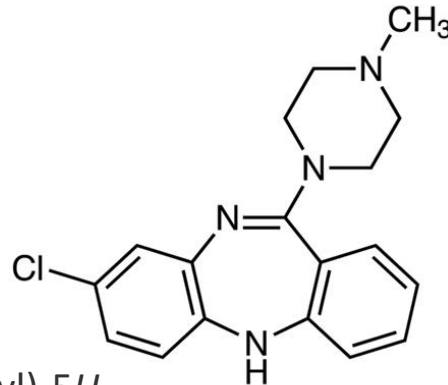
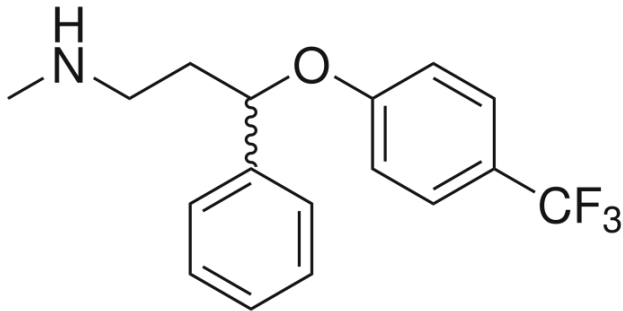


# Psychopharmacology- Introduction

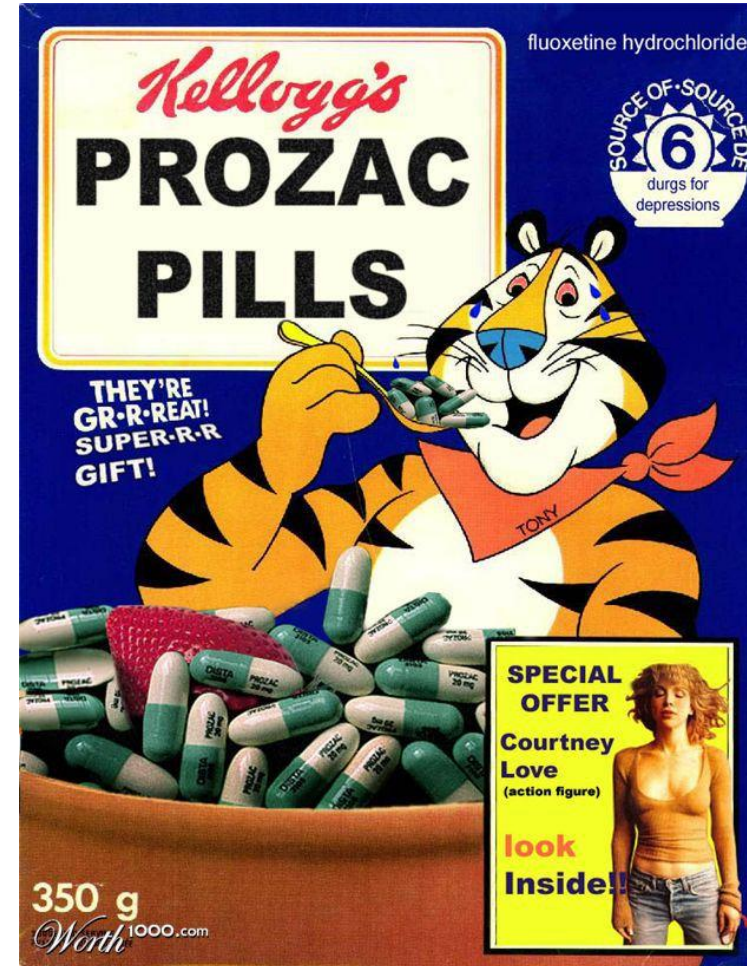
Dr Karl Coldman, Consultant Child and Adolescent Psychiatrist

Original Author:

Dr Cathy Symonds, Honorary Senior lecturer,  
University of Manchester, Consultant Liaison Psychiatry,  
Royal Bolton Hospital



•8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine



# Psychopharmacology Overview

- Introduction
- Drug development
- Key Drug trials
- Placebo Effect

# Psychopharmacology

Neuroscience + Pharmacology

= Psychopharmacology

Psychopharmacology is the critical application of knowledge of pharmacology and neuroscience in order to relieve suffering in psychiatric conditions.

