



Regional  
Affective  
Disorders  
Service

Newcastle, North Tyneside   
and Northumberland  
Mental Health NHS Trust

# Drug Treatments for Mental Illnesses: Advances, Controversies and Scandals

**Hamish McAllister-Williams**

Reader in Clinical Psychopharmacology  
and Honorary Consultant Psychiatrist  
Regional Affective Disorders Service  
RVI, Newcastle

# Agenda

- Introduction to Psychopharmacology
  - Drugs and psychiatric illness
  - The evolution of psychopharmacology
  - The place of psychopharmacology in psychiatry
- Clinical Psychopharmacology
  - Introduction to drugs
  - The practice of psychopharmacology
  - Controversies in psychopharmacology

# **Drugs and Psychiatric Illness**

# Why is the use of drugs in psychiatry different from using drugs in other branches of medicine?

- Fundamental nature of psychiatric illnesses
- Attitudes and beliefs of patients (and health care professionals)
- Pharmacological complexity of psychotropic drugs
- Drugs are but one treatment modality

# Nature of psychiatric illnesses

- “The general principles that govern treatment may be simply stated. We may begin with the axiom that a psychological illness demands psychological treatment, and that purely physical remedies can never be more than subsidiary”
  - Walshe (1947)

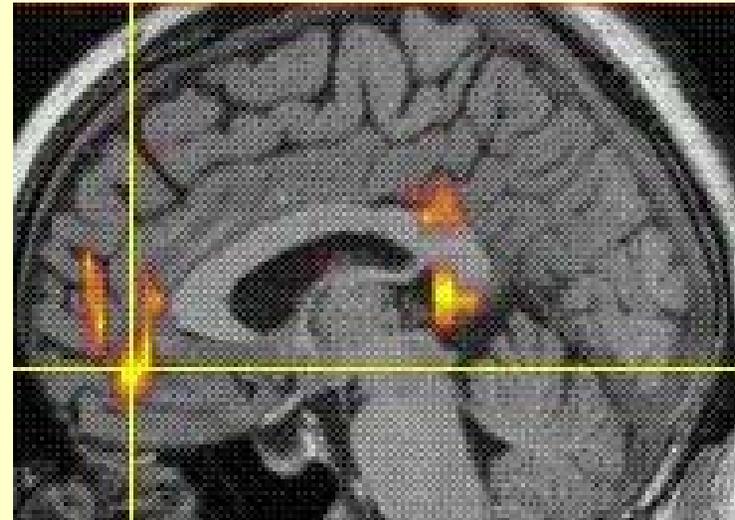
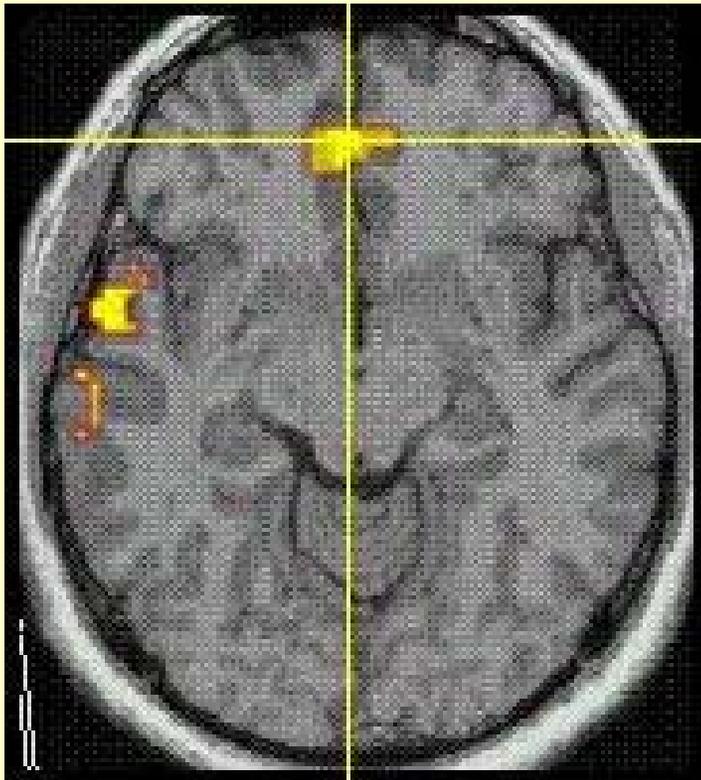
# Nature of psychiatric illness: Implications for treatment

- “...[a] psychological method of approach is both futile and harmful to the subject of a true depressive [illness]....Until his illness undergoes a spontaneous recovery he must be carefully guarded [because of the risk of suicide]”
  - Walshe 1947

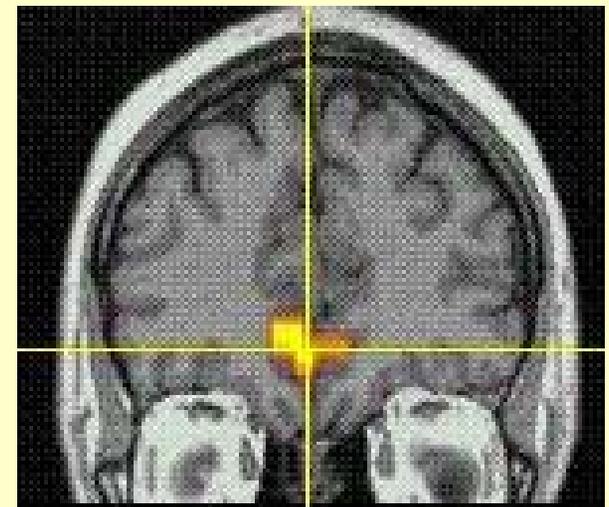
# Nature of psychiatric illnesses: Alternative views

- “The boundary between organic diseases and the so-called functional disease or neurosis is entirely imaginary....Disease is inconceivable without some physical underlying basis. The lesion need not be visible microscopically; it may be molecular or bio-chemical.”
  - Stewart (1908)

Changes in neural activity *positively* correlated (at  $p=0.001$ ) with anhedonia score in depressed subjects during happy mood induction.



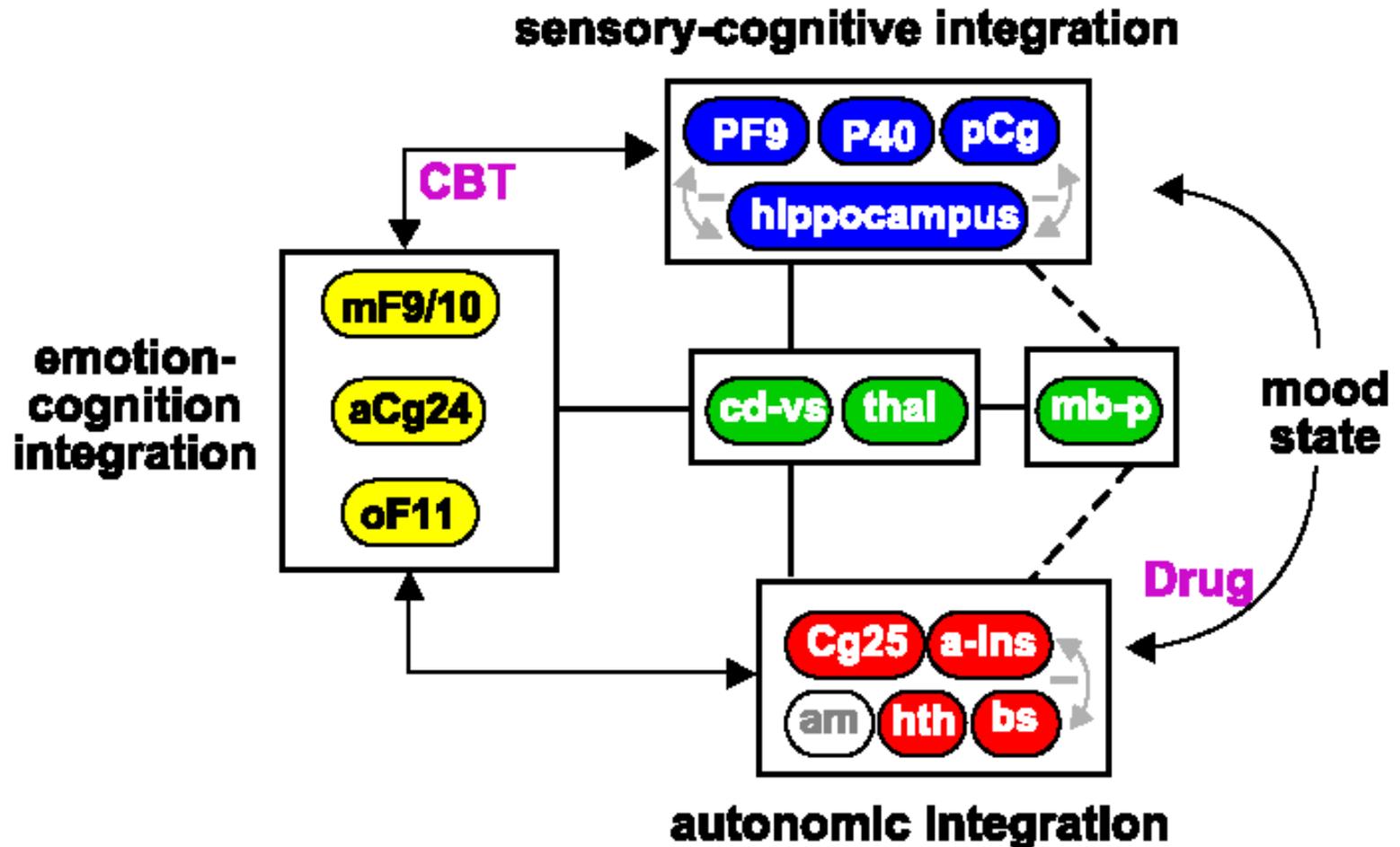
Main areas of activation: medial frontal gyrus (-5, 42.3, -10.4) and ant. part of middle temporal gyrus (-56.7, 0.4, -11.8)



# The biology of psychiatric illness: Current perspectives

- All major psychiatric illnesses have a significant genetic component
  - Multiple genes of small effect
- Neuroendocrine (e.g. HPA axis) abnormalities consistently found in different disorders
- Structural and functional neuroimaging identifying specific abnormalities in a range of loci in various disorders

# Treatment effects (Seminowicz et al. 2004)



# Models of Psychiatric Illness

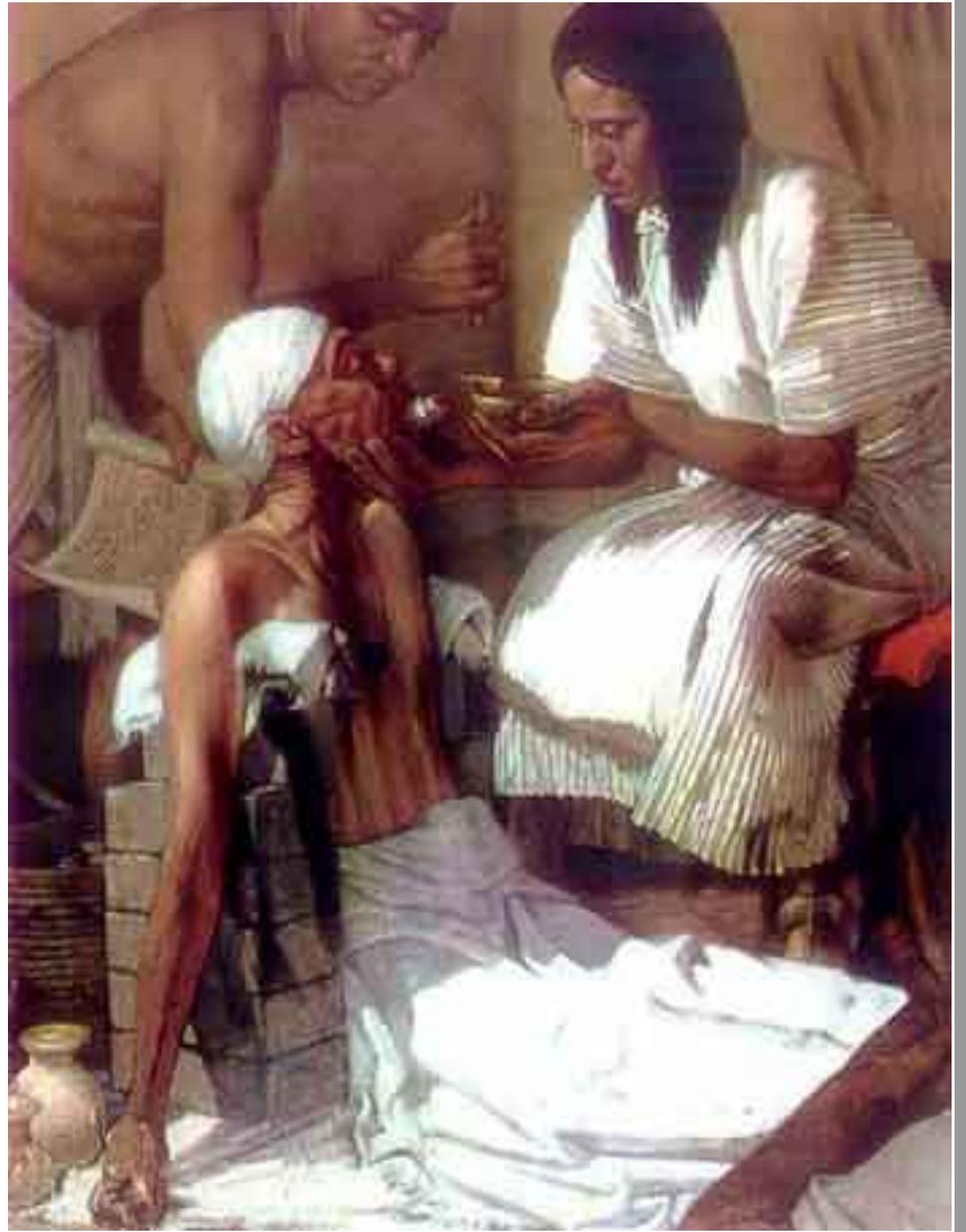
- Medical Model
  - disorders have distinct pathologies
  - psychiatry a branch of medicine
  - aetiology involves genetics and biochemistry
  - diagnosis and prescription reasonably exact and will improve
- Social Model
  - disorders problems in human relationships
  - psychiatry should be a 'helping' profession
  - drugs and ECT simply suppress distress and may be a form of social control
  - medical labels are stigmatising

# Decision to treat with drugs

- Doctor factors
  - conceptual model
  - diagnosis
  - counter transference
  - individual factors (knowledge, training, preference)
- Patient factors
  - conceptual model
  - expectations
  - knowledge base (role of media)
  - fears of medication (S.E.'s, Addiction)
  - severity of illness
  - trust in doctor

# **The Evolution of Psychopharmacology**

# Ancient Egypt 3000 - 1000 B.C.

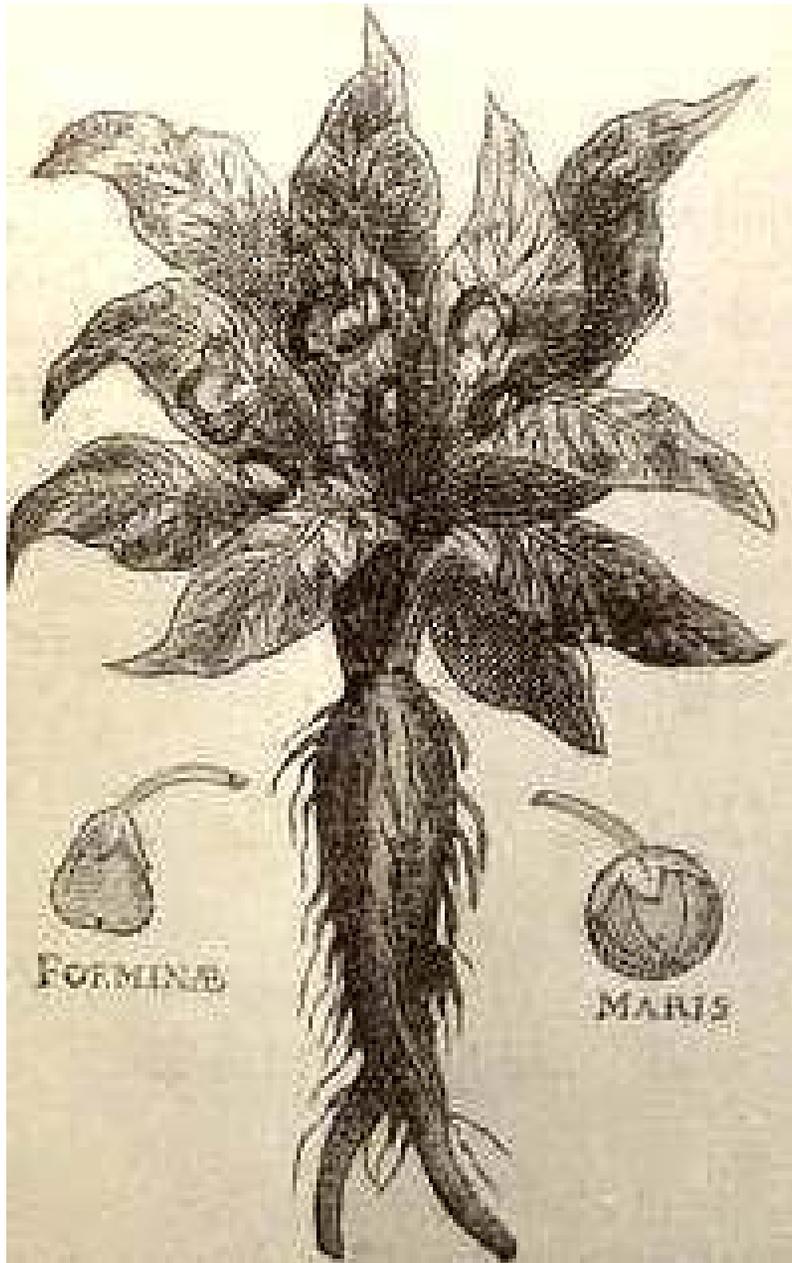


# Ancient Greece



# Ancient Greece





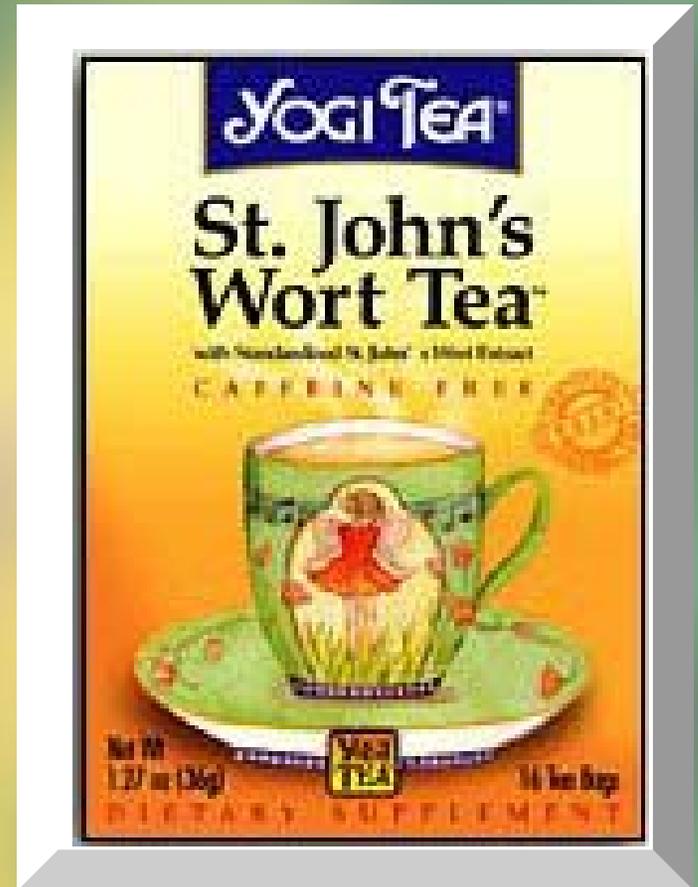
# The Dark Ages of Psychopharmacology

## Antiquity .... Until 19th Century!

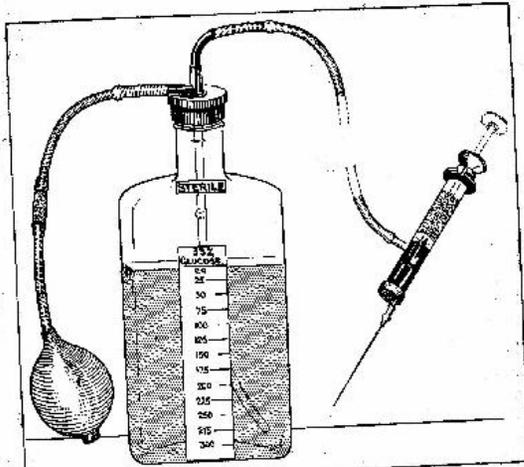
- Principles of Hippocrates lost
  - returned to ideas of possession etc
  - ideas of clinical trials ignored
- Many different treatments used including:
  - ingestion of animal, vegetable and mineral
  - physical treatments - *Torpedo*, restraint, burning at the stake

# Historical Treatment of the Patient with Severe Acute Mania





# 1900-1949



# THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—36TH YEAR.

SYDNEY, SATURDAY, SEPTEMBER 3, 1949.

No. 10.

## LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

By JOHN F. J. CADGE, M.D.,  
*Senior Medical Officer, Victorian Department  
of Mental Hygiene.*

LITHIUM SALTS enjoyed their hey-day in the latter half of last century when, commencing with their introduction by Garrod, they were vaunted as curative in gout, and so doubtless in a multitude of other so-called gouty manifestations. This followed the demonstration that lithium urate was the most soluble of the urates. It was shown that if pieces of cartilage with urate deposits were immersed in solutions of sodium, potassium and lithium carbonate, the urate was dissolved first from that piece immersed in the lithium carbonate solution.

As time went on and lithia tablets were consumed on an ever-increasing scale for an ever-increasing range of ailments, the toxic and depressant effects were more and more commonly seen.

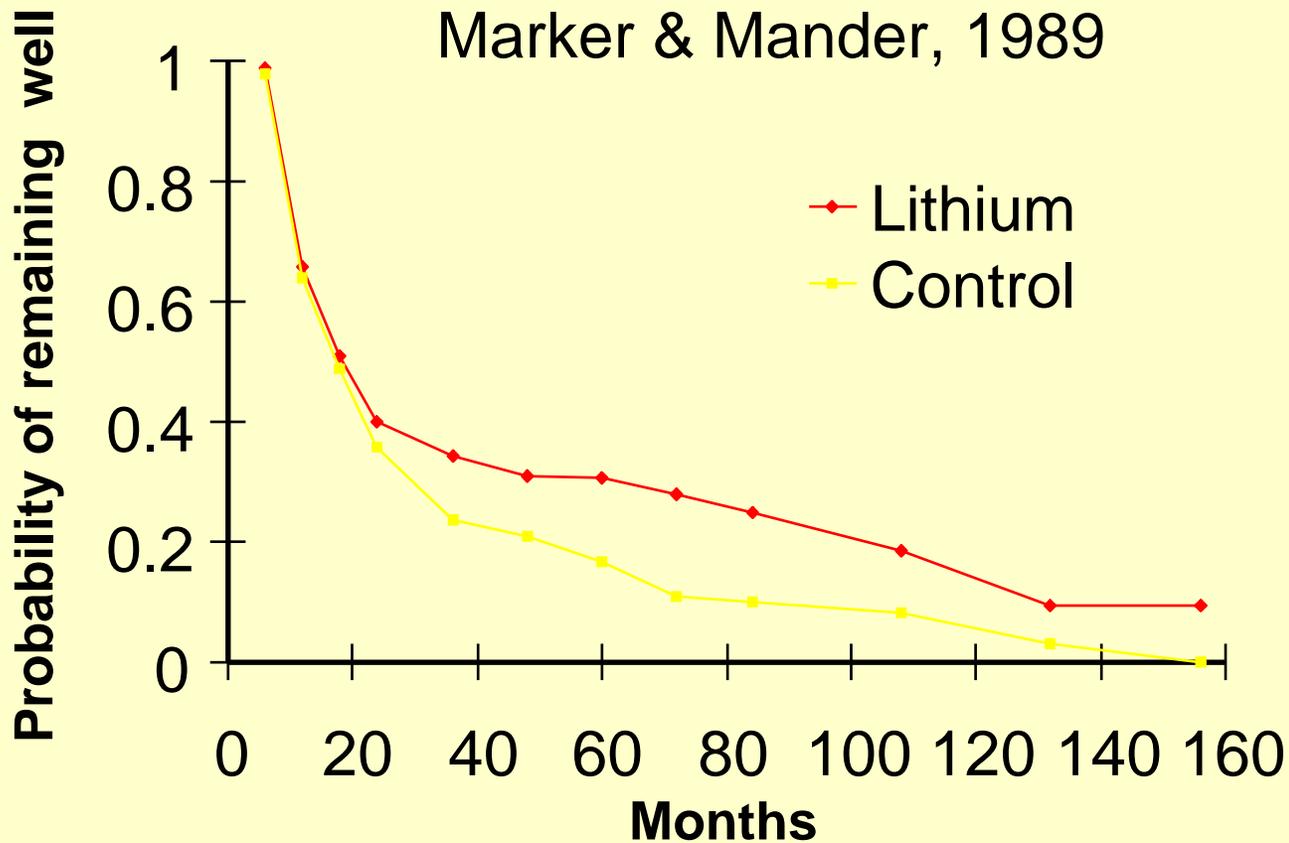
Garrod (1859) wrote of lithium carbonate: "When given internally in doses of from one to four grains dissolved in water, two to three times a day, it produces no direct physiological symptom . . . their use does not appear to be attended with any injurious consequences." And certainly, in that dosage, there should never be any toxic symptoms.

guinea-pigs, it appeared desirable to ascertain whether uric acid enhanced this toxicity. The great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen—the lithium salt. When an aqueous solution of 8% urea, saturated with lithium urate, was injected, the toxicity was far less than was expected. It looked as if the lithium ion might have been exerting a protective effect. To determine this, more observations were made, lithium carbonate being used instead of lithium urate. An 8% aqueous solution of urea kills five out of ten guinea-pigs when injected intraperitoneally in doses of 1.25 millilitres per ounce of body weight. When 0.5% lithium carbonate in an 8% urea solution was injected in the same dosage, all ten animals survived; and this argued a strong protective function for the lithium ion against the convulsant mode of death caused by toxic doses of urea.

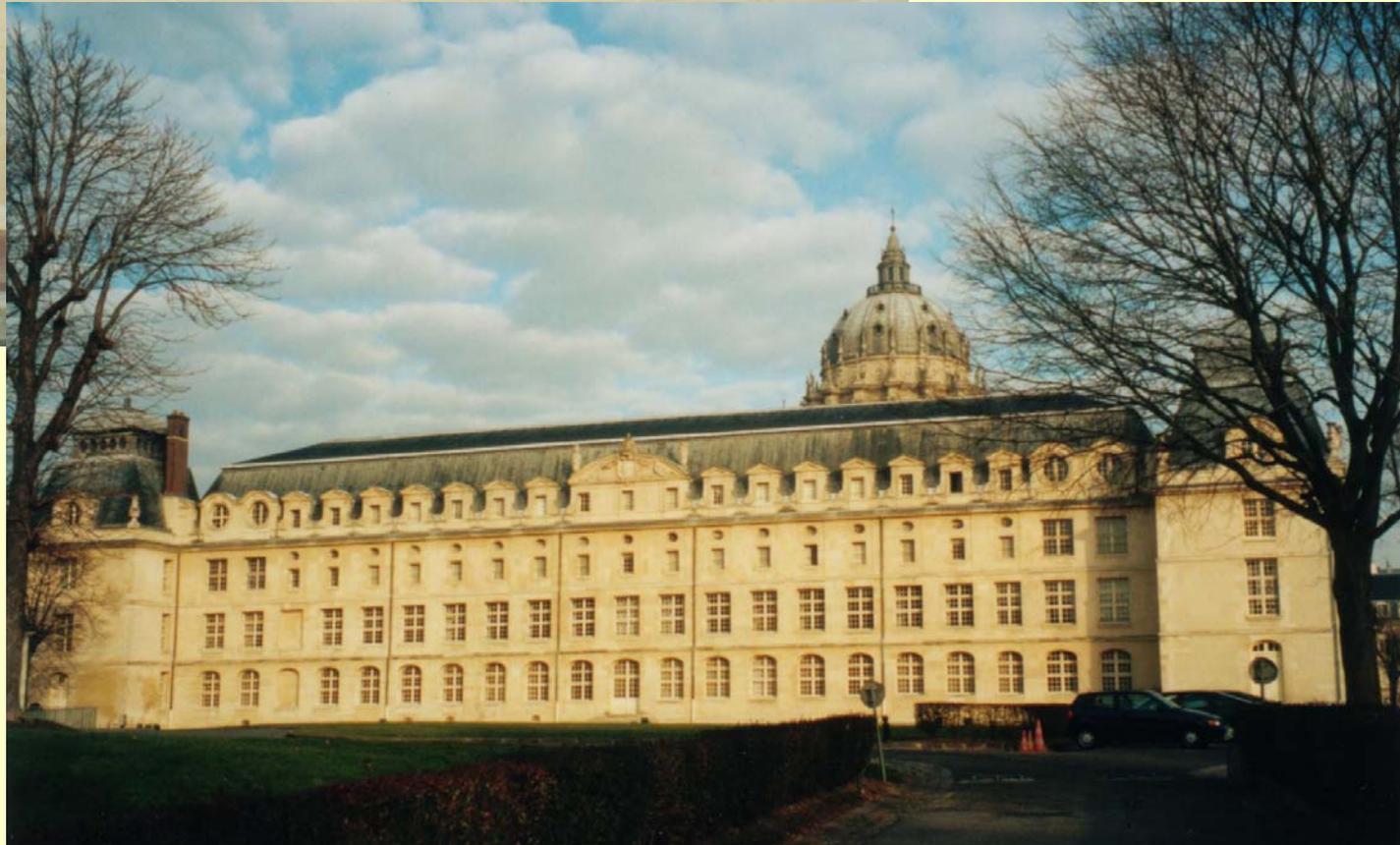
To determine whether lithium salts *per se* had any discernible effects on guinea-pigs, animals were injected intraperitoneally with large doses of 0.5% aqueous solution of lithium carbonate. A noteworthy result was that after a latent period of about two hours the animals, although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active and timid.

It may seem a long distance from lethargy in guinea-pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.

# Efficacy of Drug Treatments - Lithium Prophylaxis



HOPITAL D'INSTRUCTION DES ARMEES  
DU VAL DE GRACE

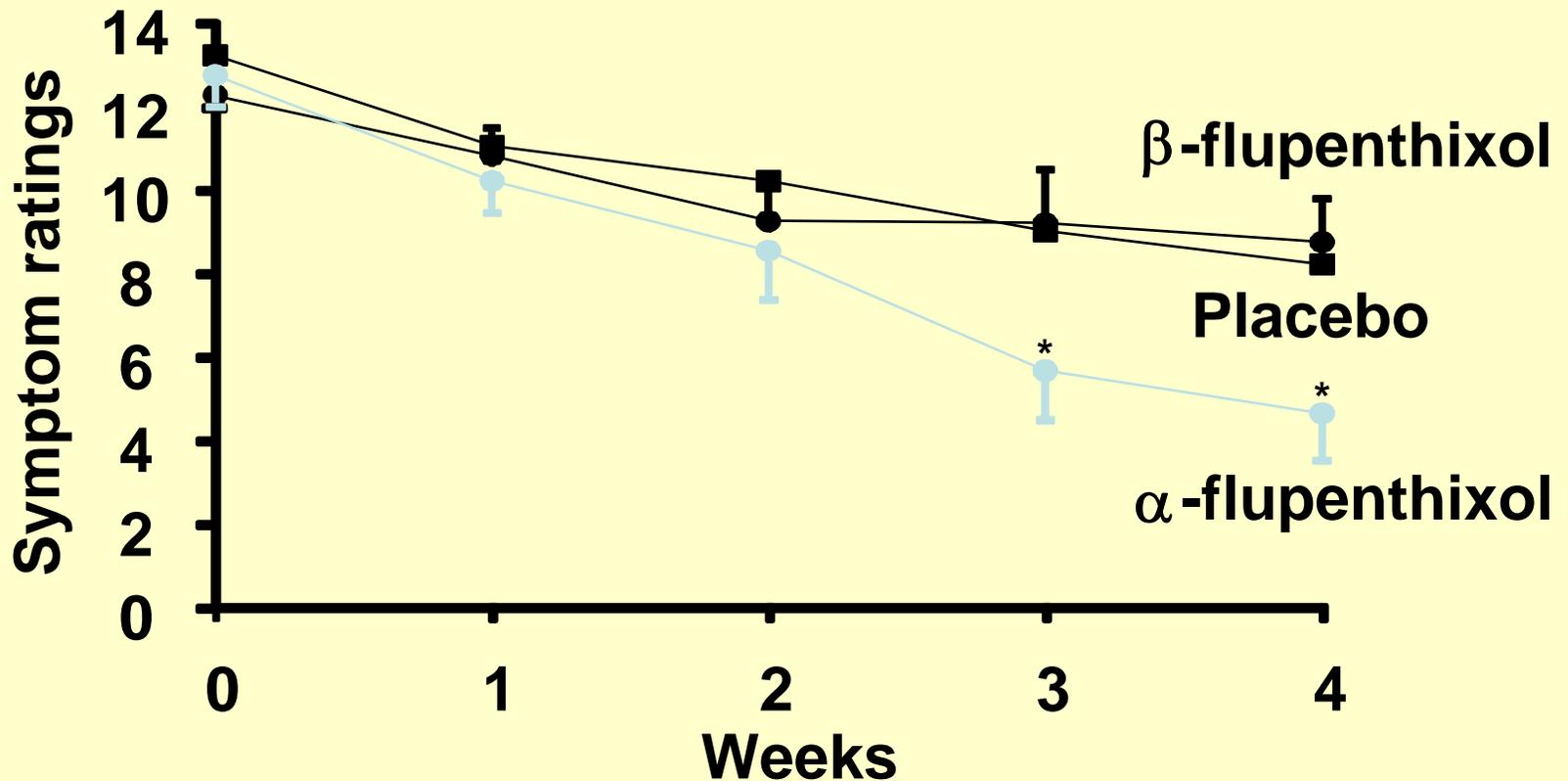


# Development of Chlorpromazine

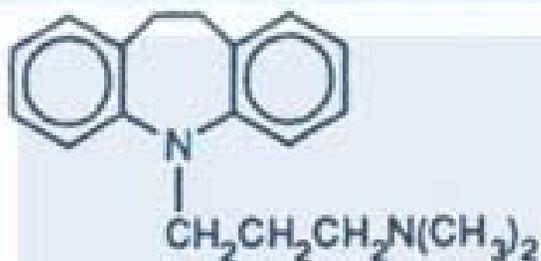
- Laborit (1949) - promethazine introduced into surgery (antihistamine)
  - Suggested tranquilized rather than sedated (neuroleptic)
- Chlorpromazine developed
- Paraire (1952), Val de Grace Hosp. Paris
- Sigwald (1953) - CPZ good in psychiatry
  - easy to use and quick acting
  - shortened hospital stays
  - useful for prophylaxis
- Used throughout the world within 5 years

