Challenging misperceptions about psychiatric drugs and understanding their role in Recovery

Joanna Moncrieff

Recovery conference March 29th 2023.

About Us

Critical psychiatry is a broad critique of mainstream psychiatry that has emerged in recent years which challenges some of psychiatry's most deeply held assumptions. It mounts a scientific challenge to claims about the nature and causes of mental disorder and the effects of psychiatric interventions, and draws on philosophy, history, anthropology, social science and mental health service users' experiences. There is no definitive 'critical psychiatry position.' It is a collection of critical perspectives intended to produce a more reflective, sceptical and patient-centred approach to the theory and practice of psychiatry.

The Critical Psychiatry Network was founded by a group of UK psychiatrists who got

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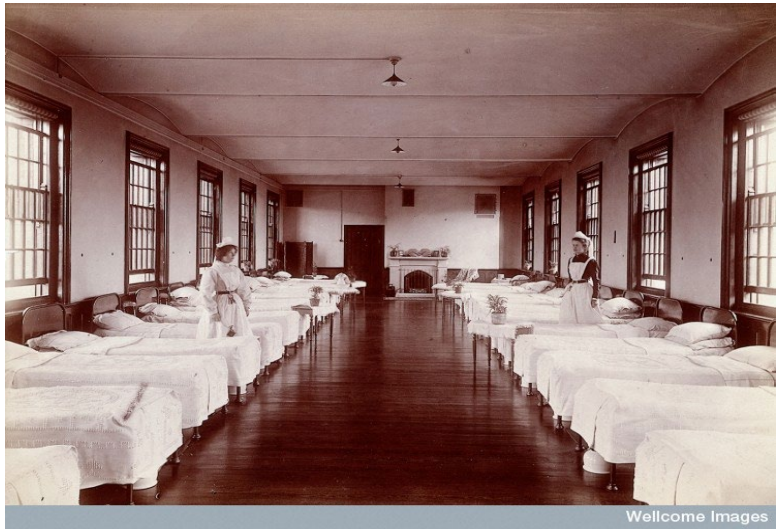
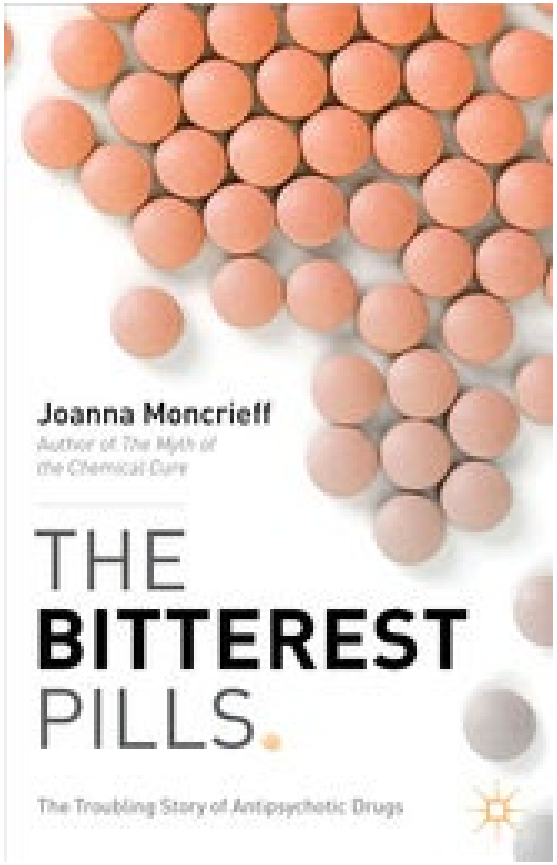
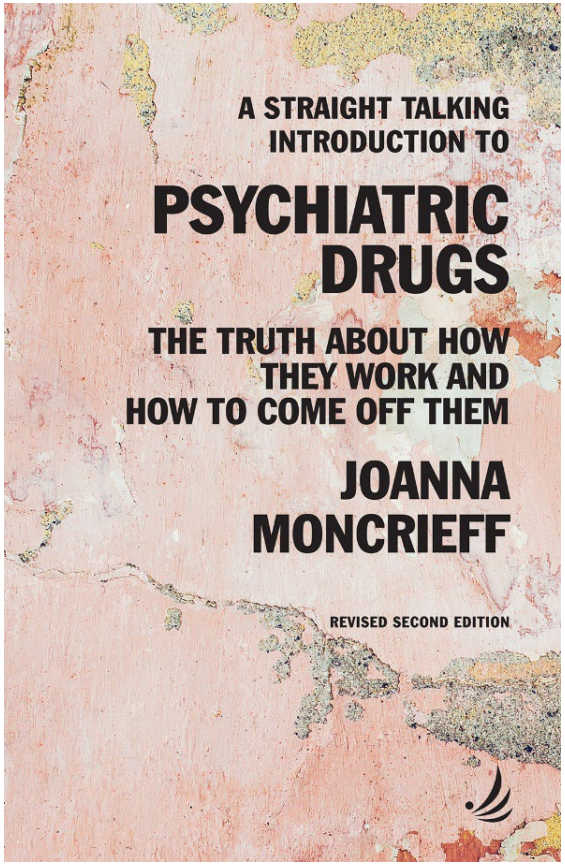
Contrasting views of ‘antipsychotics’: ‘Miracle cures’

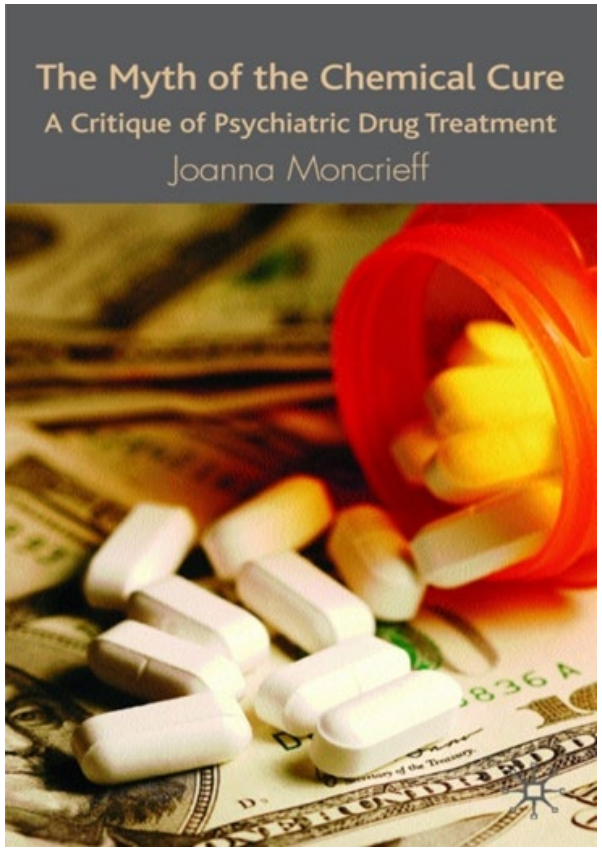
“For the first time, public mental institutions could be regarded as true treatment centres, rather than as primarily custodial facilities” Davis and Cole, 1975



- “a drug prison” “living hell” (from breggin.com)
- “a wrecking ball to the cathedral of my mind” (Oaks, 2011)
- “Satan in a flipping pill” (askapatient.com)



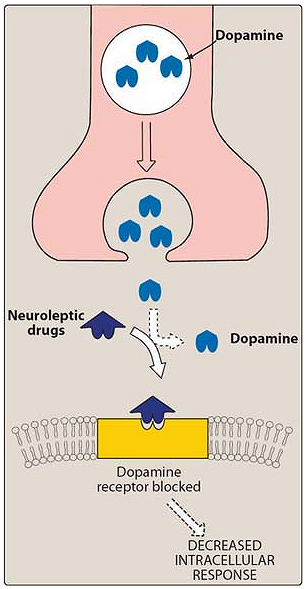




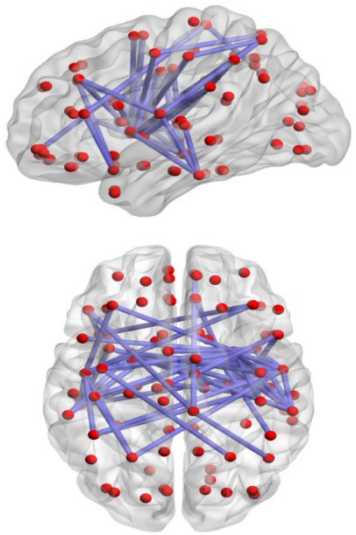
Some psychiatric drugs can be useful in some situations, but we fundamentally misunderstand what they do

The misconception:
Accepted view is that drugs correct an underlying biological abnormality – a “normalising effect” (Davis 1980)

Chemical imbalance



Abnormal neural circuitry



This view has been widely promoted by the pharmaceutical industry, and psychiatric information and texts

- ‘**imbalances of certain chemicals** in the brain are thought to lead to the symptoms of the illness. Medicine plays a ***key role*** **in balancing these chemicals**’ Pfizer, 2006, on schizophrenia

- ‘psychiatric medications can help correct imbalances in brain chemistry that are thought to be involved in some mental disorders’’ APA information leaflet, Jan 2021

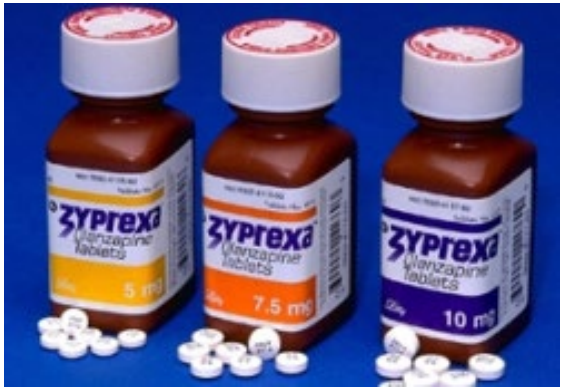
- ‘Abnormalities of serotonergic function are believed to be important in depression, anxiety, psychosis’ *Core Psychiatry*, 2008, P 582