# Psychotropic drug-A Definition

Either

- “A synthetic substance that alters endogenous neurotransmission” or
- “A substance which produces significant behavioural or affective change” or.....

# Psychotropic drug-A Definition

- “a substance that when give to a rat produces a paper”
  - FDA definition of an antidepressant depends on rat watermaze/ mouse tail dangling

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3353516/>

<https://www.viennabiocenter.org/facilities/pre-clinical-phenotyping/behavioral-tests-and-equipment/>



# Drug Development

*(Roland Kuhn and the discovery of imipramine)*

1956 – purported to approach Geigy( company) to investigate alternatives to chlorpromazine ( which at the time was very expensive)

Imipramine – differs from chlorpromazine only in one side chain

# *Roland Kuhn and the discovery of imipramine*

In 1957, published clinical observations of antidepressant effect of imipramine in a group of 40 patients (Kuhn R. Über die Behandlung depressiver Zustände mit einem Iminodibenzylderivat (G 22355) Schweiz Med Wschrft. 1957;87:1135–1140.)

“Forty patients were ultimately studied but the responses of the first three were so dramatic that the ward nursing staff and Kuhn had little doubt that the treatment was effective... Paula JF, who was depressed and deluded, started treatment on Jan 12th 1956 and six days later was completely transformed.”

**“The Antidepressant Era”  
by David Healey, 1997**

# Roland Kuhn and the discovery of imipramine

- 1 year later – repeat study on 500 psychiatric patients
- Found antidepressant effects mainly in major depression
- But also antidepressant effects in other conditions (schizophrenia/anxiety disorders)
- Identified **first** antidepressant drug

*Until mid 1950's opium treatment was standard ( lengthy and ineffective and addictive) treatment*

*For major depression, Insulin or cardiazol shock and ECT in use since 1930's and under intense discussion due to serious side effects*



# Roland Kuhn and the discovery of imipramine

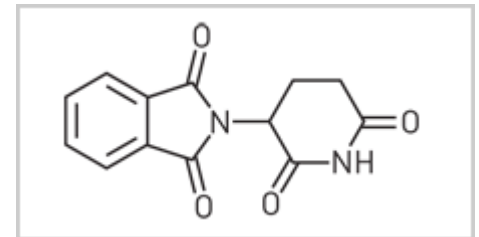
- Kuhn admitted he could not explain how imipramine worked
- As Tricyclic antidepressants were monoamine reuptake inhibitors, this led to the monoamine or catecholamine deficiency hypothesis of affective disorders

Steinberg H, Himmerich H. Roland Kuhn-100th Birthday of an Innovator of Clinical Psychopharmacology. *Psychopharmacol Bull.* 2012;45(1):48-50.

# Drug development

- **Preclinical Animal Studies:**
  - The molecule is demonstrated to have specific actions.
  - Tests are carried out on at least 2 different species
  - Mutagenicity, carcinogenicity and organ system toxicity
- **Human trials – volunteers phase 1: Is it safe?**
  - Safety, tolerability, pharmacokinetics phase
  - Administered to a small group of volunteers
  - Open, uncontrolled studies usually

2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione



Thalidomide – inhibits angiogenesis (critical for limb development)

# TGN1412 (2006)

- T cell CD28 receptor agonist
- B cell CLL and Rheumatoid arthritis
- Phase I (N=8), Northwick Park, London
- 4/6 who received drug – multiple organ failure secondary to cytokine storm

How could this happen? (macaques....

# Drug development

- **Human trials – patients phase 2: does it work?**
  - Effectiveness phase
  - Placebo controlled trials
  
- **Human trials – patients phase 3: is it any better than what is out there already?**
- How good is it and what are the common side effects
- Comparative efficacy, superiority and tolerance
- double-blind RCT

# Drug development

## **DRUG APPROVED**

- **Human trials - post-marketing surveillance phase 4:**
- Surveillance of large scale prescribing to pick up less common side effects that may lead to the drug being withdrawn
- Observational studies or randomized controlled trials.

# Shamed Glaxo reveals truth on 'suicide' drug

By **Beezy Marsh** and **Tim Utton**

BRITAIN'S biggest drugs firm caved in dramatically yesterday and revealed research which shows a leading anti-depressant can cause children to attempt suicide.