# Efficacy of Drug Treatments - Antipsychotics

Johnstone et al. 1978 - Treatment of Schizophrenia

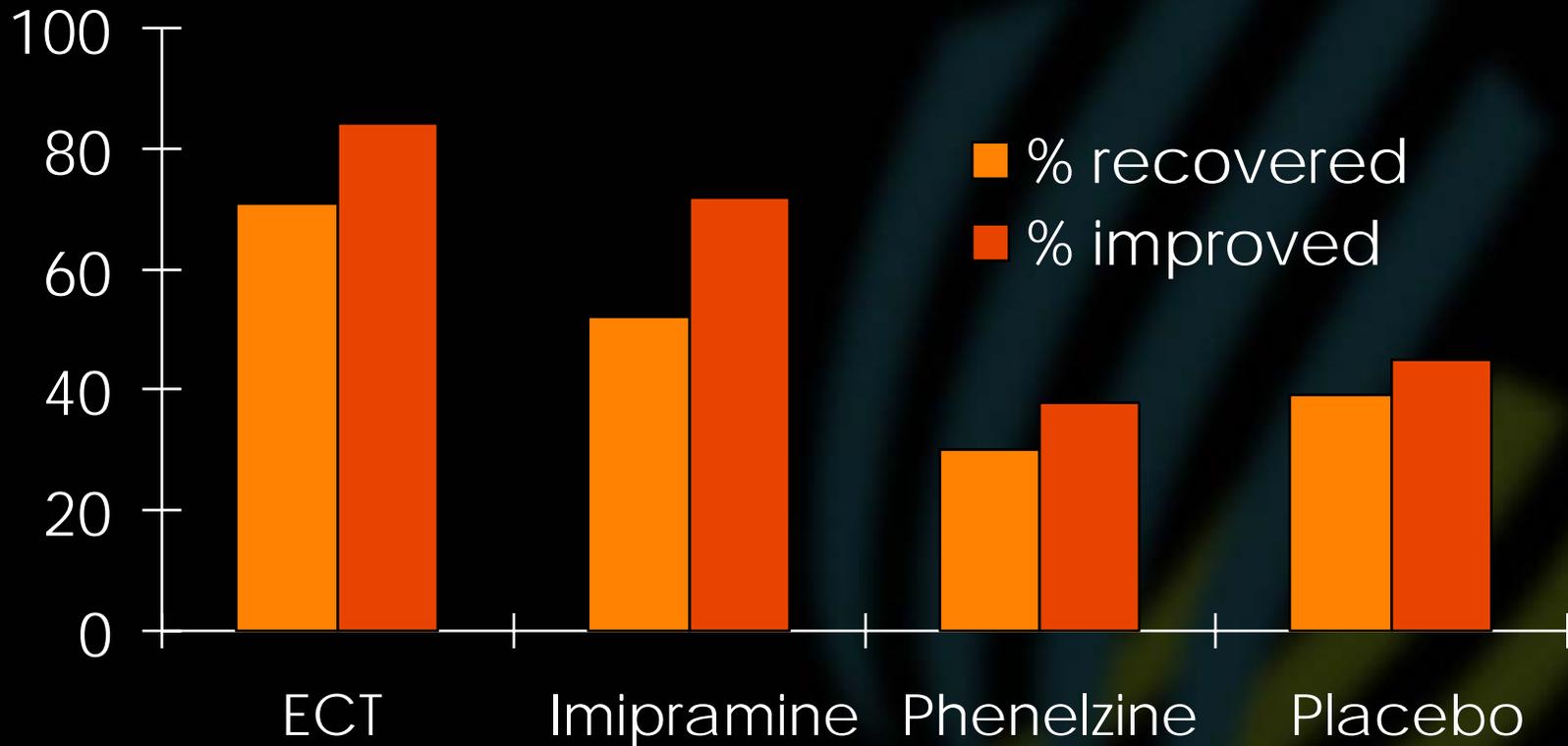


# Modern Antidepressants – 1950's

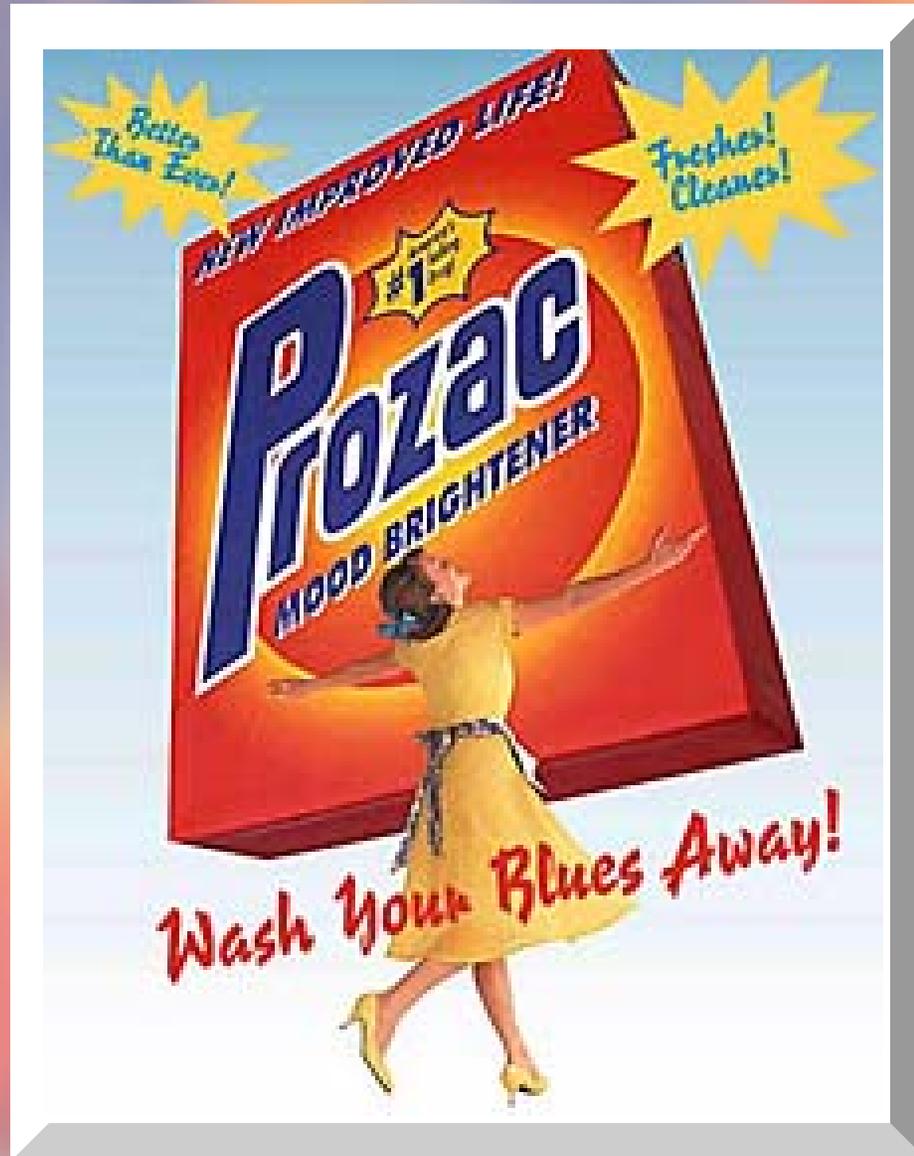


# The First RCT of Antidepressants

MRC Antidepressant Trial, 1965



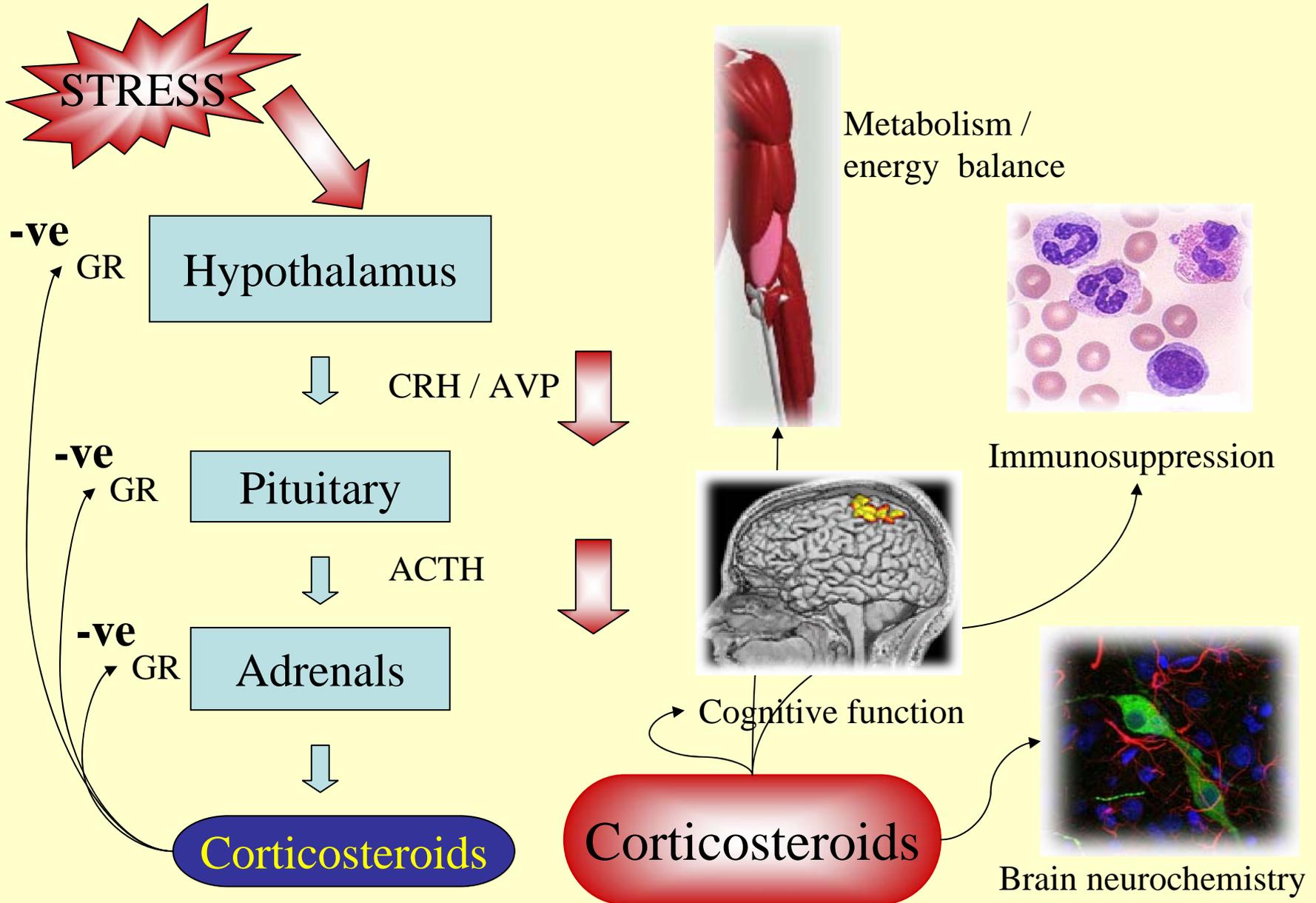
# Post TCAs and MAOIs

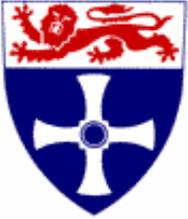


# 1977 onwards

- 1977 fluoxetine developed as SSRI
- Other drugs developed with specific pharmacology
- Depression – SSRIs, SNRIs, NaSSA
- Schizophrenia – atypicals, aripiprazole
- Bipolar disorder – anticonvulsants, atypicals
- Anxiety disorders - SSRIs
- ADHD – methylphenidate, atomoxetine
- Dementia – Cognitive enhancers
- Drugs and Alcohol – bupropion, acamprosate

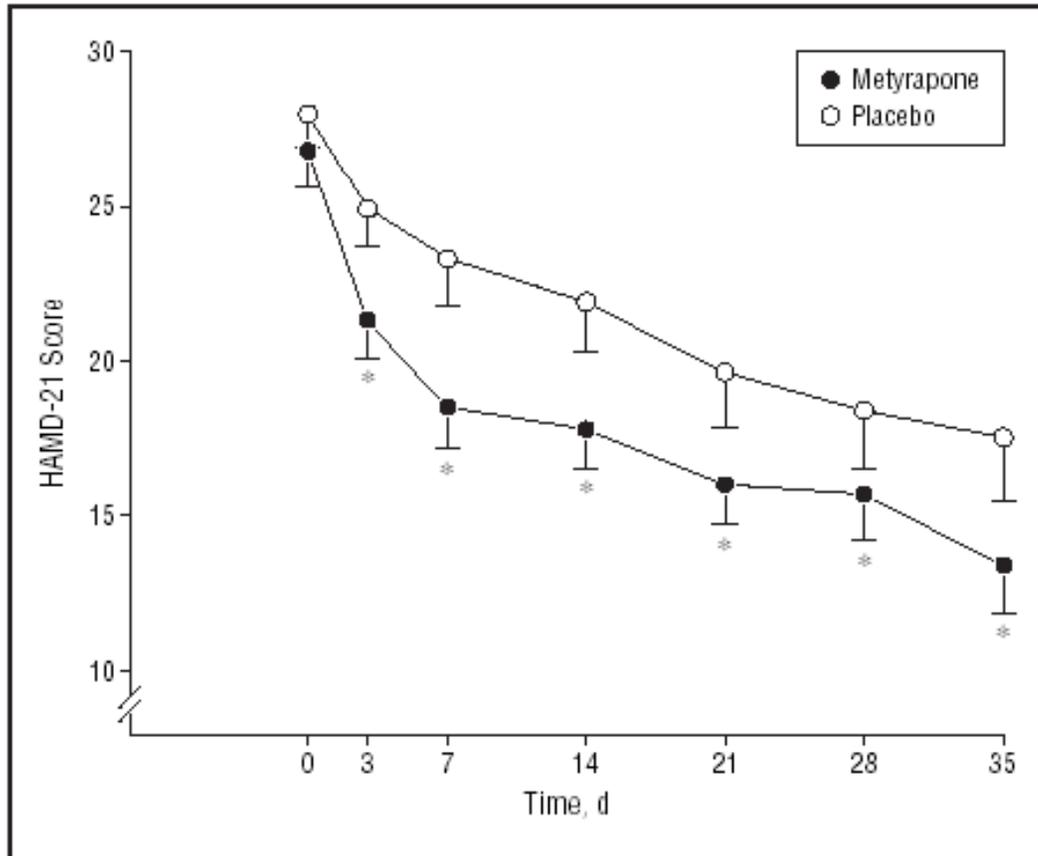
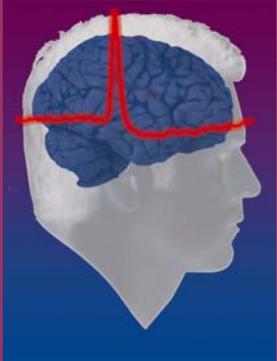
# HPA Axis and Stress





# Metyrapone augmentation of antidepressants (Jahn et al. 2004)

Psychobiology  
Research Group



n = 63

Antidepressants  
= nefazadone or  
fluvoxamine

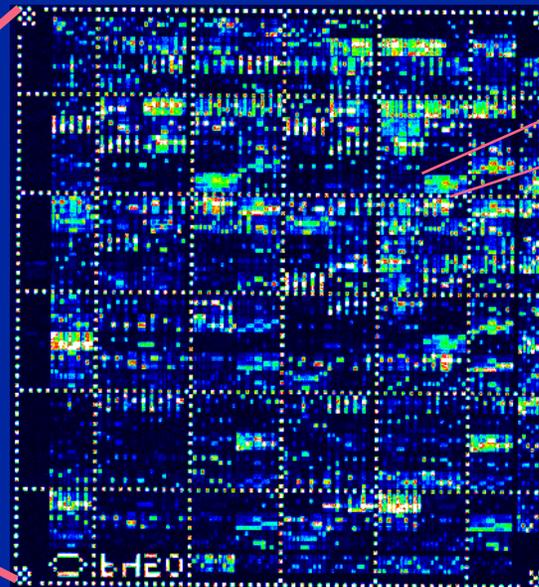
**Figure 2.** Hamilton Rating Scale for Depression, 21-item version (HAMD-21) scores for the metyrapone group (solid circles) and the placebo group (open circles) for days 0, 3, 7, 14, 21, 28, and 35 on the intention-to-treat sample. Data are presented as mean  $\pm$  SEM. Asterisks indicate time points with significant group differences. The y-axis is cut below a HAMD score of 10.

# The AmpliChip tests are based on Affymetrix microarray technology

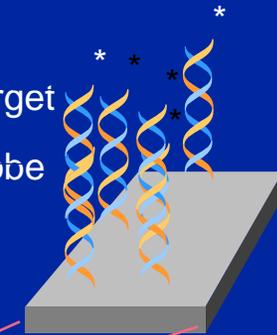
## *AmpliChip CYP450 CE-IVD*



**CYP450 2D6 & 2C19**



labeled DNA target  
Oligonucleotide probe

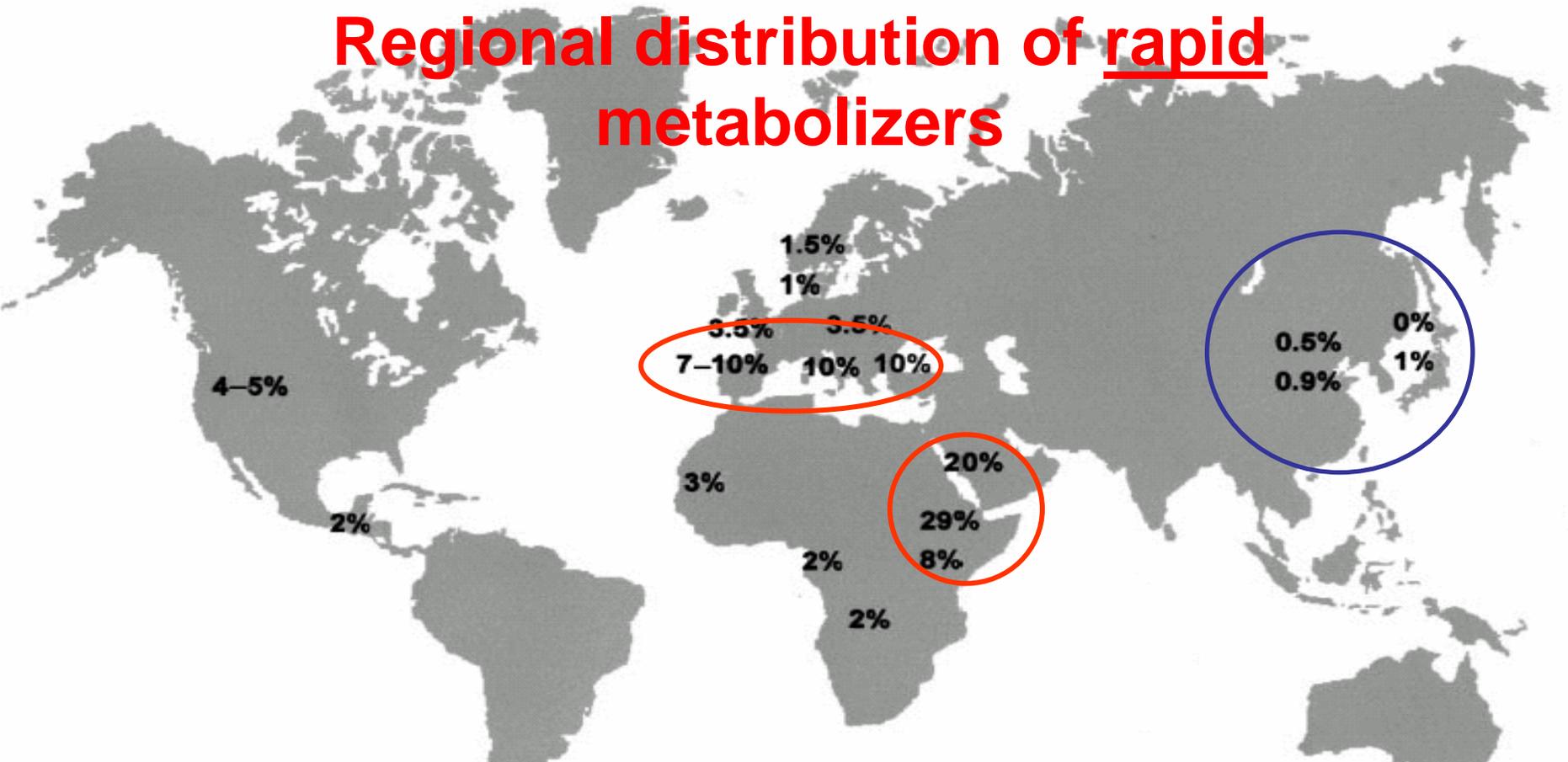


To address the relevant genetic variations, each array contains over 15,000 different probes complementary to sense and anti-sense P450 genomic DNA. Probes range in length from 18mer to 22mer

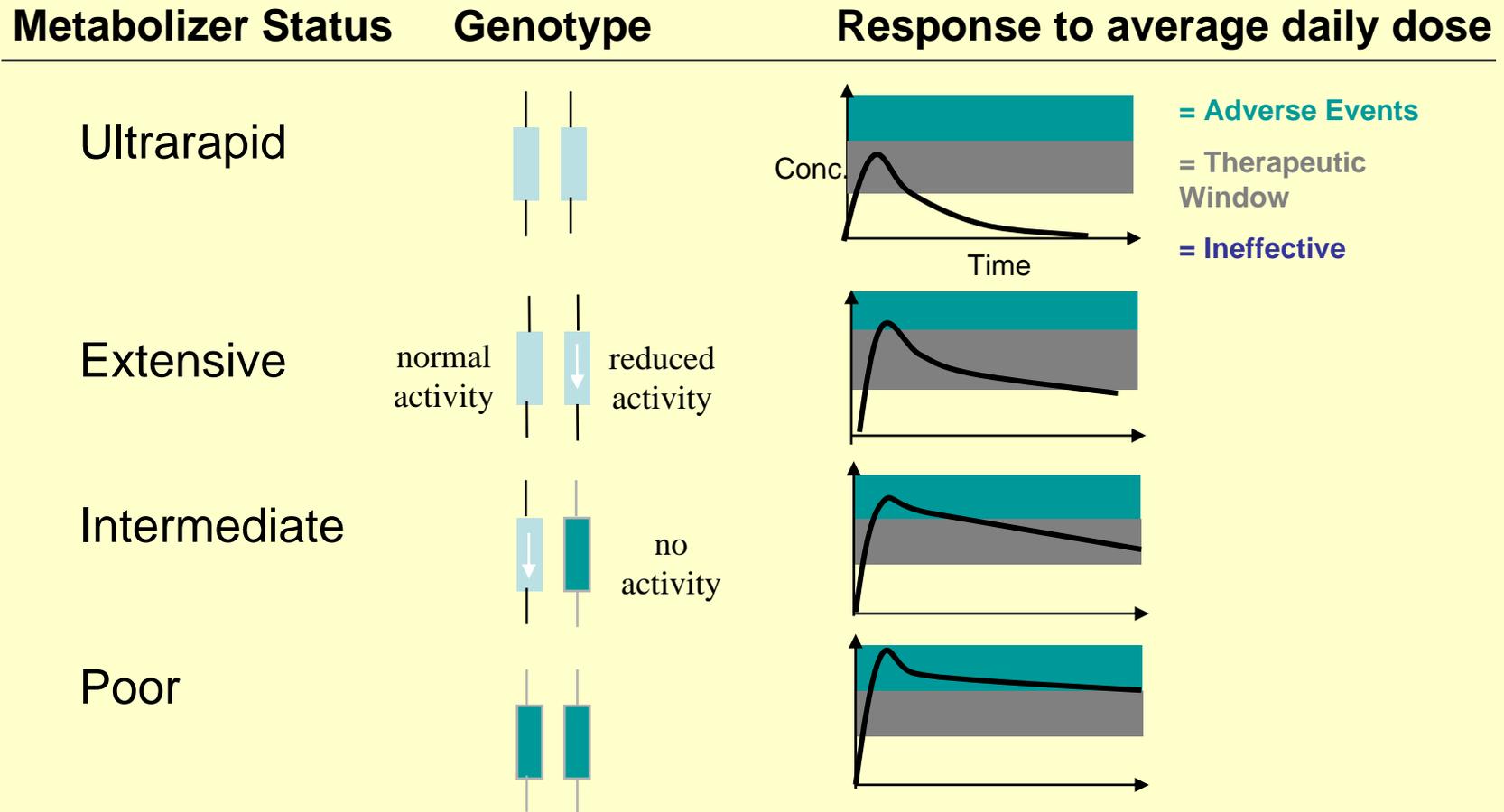


AMPLI@CHIP

# Regional distribution of rapid metabolizers

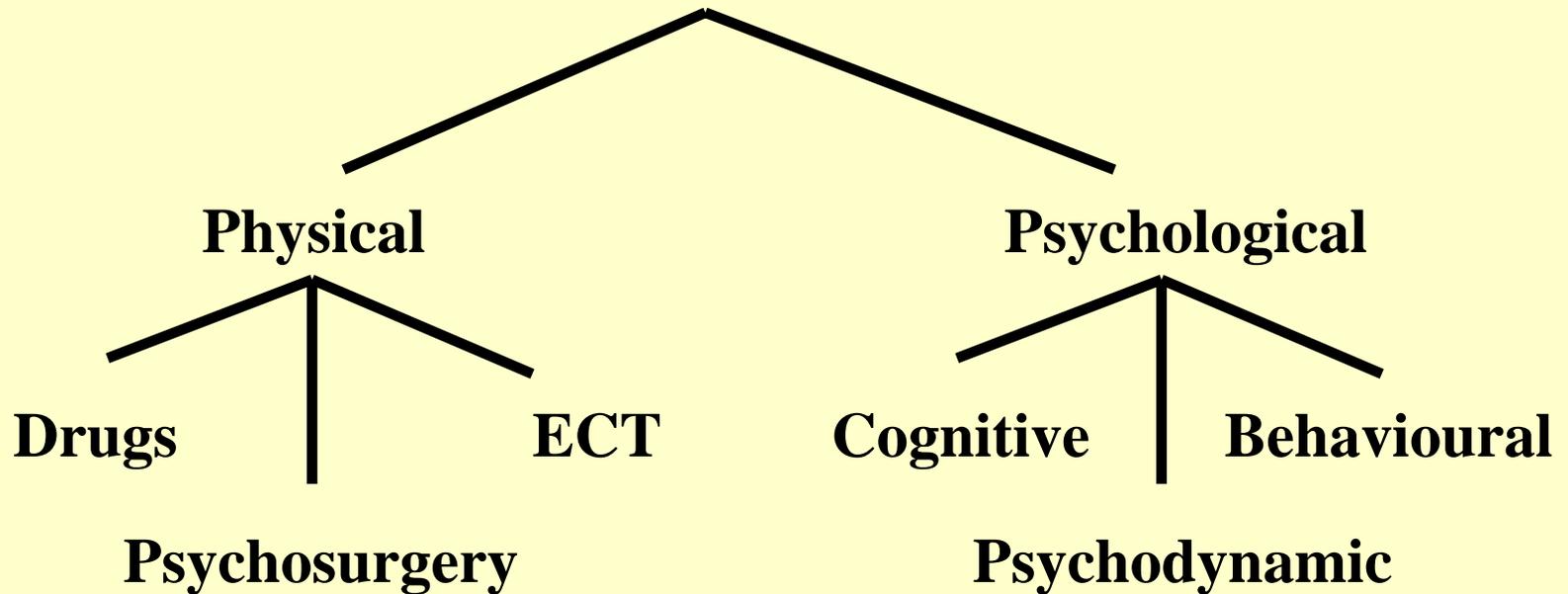


# Drug Concentrations by Genotype



# **The Place of Psychopharmacology in Psychiatry**

# Treatments in Psychiatry



# Non-pharmacological strategies

- Schizophrenia
  - Brief CBT for schizophrenia (Turkington et al. (2002) B.J.Psych 180, 523-527)
  - CPN delivered CBT of up to 6 X 1hr sessions
    - Assessment and engagement, developing explanations, symptom management, adherence, core beliefs in relapse prevention
  - Improvement in symptomatology and insight

# Non-pharmacological strategies: Bipolar disorder

- Relapse signature identification
- Perry et al. 1999 BMJ 318: 149-153
  - 69 patients RCT
  - 7-12 individual sessions from research psychologist identifying relapse signature
  - Results:
    - Time to 25% relapse with mania: 65/52 vs 17/52
    - No significant effect on time to depressive relapse
    - Significantly improved social functioning and employment
- See Morriss (2004) APT 10, 18-26

# Importance of Psychopharmacology

- Main therapeutic tool employed by most psychiatrists
- Effective but potentially toxic drugs, some of which have a narrow therapeutic ratio
- We are in a current state of great flux with regard to available drugs and guidelines
- But...
  - knowledge levels generally not good leading to less than effective use and increased risks for patients
  - often flippantly dismissed