Models of drug action

Disease centred model	Drug centred model
Drugs correct an abnormal brain state	Drugs *create* an abnormal/altered brain state
Therapeutic effects arise from drugs effects on the biological mechanisms that produce symptoms	Useful effects are a consequence of drug-induced changes to normal brain functioning being superimposed on symptoms (unwanted thoughts, feelings and behaviour)
Example (general medicine): asthma treatments, aspirin, paracetamol	Examples: alcohol for social anxiety, opiate anaesthetics

The drug centred model highlights the fact that psychiatric drugs are **psychoactive substances**

- Change the normal state of the body and the brain
- Changes are manifest in changes in mental activity (sensation, thought, emotion), behaviour and physical functioning
- Linked *physical* alterations (eg drug-induced sedation has mental and physical components)
- Can produce euphoria **or** dysphoria to different degrees and with individual variation/preference



Drug-induced changes

Short-term use:

- Immediate changes
- Persistent changes

Long-term use:

- Long-term changes due to drug impact
- Adaptations

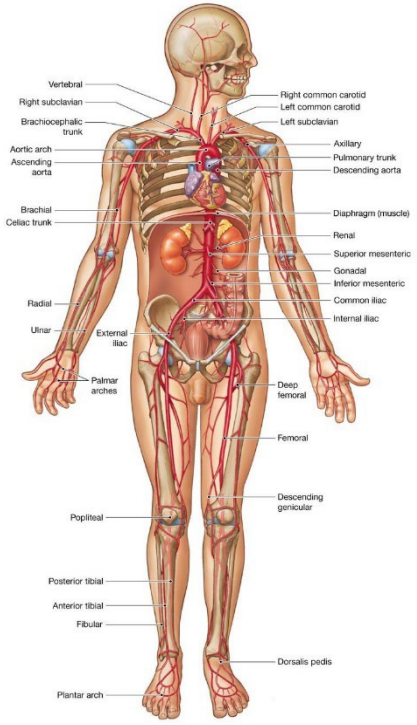
Withdrawal

Withdrawal effects- short and long-lasting

Legacy effects

Persistent changes (after drug has been reduced or stopped)

NB Changes occur at level of the body and brain and are manifested in mental and physical changes and symptoms



Drug-induced changes e.g. haloperidol

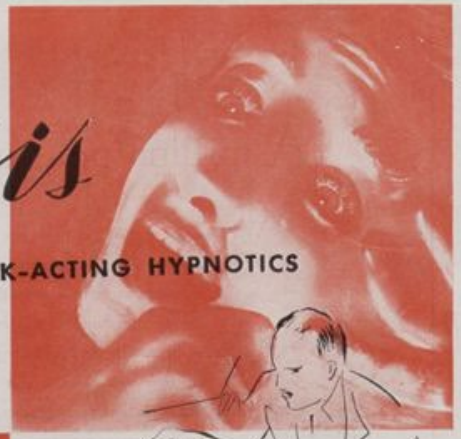
effect	mechanism	Experience/symptom
Immediate changes	DA_2 blockade and other neurotransmitter changes	Sedation, reduced mental activity and emotional reactivity, Parkinsonism
Long-term changes	DA_2 blockade etc ? adaptive increase in dopamine activity and other NT changes Reduced brain volume	Sedation, reduced mental activity and emotional reactivity, Parkinsonism Tardive dyskinesia Super-sensitivity psychosis ?
Withdrawal	Rebound increase in dopamine and other neurotransmitter activity	Agitation, insomnia, Psychosis
Persistent effects	? increased dopamine activity/other NT changes; ? structural damage	Tardive dyskinesia

Prior to the 1950s, drugs understood as acting according to a drug-centred model

WHEN

Crisis

DEMANDS QUICK-ACTING HYPNOTICS



Both medications are supplied in two potencies

PENTOBARBITAL SODIUM
and Benzyl Alcohol

2½ grs. in 1 cc. Ampul Solution
5 grs. in 2 cc. Ampul Solution

PHENOBARBITAL SODIUM
and Benzyl Alcohol

2½ grs. in 1 cc. Ampul Solution
5 grs. in 2 cc. Ampul Solution

For Intramuscular Use

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

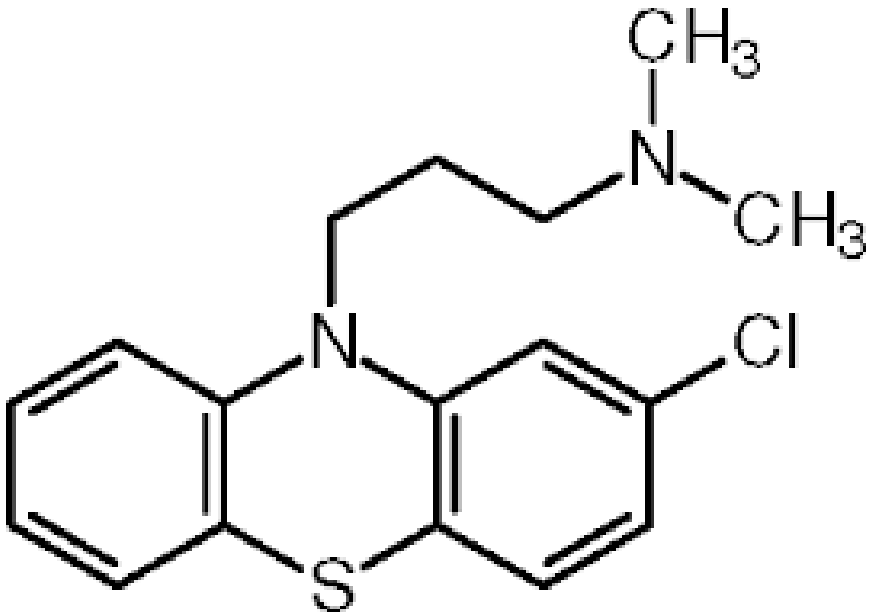
***Phenobarbital**
Sodium and Benzyl Alcohol

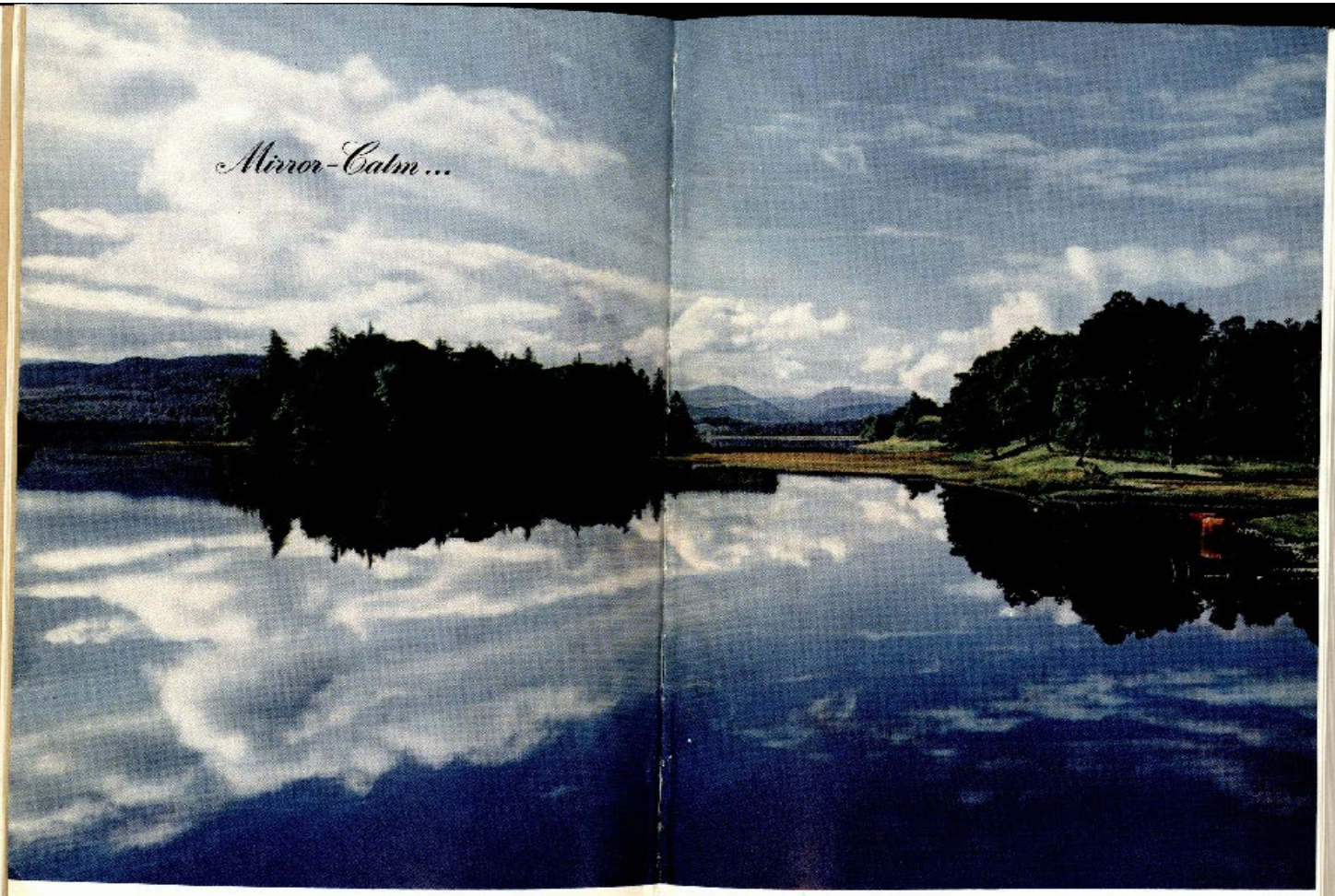
LAKESIDE

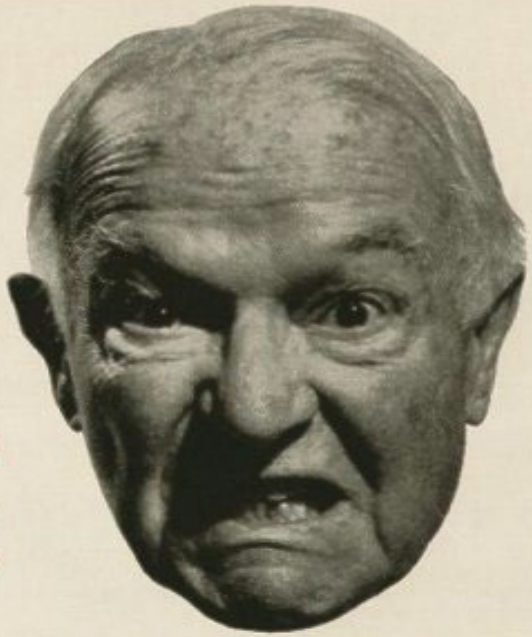
‘Antipsychotics’/neuroleptics

- When the first ‘antipsychotics’ (e.g. chlorpromazine) were introduced into psychiatry in France in 1952, they were initially regarded as special sorts of sedative

- Referred to as “neurological inhibitors,” then as a “neuroleptics” and major tranquilisers







Tyrant in the house?