In an astonishing U-turn, Glaxo-SmithKline finally published full details of nine scientific studies and two clinical reviews which expose the dangers posed to under-18s who take Seroxat.

Children on Seroxat are twice as likely to have suicidal thoughts than those on a dummy pill, it emerged.

Alarming, one study showed six youngsters on Seroxat wanted to kill themselves, compared to just one taking a placebo pill.

The drug was also linked to distressing side effects including hostility, insomnia, dizziness, tremors and emotional irritability.

Campaigners say the damning findings were suppressed for up to a decade while thousands of teenagers and children as young as six continued to be given the pills to ease depression.

## 'A bright and public light'

At one point, doctors had even hailed Seroxat as a 'wonderdrug' to help people overcome shyness.

The firm is facing a major lawsuit amid allegations that drug regulators were duped into thinking Seroxat - which is worth £2 billion a year to Glaxo - was safe for children.

## The who

**'It was like prescribing him a loaded gun'**

**JAMIE HOOLE** killed himself two months after he started taking Seroxat.

The talented pianist and artist was prescribed the drug after he lost his self-confidence and began to withdraw from everyday life.

More than a year after he hanged himself, his mother Jean Bambrough is convinced her son would still be alive had he not been on the drug.

Miss Bambrough, 43, a personal assistant from Northwood, North-West London, said: 'It was like prescribing him a loaded gun.'

Jamie, a builder, turned to self-harm - cutting his arms, legs and stomach with a knife. Not long after, his 13-year-old brother Daniel came home to find him hanging by a belt.

Adrian Keegan, 19, had been taking Seroxat for just 26 days when he committed suicide.

He was diagnosed with depression after his relationship with his girlfriend broke down and was prescribed the drug by his GP in 2001.

His father Christopher found his body hanging in his flat. Mr Keegan, from Market Drayton, Shropshire, said: 'There needs to be

British GPs were banned from prescribing Seroxat to children.

She was first prescribed the drug as a 16-year-old GCSE pupil. Her personality rapidly changed and she began to harm herself.

After coming off the drug, she secretly began taking it again two years later to help her depression.

After 17 days, she hanged herself. Her mother Stephanie, 44, from Newhaven, East Sussex, said: 'Words cannot describe what we've been going through.'

Lucy Sullivan was prescribed Seroxat for depression but weaned herself off it after she tried to kill herself by slitting her wrists.

Now the 24-year-old blames it for depriving her of 18 months of her life. Soon after she began taking the drug at 19 for clinical depression, her personality changed for the worse.

She became violent, lost touch with her friends and lacked the will to find another job after she was made redundant.

After almost 18 months on the drug, Miss Wilson, from Bromsgrove, Worcestershire, tried to kill



# Suicide

**Objective:** In March 2004 the U.S. Food and Drug Administration (FDA) warned physicians and patients regarding increased risk of suicide with 10 newer antidepressant drugs. The authors used population-based data to evaluate the risk of suicide death and serious suicide attempt

**Results:** In the 6 months after the index prescription of antidepressant treatment, 31 suicide deaths (40 per 100,000 treatment episodes) and 76 serious suicide attempts (93 per 100,000) were identified in the study group. The risk of suicide attempt was 314 per 100,000 in children and adolescents, compared to 78 per 100,000 in adults. The risk of death by suicide was not significantly higher in the month after starting medication than in subsequent months. The risk of suicide attempt was highest in the month before starting antidepressant treatment and declined progressively after starting medication. When the 10 newer antidepressants included in the FDA advisory were compared to older drugs, an increase in risk after starting treatment was seen only for the older drugs.

**Conclusions:** The risk of suicide during acute-phase antidepressant treatment is approximately one in 3,000 treatment episodes, and risk of serious suicide attempt is approximately one in 1,000. Available data do not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs.

*(Simon et al Am J Psychiatry 2006; 163:41–47)*

# Suicide attempts and treatment

**Objective:** This study compared the time patterns of suicide attempts among outpatients starting depression treatment with medication or psychotherapy.

**Method:** Outpatient claims from a prepaid health plan were used to identify new episodes of depression treatment beginning with an antidepressant prescription in primary care (N=70,368), an antidepressant prescription from a psychiatrist (N= 7,297), or an initial psychotherapy visit (N= 54,123). Outpatient and inpatient claims were used to identify suicide attempts or possible suicide attempts during the 90 days before and 180 days after the start of treatment.

