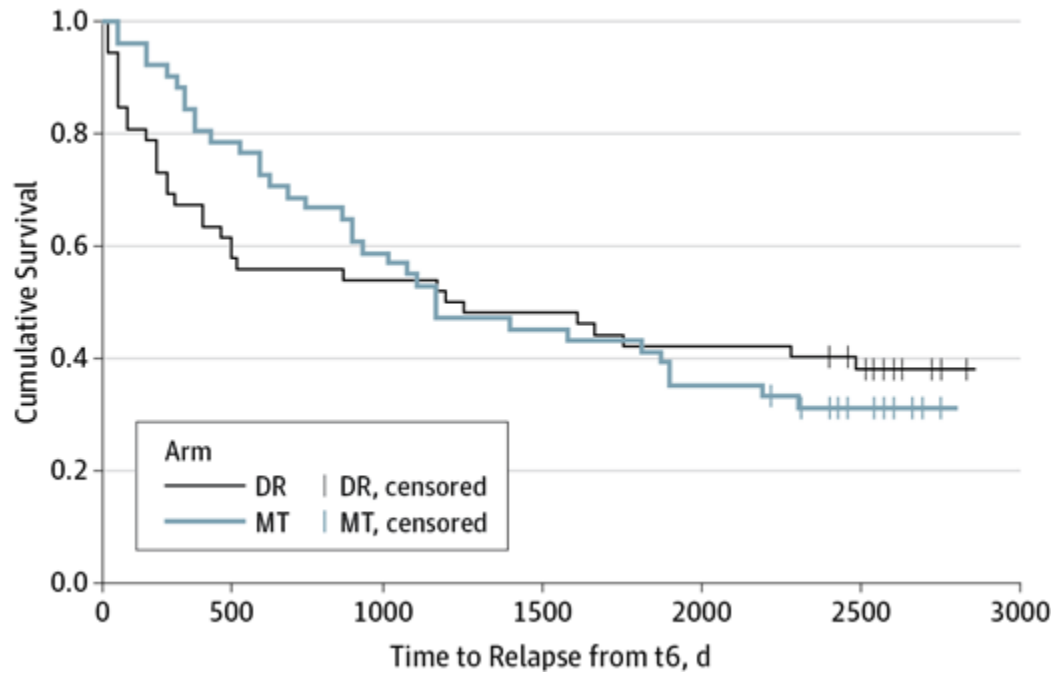
Characteristic	No. (%)		Total Sample (n = 103)
	DR (n = 52)	MT (n = 51)	
Recovery	21 (40.4)	9 (17.6)	30 (29.1)
Remission			
Symptomatic	36 (69.2)	34 (66.7)	70 (68.0)
Functional	24 (46.2)	10 (19.6)	34 (33.0)

Abbreviations: DR, dose reduction/discontinuation; MT, maintenance treatment.

Figure Legend:

Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

Wunderink et al, 2013



Antipsychotics and brains: there is now conclusive evidence that antipsychotics produce brain shrinkage: **Animal studies**

