Newcastle University

Regional Affective Disorders Service

NHS

Northumberland, Tyne and Wear NHS Trust

Psychopharmacology

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Intro

- NOT a comprehensive review of everything you need to know about drug treatments of mental illness!
- Remember:
  - 30% of patients visiting their GP have mental health problems
  - 20-50% of patient in hospital out-patient clinics have mental health problems
  - This is NOT some highly specialised area that you only need to have a vague knowledge of
  - All doctors need to know something about psychotropic drugs

Plan

- General comments
- Brief overview of major groups of psychotropics
  - Antidepressants
  - Hypnotics/anxiolytics
  - Antipsychotics
  - “Mood Stabilisers”

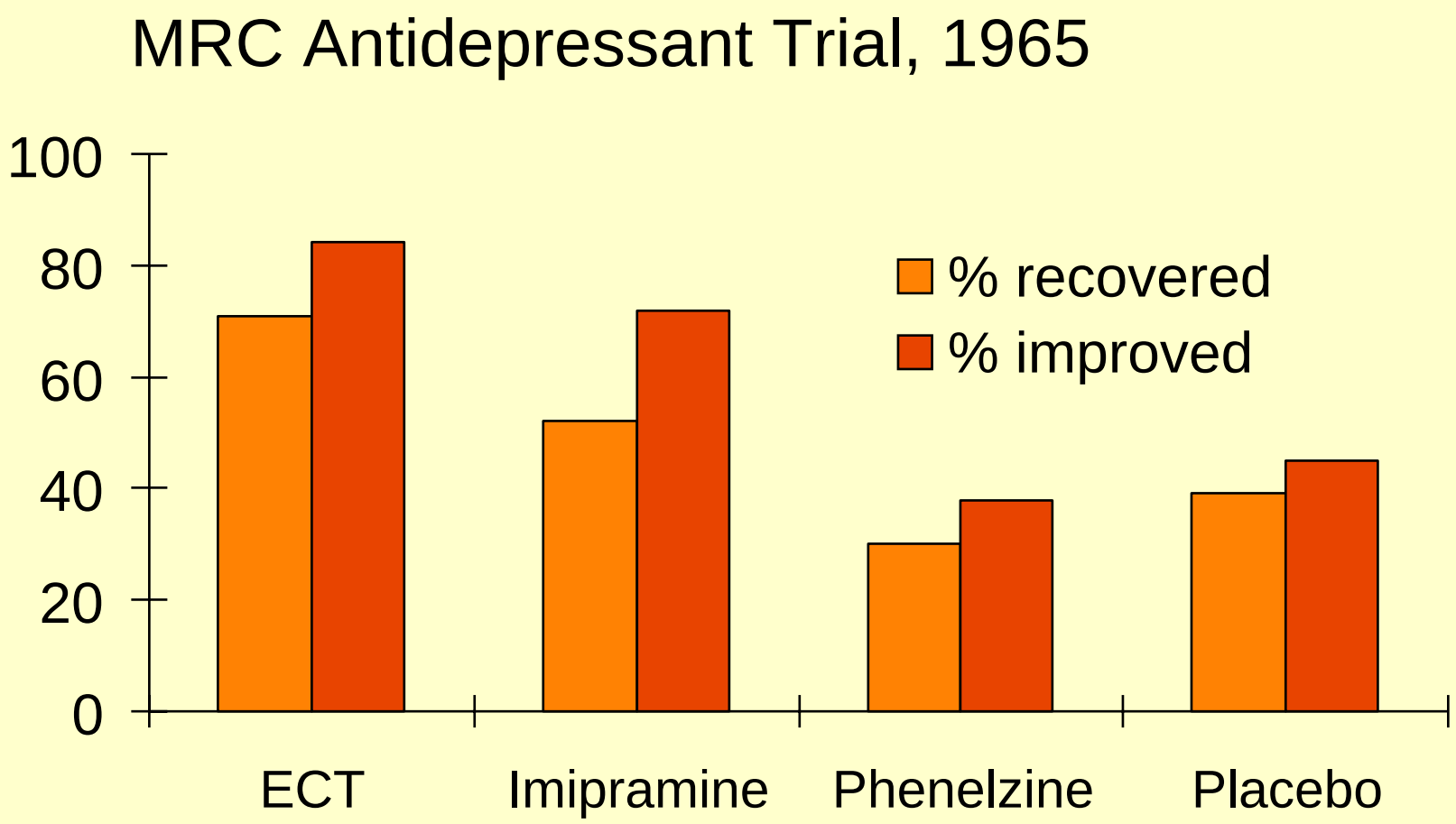
- NOT
  - Anti-dementia drugs
  - Drugs used in addictions
  - Drugs used for ADHD