**Results:** Overall incidence of suicide attempt was highest among patients receiving antidepressant prescriptions from psychiatrists (1,124 per 100,000), lower among those starting psychotherapy (778 per 100,000), and lowest among those receiving antidepressant prescriptions in primary care (301 per 100,000). The pattern of attempts over time was the same in all three groups: highest in the month before starting treatment, next highest in the month after starting treatment, and declining thereafter. Results were unchanged after eliminating patients receiving overlapping treatment with medication and psychotherapy. Overall incidence of suicide attempt was higher in adolescents and young adults, but the time pattern was the same across all three treatments.

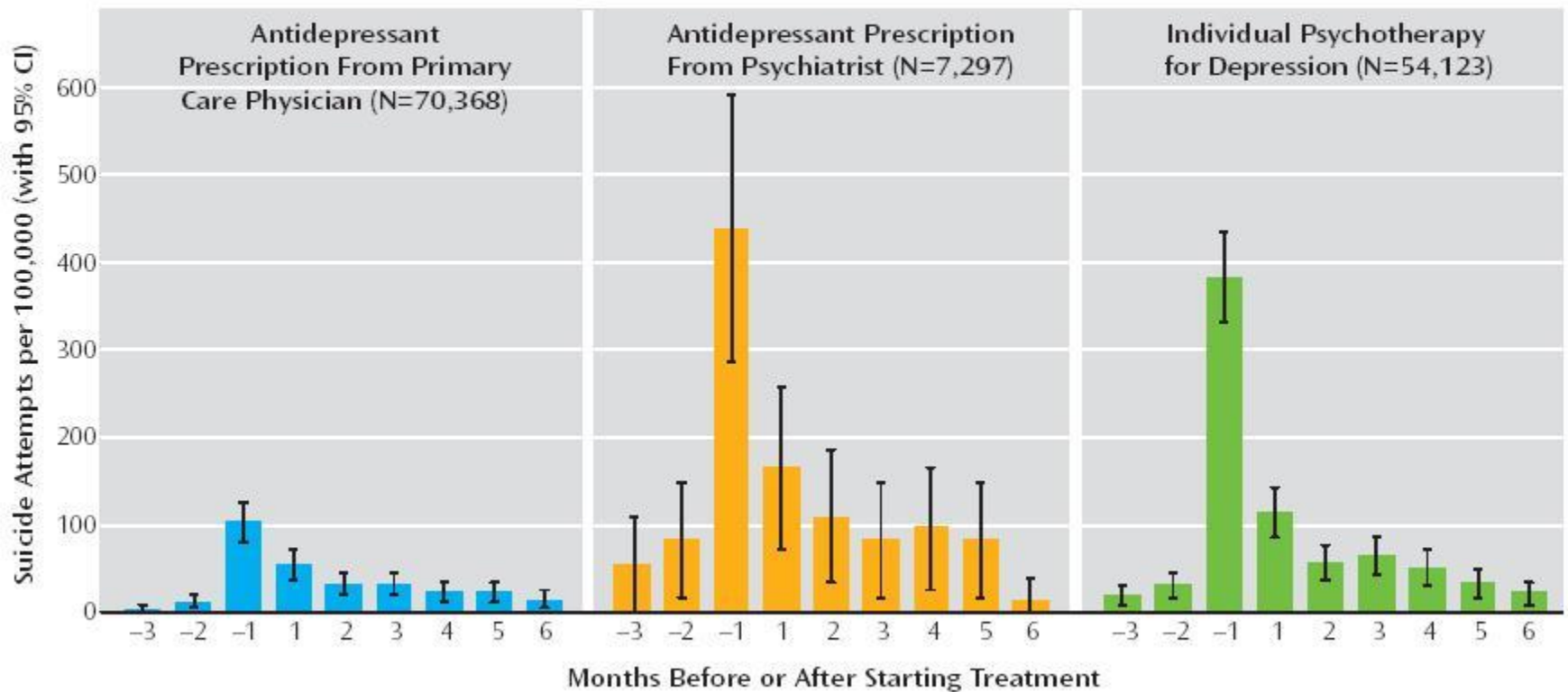
**Conclusions:** The pattern of suicide attempts before and after starting antidepressant treatment is not specific to medication. Differences between treatments and changes over time probably reflect referral patterns and the expected improvement in suicidal ideation after the start of treatment.