# **Introduction to drugs**

# Main Groups of Drugs

- Antidepressants
  - TCA's, MAOI's, SSRI's, Others
- Mood stabilisers
  - Lithium, carbamazepine, sodium valproate
- Anxiolytics/hypnotics
  - benzodiazepines (antidepressants)
- Antipsychotics
  - classical and atypical
- Drugs used in addictions
- “Anti-dementia” drugs

# Antidepressants - SSRI's

- e.g. fluoxetine, citalopram, paroxetine, sertraline
- Inhibit 5-HT uptake
- Effective for acute episodes plus prophylaxis in depression, anxiety, OCD, panic, ?bulaemia
- S/E's - nausea and anxiety (short lived), sexual dysfunction (long term)
- Especially good in physically ill, elderly, suicidal
- Good first line treatments

# Antidepressants - TCA's

- e.g. amitriptyline, imipramine, lofepramine
- Inhibit 5-HT and NA uptake
- Effective for acute episodes plus prophylaxis
- S/E's - dry mouth, constipation, sedation, postural hypotension, cardiotoxicity
- Not good in physically ill, elderly, suicidal
- Lofepramine reasonable first line treatment
- Amitriptyline useful in TRD

# Antidepressants - MAOI's

- e.g. phenelzine, tranylcypamine
- Inhibit MAO (breaks down NA and 5-HT)
- Effective for depression (?esp. if with anxiety).
- S/E's - postural hypotension, insomnia, oedema, dependency (tranylcypromine)
- Eating restrictions - wine, cheese, game
- Especially used in atypical depression and TRD

# Antidepressants - Others

- Many others that don't fit main groups e.g.
- Venlafaxine, duloxetine (SNRIs)
  - Block 5-HT and NA uptake
  - ? Good for treatment resistance. S.E.'s like SSRI
  - Problems with discontinuation (c.f. paroxetine)
- Trazodone
  - Sedative. ? efficacy. Few S.E.'s plus safe in overdose. Sometimes combined with SSRI
- Mirtazepine
  - Sedative and causes weight gain. ?Useful in TRD (combined with SSRI or SNRI)
- Reboxetine
  - Noradrenaline uptake blocker. Well tolerated

# Mood Stabilisers - Lithium

- ? mechanism of action
- Effective in treatment of mania, treatment of resistant depression (with antidepressant) and prophylaxis (bipolar illness)
- Narrow therapeutic index (therefore blood levels done)
- S/E's - tremor, kidney damage, thyroid damage (therefore regular blood checks)

# Other Mood Stabilisers

- e.g. Valproate, carbamazepine and lamotrigene
- ? Mechanism of action
- Usually used if lithium doesn't work (instead of lithium or in addition) or for 'rapid cycling disorder' for which they are probably better
  - Lamotrigene for bipolar depression
- S/E's – GI upset, dizziness, sedation (esp. carbamazepine), ataxia, confusion, skin rashes (esp lamotrigene)
- NB teratogenetic effects of valproate, carbamazepine and lithium

# Anxiolytics/hypnotics

- Benzodiazepines e.g. diazepam, lorazepam, chlordiazepoxide
- Relieve anxiety immediately, good for short term use
- Hypnotics are simply BZs with short **half lives**
- S/E's - very few except dependency
- **However** antidepressants are the drugs of choice for treating anxiety but take longer to work

# Antipsychotics - Classical

- e.g. chlorpromazine, haloperidole
- block D<sub>2</sub> receptors
- Antipsychotic and sedative
- S/E's - movement disorders, dry mouth, constipation, sedation, postural hypotension, cardiotoxicity
- Used in schizophrenia, mania, psychotic depression

# Antipsychotics - Atypicals

- More recently introduced drugs. All different
- Some more dopamine selective
  - e.g. sulpiride, amisulpride
- Most combined 5-HT<sub>2</sub> and D<sub>2</sub> antagonists
  - e.g. clozapine, risperidone, olanzapine, quetiapine
- Now first line antipsychotics for schizophrenia and mania (?+ other effects in bipolar disorder)
- Less side effects (generally but esp. EPS), but more weight gain and metabolic syndrome
- ?? more effective (esp negative and mood Sx)
- Clozapine used for TRS, but risk of blood disorders
- Depot risperidone available
- Expensive

# Drugs used in additions

- Drugs used to substitute for drugs of addiction aimed at harm reduction
  - Methadone for opiate addiction
  - Nicotine patches for smoking
- Drugs to facilitate abstinence
  - decrease cravings:
    - Acamprosate for alcohol
    - Bupropion for smoking
  - “behavioural” therapy
    - Disulfiram for alcohol

# Drugs used in dementia

- Findings suggest a reduction in acetylcholine in Alzheimer's disease
- ACh broken down in synapse by acetylcholinesterase
- Donepezil, rivastigmine and galantamine inhibit AChesterase
- Side effects – GI disturbance
- Magnitude of effects?

# Clinical Management

- Identify syndrome – make a diagnosis!!!!

# Diagnosis

---

- Use checklist based on ICD-10
  - Symptoms present for most of the day for 2/52
  - 4 symptoms = mild
  - 5-6 = moderate
  - 7+ = severe (+/- psychotic symptoms)

# Assessing severity of depression (Appendix E)

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- Key symptoms
  - Persistent low mood
  - Loss of interest or pleasure
  - Fatigue or low energy
- If any of above then ask about:
  - Disturbed sleep
  - Poor concentration or indecisiveness
  - Low self confidence
  - Poor or increased appetite
  - Suicidal thoughts or acts
  - Agitation or slowing of movement
  - Guilt or self blame

# Diagnosis of Depression

## DSM-IV Criteria

- **5 or more** of the following over a two week period:
  - \*depressed mood
  - \*markedly diminished interest or pleasure in all activities
  - weight loss, decreased or increased appetite
  - insomnia or hypersomnia
  - psychomotor agitation or retardation
  - fatigue or loss of energy
  - feelings of worthlessness or inappropriate guilt
  - diminished ability to think or concentrate
  - recurrent thoughts of death or suicide
- N.B. must have one of symptoms marked with \*

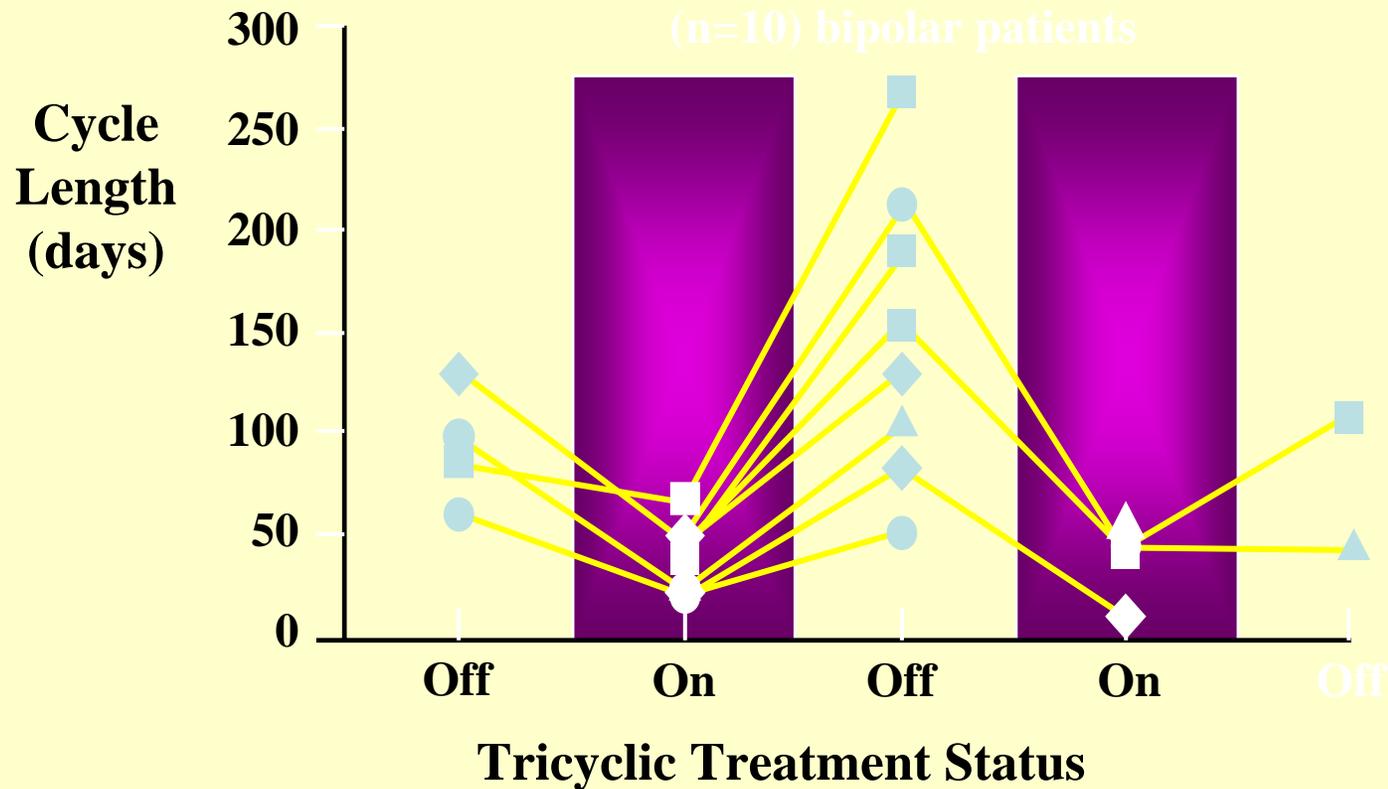
# Epidemiology of depression: ICD vs DSM

- One year prevalence of depression in rural Udmurtia
  - Pakriev et al. 1998
  - 855 people administered CIDI
  - By ICD-10 criteria – 30.5% depressed
  - By DSM-III-R criteria – 22% depressed

# Diagnostic dilemmas in depression

- “Normal” misery vs depression
- Unipolar vs bipolar disorder
  - Between 9 and 24% of unipolar depression patients end up with a different diagnosis, mainly bipolar affective disorder (Angst & Preisig, 1995)

# Tricyclic-Induced Shortening of Bipolar Cycle Length (n=10)



# Clinical Management

- Identify syndrome – make a diagnosis!!!!
- Educate patient and others

# Some questions asked by patients when starting psychotropic drugs

1. Do they work?
2. Why can't I just pull myself together?
3. How do they work?
4. Will they alter my mind?
5. Will they alter my personality?
6. How long will I have to take them for?
7. Do they always work?
8. What side effects do they have?
9. What happens when I stop them?

# Clinical Management

- Identify syndrome – make a diagnosis!!!!!!
- Educate patient and others
- Select treatment
  - Assessment of risk/benefits
  - Consideration of costs
  - Full discussion with patient
  - Informed choice by patient

# Clinical Management

- Identify syndrome – make a diagnosis!!!!
- Educate patient and others
- Select treatment
  - Assessment of risk/benefits
  - Consideration of costs
  - Full discussion with patient
  - Informed choice by patient
- Monitor response and adjust treatment

# Monitoring Patients: CGI severity

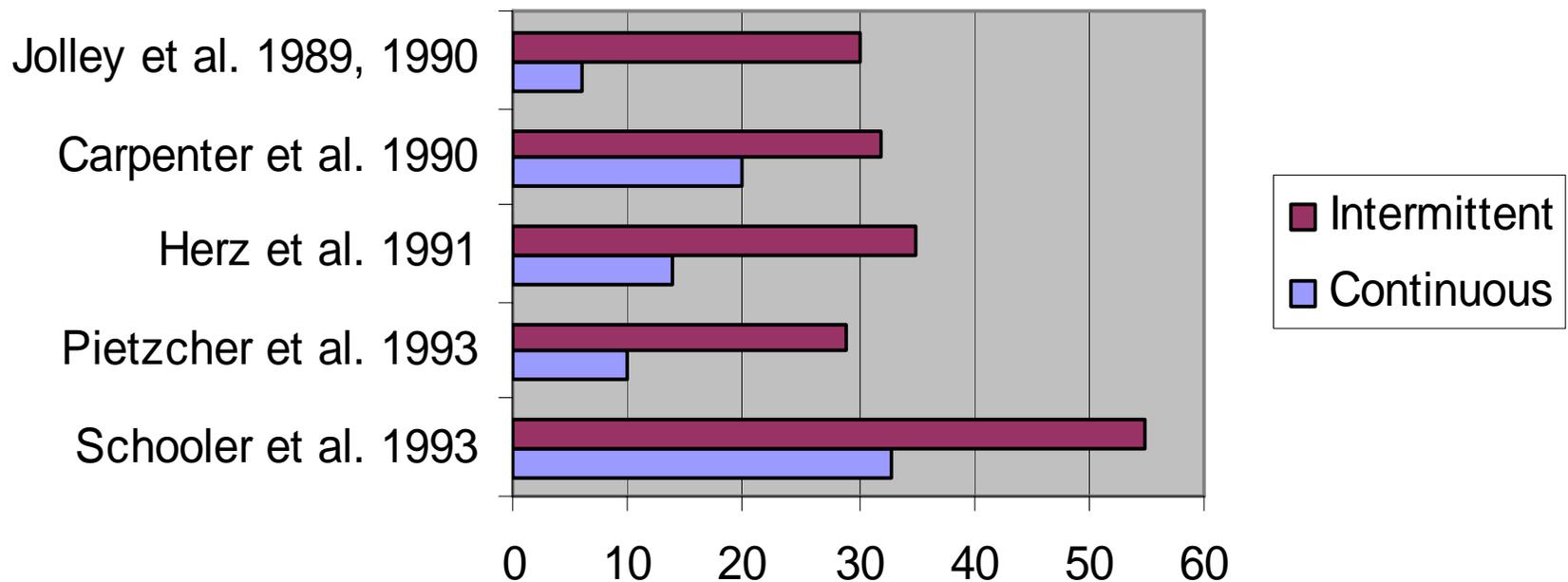
- Simple 7-point scale
  - Done considering your total clinical experience of patients with the same condition
  - Relate to specific time period
- 1: Normal not ill
  - 2: Minimally ill
  - 3: Mildly ill
  - 4: Moderately ill
  - 5: Markedly ill
  - 6: Severely ill
  - 7: Very severely ill

# Clinical Management

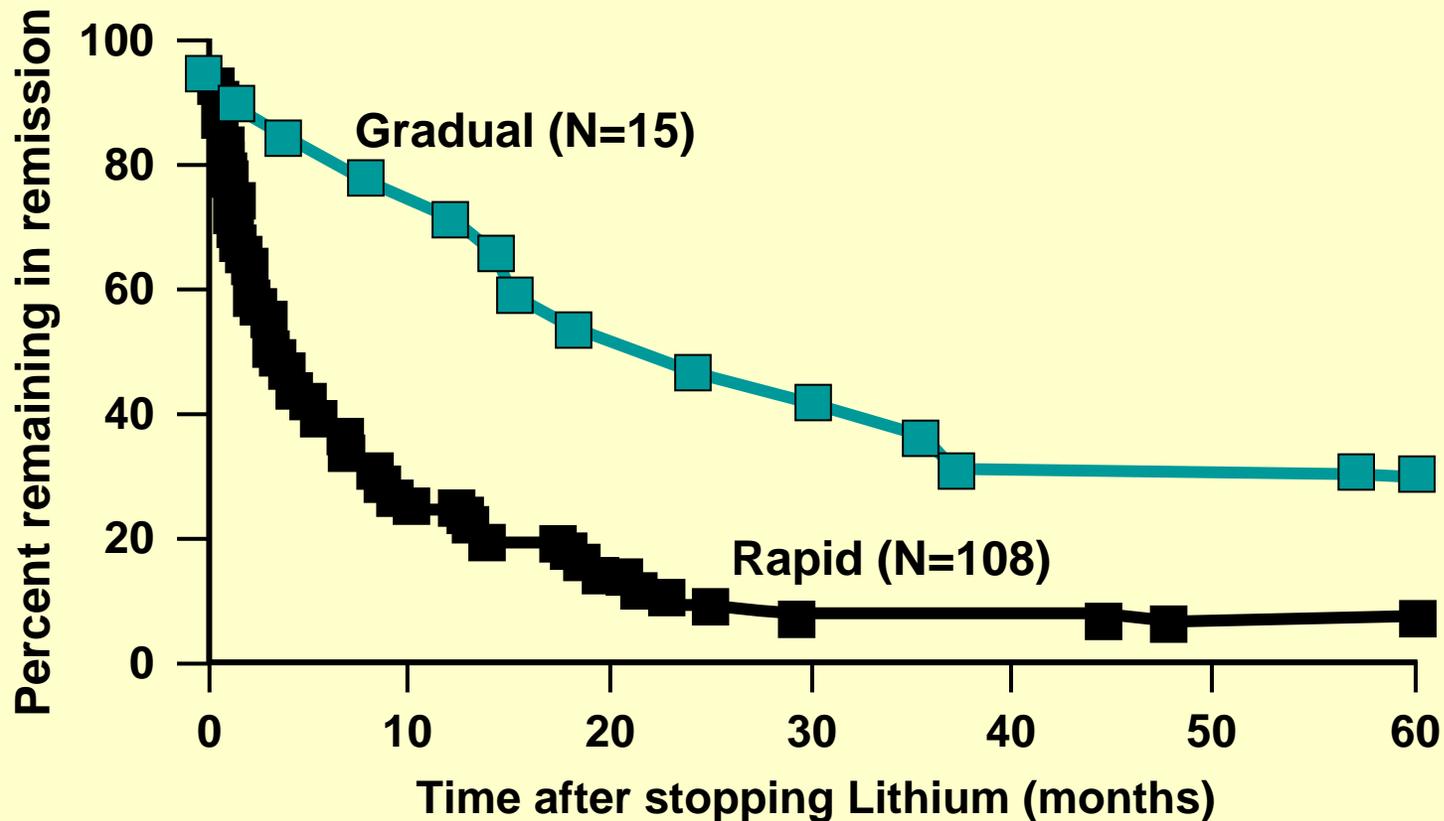
- Identify syndrome – make a diagnosis!!!!
- Educate patient and others
- Select treatment
  - Assessment of risk/benefits
  - Consideration of costs
  - Full discussion with patient
  - Informed choice by patient
- Monitor response and adjust treatment
- Maintenance treatment

# Continuous versus intermittent antipsychotic therapy

Relapse rates (%) over 1 year of continuous or intermittent maintenance therapy with conventional antipsychotics