- See
  - www.staff.ncl.ac.uk/r.h.mcallister-williams
  - “Presentations” and then “Medical Student Senior Rotation, Autumn, 2007”

The science of psychopharmacology

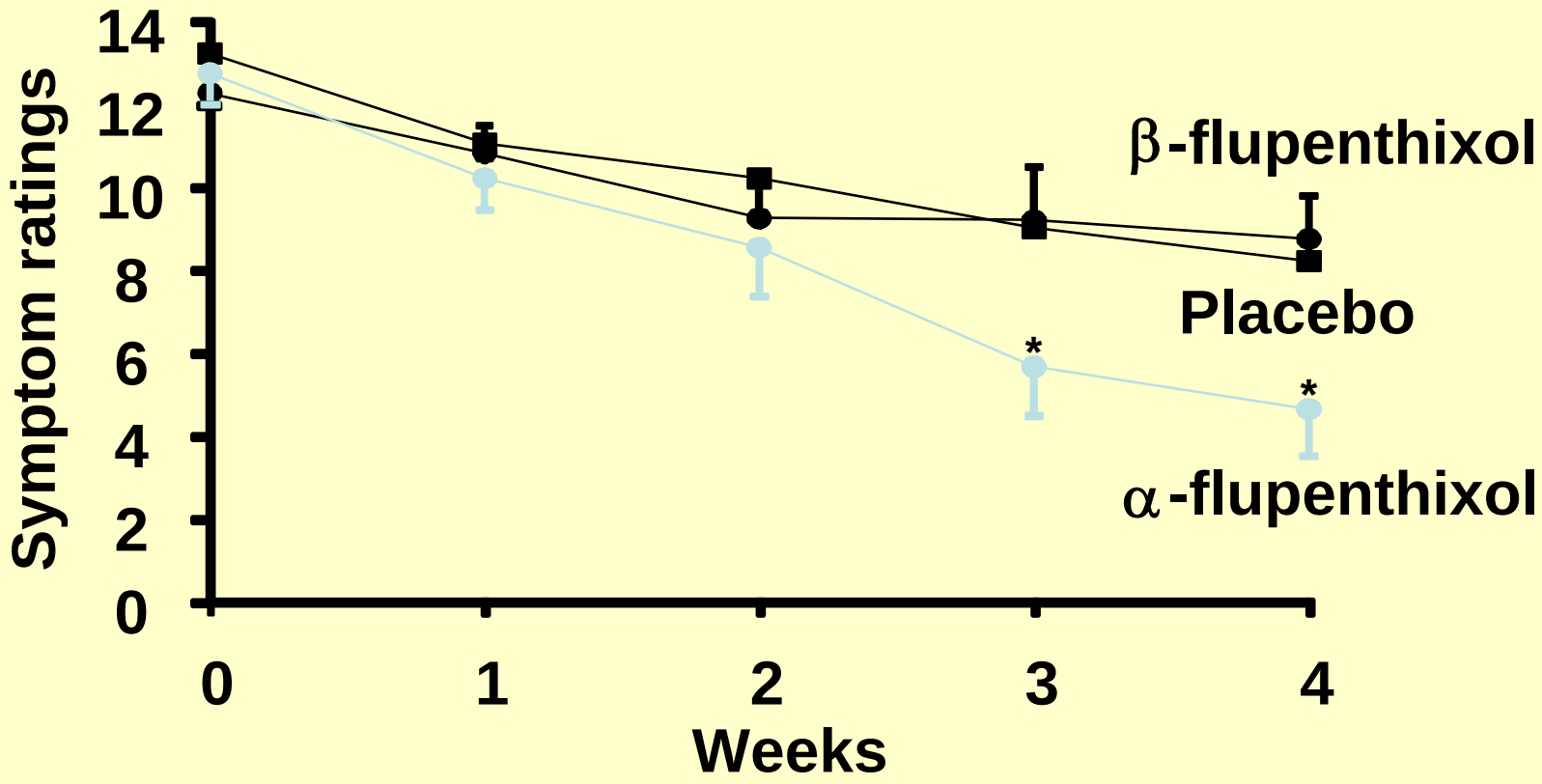
Three classic studies

Efficacy of Drug Treatments - Antidepressants

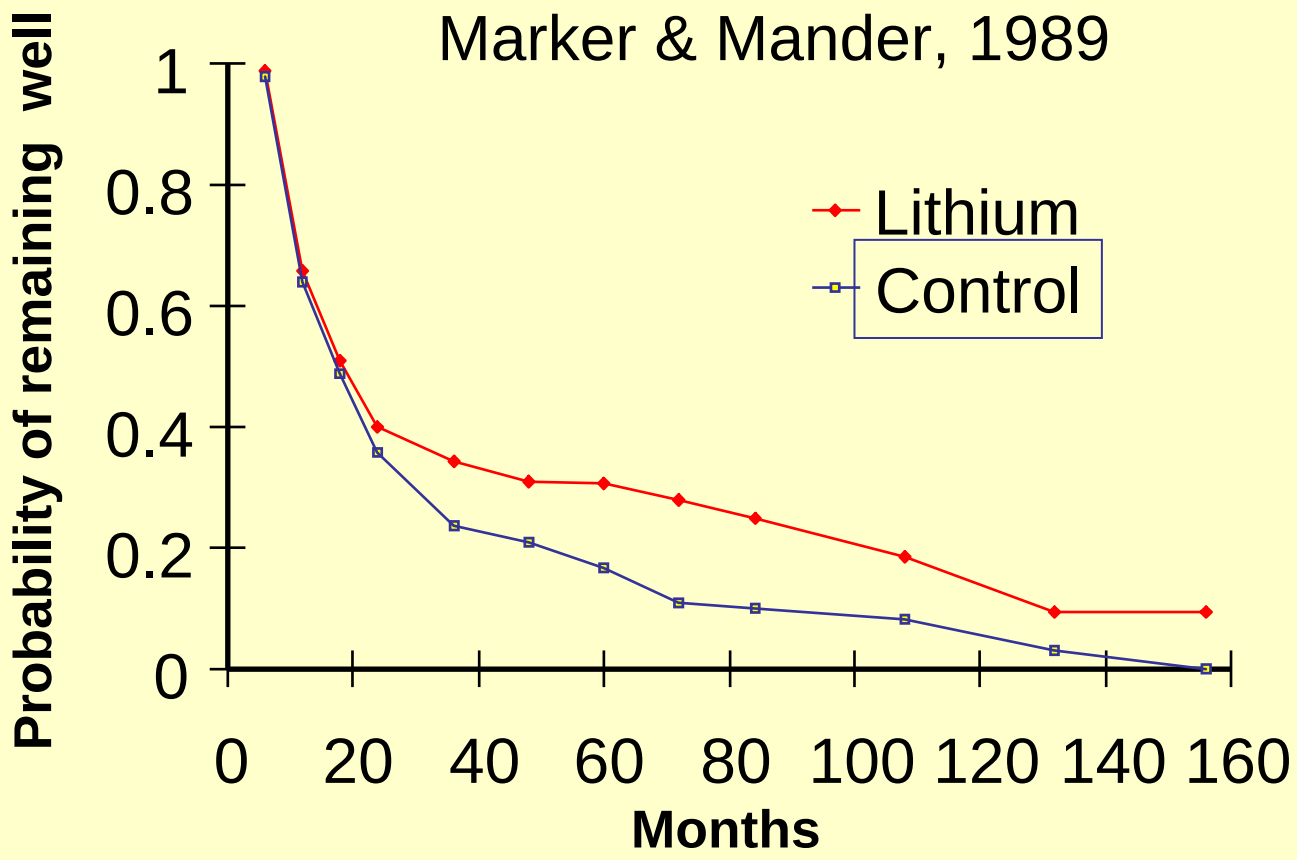


Efficacy of Drug Treatments - Antipsychotics