*(Simon and Savarino Am J Psychiatry 2007; 164:1029–1034)*

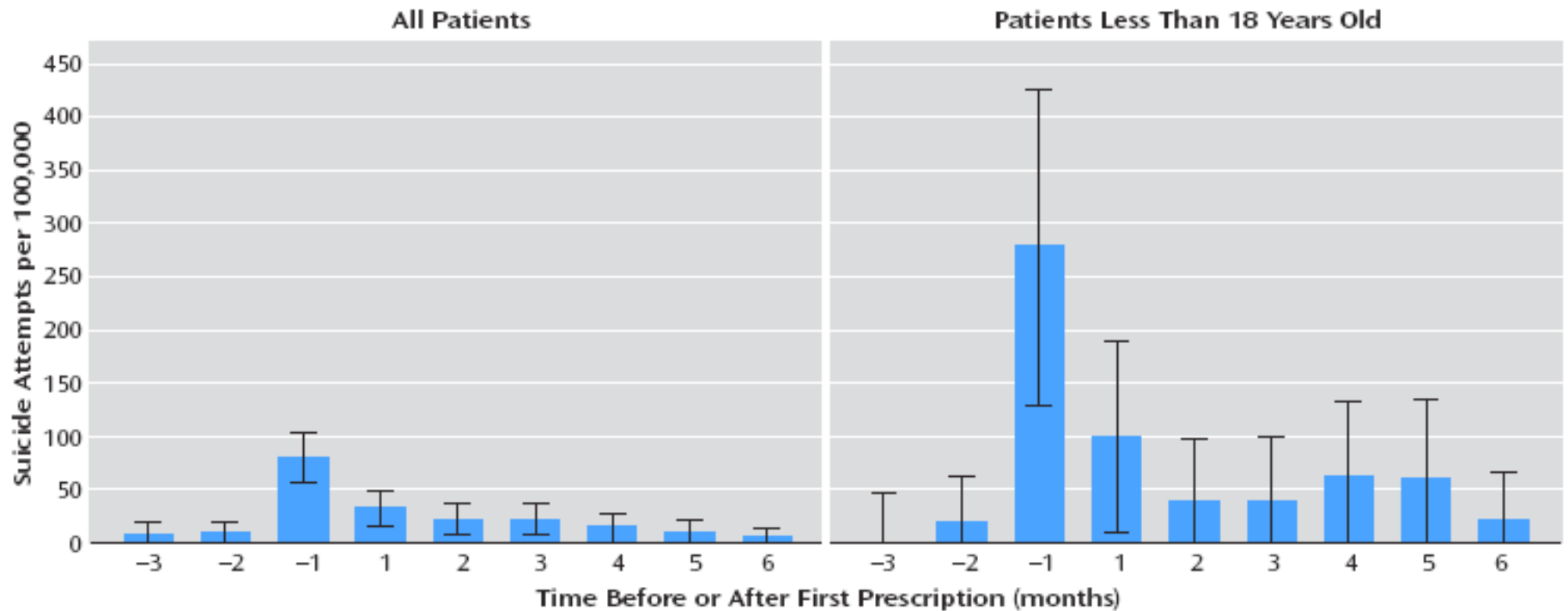


# Suicide attempts and treatment

FIGURE 1. Risk of Suicide Attempt or Possible Suicide Attempt Before and After Starting Treatment Among Adolescents and Adults Receiving New Antidepressant Prescriptions From Primary Care Physicians, Receiving New Antidepressant Prescriptions From Psychiatrists, or Starting Individual Psychotherapy for Depression



# Suicide attempts and treatment related to age



<sup>a</sup> Bars indicate 95% confidence intervals.