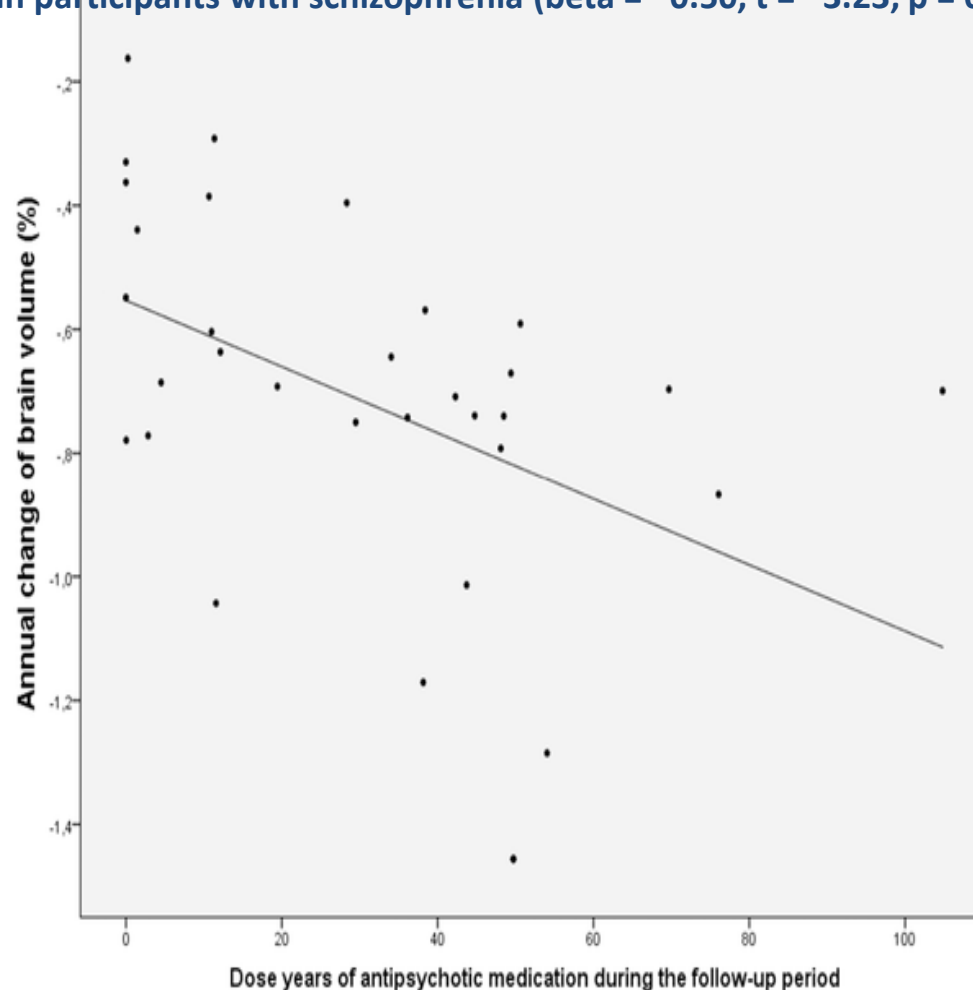


- Dorph-Petersen et al, 2007: Macaque monkeys, 18 months.

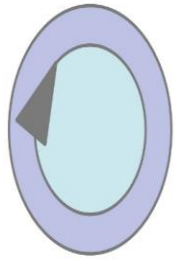
Brains of drug treated monkeys were 8-11% lighter

- Vernon et al, 2011: Rats treated for 8 weeks. 6-8% decrease in WBV, mostly in frontal cortex

Figure 3. Linear regression between dose years (equivalent to daily 100 mg chlorpromazine) of antipsychotic medication and annual change in brain volume (%) in participants with schizophrenia (beta = -0.50 , $t = -3.23$, $p = 0.003$).



Veijola J, Guo JY, Moilanen JS, Jääskeläinen E, Miettunen J, et al. (2014) Longitudinal Changes in Total Brain Volume in Schizophrenia: Relation to Symptom Severity, Cognition and Antipsychotic Medication. PLOS ONE 9(7): e101689. <https://doi.org/10.1371/journal.pone.0101689>
<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0101689>