Johnstone et al. 1978 - Treatment of Schziophrenia



Efficacy of Drug Treatments - Lithium Prophylaxis



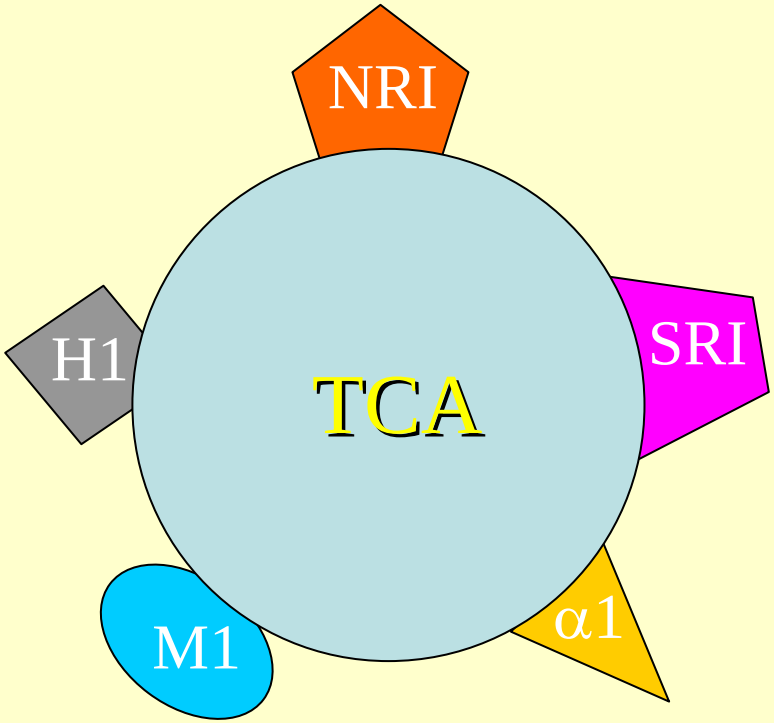
The clinical use of psychotropic drugs

- Idiosyncratic reactions
  - e.g. amphetamine, SSRIs and migraine
- Lack of therapeutic ranges for drugs
  - e.g. most antidepressants