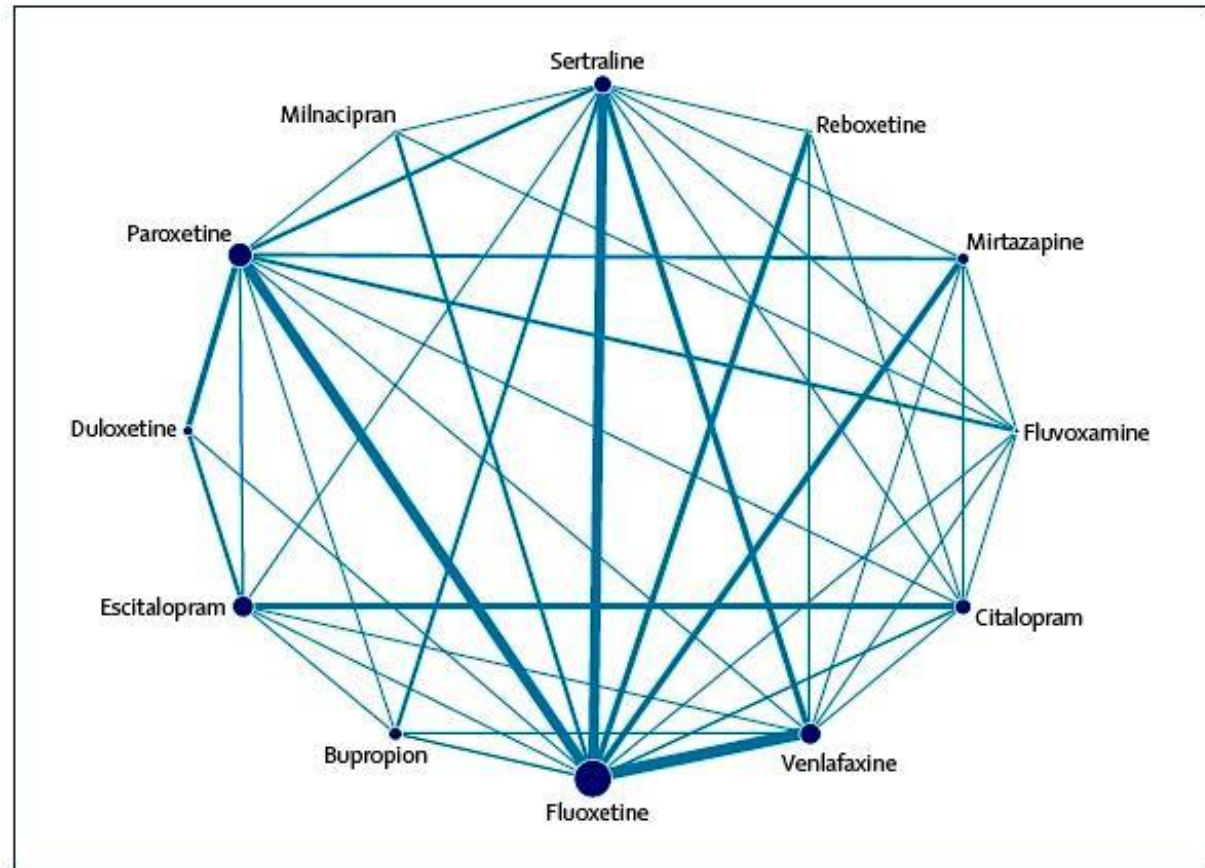
# Exam: drugs that got through trials

Nefazadone	Serotonin antagonist and reuptake inhibitor
Pimozide	1 <sup>st</sup> gen antipsychotic
Thioridazine	Withdrawn worldwide 2005 Severe cardiac arrhythmias
Sertindole	Atypical antipsychotic
Mianserin	Atypical antidepressant - <u>tetra</u> cyclic
Tranlycypromine	MAOi
Clozapine	dopamine D1, dopamine D2, 5-HT2A, alpha1-adrenoceptor, and muscarinic-receptor antagonist.)
Lithium	Salts

# Trials to know

- CATIE
- CUtLASS
- EUFEST
- STAR – D
- SADHART

CIPRIANI



**Figure 2: Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)**  
The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

# CATIE

- **CATIE** (*Clinical Antipsychotic Trials of Intervention Effectiveness*) - **FGA vs 2nd gen. antipsychotic**

## Phase 1 (N= 1493)

- 18 month study
- PERPHENAZINE VS OLZ/RISP/QUET/ZIP
- Olanzapine lowest discontinuation rate and lowest hospitalisation rate for relapse. Highest rate of metabolic side effects.
- Perphenazine was as tolerable and efficacious as 2nd gen. antipsychotic