'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.

On 'Thorazine' therapy, the patient often forms more regular eating and sleeping habits and improves in his personal hygiene. As the patient becomes more tractable and cooperative, he is able to live a composed and useful life.

THORAZINE*

chlorpromazine, S.K.F.

one of the fundamental drugs in medicine

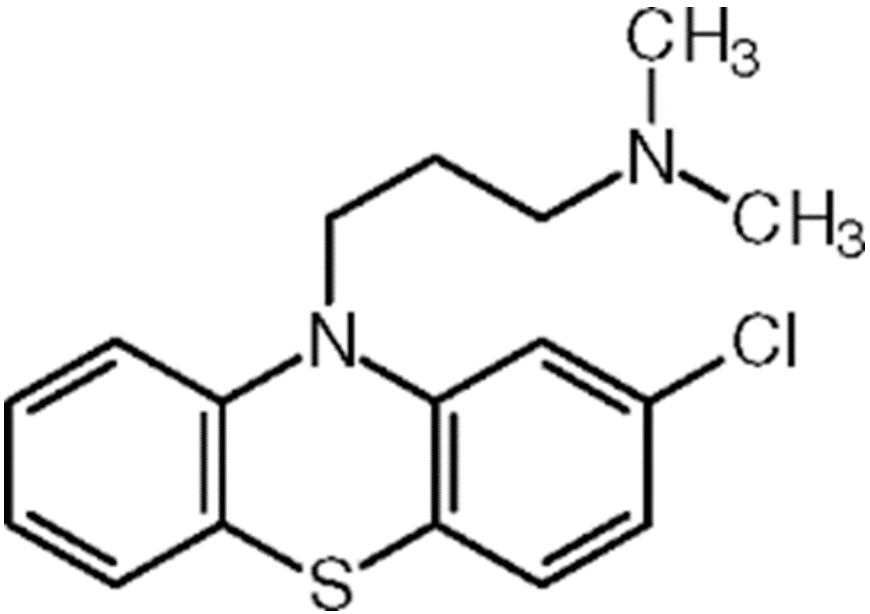
Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

Specificity of neuroleptics/antipsychotics

- During the 1960s they came to be seen as working in a more targeted or specific manner

- “they appear to do more than tranquilise” (Henderson & Gillespie 1962).



By 1970 they were regarded as disease-centred treatments that targeted the biological basis of psychiatric symptoms

in acute schizophrenia

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

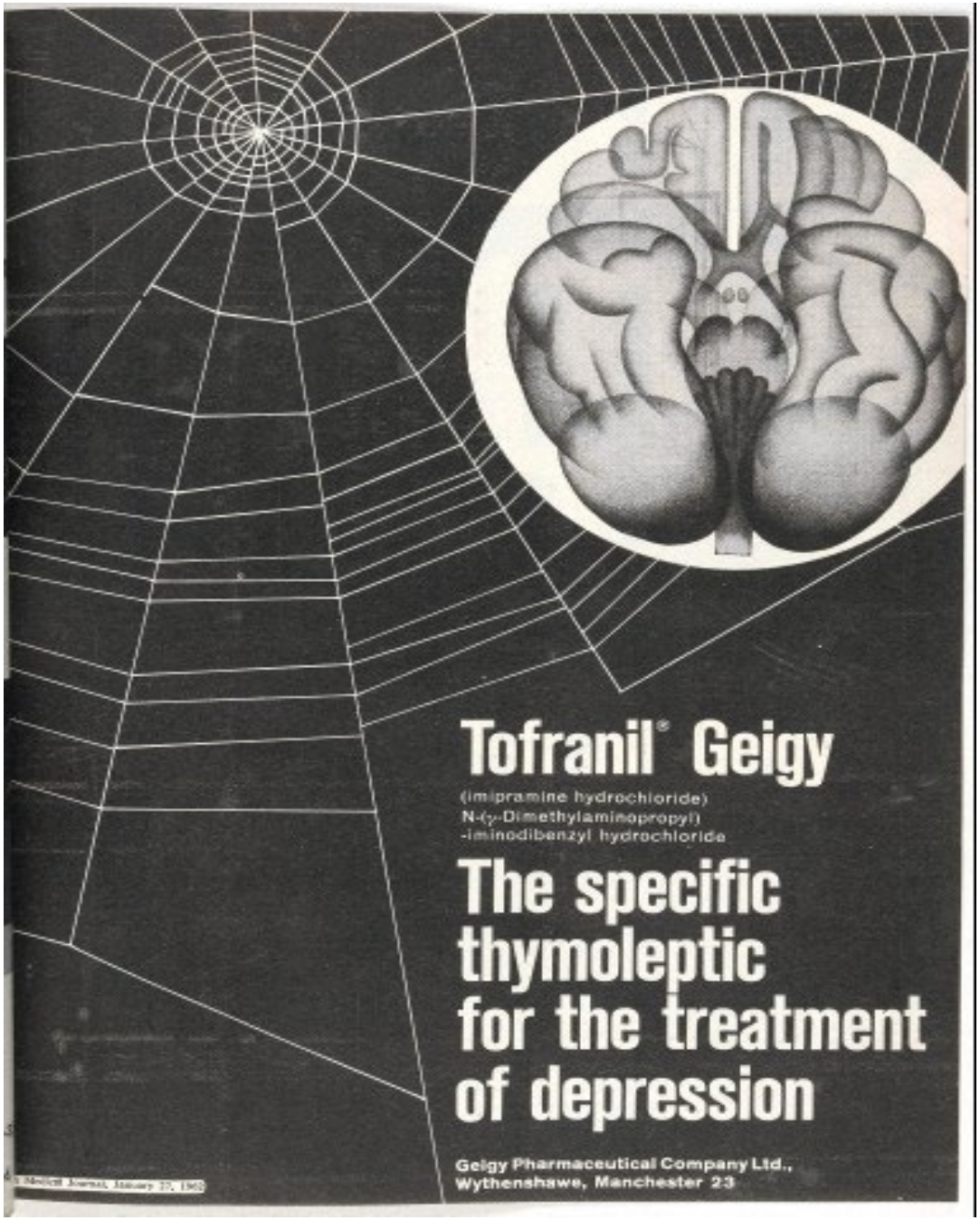
1 Canadian Medical Association Journal 84, 152, 1961. 2 Journal of the Arkansas Medical Society 58, 310, 1962. 3 American Journal of Psychiatry, 118, 740, 1962.

Sandoz Products Limited, Sandoz House, 23 Great Castle Street, London, W1N 8AE
Melleril is a registered trade mark.

SANDOZ

Specificity of antidepressants

- Early antidepressants were described as being similar to stimulants
- By 1960s, antidepressants “appear to act specifically against depressive symptoms” (Dally, 1967)


Tofranil® Geigy
(imipramine hydrochloride)
N-(γ-Dimethylaminopropyl)
-iminodibenzyl hydrochloride
The specific thymoleptic for the treatment of depression
Geigy Pharmaceutical Company Ltd.,
Wythenshawe, Manchester 23

Drug classification and terminology reflect these changes:

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)

Evidence for disease-centred model of drug action

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

Ideas about mental disorders being caused by deficiencies or abnormalities of brain chemicals (e.g. serotonin, noradrenalin, dopamine etc) have not been substantiated

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

References:

Moncrieff, J (2009) A critique of the dopamine hypothesis of schizophrenia and psychosis. *Harvard Review of Psychiatry*, 17 (3) 214-225

Kendler, K. S., & Schaffner, K. F. (2011). The dopamine hypothesis of schizophrenia: An historical and philosophical analysis. *Philosophy, Psychiatry, & Psychology, 18*(1), 41–63. https://doi.org/10.1353/ppp.2011.0005