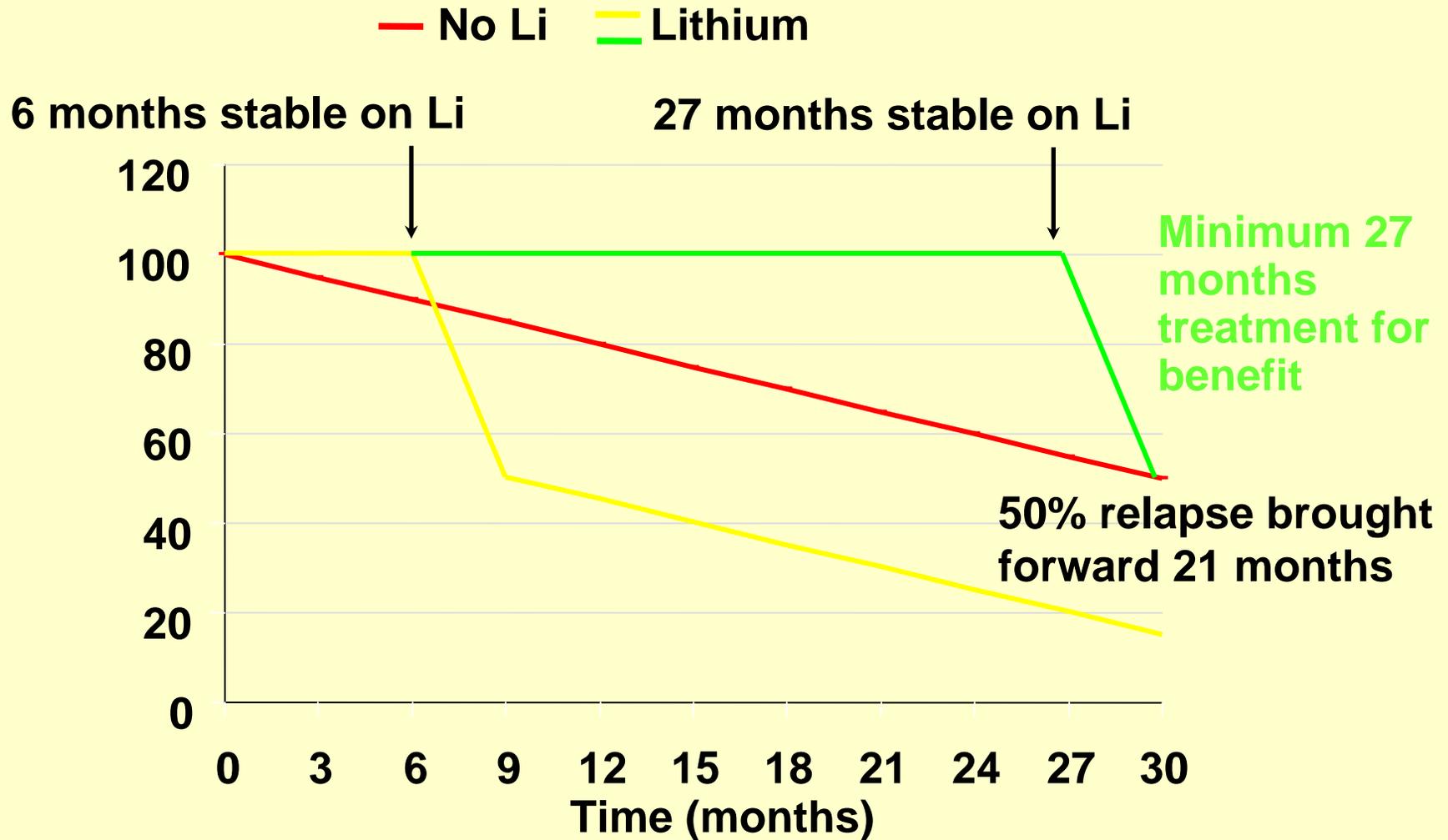


# Consequence of Rapid Discontinuation of Lithium in Bipolar I Patients



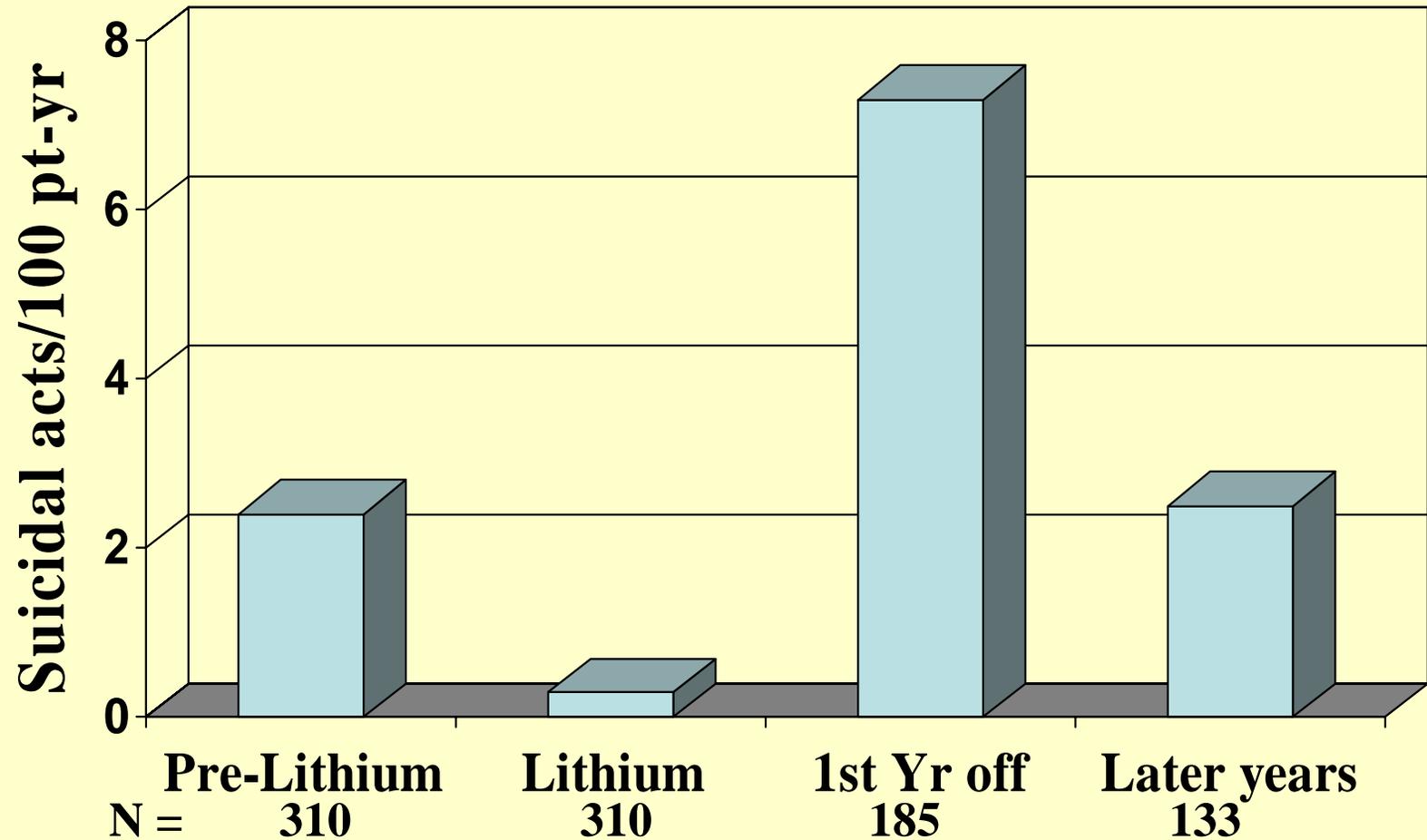
*From Suppes et al, 1991.*

# Effect of lithium withdrawal



Goodwin (1994)

# Consequences of lithium discontinuation



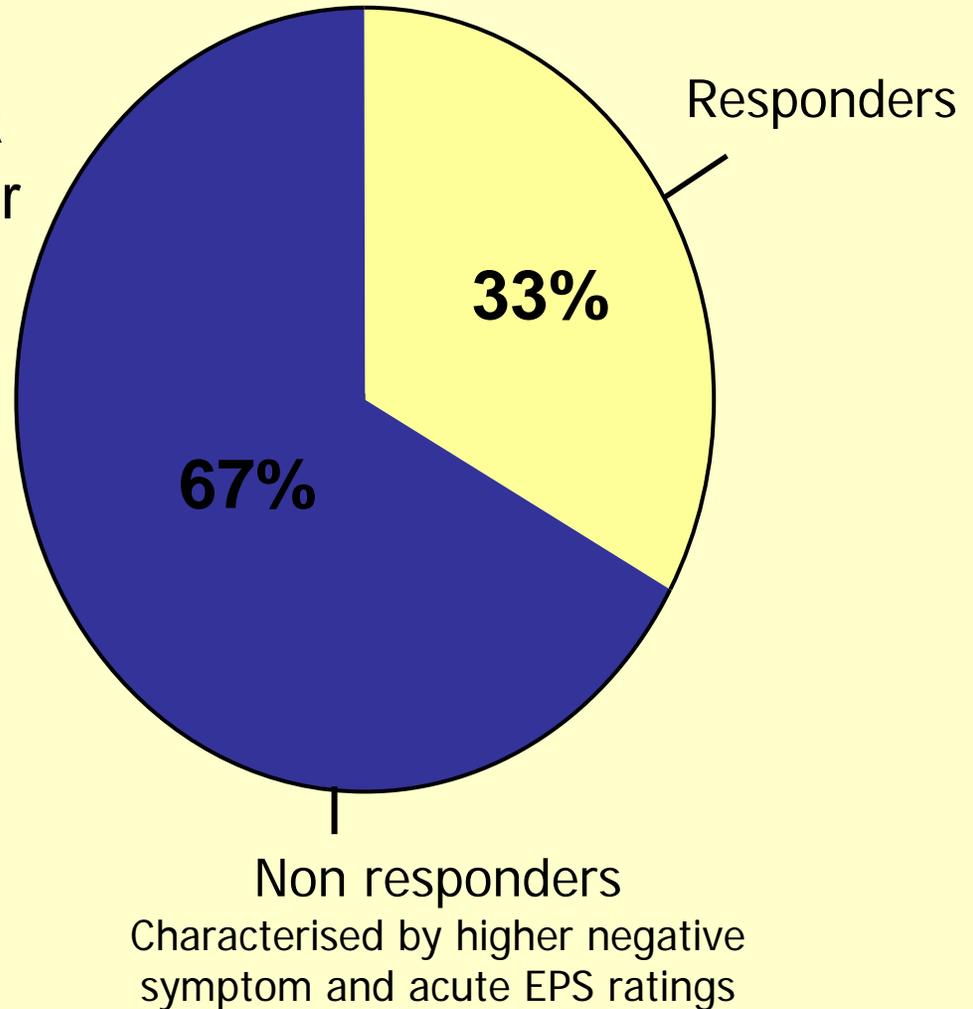
# Clinical Management

- Identify syndrome – make a diagnosis!!!!
- Educate patient and others
- Select treatment
  - Assessment of risk/benefits
  - Consideration of costs
  - Full discussion with patient
  - Informed choice by patient
- Monitor response and adjust treatment
- Maintenance treatment
- Non-response strategy

# Treatment with FGA

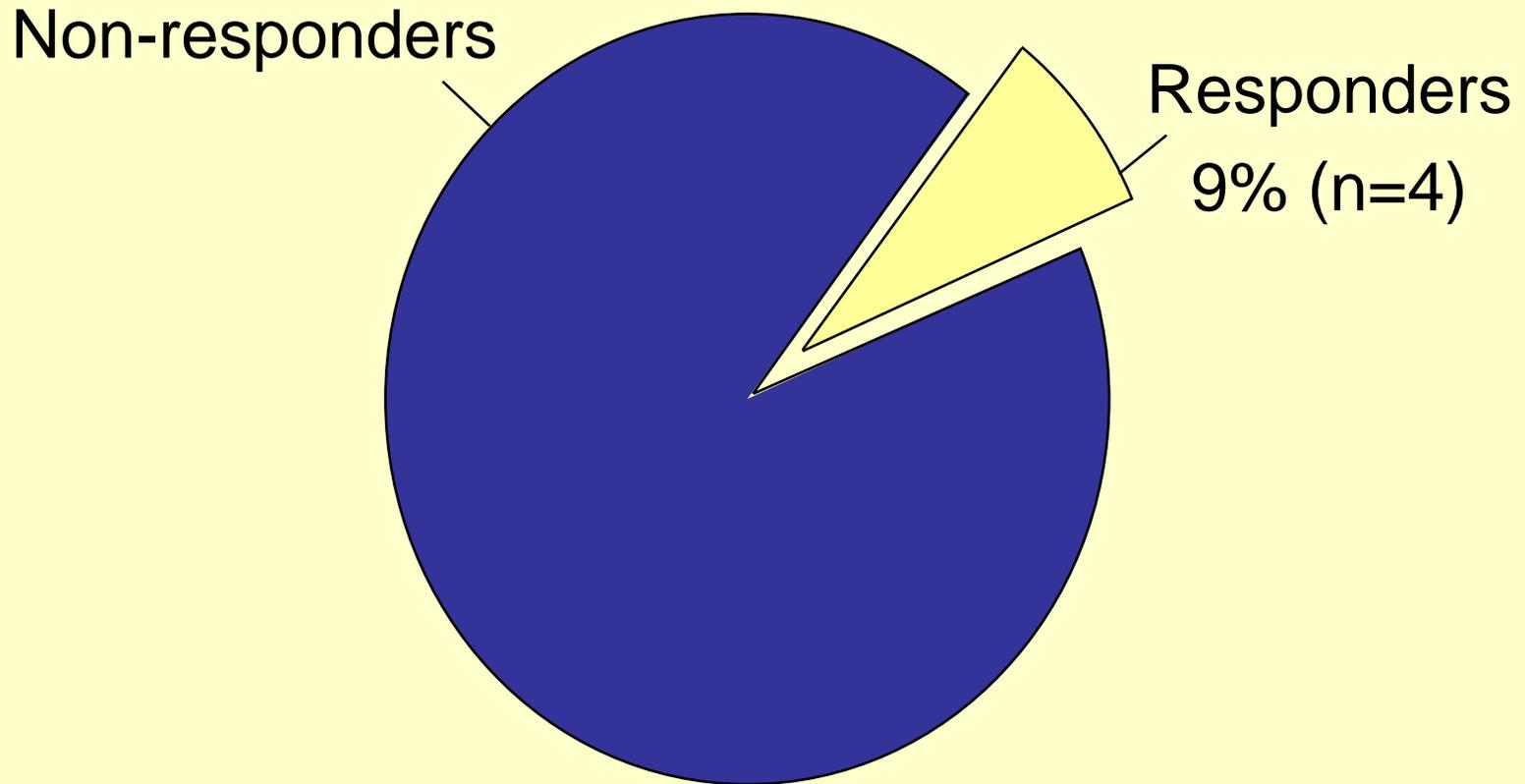
## Outcome At 4 Weeks (N=109)

- Patients with schizophrenia and schizoaffective disorder treated for 4 weeks
  - Fluphenazine 20 mg and benztropine 2 mg bd
- Strict criteria for treatment response
  - No symptom on psychosis subscale of the Brief Psychiatric Rating Scale (BPRS) rated higher than 'mild'



# Treatment with FGA

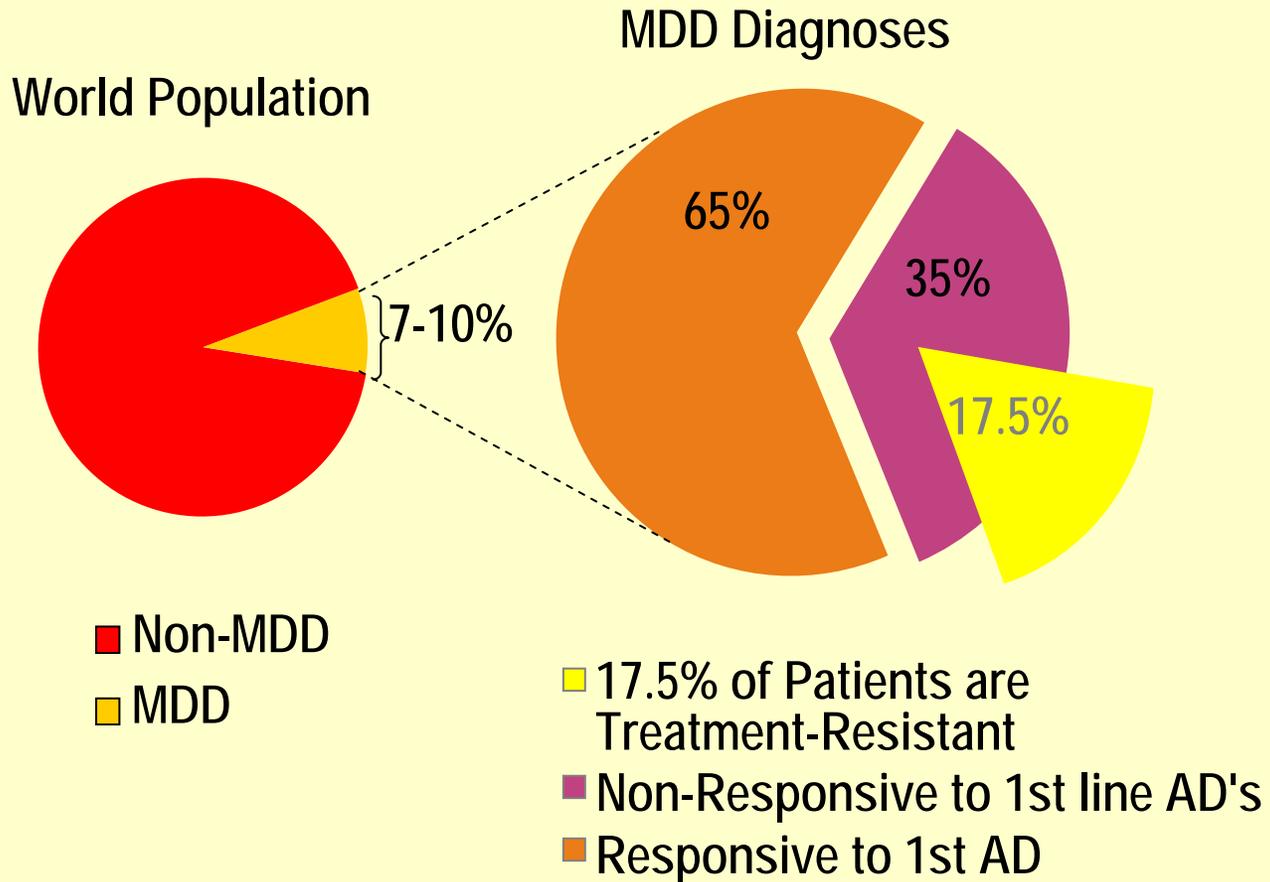
## Additional Responders At Week 8 (N=47)



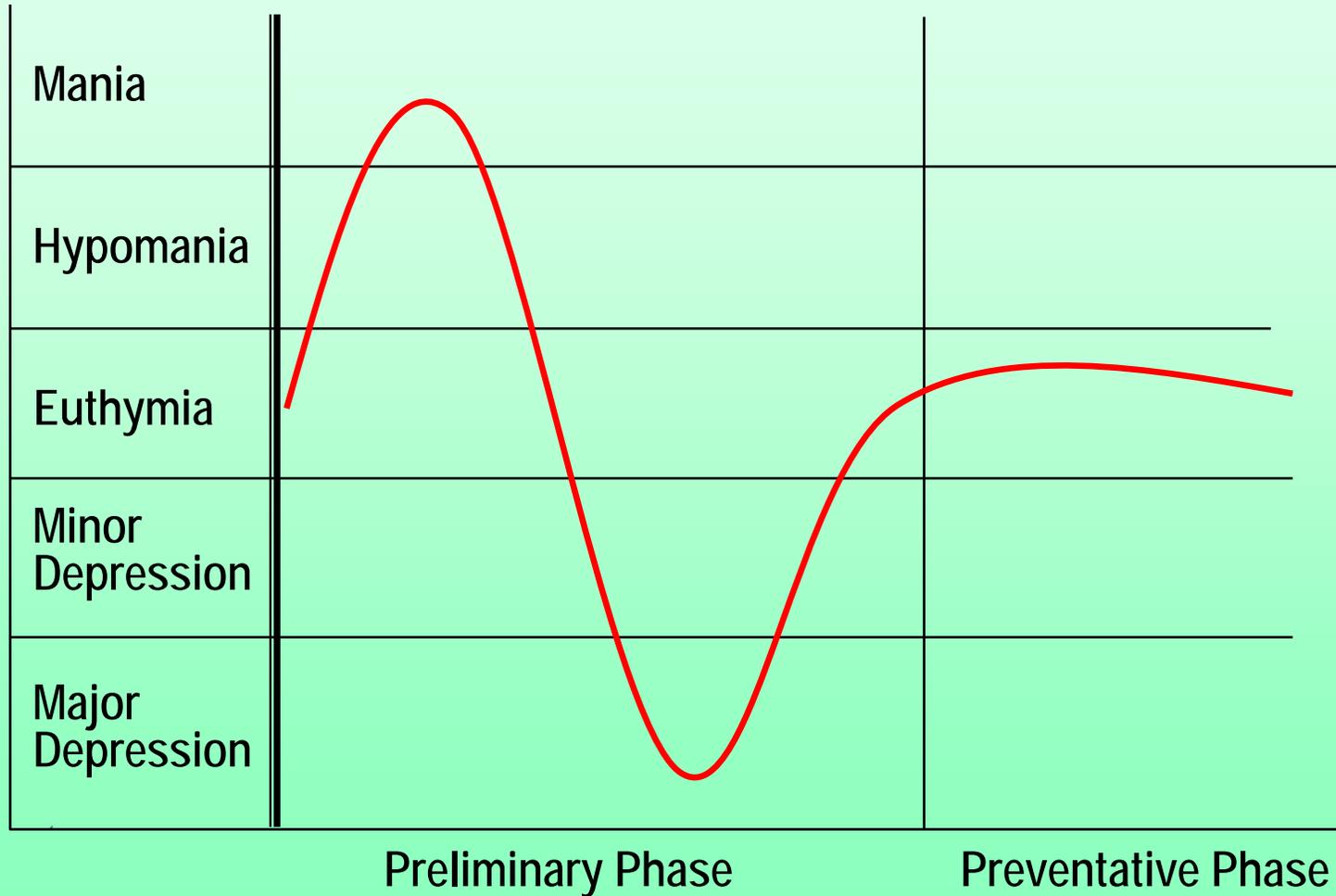
- No superiority for any of the specific alternative treatments studied