# CATIE

Phase 2 for patients discontinuing first drug

– Efficacy pathway (cloz vs another 2nd gen. antipsychotic, N=99)

- Clozapine well tolerated (44% vs 18% remained on it for duration)

– Tolerability pathway (zip vs another 2nd gen. antipsychotic, N=444)

- Olz and Risp did well

- <http://www.nimh.nih.gov/funding/clinical-trials-for-researchers/practical/catie/phase1results.shtml>

# CUtLASS

- CUtLASS – (*Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study*)
- UK version. Smaller, open studies.
- N=1227
- first-generation v. second-generation drug other than clozapine (AMI/OLZ/QUET/RISP)
- Primary outcome was quality of life at 1 year and symptoms were the main secondary outcome
- No significant advantages from using 2nd gen. antipsychotic

# CATIE and CUtLASS

CUtLASS-2 (like CATIE phase 2)

- Clozapine ‘rocks’ in the UK too for treatment resistant SCZ

## Are FGA results surprising?

NB - Low potency typicals used in CUTLASS (mostly sulpiride – very much like a 2<sup>nd</sup> gen antipsychotic)

*CATIE and CUtLASS: can we handle the truth? Lewis and Lieberman (British Journal of Psychiatry 2008, 192: 161-163)*



# EUFEST Kahn et al. The Lancet 2008

Method: n=498, **FIRST-EPIISODE** schizophrenia, schizophreniform, schizoaffective

1 year, randomised **OPEN** trial comparing amisulpride, quetiapine, olanzapine and ziprasidone with **LOW-DOSE** haloperidol (1-4mg/day).

Primary outcome: Premature study discontinuation due to any reason

Results: amisulpride and olanzapine lowest discontinuation rate (overall and dropout due to inefficacy). Haloperidol most EPS despite low doses. Olanzapine most weight gain.

# Trials

- SADHART (Sertraline AntiDepressant Heart Attack Trial 2002)
  - 369 patients randomized to placebo or sertraline in flexible dosages ranging from 50 mg/day to 200 mg/day for 24 weeks,
  - Sertraline is safe and efficacious in depressed patients with ischemic heart disease
  - Underpowered re: detecting mortality difference between sertraline and placebo.
- SADHART-CHF (2010)
  - 469 patients were randomized (n = 234 sertraline, n = 235 placebo)
  - Left ventricular ejection fraction  $\leq 45\%$ , New York Heart Association functional class II to IV
  - Safe but no more effective than placebo

# STAR\*D – basis of iterative algorithm for treatment of depression

- Level 1 results include 2,876 outpatients, ages 18-75 years, from 41 clinical sites across the USA. Citalopram for 12-14wk
  - 28% remission within 7 weeks (mean dose 55mg!)
  - 10-14% partial response

NB - non randomised. major incentive for patients taking part in this trial is that they got free healthcare within their local health system.