R A D A R

Research into Antipsychotic
Discontinuation And Reduction

The RADAR trial



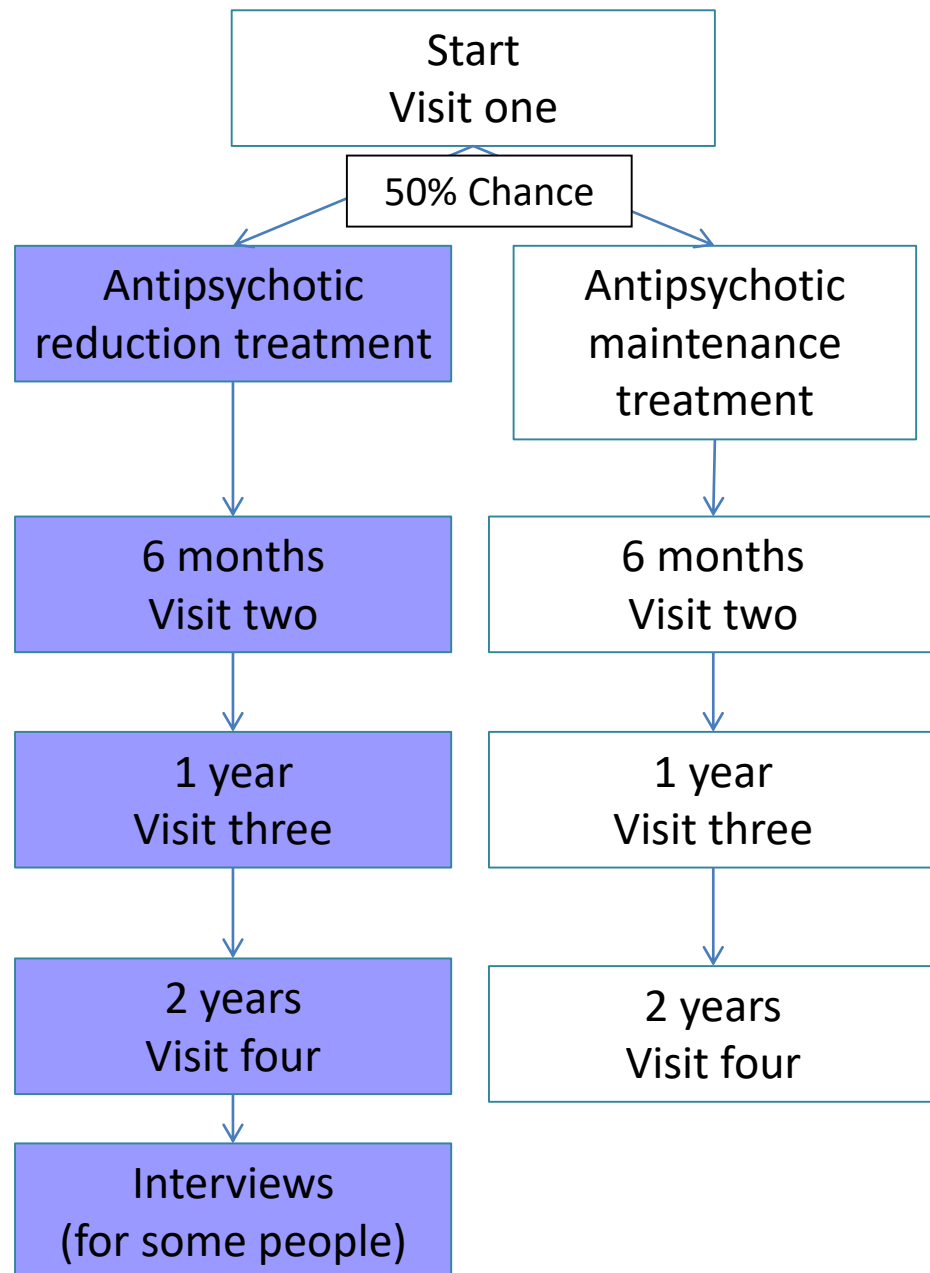
*National Institute for
Health Research*

- Randomised controlled trial of gradual antipsychotic reduction and discontinuation vs maintenance in people with recurrent or long-term non-affective psychosis or schizophrenia
- 402 participants; 2 year follow-up initially
- Outcomes: social functioning; relapse; symptoms; neuropsychological performance; adverse effects; service use etc