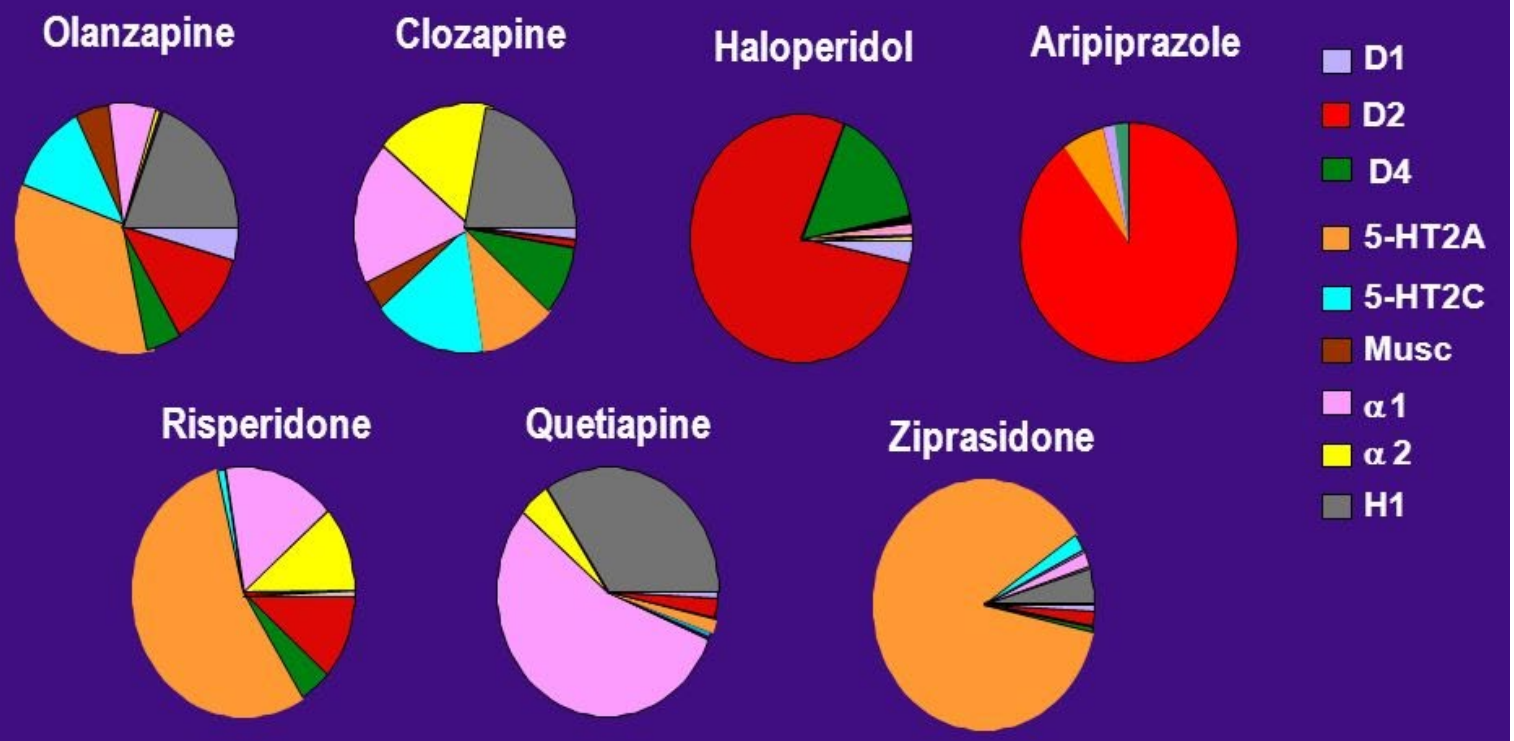
‘Antipsychotics, dopamine D_2 receptor occupancy and clinical improvement in schizophrenia: a meta-analysis’ Yilmaz et al, 2012

- **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 D_2 occupancy was limited to less than 80% in order to control for the appearance of extrapyramidal symptoms, **high D_2 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 D_2 occupancy is a contributing factor for the mechanism of antipsychotic effect in SCZ **for some but not all antipsychotic medications**.

Receptor Binding Profiles



Bymaster FP, et al. *Neuropsychopharmacology*. 1996;14(2):87-96.
Schotte A, et al. *Psychopharmacology (Berl)*. 1996;124(1-2):57-73.

Molecular Psychiatry www.nature.com/mp

SYSTEMATIC REVIEW OPEN

Check for updates

The serotonin theory of depression: a systematic umbrella review of the evidence

Joanna Moncrieff[1,2]✉, Ruth E. Cooper[3], Tom Stockmann[4], Simone Amendola[5], Michael P. Hengartner[6] and Mark A. Horowitz[1,2]

The serotonin hypothesis of depression is still influential. We aimed to synthesise and evaluate evidence on whether depression is associated with lowered serotonin concentration or activity in a systematic umbrella review of the principal relevant areas of research. PubMed, EMBASE and PsycINFO were searched using terms appropriate to each area of research, from their inception until December 2020. Systematic reviews, meta-analyses and large data-set analyses in the following areas were identified: serotonin and serotonin metabolite, 5-HIAA, concentrations in body fluids; serotonin 5-HT_{1A} receptor binding; serotonin transporter (SERT) levels measured by imaging or at post-mortem; tryptophan depletion studies; SERT gene associations and SERT gene-environment interactions. Studies of depression associated with physical conditions and specific subtypes of depression (e.g. bipolar depression) were excluded. Two independent reviewers extracted the data and assessed the quality of included studies using the AMSTAR-2, an adapted AMSTAR-2, or the STREGA for a large genetic study. The certainty of study results was assessed using a modified version of the GRADE. We did not synthesise results of individual meta-analyses because they included overlapping studies. The review was registered with PROSPERO (CRD42020207203). 17 studies were included: 12 systematic reviews and meta-analyses, 1 collaborative meta-analysis, 1 meta-analysis of large cohort studies, 1 systematic review and narrative

- Serotonin in body fluids
- Serotonin metabolite in CSF
- Serotonin receptors
- Serotonin transporter protein (SERT)
- Tryptophan depletion studies
- SERT gene studies and gene-stress interaction studies

The drug-centred model of antipsychotic action:

what sort of mental and behavioural alterations do antipsychotics produce?

Antipsychotic drug-induced effects

- Animal/healthy volunteers studies[1-7]

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 & Farquhar, 1999

Patient accounts of the alterations produced by ‘antipsychotics’

Comments from ‘askapatient.com’

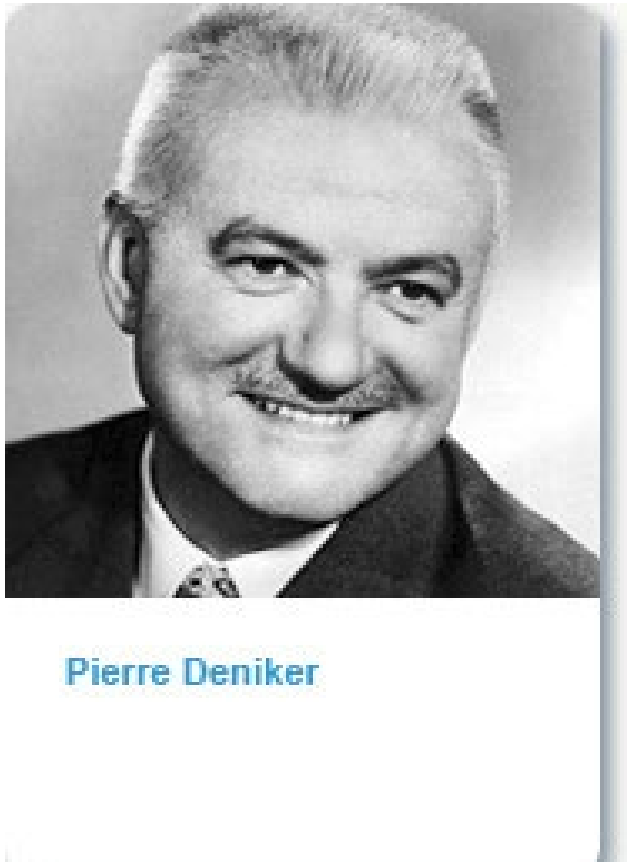
- *Mental and physical stagnance*
- *Emotionally empty, dead inside*
- *A weird spacey empty feeling*
- *Lethargy and indifference*

(Moncrieff et al, 2008)

In 1950s Deniker (and others) proposed that ‘antipsychotics’ (early ones) worked because they produced a mild form of Parkinson’s disease

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.



“the apparent **indifference**, or **delay in response** to external stimuli, the **emotional and affective neutrality,** the **decrease in both initiative and preoccupation** without alteration of conscious awareness or in intellectual faculties, constitute the psychic syndrome due to treatment”

Delay & Deniker, 1952

Early observations of drug-induced effects of antipsychotics

‘From the beginning it was evident that no lines of demarcation could be drawn between therapeutic degrees of reduced psychomotor activity and early symptoms of parkinsonism…

Clinical evidence therefore, indicated that the therapeutic function of chlorpromazine and reserpine could not be separated from their modifying influence on the function of the subcortical motor system in transacting volitional, affective and intentional functions’ (Freyhan, 1959) (P10).

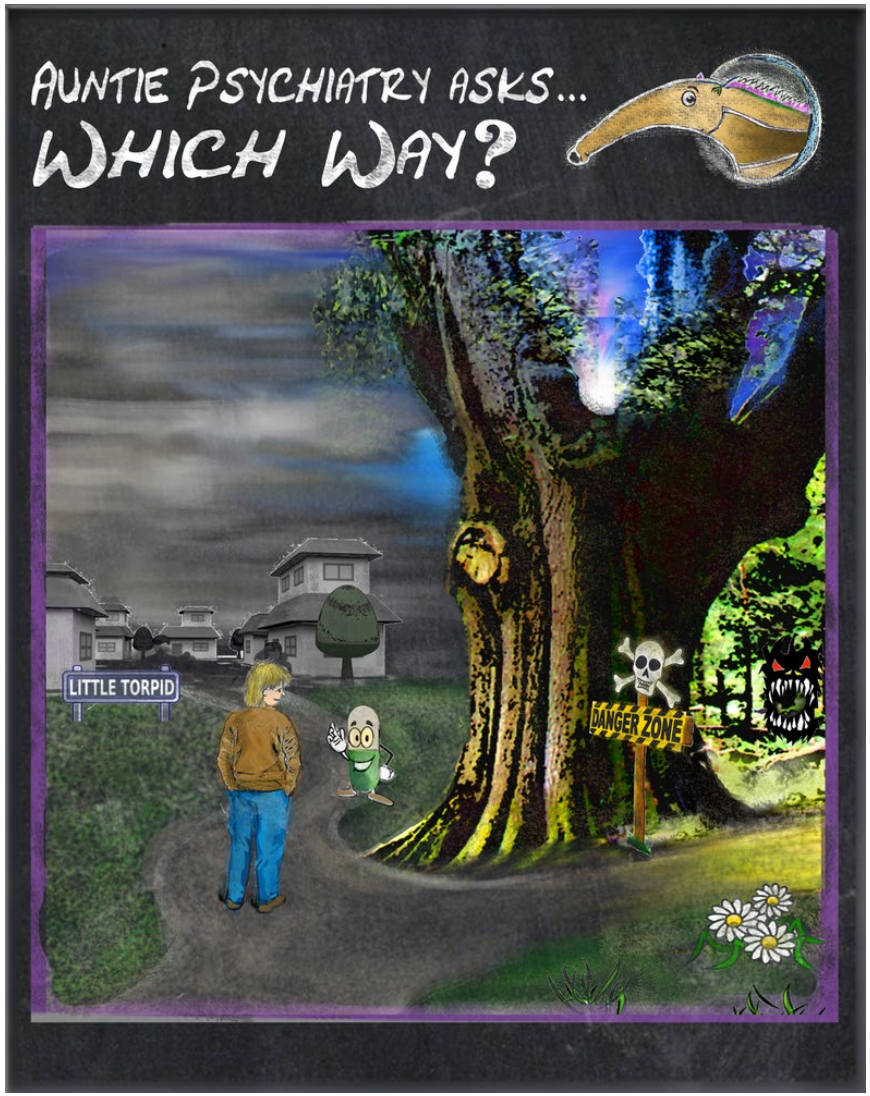
Impact on symptoms

Dimension of psychotic experience	Reduction in dimension after 6 weeks of antipsychotic treatment
Behavioural impact	64%
Cognitive preoccupation	51%
Emotional involvement	56%
Conviction	25%
External perspective	0