- Enormous dosage ranges
  - e.g. 10mg – 1500mg chlorpromazine per day
- High rates of non-response
- Multiple classes of drugs
- Polypharmacy

Antidepressants

- TCAs
- SSRIs
- NaRIs
- SNRIs
- Antagonists
- MAOIs
- …..and others currently available plus ones on the way

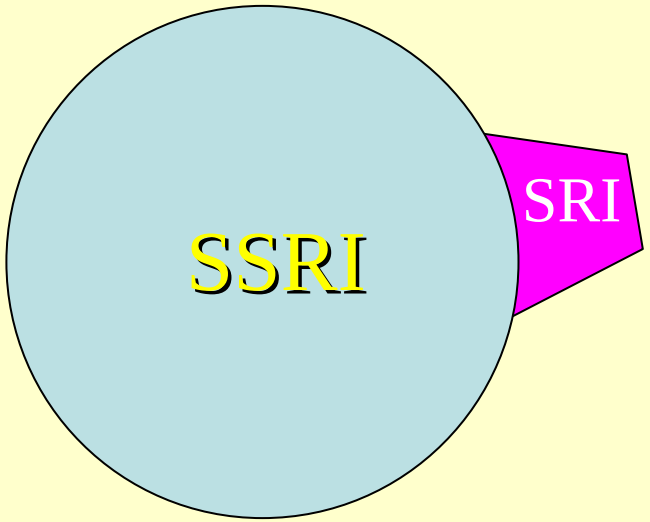
Tricyclic Antidepressants (TCAs)