RADAR Trial: what will happen

Antipsychotic reduction treatment

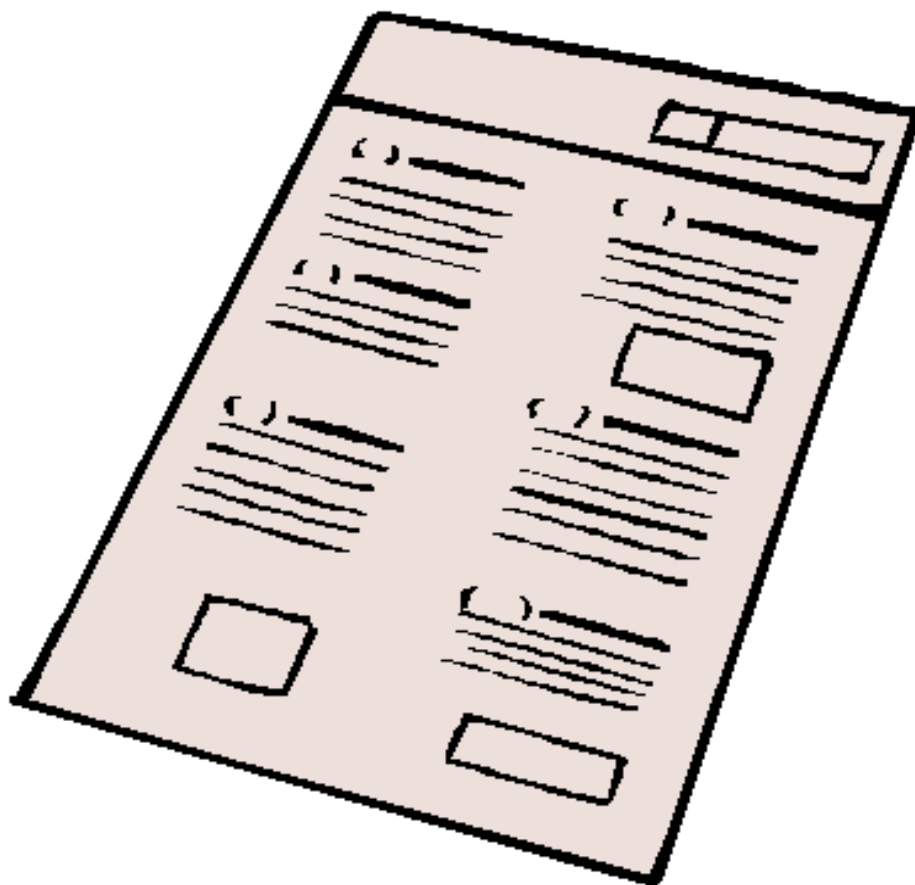
- Participants will, with their psychiatrist, reduce and, potentially, stop taking their antipsychotic medication.
- The reduction can be done more slowly or quite quickly over ~ 6-12 months
- At the end of the study, some people who received the antipsychotic reduction treatment will be asked to talk to a member of the research team about their experience of taking part in the study



Treatment of bipolar disorder from a drug-centred perspective: classical “manic depression” (bipolar 1)

- ‘Neurosuppressants’ (lithium, valproate, antipsychotics) reduce symptoms of acute mania
- They may reduce the recurrence of mania, but trials are flawed (discontinuation effects)
- Naturalistic studies show rates of relapse are higher now than pre-1950s (Winokur et al, 1975; Healy et al, 2005)
- No logical reason why these drugs would reduce the occurrence of depression and may exacerbate it
- No evidence that they reduce mood variability (in fact negative trials with lithium)

Bipolar symptoms test



Why did the disease-centred model of drug action catch on?

- Professional interests
- Pharmaceutical industry
- Politics

Professional interests



Distinguishing psychiatric treatment from recreational drug use



COUNTERTHINK




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The benzodiazepine crisis



- ‘antipsychotic medicines are believed to work by balancing the chemicals found *naturally* in the brain’
- Eli Lilly, zyprexa.com, 2011





Prescribe early, because what she loses, she could lose forever.

Help stop the spiral of decline

Risperdal CONSTA 
risperidone LONG-ACTING INJECTION

ABBREVIATED PRESCRIBING INFORMATION: Risperdal[®] Consta[™] Injection (Risperidone) Please read Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** Prolonged release injection containing risperidone. Three strengths available. **Uses:** Schizophrenia. Other psychotic conditions, in which positive and/or negative symptoms are prominent. Not licensed for behavioural symptoms of dementia. **Dosage (IM): Adults:** 25 mg every two weeks (alternate buttocks); consider 37.5 mg if stabilised on more than 4 mg/day oral. Consider 12.5 mg increase after four weeks. Maximum: 50 mg every two weeks. Ensure prior tolerability with oral risperidone. Supplement with oral risperidone for first three weeks as appropriate. **Elderly:** 25 mg every two weeks, plus oral cover as above. **Renal and hepatic impairment:** Caution. 25 mg every two weeks if minimum 2 mg oral tolerated following titration. **Children and adolescents under 18 years:** Not studied. **Contraindications:** Hypersensitivity to the product or diluent. **Warnings and Precautions:** Not recommended for behavioural symptoms of dementia because of three-fold risk of