*Kinon BJ, Kane JM, Johns C, et al. Psychopharmacol Bull. 1993;29(2):309-314*

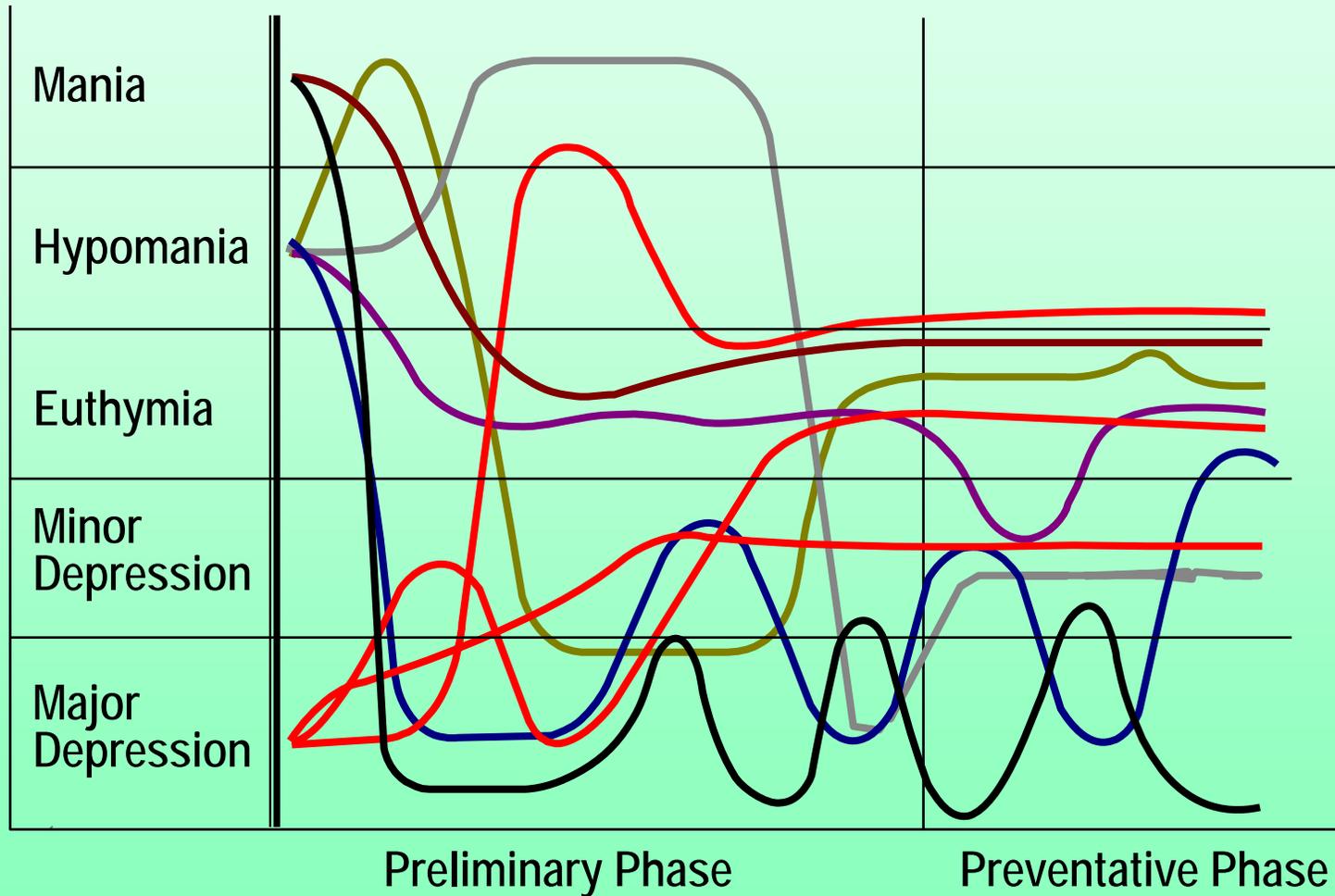
# Epidemiology of treatment resistant depression



# The course of Bipolar Disorder



# The course of Bipolar Disorder



# Some general principles of managing difficult to treat patients

1. Reassessment of diagnosis
  2. Reassessment of comorbidity, maintaining factors etc
  3. Assess concordance
- 
- Assessment
- 

4. Collaborative approach
  5. Education of all
  6. Instillation of hope
  7. Do something
  8. Non-pharmacological strategies
  9. Have clear pharmacological plans
- 
- General Issues
- 

10. Have adequate trials of medication
  11. Monitor response assiduously and objectively
  12. Take care with change overs
  13. Avoid polypharmacy where possible
  14. Maintenance therapy
- 
- Pharmacology

# Compliance with Drug Treatment

- Not good -
  - Thomson et al. (1982) - 20% stopped within 3 weeks
  - Johnson (1973) - 3/4 stopped by one month
- Why?
  - S.E.'s
  - patient not convinced
  - get better/worse
  - long delay in improvement
  - worried addictive/alter personality

# Improving compliance

- trust in doctor
- acceptance of biological model
- acceptance of illness
- explanation of risk and benefits
- simple therapeutic regimen
- written information
- regular follow up
- role of psychologist and other members of the MDT

# **NICE Clinical Guideline 1** **December 2002**

**Core interventions in the  
treatment and management  
of schizophrenia in primary  
and secondary care**

**NHS**

*National Institute for  
Clinical Excellence*

# Acute Episode

---

- Informed choice by patient
  - If not able to do this then atypical
- If on typical and SEs are problematic or Sx control is inadequate, then atypical (otherwise remain on conventional)
- Single drug within BNF limits
  - Avoid high doses and loading doses
- Treatment trials should be for periods of 6-8 weeks
- Progress, SEs and user satisfaction should be monitored closely
- Treat for 1-2 years, withdraw slowly and monitor for 2 years after withdrawal

# NICE: Treatment resistant schizophrenia

---

- Establish that there have been adequate trials of antipsychotics
- If Sx unresponsive to a conventional then use an atypical before consider TRS
- If TRS (min 2 antipsychotics each for 6-8/52, at least one atypical) consider clozapine sooner rather than latter
- Avoid multiple antipsychotics except for pts who have not fully responded to clozapine

# NICE: Relapse prevention

---

- Oral drugs as per acute episode
- Risk assessment by clinician and MDT regarding concordance and need for depot
- Depots
  - Use if patient chooses this or problems with concordance
  - Use within BNF dose limits
  - Use test doses as set out in BNF
  - Regular review as per orals
  - NB Risperdal consta guidelines exist (consultants only)

# **NICE Clinical Guideline 23** **December 2004**

**Depression: management of  
depression in primary and  
secondary care**

**NHS**

*National Institute for  
Clinical Excellence*

# NICE Guidance

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- **Stepped care**
- Step 1: Recognition of depression
- Step 2: Depression in primary care – mild depression
- Step 3: Depression in primary care – moderate to severe
- Step 4: Mental health services – refractory, recurrent, atypical and psychotic depression
- Step 5: Depression requiring inpatient care

# Step 2: Mild depression in primary care

---

- Antidepressants
  - Not recommended for initial treatment
  - If symptoms persist after other interventions [C]
  - If past history of moderate to severe depression [C]

# Step 3: Moderate to severe depression in primary care

---

- Antidepressants
  - Should be routinely offered [A]
  - Address common concerns [GPP]
  - Inform about potential side effects [C]
  - Inform about time delay in response [GPP]
  - Review at regular intervals [GPP]
  - Continue for at least 6 months from remission [A]
  - After 6 months review need for medication [GPP]

# Step 3

---

- Choice of antidepressant
  - SSRI in routine care [A]
  - Consider fluoxetine (since generic and long half life, but NB drug interactions) or citalopram (since generic) [C]
  - If SSRI leads to agitation or akathisia then consider switch or benzodiazepine with review in 2/52 [C]
  - If fails to respond to first drug check concordance [GPP]
  - If response inadequate consider increasing dose to BNF limits [C]
  - If not effective switch antidepressant [C]
  - Reasonable alternative to SSRIs = mirtazepine, but consider moclobemide, reboxetine, tricyclics [B]

# Step 3

---

- Choice of antidepressant (cont.)
  - Mirtazepine – warn about sedation and weight gain [A]
  - Moclobemide – ensure previous drug washed out [A]
  - Reboxetine – relative lack of data [B]
  - Tricyclics – poor tolerability, cardiotoxicity and toxicity in OD [B]
    - If used, lofepramine good choice [C]
    - If respond at low dose, maintain this [C]
    - Gradually increase dose, monitoring for SEs, if lack of efficacy [GPP]
  - Venlafaxine

# Step 3: Atypical Depression

---

- Atypical Depression
  - Overeating, over-sleeping, interpersonal rejection and over-sensitivity
  - More often female and young onset
  - Comorbid panic, substance misuse and somatisation common
  - Treat with SSRI [C]
  - Refer if don't respond and functionally impaired [GPP]

# Step 3

---

- Monitoring of antidepressants
  - Monitor for akathisia and increased anxiety in early stages of treatment with an SSRI [GPP]
  - If risk of suicide or < 30yrs old review after 1/52, then close monitoring (e.g. by phone)
    - Everyone else review after 2/52 then every 2-4/52 for 3/12

# Step 4 - Refractory depression

---

- Failure to respond to 2 or more ADs
- Consider everything in step 3. [GPP]
- Drugs
  - Lithium augmentation (even after 1 AD) – NB SEs and toxicity [C]
  - Don't augment with BZs [C]
  - ADs plus CBT
  - Venlafaxine up to BNF limits [C]
  - SSRI + mianserin or mirtazepine [C]
    - Monitor carefully for SEs [GPP]
    - Use mianserin with caution esp. in elderly – agranulocytosis [C]
  - Consider phenelzine [C]
  - Carbamazepine, lamotrigine, buspirone, pindolol, valproate, thyroid hormone augmentation not recommended routinely [B]
  - If thinking of other strategies, think of second opinion or tertiary referral – document discussions in notes [C]

# Step 4 – recurrent depression

---

- If 2 or more episodes consider ADs for 2 years [B]
- Re-evaluate risk factors when thinking about going beyond 2 years [GPP]
- Use same dose of AD as for acute treatment [C]
- AD + Li
  - Continue for at least 6/12 [B]
  - If stop one, stop Li [C]
- Li not recommended as sole agent [C]

# BAP Guidelines for the management of Bipolar Disorder



[www.bap.org.uk](http://www.bap.org.uk)



# Outline

---



- Fundamentals of patient management
  - Diagnosis
  - Access to services and the safety of the patient and others
  - Enhanced care
- Treatment of different phases of bipolar illness
  - Acute Manic or Mixed Episodes
  - Acute Depressive episode
  - Long-term treatment
  - Treatment in special situations



# Acute Manic or Mixed Episodes

---

- Initiate oral administration of an (atypical) antipsychotic or valproate (A)
- For less ill manic patients lithium or carbamazepine may be considered as a short term treatment (A).
- To promote sleep consider adjunctive benzodiazepine (B)
- Antidepressants should be tapered and stopped (B)

# Acute Manic or Mixed Episodes

---



If symptoms uncontrolled and/or mania is very severe

- Add another first-line medicine.
  - Consider the combination of lithium or valproate with an antipsychotic (A).
  - Consider clozapine in more refractory illness (B).
  - ECT may be considered for manic patients who are severely ill and/or whose mania is treatment resistant and patients with severe mania during pregnancy (C).

# Outline

---



- Fundamentals of patient management
  - Diagnosis
  - Access to services and the safety of the patient and others
  - Enhanced care
- Treatment of different phases of bipolar illness
  - Acute Manic or Mixed Episodes
  - Acute Depressive episode
  - Long-term treatment
  - Treatment in special situations

# Acute Depression

---



- Treat with an antidepressant (e.g. SSRI) and an anti-manic drug (e.g. lithium, valproate or an antipsychotic) together (B).
- Antidepressant monotherapy is not recommended for patients with a history of mania (B).
- Consider adding antipsychotic especially if psychotic symptoms present (A)
- Consider ECT for patients with high suicidal risk, psychosis, severe depression during pregnancy or life-threatening inanition (A).

# Outline

---



- Fundamentals of patient management
  - Diagnosis
  - Access to services and the safety of the patient and others
  - Enhanced care
- Treatment of different phases of bipolar illness
  - Acute Manic or Mixed Episodes
  - Acute Depressive episode
  - Long-term treatment
  - Treatment in special situations



# Long-term treatment

---

## Choice of long-term treatments

- Consider lithium monotherapy (A)
  - Lithium protects against both mania and depression, but is more effective at preventing mania (Ia)
  - Long term treatment with lithium decreases the risk of suicide (I)
  - If lithium ineffective or poorly tolerated
    - Valproate protects against mania (and depression) (Ia)
    - Olanzapine protects against mania (and depression) (Ia)
    - Carbamazepine is less effective than lithium (Ib) but may be used especially in non-classical illness (B).  
Oxcarbazepine has fewer pharmacokinetic interactions
    - Lamotrigine protects against depression (and mania) (Ia)
  - Acute response to an agent favours its use long term (B)

# **NICE Clinical Guideline 22** **December 2004**

**Anxiety: Management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in primary, secondary and community care**

**NHS**

*National Institute for  
Clinical Excellence*

# Management of anxiety in adults in primary and secondary care: Steps 2 - 4

---

- Choose one out of:
  - Psychological interventions
  - Pharmacological therapy
  - Self-help
- If fail two types of intervention – refer into secondary care

# NICE Anxiety Guidelines

## Panic Disorder

### Pharmacotherapy

---

- NOT benzodiazepines
- SSRI licensed for panic (citalopram, escitalopram, paroxetine)
- If SSRI not suitable or patient fails 12/52 course consider imipramine or clomipramine
- Long term treatment and doses at the higher end of the dose range may be needed

# NICE Anxiety Guidelines

## GAD

### Pharmacotherapy

---

- Don't use benzodiazepines beyond 2-4 weeks
- Offer an SSRI
- If no response after 12 weeks try another SSRI
- Long term treatment and doses at the higher end of the dose range may be needed

# NICE anxiety: Step 5

---

- Holistic
- CBT with experienced therapist
- “consider a full exploration of pharmacotherapy”
- Refer to tertiary centres

# **Controversies in Psychopharmacology**

# Psychopharmacological Problems and Controversies

- **Cost of drugs**

# Cost of drugs

<b>Drug (dose/day)</b>	<b>Cost per month</b>
Venlafaxine 150 mg	£39.03
Duloxetine 60 mg	£27.72
Escitalopram 20 mg	£25.20

# Summary of remission rates for antidepressant drug classes

Rate	Drug class	Patients	Overall rate	Studies	n
Remission	Venlafaxine <sup>1</sup>	3% in-patients, 97% out-patients	45%	8	851
	SSRIs <sup>1</sup>	3% in-patients, 97% out-patients	35%	8	748
	TCAs <sup>2</sup>	out-patients	28%	1	71

**P Values**

venlafaxine vs SSRI (1) : p < 0.001

SSRI vs TCA (2) : p = 0.209

**TCA Response  
Data**



**Mental Health**

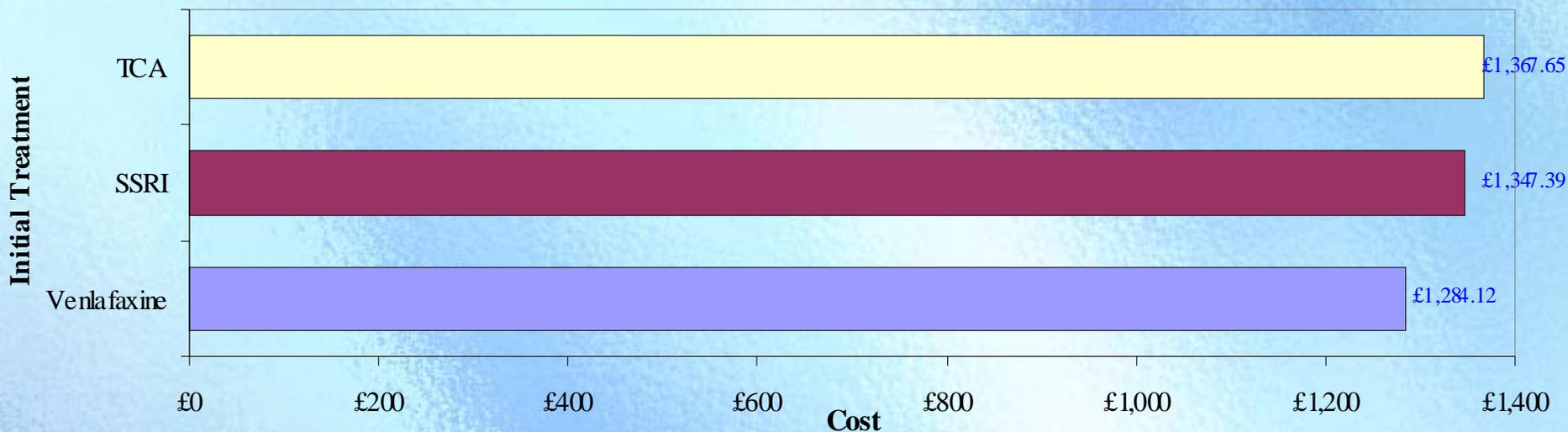
Prescribing information is available at this meeting.



ZEFE087/0701

# Average Expected 6-month per-patient cost

Average Modelled Expected per Patient Cost at 6 Months



Mental Health

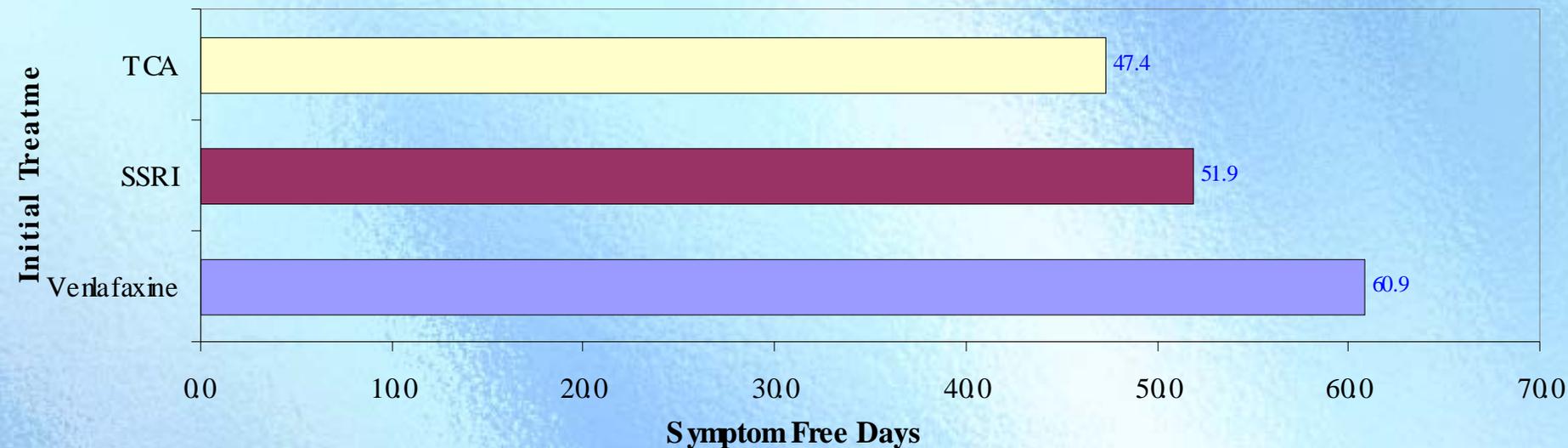
Prescribing information is available at this meeting.



ZEFE087/0701

# Average Expected per-patient Symptom Free Days (SFDs) during 6 months (182 days) of treatment

Average Expected Symptom Free Days per Patient



Mental Health

Prescribing information is available at this meeting.



ZEFE087/0701

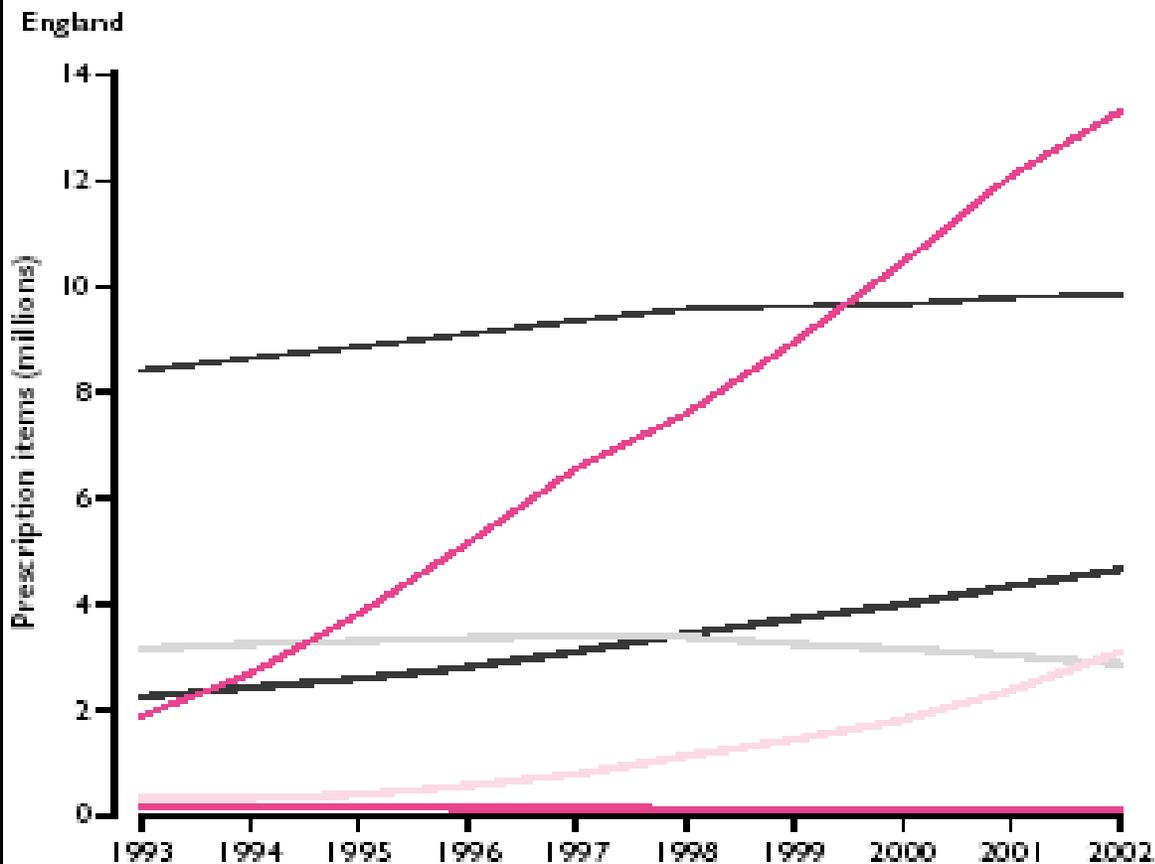
# Average Expected Cost per Symptom Free Day