The main impact of antipsychotics is on behavioural disturbance, emotional state and cognitive preoccupation

Mizrahi et al, 2006

“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)



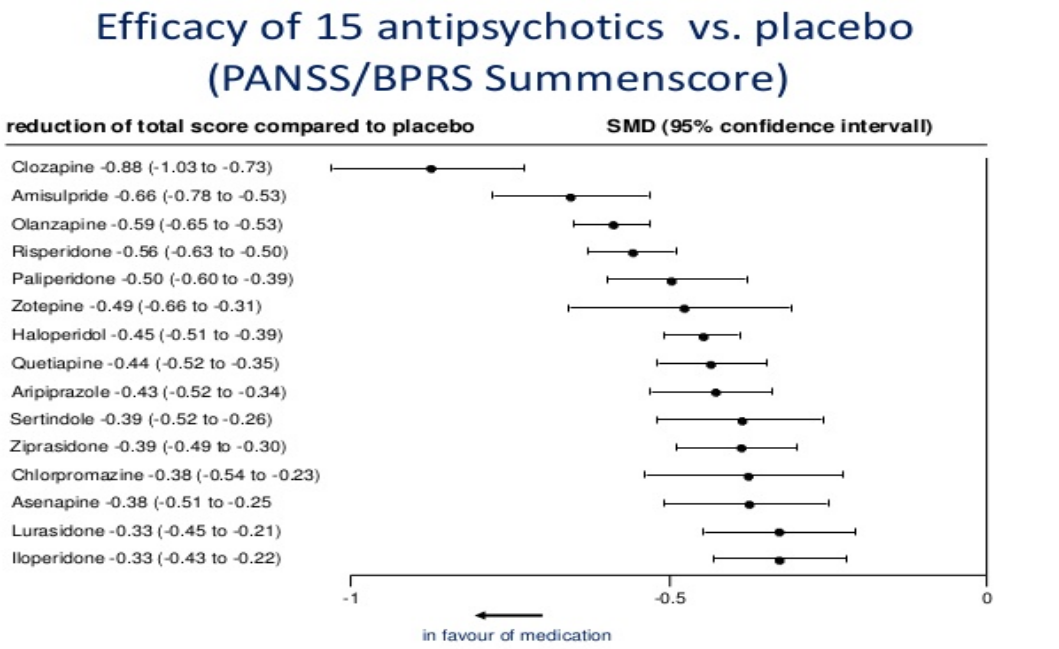
“Rottenly normal” (Oliver Sack’s brother)

A drug centred approach to the treatment of psychosis

- Immediate effects of antipsychotics may be useful to suppress acute psychotic symptoms- but they are disliked and alternative approaches may be possible (Francey et al, 2020)

- ? Benefits of long-term treatment are less clear

Efficacy of antipsychotics



Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Are antipsychotics needed for an acute episode of psychosis?

- Minimal medication approaches have had some success in the past: e.g. the Soteria project (reviewed by Cooper et al, 2020)
- Recent pilot trial (Francey et al, 2020) showed no difference between placebo and antipsychotics on primary outcome at 6 months (SOFAS) in context of intensive, high quality psychosocial care

Evidence for the benefits of long-term treatment with antipsychotics

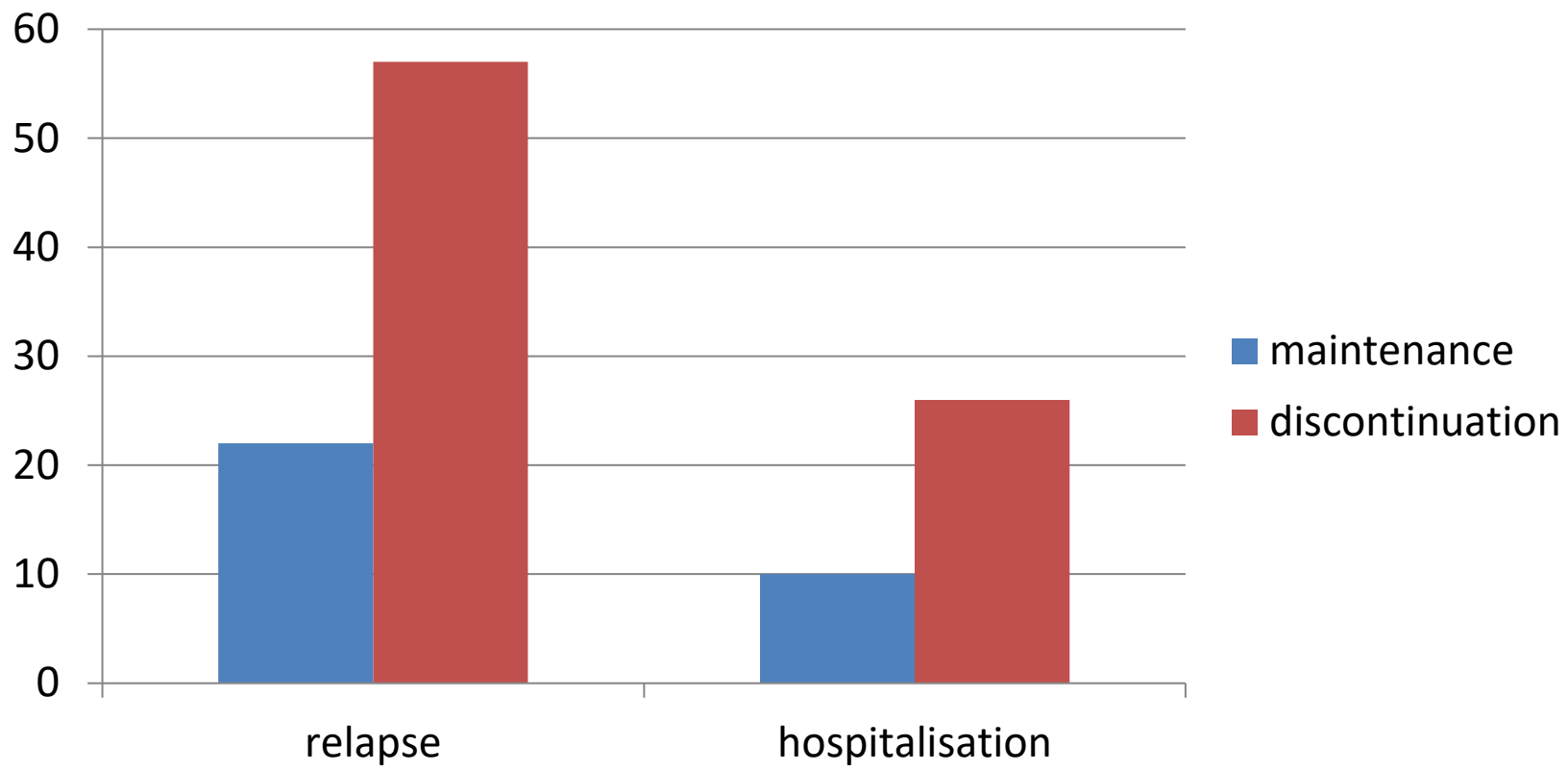
Leucht et al, 2012.

- Meta-analysis: 65 RCTs, total n = 6493 patients
- Relapse - maintenance treatment: 22%
- Relapse - antipsychotic discontinuation: 57%

Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis

Stefan Leucht, Magdolna Tardy, Katja Komossa, Stephan Heres, Werner Kissling, Georgia Salanti, John M Davis

RCTs of antipsychotic discontinuation show that it is associated with higher relapse rates compared to maintenance treatment (Leucht et al, 2012)



Limitations of antipsychotic maintenance studies

- Evidence consists of antipsychotic d*iscontinuation* 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

Cohort studies finding better outcomes for people with psychosis not taking antipsychotic medication compared with those taking continuous antipsychotic medication:

- Harrow et al, 2007; 2012 (Chicago)
- Morgan et al, 2014 (AESOP study)
- Wils et al, 2017 (OPUS trial)
- Moilenan et al, (Northern Finnish birth cohort, 2016)