cerebrovascular adverse events. If history of CVA/TIA, consider risk carefully. Care with other risk factors for cerebrovascular disease. Orthostatic hypotension. Cardiovascular disease. Drugs prolonging QT. Reduce dose if hypotension. If tardive dyskinesia consider stopping all antipsychotic drugs. Parkinson's disease. Epilepsy. If Neuroleptic Malignant Syndrome, stop all antipsychotics. Monitoring in diabetics and those with risk factors for diabetes advisable. Advise of potential for weight gain. Advise not to drive or operate machinery if alertness affected. Acute withdrawal symptoms, recurrence of psychoses. Recommend gradual withdrawal. Care when using Risperdal and furosemide in elderly patients with dementia. **Pregnancy:** If benefits outweigh risks. **Lactation:** Avoid. **Interactions:** Centrally acting drugs, dopamine agonists, hepatic enzyme-inducing drugs. Fluoxetine, paroxetine or haloperidol. **Side Effects:** weight gain or decrease, fatigue, extrapyramidal symptoms, depression, nervousness, sleep disorder, apathy, impaired concentration, abnormal vision, hypotension, syncope, rash, pruritus, peripheral oedema, injection site reaction. Symptoms of hyperprolactinaemia such as nonpuerperal lactation, amenorrhoea, abnormal sexual

function, ejaculation failure, decreased libido and impotence. **Very rarely:** hyperglycaemia and exacerbation of pre-existing diabetes. **Occasionally reported:** tardive dyskinesia and seizures, increased or decreased white blood cell count; increases in hepatic enzymes. **Withdrawal reactions:** associated with antipsychotic drugs. **Legal Category:** POM. **Active Ingredient:** Risperidone. **Presentations, Pack Sizes, Product Licence Numbers and Basic NHS Costs:** 25 mg prolonged-release injection (PL 0242/0375) 1 dose: £82.92; 37.5 mg prolonged-release injection (PL 0242/0376) 1 dose: £115.84; 50 mg prolonged-release injection (PL 0242/0377) 1 dose: £148.55. **Further Information Available from Product Licence Holder:** Janssen-Cilag Ltd., Sanderton, High Wycombe, Buckinghamshire HP14 4HJ UK. ©-2006 Janssen-Cilag Ltd. *Registered trademark. AP1VER060305C Abbreviated Prescribing Information last updated 06th March 2006. RISP/C/06-0038. January 2007.

Information about adverse event reporting can be found at www.yellowcard.gov.uk Adverse events should also be reported to Janssen-Cilag Ltd.

Political influence



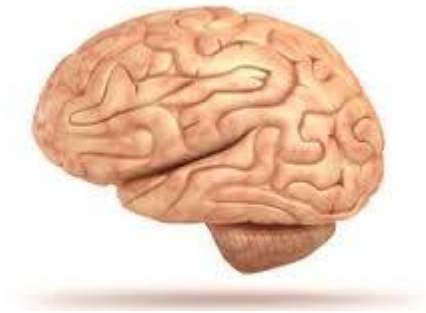
Mental Health Act

Conclusions

- Drugs prescribed for mental distress or disorder do not reverse or target an underlying disease or abnormality or chemical imbalance
- They produce altered physical and mental states, and have unpredictable and under-researched effects, especially in the long-term
- These alterations interact with mental symptoms in various ways- sometimes with beneficial effects, but may have harmful effects

A new approach to use of drugs for mental health problems

Disease centred model
- assumes benefit



Drug centred model - more
cautious, assumes harm



The dopamine hypothesis of schizophrenia and psychosis: the evidence

- Effects of antipsychotics (dopamine not central for all antipsychotics) (Yilmaz et al, 2012)
- Stimulant induced psychosis (not pinned down to dopamine)
- Measures of dopamine and dopamine receptors are negative or drug-induced
- Other studies of dopamine activity inconsistent and confounded by stress, arousal, movement etc

‘Antipsychotics, dopamine D₂ receptor occupancy and clinical improvement in schizophrenia: a meta-analysis’ Yilmaz et al, 2012

- **RESULTS:** The first step of the meta-analysis confirmed the positive relationship between antipsychotic medication and clinical improvement in SCZ (ES=1.36; 95% CI: 1.13-1.60). The second step of our analysis revealed that when D₂ occupancy was limited to less than 80% in order to control for the appearance of extrapyramidal symptoms, **high D₂ occupancy was correlated with reduction in clinical scores (r=0.4, p<0.001) for medications other than clozapine or quetiapine.**
- **Actually NO association found even excluding quetiapine and clozapine until an outlier study was excluded**
- **CONCLUSIONS:** Our results suggest that D₂ occupancy is a contributing factor for the mechanism of antipsychotic effect in SCZ **for some but not all antipsychotic medications.**