Average Expected Cost per SFD



Figure 3

Prescription items (millions) for selected antidepressants, 1993–2002



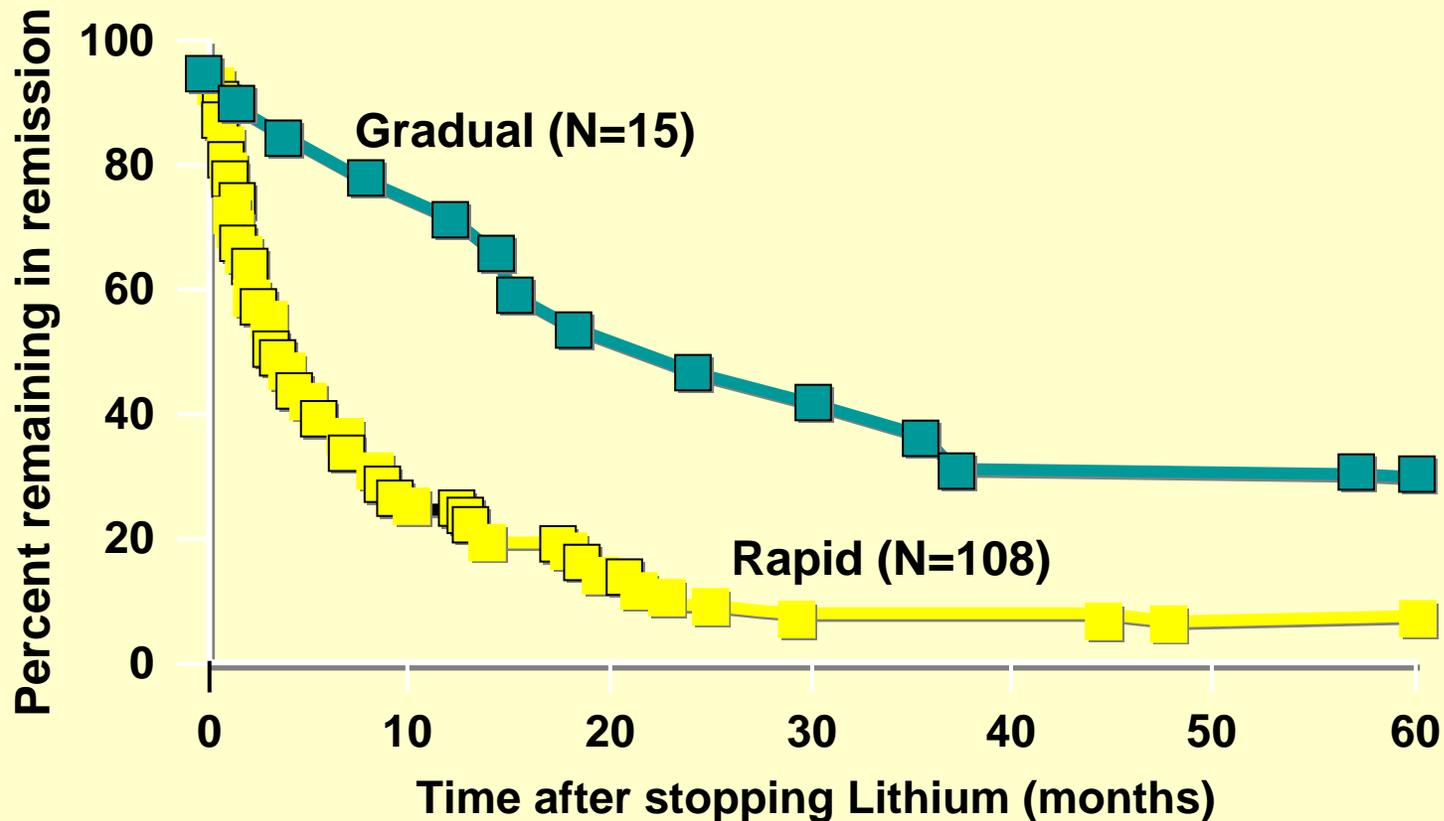
- |   |   |
|---|---|
| — Tricyclic & related antidepressants (TCA) | — Monoamine oxidase inhibitors (MAOI)             |
| — Amitriptyline                             | — Selective serotonin re-uptake inhibitors (SSRI) |
| — Dothiepin                                 | — Other antidepressants                           |

# Psychopharmacological Problems and Controversies

- Cost of drugs
- **Aren't drugs really harmful?**

# Harmful Medication

## Consequence of Rapid Discontinuation of Lithium in Bipolar I Patients

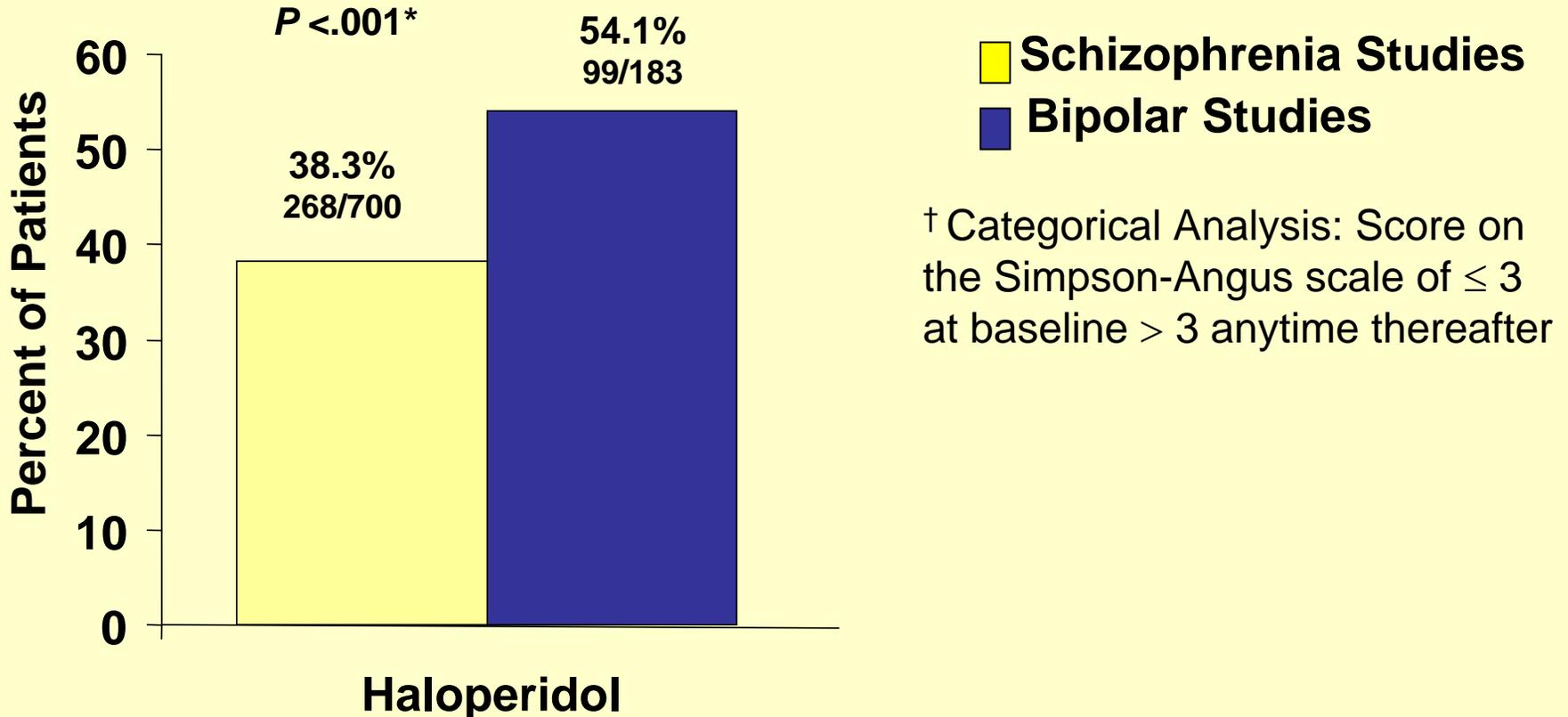


*From Suppes et al, 1991.*

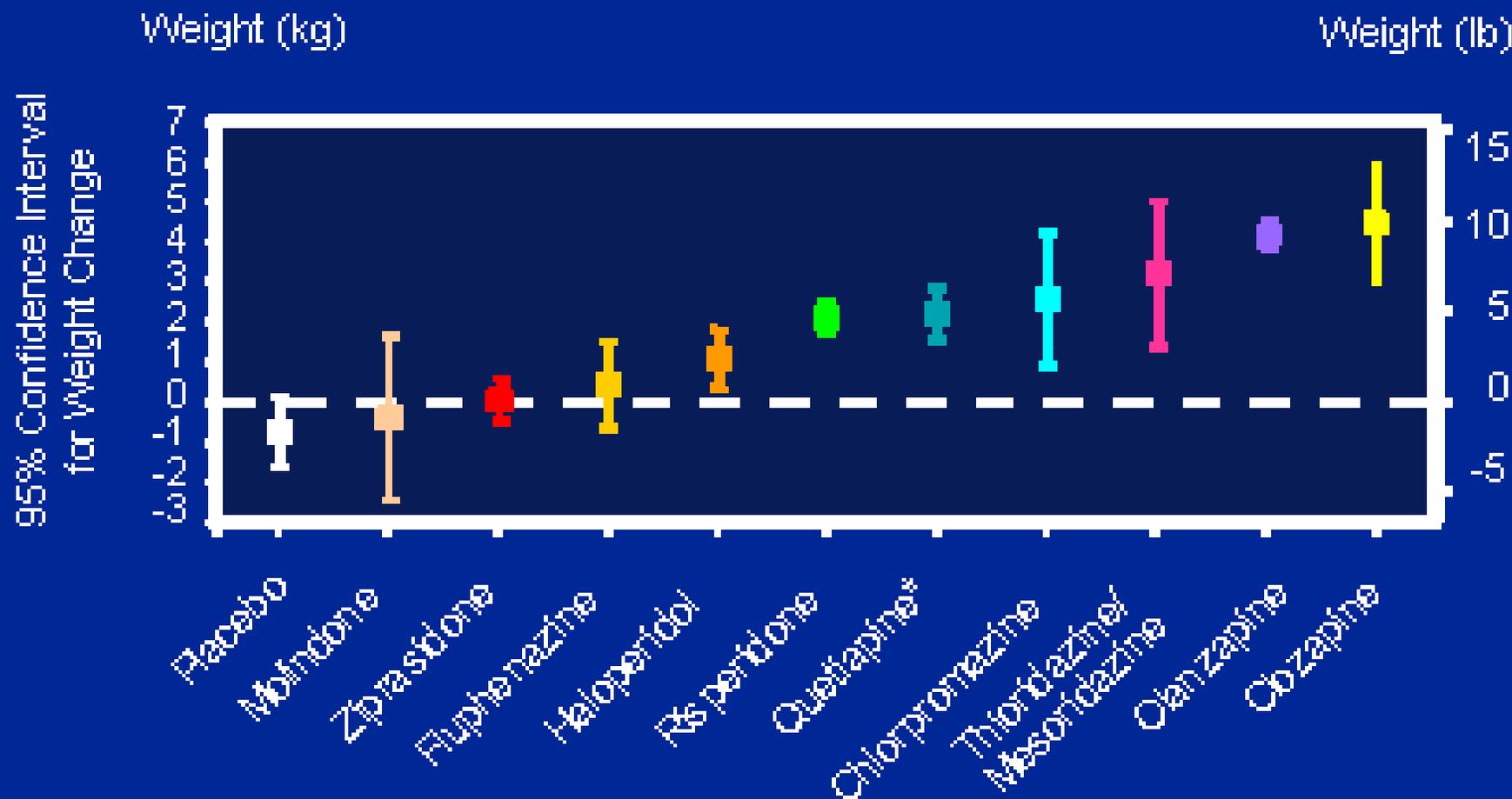
# Harmful Medication

## EPS Rates Schizophrenia vs Bipolar disorder

Treatment-Emergent Parkinsonism†



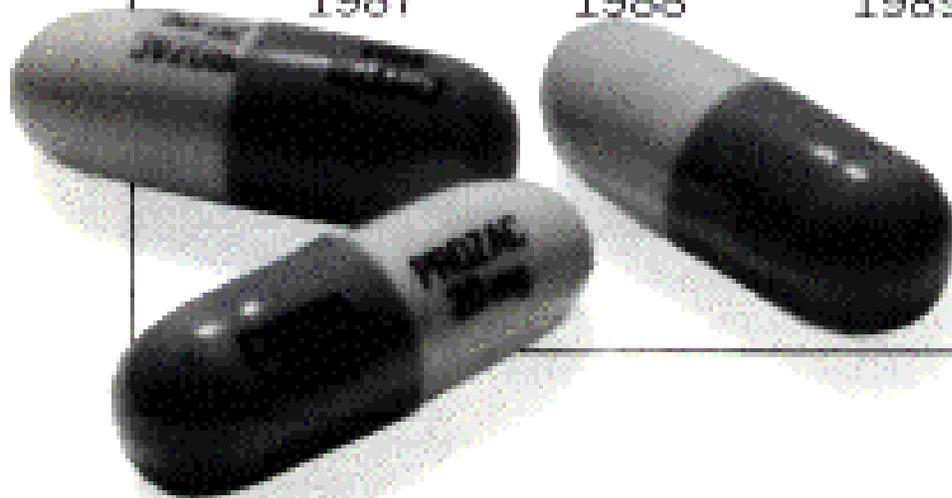
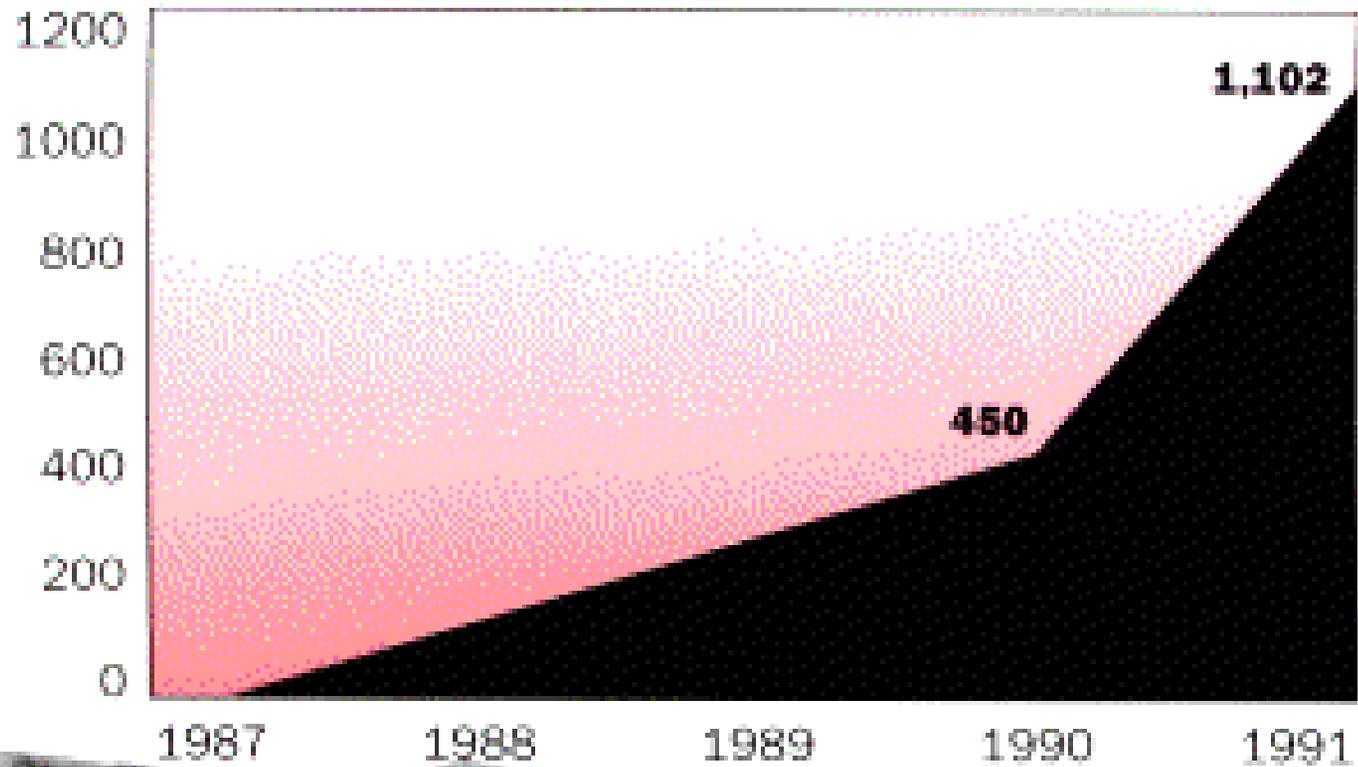
# Metaanalysis of Antipsychotic-Related Weight Gain Estimate at 10 Weeks



\*Maximum duration for quetiapine was 6 weeks; 10-week estimates not reported.  
 Allison DB et al. *Am J Psychiatry*. 1999;156:1686-1696.

# Total Prozac-Related Deaths

1991 One-Year Increase = 145%



## THE LETHAL DANGERS OF THE PSYCHIATRIC DRUGS PROZAC & RITALIN

### Prozac

Prozac is hailed as a 'wonder-drug'. However, as far back as September 1993, the U.S. Food & Drug Administration had received 28,623 reports of adverse reactions to Prozac; more than for any other product in the last 24 years.

A September 1989 article in the Journal of Clinical Psychiatry, estimated that between 10%-25% of persons on Prozac experience 'akathisia', a drug-induced insanity which includes hallucinations, aggression, self-destructive outbursts, suicide, hostility and rage. Add to this the reports of 1,885 attempted suicides and 1,734 deaths (1,089 by suicide), and the real 'wonder' of Prozac emerges.

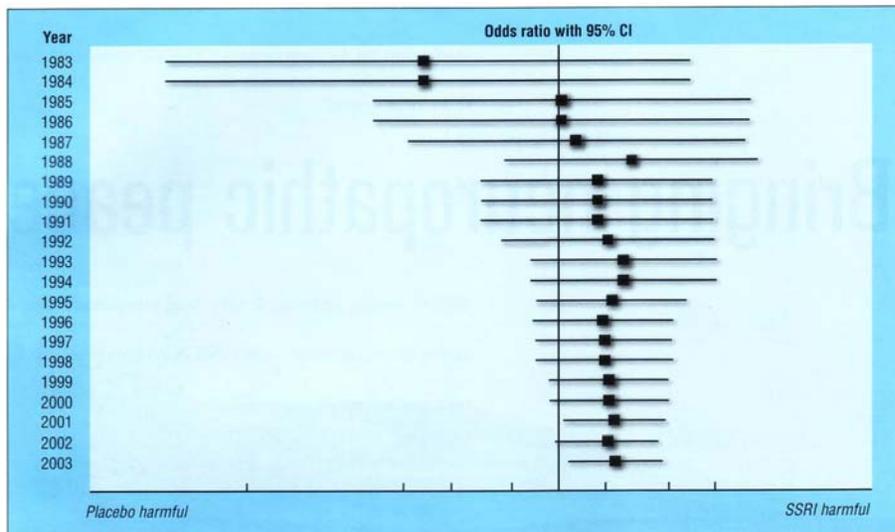
# Akathisia

- “...a subjective experience of motor unease with a feeling of being unable to sit still, a need to get up and move about, to stretch the legs, tap the feet, rock the body.”
  - Sims “Symptoms of the Mind” 1988

# BMJ, Feb 19, 2005

# BMJ

3303-373-428 No 7488 19 FEBRUARY 2005 Clinical research ISSN 0959-8138



## Do SSRIs cause suicide?

Three studies offer new insights for clinical practice p373, p385, p389, p396

Risk assessments for repeated self harm are inaccurate p394

Improving discussion of trial participation with cancer patients p400

Locked-in syndrome p406

Antibiotics for suspected haemolytic uraemic syndrome? p409

Teaching cultural diversity p403

# Psychopharmacological Problems and Controversies

- Cost of drugs
- Aren't drugs really harmful?
- **Do drugs really work?**

# RCTs and depression

- Around 30-40% patients in placebo arms of RCTs respond within 6/52 (c.f. 60-65% for drug)
  - Reasons include spontaneous recovery and supportive care
  - Rate of spontaneous recovery increases with decreasing severity of illness
  - Placebo response correlates with year of publication
- 40% drop outs from RCTs
  - ITT analysis biased against active treatment
- Most RCTs funded by industry
  - 4X as likely to be positive cf independent study
  - Publication bias
- Problem of RCTs for psychological therapies

# BMJ 16<sup>th</sup> July, 2005

Downloaded from [bmj.com](http://bmj.com) on 15 July 2005

## Education and debate

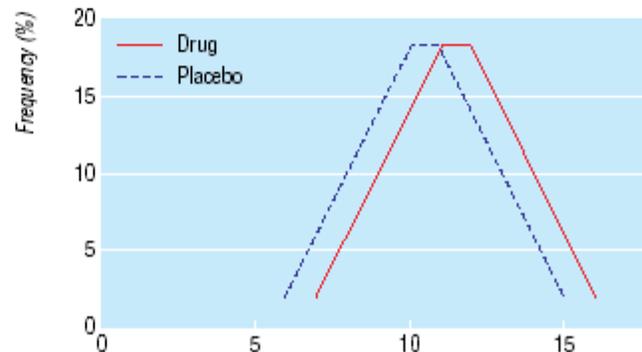
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### Efficacy of antidepressants in adults

Joanna Moncrieff, Irving Kirsch

Most people with depression are initially treated with antidepressants. But how well do the data support their use, and should we reconsider our strategy?