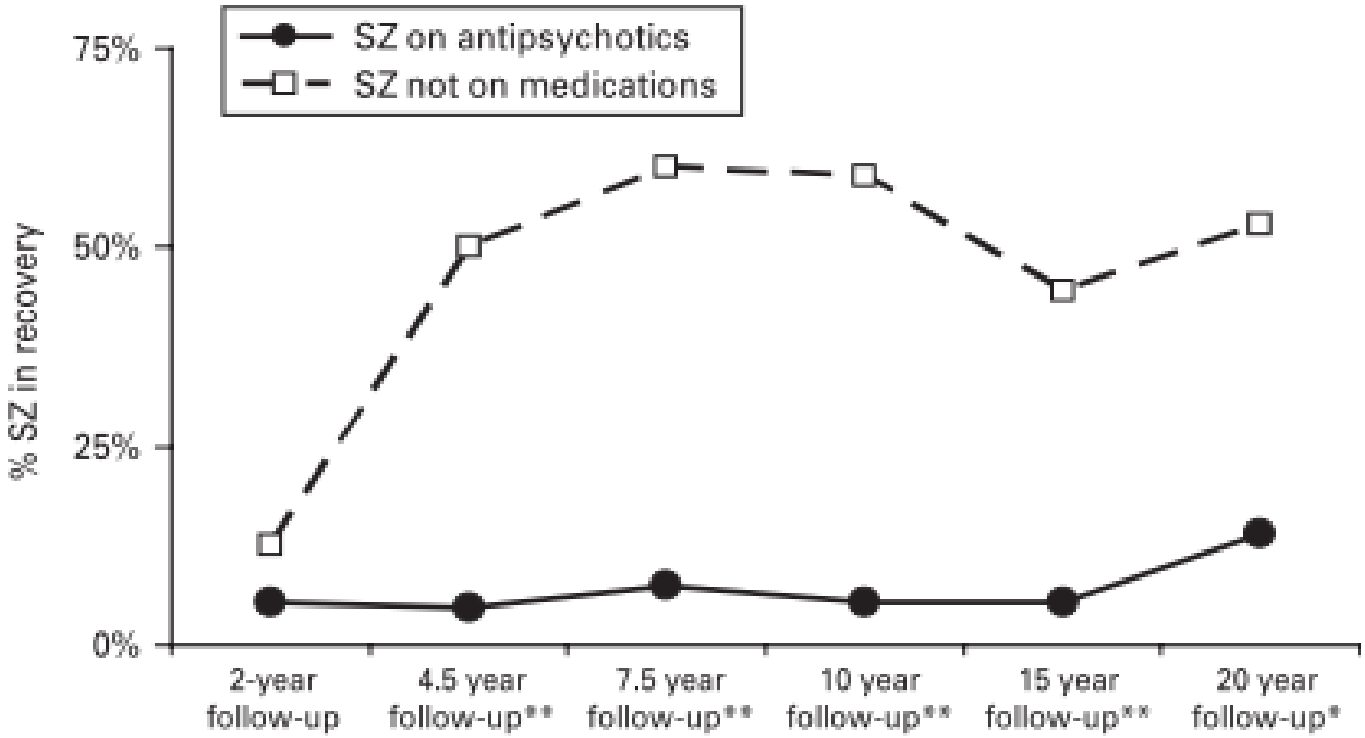
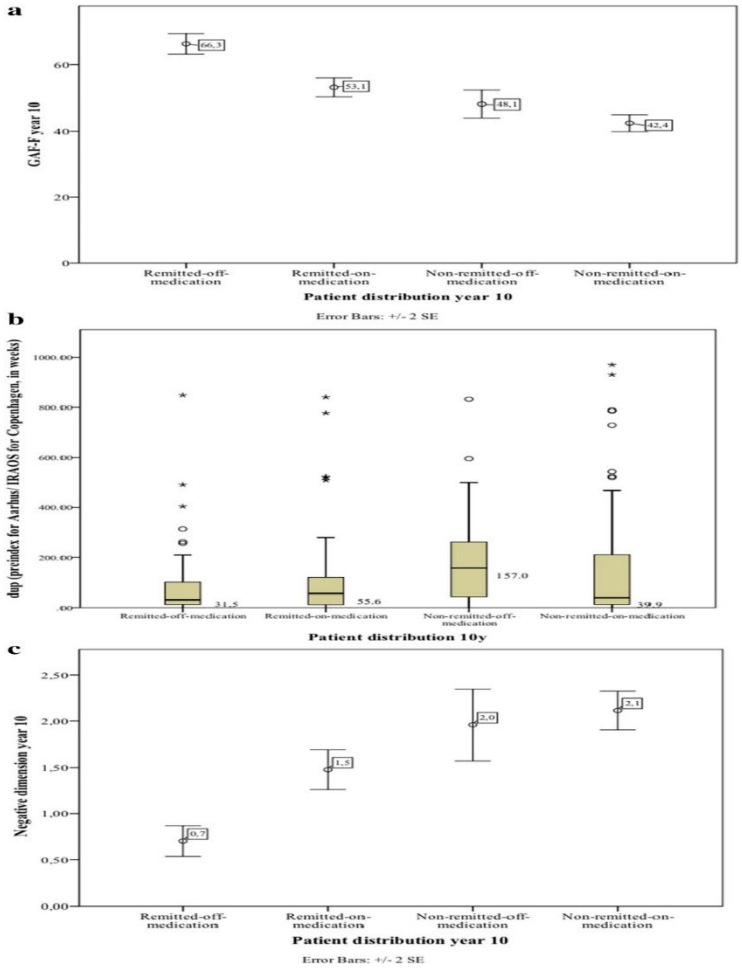


Figure 1. Relationship between recovery and use of antipsychotics in schizophrenia (SZ). *p < 0.01, **p<0.001

Harrow et al, 2012



Wunderink et al, 2013 - 7 year follow-up

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. (%)		
	DR (n = 52)	MT (n = 51)	Total Sample (n = 103)
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

But long-term outcomes may be different: Wunderink et al, (2013): 7 year follow-up of a randomised trial

- DR = dose reduction/ discontinuation
- MT = maintenance treatment

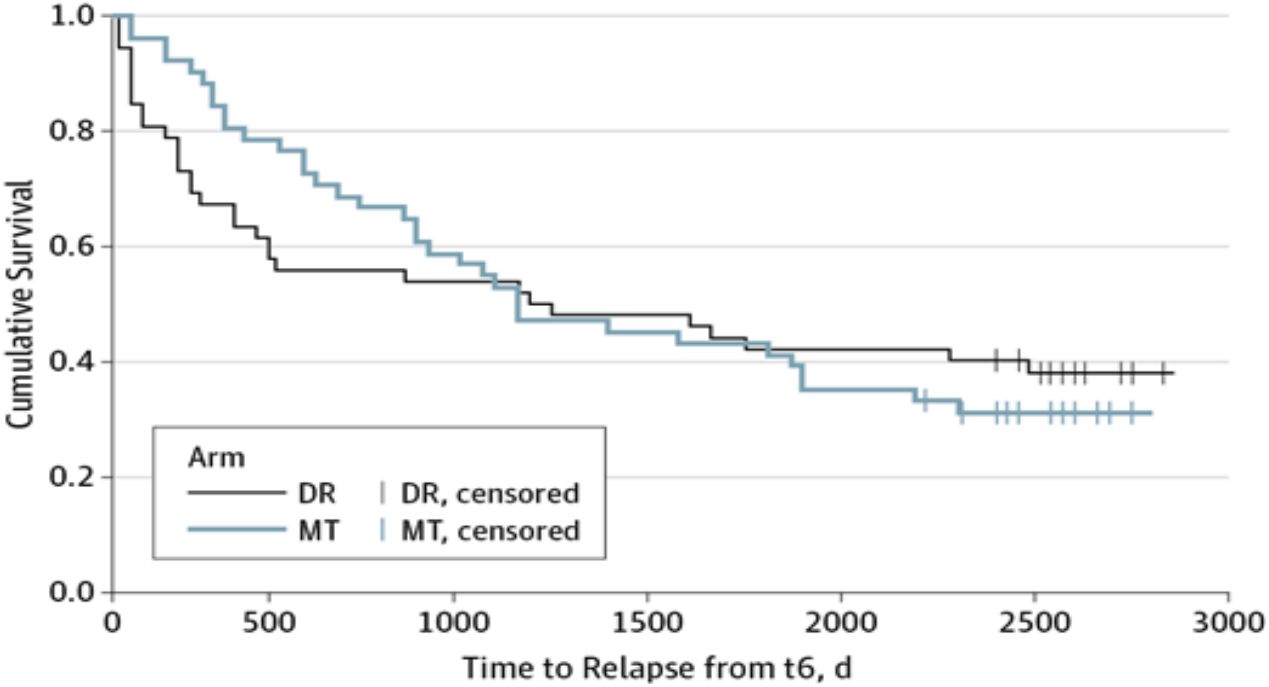


Figure 1. Time to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18-months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT)

Wunderink et al, 2013

Long-term effects of discontinu

https://www.ncbi.nlm.nih.gov/pubmed/29551618

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Lancet Psychiatry. 2018 May;5(5):432-442. doi: 10.1016/S2215-0366(18)30090-7. Epub 2018 Mar 15.

Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial.

Hui CLM[1], Honer WG[2], Lee EHM[3], Chang WC[4], Chan SKW[4], Chen ESM[3], Pang EPF[5], Lui SSY[6], Chung DWS[7], Yeung WS[8], Ng RMK[9], Lo WTL[10], Jones PB[11], Sham P[12], Chen EYH[4].

Author information

Abstract

BACKGROUND: The long-term consequences of discontinuing antipsychotic medication after successful treatment of first-episode psychosis are not well studied. We assess the relation between early maintenance therapy decisions in first-episode psychosis and the subsequent clinical outcome at 10 years.

METHODS: This is a 10 year follow-up study, spanning Sept 5, 2003, to Dec 30, 2014, of a randomised, double-blind trial in seven centres in Hong Kong in which 178 patients with first-episode psychosis with full positive symptom resolution after at least 1 year of antipsychotic treatment were given maintenance treatment (n=89; oral quetiapine 400 mg daily) or early treatment discontinuation (n=89; placebo) for 12 months. After the trial, patients received naturalistic treatment. Overall this cohort of patients will have received about 3 years of treatment before entering the follow-up phase of the study: about 2 years of maintenance treatment before study entry and 1 year of treatment in the trial. The primary outcome of this follow-up was the proportion of patients in each group (including those for whom direct follow-up was not available) with good or poor long-term clinical outcomes at 10 years, with poor outcome defined as a composite of persistent psychotic symptoms, a requirement for clozapine treatment, or death by suicide. The randomised trial was registered with ClinicalTrials.gov, number NCT00334035, and the follow-up study was registered with ClinicalTrials.gov, number NCT01926340.

FINDINGS: Poor 10 year clinical outcome occurred in 35 (39%) of 89 patients in the discontinuation group and 19 (21%) of 89 patients in the maintenance treatment group (risk ratio 1·84, 95% CI 1·15-2·96; p=0·012). Suicide was the only serious adverse event that occurred in the follow-up phase (four [4%] patients in the early discontinuation group vs two [2%] in the maintenance group).

INTERPRETATION: In patients with first-episode psychosis with a full initial response to treatment, medication continuation for at least the first 3 years after starting treatment decreases the risk of relapse and poor long-term clinical outcome.