# Star\*D level 2 (N=1469)

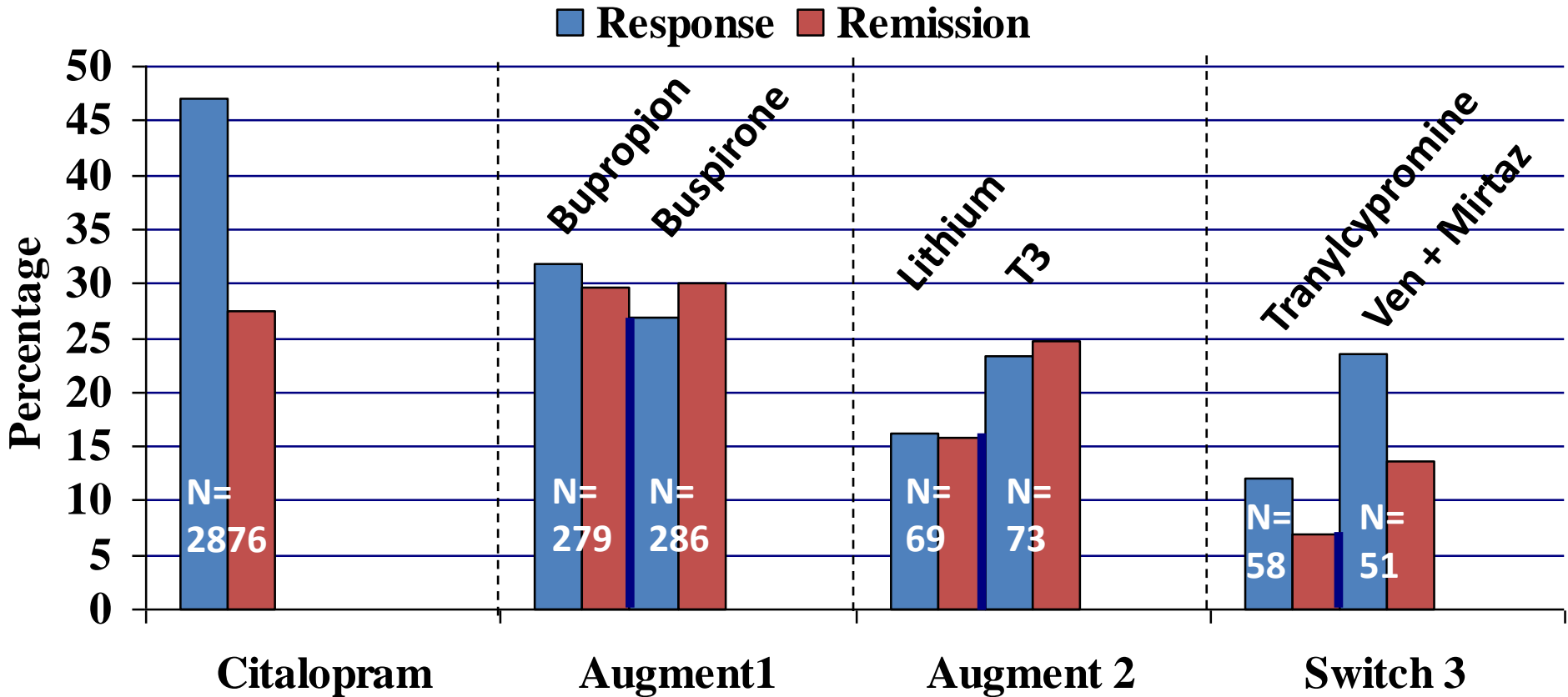
- Medication Switch: switch to sertraline, venlafaxine XR, bupropion SR. (25% remission)
- Medication Augmentation: add to citalopram either (a) buspirone, (b) bupropion SR. (33% remission)

# STAR\*D – basis of iterative algorithm for treatment of depression

- Level 3 results n=377
  - Switch to Mirtazepine/Nortriptyline : 15% remission
  - Augment with Lithium / T3 : 10-20% remission
- Level 4 results n=142
  - Switch to Mirtazepine/Venlafaxine combo
  - Switch to Tranylcypromine
  - M/V option better tolerated. 10% remission

# Outcome of STAR\*D: augmentation

Entry: 80% recurrent or chronic depression. Mean episodes: 6, Mean duration 25 months.



Trivedi et al 2006; Madhukar et al 2006; Nierenberg et al 2006; McGrath et al 2006

# Placebo (response)

- May be inert or active and may cause adverse effects
- 20-60 percent in depression, mania and anxiety disorders
- 20-50 percent in chronic schizophrenia
- What factors determine propensity to respond to a placebo?

# Factors influencing response to placebo

- Clinician reputation and relationship with patient
- Clinical setting
- Patient's expectations and response to treatment in the past
- Surgery > Injections > lots of large capsules vs 1-2 small tablets
- Strong tasting or noxious smelling
- Colour (GREEN ANXIOLYTICS AND YELLOW ANTIDEPRESSANTS)
- Length of "treatment" (placebo sag -refers to the attenuation of the placebo effect with repeated use (Peck & Coleman, 1991) )



# Factors influencing response to placebo

- Severe pain
- Mild depression
- Real vs experimentally induced conditions
- Conditions: pain, autonomic sensations, neurohumoral disorders (hypertension, palpitations, nausea)
- Chronic illness = lower placebo response

# Why do placebos work?

- **1. Natural remission** – patient simply gets better. as most diseases relapse and remit. Placebo use is mere coincidence.
- **2. Measurement regression:** When a continuous variable is measured repeatedly in a sample, successive measurements get closer to the population mean
- **3. Conditioning theory:** Response to placebo is simply a conditioned response – “when I take pills I get better”.

Thank You!

Questions?