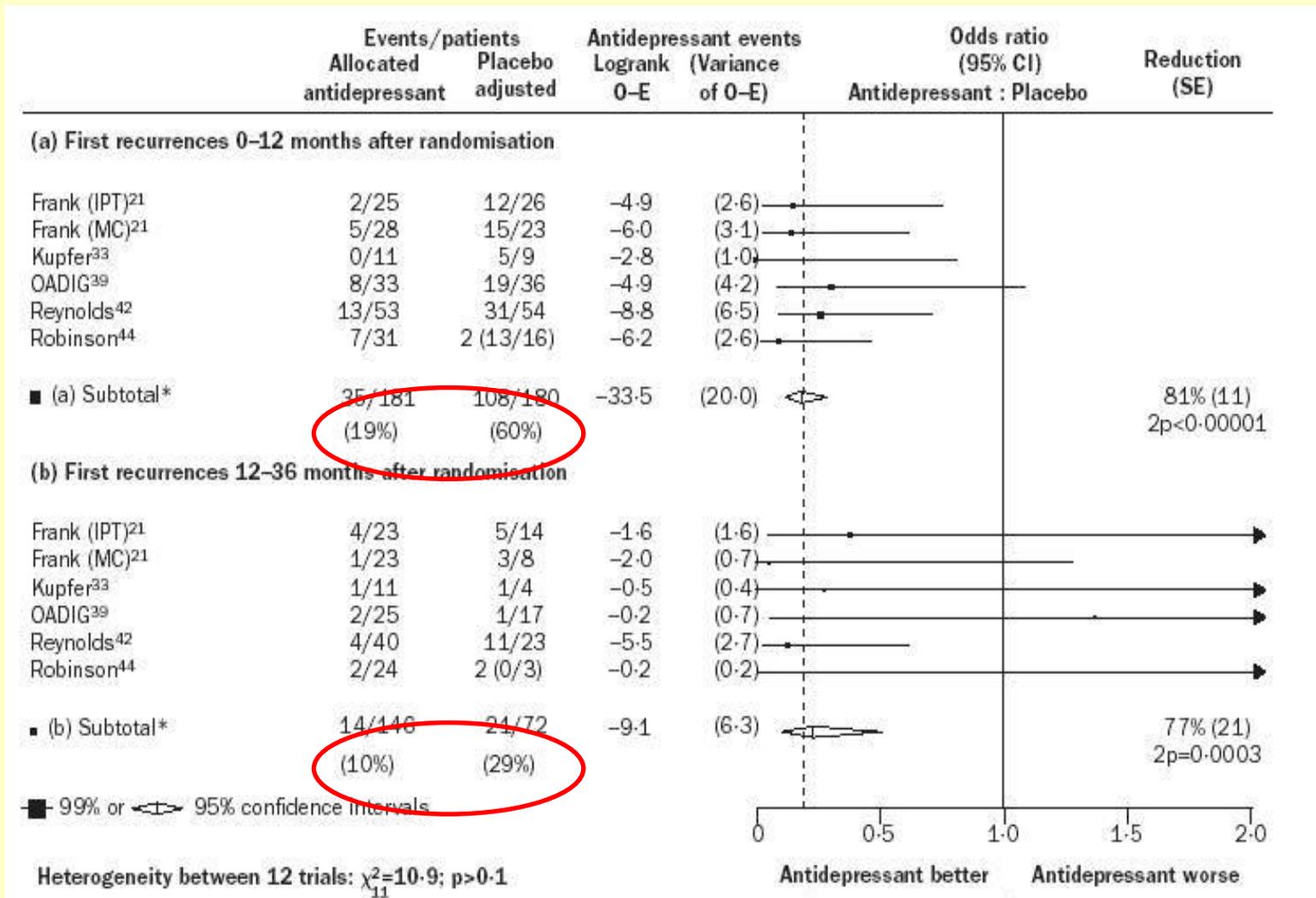
The National Institute for Health and Clinical Excellence (NICE) recently recommended that antidepressants, in particular selective serotonin reuptake inhibitors, should be first line treatment for moderate or severe depression.<sup>1</sup> This conclusion has broadly been accepted as valid.<sup>2</sup> The message is essentially the same as that of the Defeat Depression Campaign in the early 1990s, which probably contributed to the 253% rise in antidepressant prescribing in 10 years.<sup>1</sup> From our involvement in commenting on the evidence base for the guideline we believe these recommendations



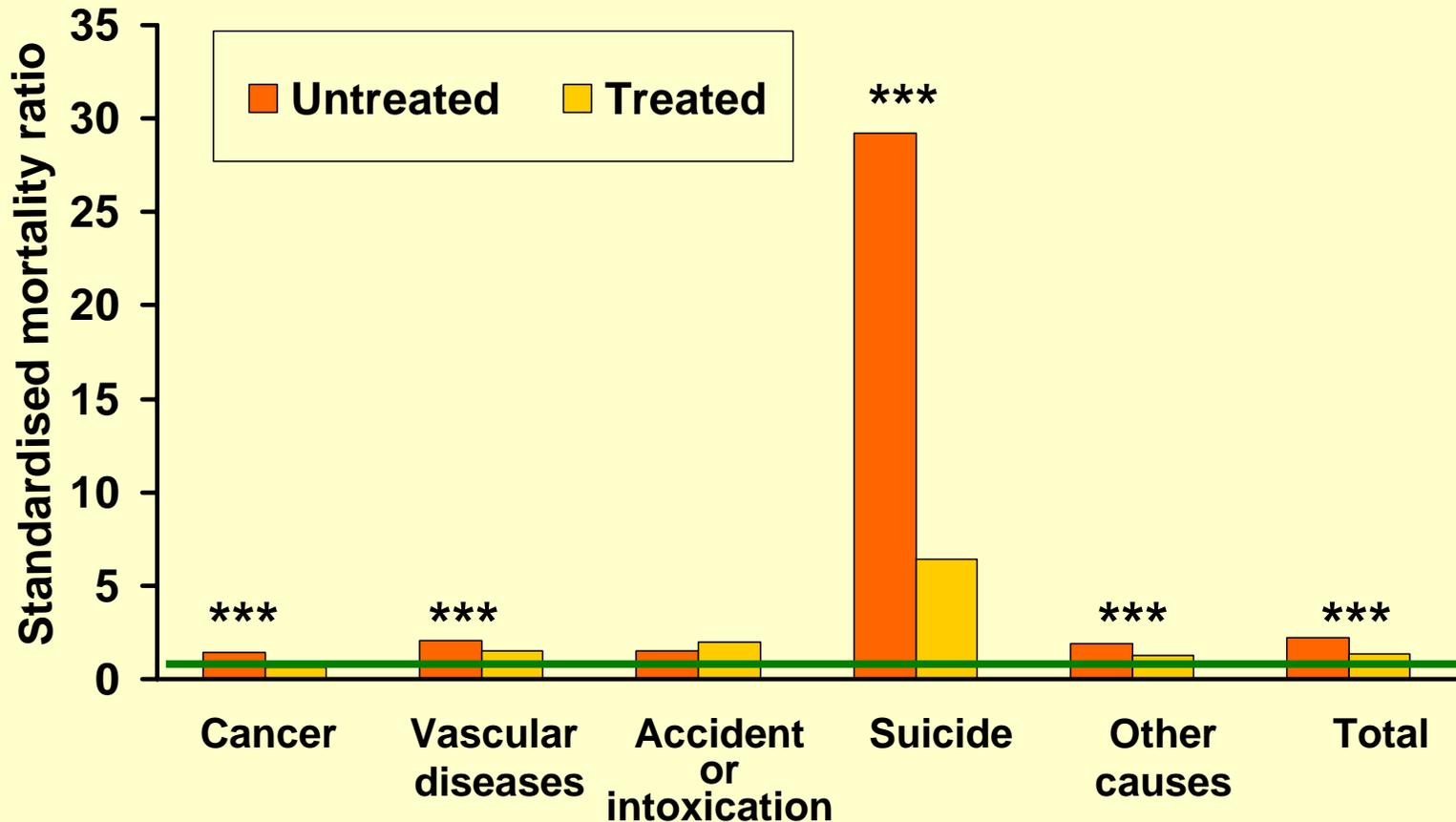
Department of  
Mental Health  
Sciences, University  
College London,  
London W1N 8AA  
Joanna Moncrieff  
*senior lecturer in  
social and community  
psychiatry*

School of Health  
and Social work,  
University of  
Plymouth,  
Plymouth

# Reduction in the risk of relapse with continuation of antidepressants



# Mortality in bipolar disorder



220 bipolar inpatients followed-up for 22 years or more

\*\*\*p<0.001 vs treated patients

Angst et al 2002

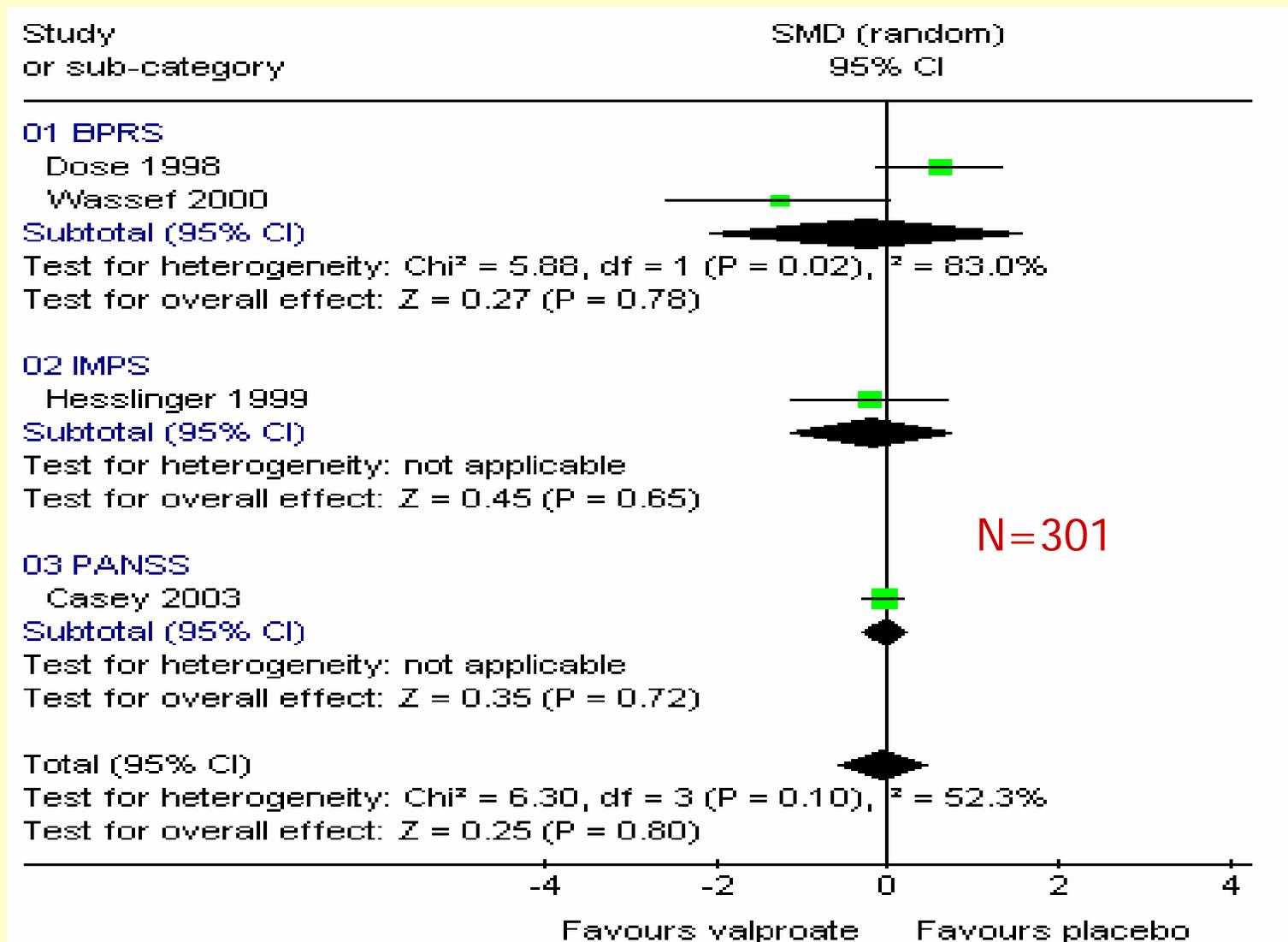
# Psychopharmacological Problems and Controversies

- Cost of drugs
- Aren't drugs really harmful?
- Do drugs really work?
- **Treatment resistance**

# Psychopharmacological Problems and Controversies

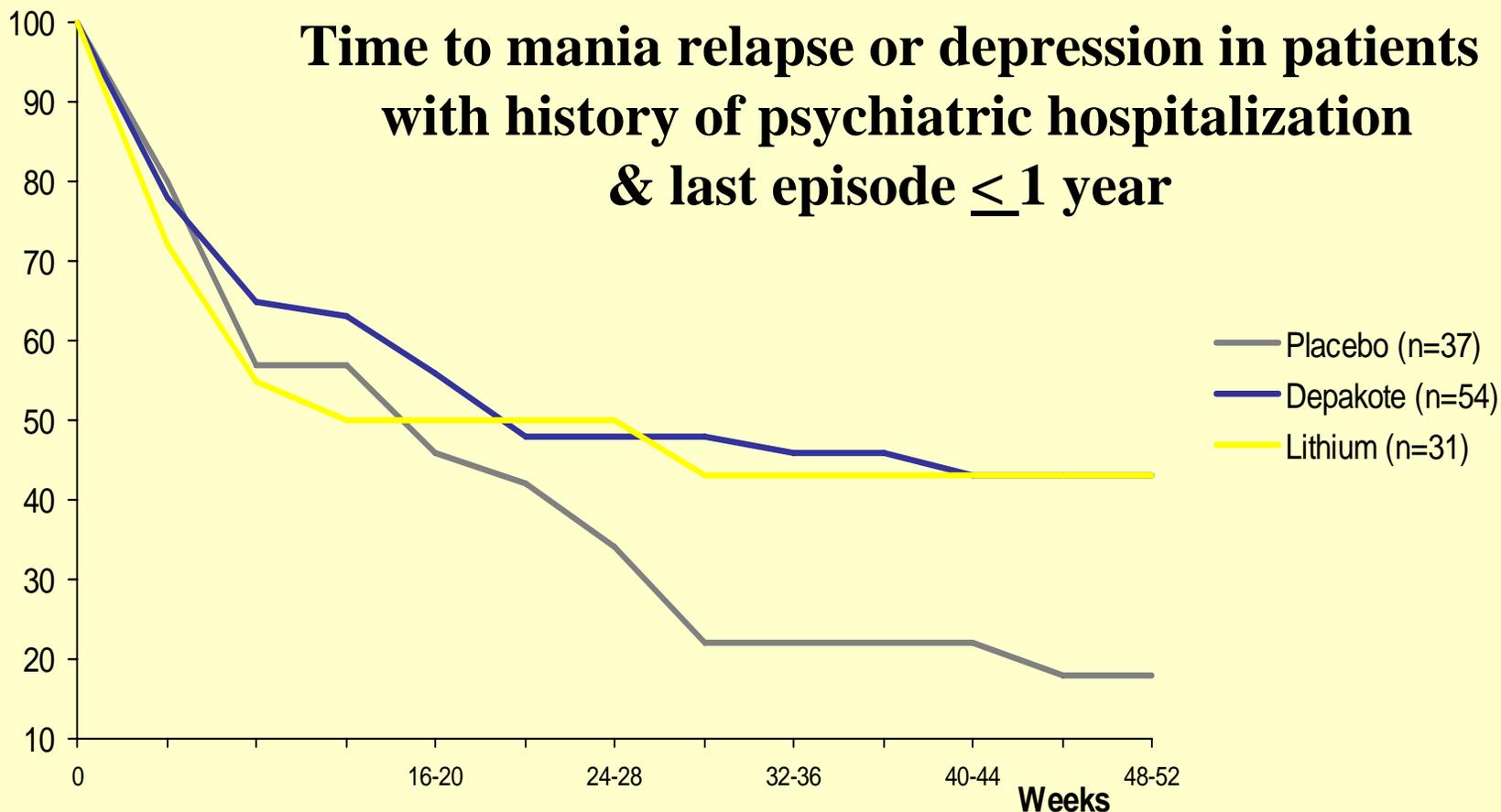
- Cost of drugs
- Aren't drugs really harmful?
- Do drugs really work?
- Treatment resistance
- **Poor evidence base**

# Treatment-resistant Schizophrenia: Valproate Augmentation



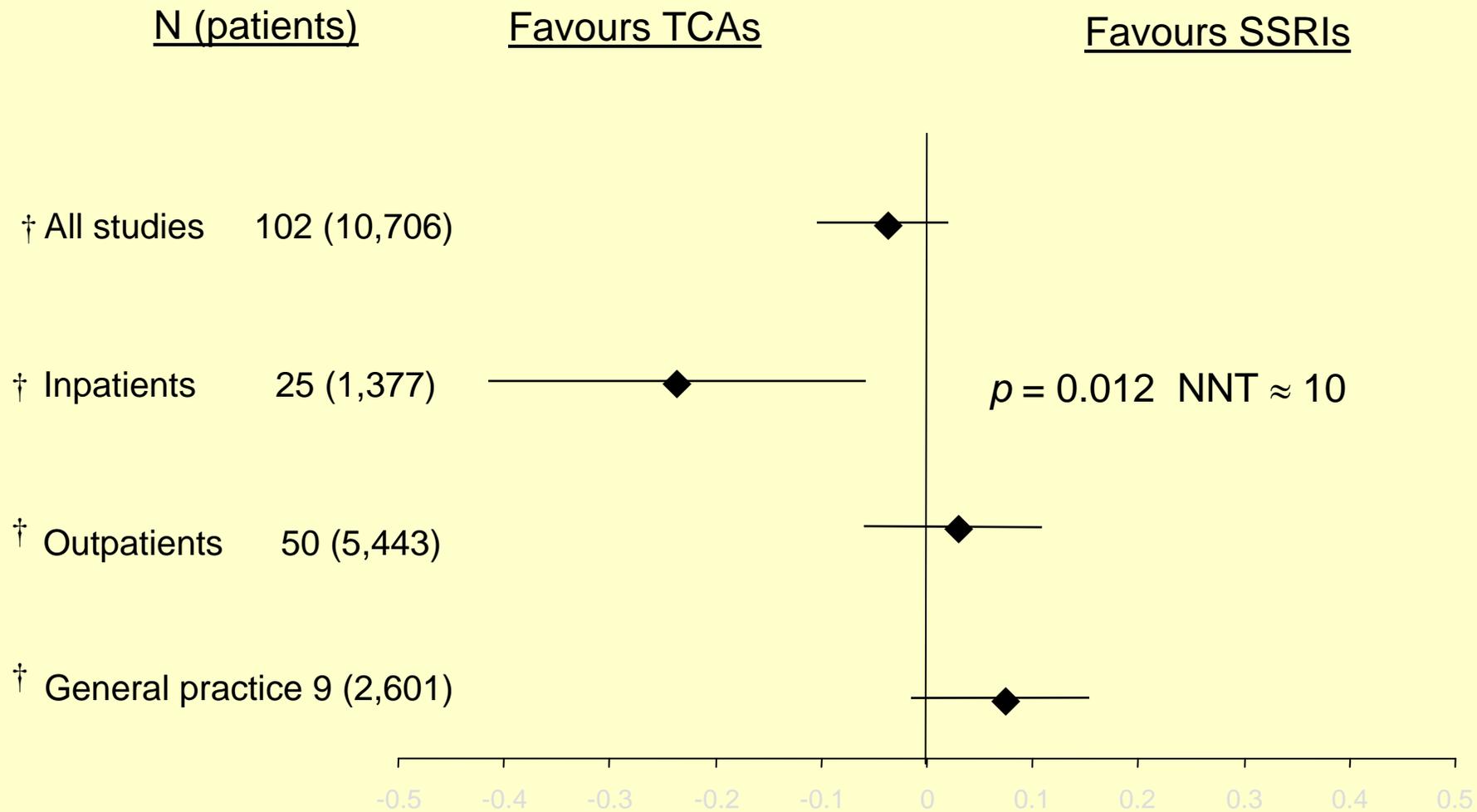
# Evidence base for use of valproate for prophylaxis in bipolar disorder

% Symptom Free



**Evidence base regarding  
decision to switch class of  
antidepressant after failure to  
respond to first line treatment....**

# Efficacy: SSRIs versus TCAs



Relative effect size (95% CI)

**Anderson 2000**

- Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of **49** completed trials in **14,236** patients.
- American Journal of Cardiology. 97(1):61-7, 2006 Jan 1.

# Evidence for NICE level 2 interventions for mild depression

- Guided self help effect on symptom levels
  - $N = 2, n = 57$
- Exercise on symptom levels
  - $N = 4, n = 146$
- Running versus mixed exercise
  - $N = 1, n = 18$



# Psychopharmacological Problems and Controversies

- Cost of drugs
- Aren't drugs really harmful?
- Do drugs really work?
- Treatment resistance
- Poor evidence base
- **Institutionalised bias against psychopharmacology**

# Royal College of Psychiatrists: Structure of the College

- Faculties
  - e.g. General and Community, Old age, Child and Adolescent, Forensics
- Sections
  - e.g. Perinatal psychiatry
- Special Interest Groups
  - e.g. Computers in Psychiatry, Gay and Lesbian, Spirituality

# Conclusions

- Psychopharmacology is an evolving area of treatment
- Psychopharmacology is the main therapeutic tool of psychiatrists but has poor professional recognition
- The practice of psychopharmacology is complex with many problems
  - Many controversies exist (rightly or wrongly)
  - The worst controversy is that the evidence base is so poor

“The study of MEDICINE is prosecuted under two relations, namely as a *Science* and as an *Art*”

The Science and Practice of  
Medicine  
W. Aitken  
1872