FUNDING: Food and Health Bureau, Research Grants Council of Hong Kong, and AstraZeneca.

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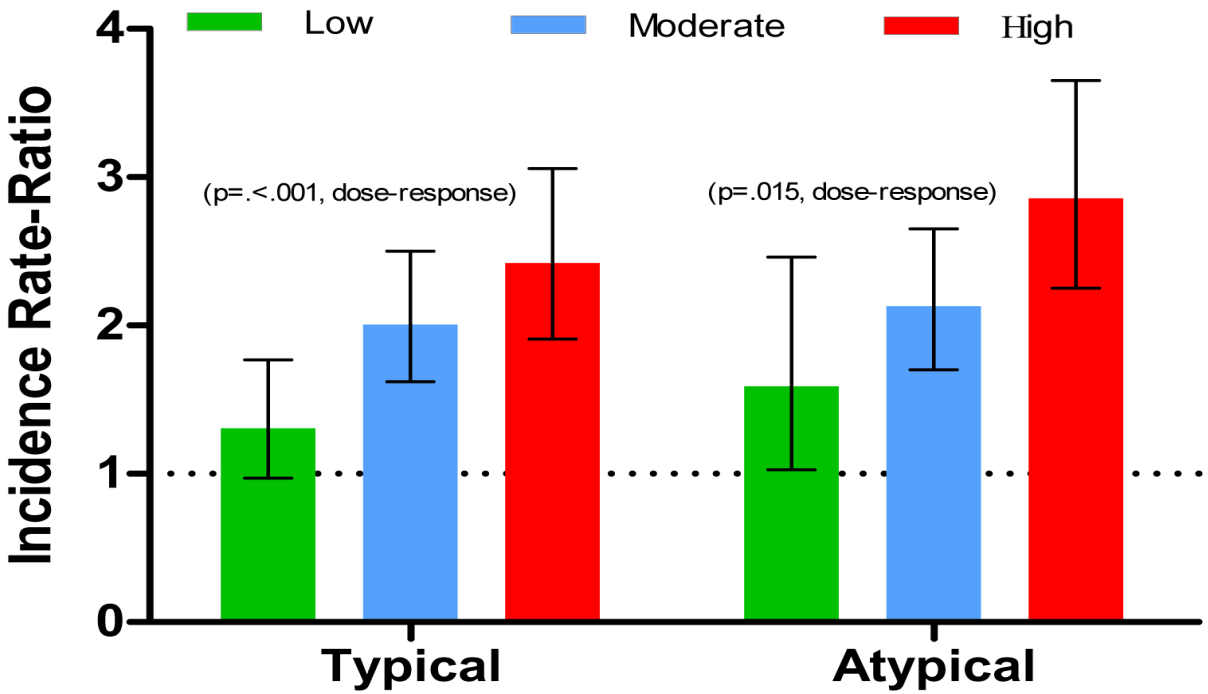
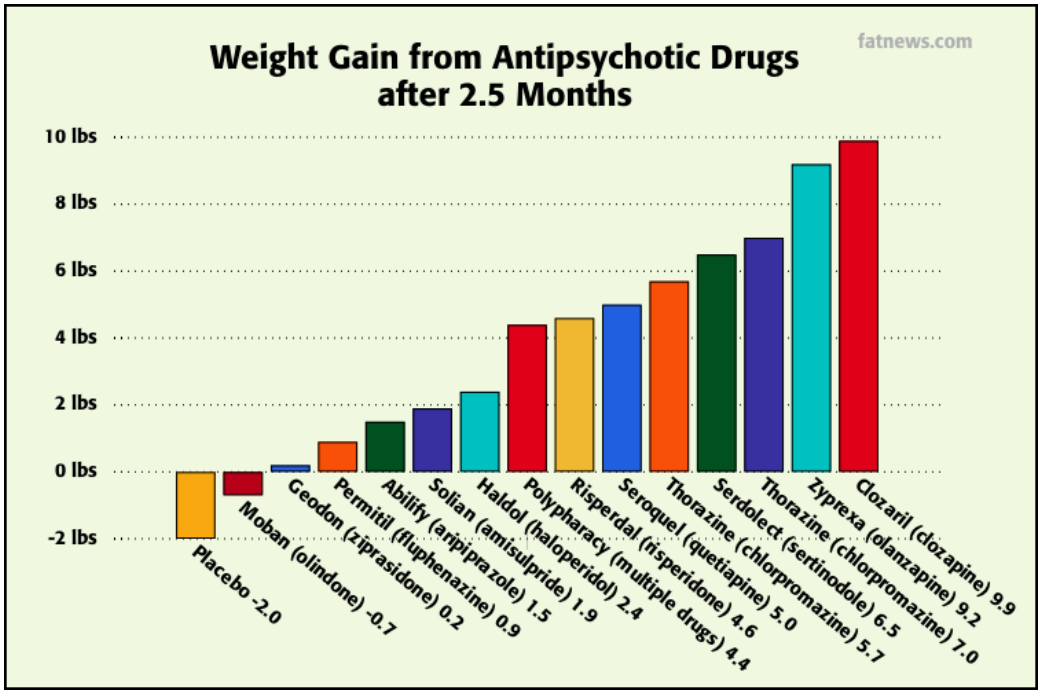
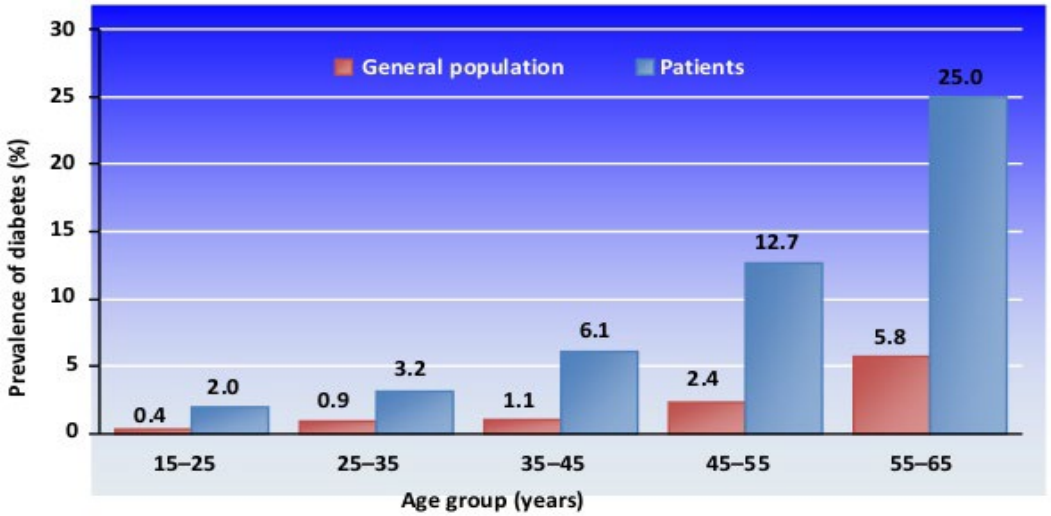
Antipsychotics and sudden death. Ray et al, 2009, NEJM



	Typical			Atypical		
Deaths	46	104	105	22	108	93
Person-years	21,438	33,671	31,626	10,435	41,513	27,641
IRR	1.31	2.01	2.42	1.59	2.13	2.86
95% CI	0.97-1.77	1.62-2.50	1.91-3.06	1.03-2.46	1.70-2.65	2.25-3.65


Weight Gain from Antipsychotic Drugs
after 2.5 Months
fatnews.com
10 lbs
8 lbs
6 lbs
4 lbs
2 lbs
0 lbs
-2 lbs
Placebo -2.0
Moban (olindone) -0.7
Geodon (ziprasidone) 0.2
Permitil (fluphenazine) 0.9
Abilify (aripiprazole) 1.5
Solian (amisulpride) 1.9
Haldol (haloperidol) 2.4
Polypharacy (multiple drugs) 4.4
Risperdal (risperidone) 4.6
Seroquel (quetiapine) 5.0
Thorazine (chlorpromazine) 5.7
Serdolect (sertindole) 6.5
Thorazine (chlorpromazine) 7.0
Zyprexa (olanzapine) 9.2
Clozaril (clozapine) 9.9

Prevalence of diabetes in schizophrenia compared to general population



De Hert et al 2006

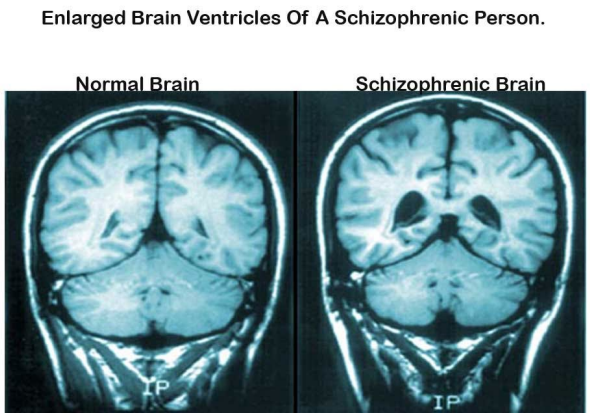
Sexual side effects very common

Antipsychotic Drugs	Sexual side effects in Men	Sexual side effects in women
Risperidone	Erectile or ejaculatory dysfunction Azoospermia Gynaecomastia	Infertility Decreased libido
Olanzapine	Reduced libido Erectile or ejaculatory dysfunction	Reduced libido Decreased lubrication
Amisulpride	Gynaecomastia Reduced libido	Amenorrhea
Haloperidol	Decreased libido Erectile dysfunction Ejaculatory disorder	Decreased libido Arousal disorder
Clozapine	Gynaecomastia Decreased libido	Decreased libido Impaired arousal
Quetiapine	Decreased libido Impaired arousal	Decreased libido Impaired arousal
Arpiprazole	Decreased libido Ejaculatory dysfunction	Arousal difficulty Delayed orgasm

Table 1: Sexual side effect of both typical and atypical antipsychotic drugs.

Antipsychotics and brains: evidence of brain volume reduction with antipsychotics

- Cross-sectional studies
- Longitudinal studies
- Animal studies
- Meta-analyses



Antipsychotics cause 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

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Increasing expectations and knowledge require a more subtle use of prophylactic antipsychotics

Robin M. Murray [1] and Marta Di Forti [1]

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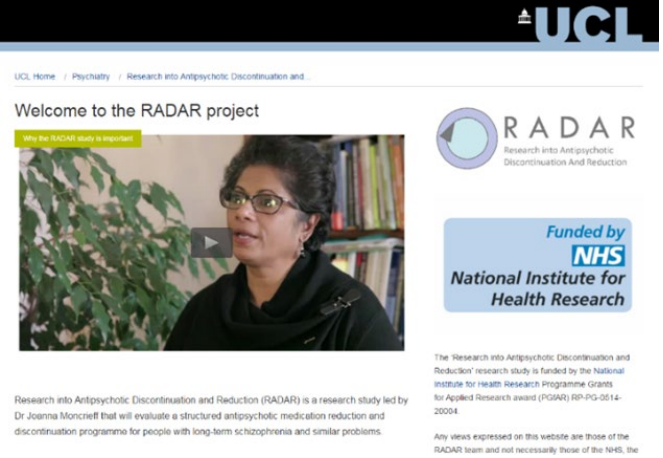
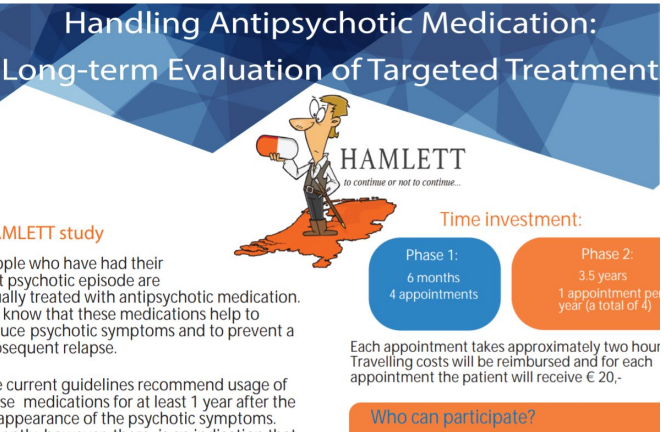
Those who comment on the use of antipsychotics in 2018 face two challenges. The first stems from rising expectations. The move from incarceration of psychotic people in asylums to care in the community has transformed the lives of many in Western European countries. Undoubtedly, antipsychotics played a major role in facilitating this. Furthermore, there is overwhelming evidence that antipsychotics are essential in acute psychosis and that many patients will benefit from taking them for a period thereafter.

However, as care has improved, so expectations of recovery have increased. This has been accompanied by calls for patients and relatives to have a greater voice in planning care. In some countries, their representatives have been incorporated into policy making1. In others, patients have been relegated to shouting their criticisms from offstage. One example of the latter is the website "Mad in America" (https://www.madinamerica.com); a brief look should cause any psychiatrist to reflect on why antipsychotics attract such opprobrium from many of those they are intended to help.

It is in this context that the prescription of antipsychotics for prevention of recurrence, rather than treatment of active symptoms, should be considered. Drugs intended to be taken prophylactically need to be extremely safe and tolerable; witness the arguments concerning the pros and cons of statins. In recent years, concern has been raised about the risk/benefit ratio of prophylactic antipsychotics2. The paper by Correll et al3 is the second of two responses from the psychopharmacological establishment, and takes a less dogmatic approach than its predecessor4.

Correll et al accept that most antipsychotics increase the risk of obesity and the metabolic syndrome. Their review addresses, but fails to resolve, the paradox that we clinicians commonly see the adverse effects of antipsychotics on the physical health of our patients, yet mortality appears to be lower in those patients who





Antipsychotic reduction and discontinuation trials ongoing:

RADAR trial, UK

HAMLETT trial, the Netherlands;

REDUCE trial, Australia;

TAILOR study, Denmark;

Gadem trial, Taiwan

Bipolar disorder: what is it?

- Classical ‘manic depression’ (bipolar 1)
- Bipolar II
- Bipolar spectrum disorder
- ‘Mood instability’
- Paediatric bipolar disorder

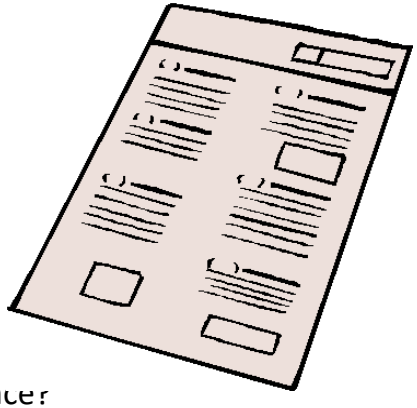
Bipolar expansion

- 20th century: Manic depression (classical bipolar 1) affects less than 1 in 1000 people (Healy et al, 2008)

- Angst et al 1998 suggest: 5% have bipolar 1; 11% have bipolar 2

- Angst et al 2003 suggest; 24% have ‘bipolar spectrum’

Bipolar symptoms test



- Does your self confidence range from great self doubt to equally great over-confidence?
- Are there great variations in the quantity and quality of work you produce?
- Do you have periods of dullness and other periods of creative thinking?

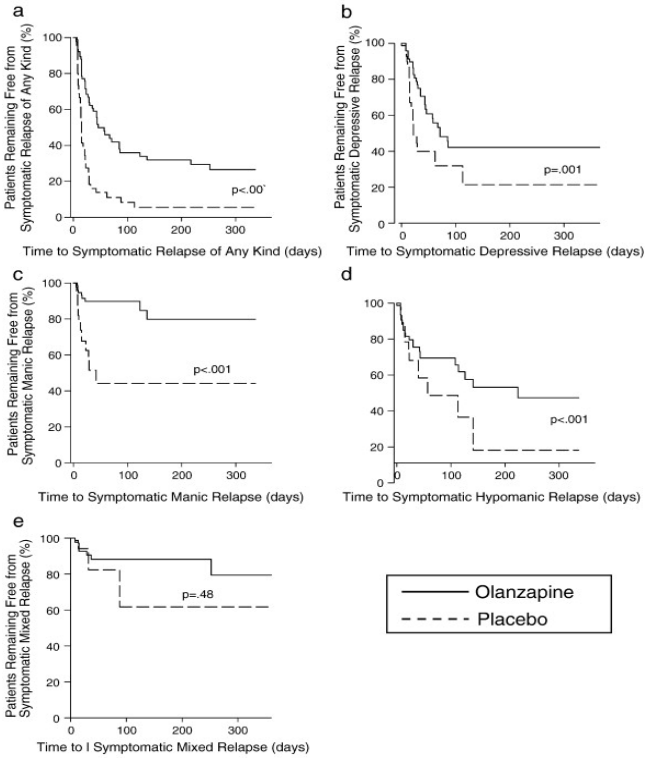
‘symptoms’ are on a continuum with ordinary character traits and everyday mood variation and functioning- therefore anyone can view themselves as having it


MOOD SWINGS SETTING YOUR TONE?
Don't let bipolar disorder distort your life.
Ask a doctor if Abilify is right for you.
ABILIFY®
RESONATE FOR THE RIGHT REASON

There's no such thing as a 'mood stabiliser'

- Concept established by Abbot Laboratories to market Depakote in 1990s (Harris et al, 2003)
- All so called 'mood stabilisers' are sedative agents
- Volunteers studies show lithium does not reduce mood fluctuations (and no research on other medications)
- Research on 'mood stabilisers' shows that continuation treatment reduces the risk of relapse (mostly of mania) compared with discontinuation in people with classical manic depression or bipolar 1
- Significant discontinuation effect
- Almost no research in people who have other types of bipolar disorder

Discontinuation effects in a maintenance treatment trial



The drug-centred model of antidepressant action:

what sort of mental and behavioural alterations do antidepressants produce?

Antidepressant-induced alterations: volunteer studies and patient reports of alterations

Tricyclics

- Sedation
- Cognitive impairment
- Dysphoria

SSRIs

- More subtle
- Emotional numbness
- Reduced libido and other sexual dysfunction
- Lethargy
- Agitation especially in younger people (possibly associated with suicidal impulses and aggression)
- Dysphoria at higher doses

SSRI antidepressants

Type of change	mechanism	experience
Immediate changes	? Increased serotonin activity	Emotional blunting, sexual dysfunction, lethargy, agitation
Long-term effects	?	Emotional blunting, sexual dysfunction, lethargy – maybe worsening
Withdrawal effects	?	agitation, anxiety, dizziness, loss of balance etc
Persistent effects	?	sexual dysfunction, others?

The drug-centred model of antidepressant action

- Interaction of psychoactive effects and symptoms may lead to lessening or obscuring of symptoms e.g. emotional numbness may reduce intensity of emotions

- Placebo and amplified placebo effects also relevant

Are these effects useful in depression?

- Difference between antidepressants and placebo is 0.3 SMD
- Equates to around 2 points on Hamilton Rating Scale for depression (maximum points 54)

Implications of different models of drug action: the disease-centred model

Drugs reverse or ameliorate an unwanted biological process or ‘disease’ that gives rise to symptoms

Forced treatment justified because most people agree that disease is a bad thing and that brain disease can affect judgement

Implications of the Drug-centred model

Psychoactive drugs change people's usual selves or character to varying extents

Forced treatment means that **other people** prefer the drug-induced state to the individual's previous behaviour – when 'treatment' is given long-term this can be thought of as **character modification** using drugs

Democratic, consensual drug treatment

- Psychoactive drugs change people's usual selves or character to varying extents
- People's response to drug-induced effects vary (how much they like them, whether they find them useful)
- Antipsychotics can reduce psychotic symptoms and anxiety, but also suppress emotions and general thinking
- If the drug is prescribed to help the individual (not for social control) then the individual has to find the drug effects preferable (less disabling and unpleasant) to their symptoms

Why these issues are important

"Unfortunately, my personality has been so stifled that I sometimes think that the richness of my pre-injection days - even with brief outbursts of madness - is preferable to the numbed cabbage that I have become. I am advised by all doctors to continue with my injections and will do so, but in losing my periods of madness **I have to pay with my soul, and the price of health seems twice as high as Everest.**"

Peter Wescott, 1979, BMJ