N.B. also effects on cardiac and neuronal membrane excitability

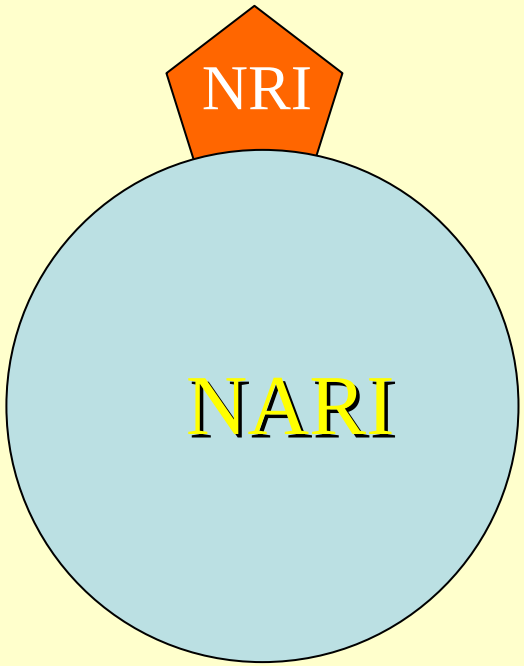
- e.g. amitriptyline, lofepramine, imipramine
- Inhibit 5-HT and NA uptake
  - Produces therapeutic effect
- Block of M_1, H_1, α_1 receptors produces side effects
- Poorly tolerated and toxic in overdose (except lofepramine)
- ?Amitriptyline more potent than SSRIs for severe depression

Selective Serotonin Reuptake Inhibitors (SSRIs)



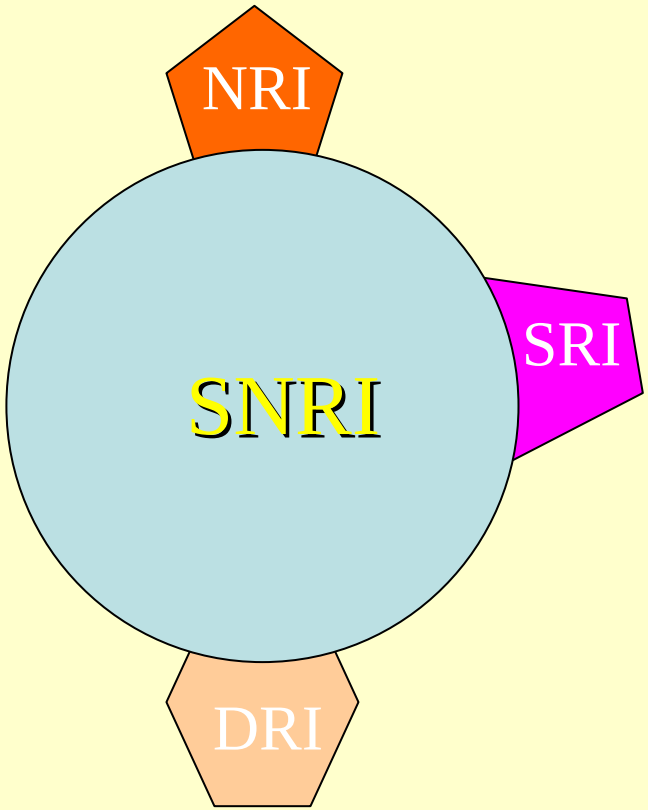
- e.g. fluoxetine, paroxetine, sertraline, citalopram, escitalopram
- Inhibit 5-HT uptake
  - Produces therapeutic benefit
    - depression
    - OCD, Panic, anxiety
  - Produces side effects
    - Nausea
    - Early increased anxiety
    - Sexula dysfunction
- Well tolerated and good first line treatments

Noradrenaline Reuptake Inhibitors (NaRIs)



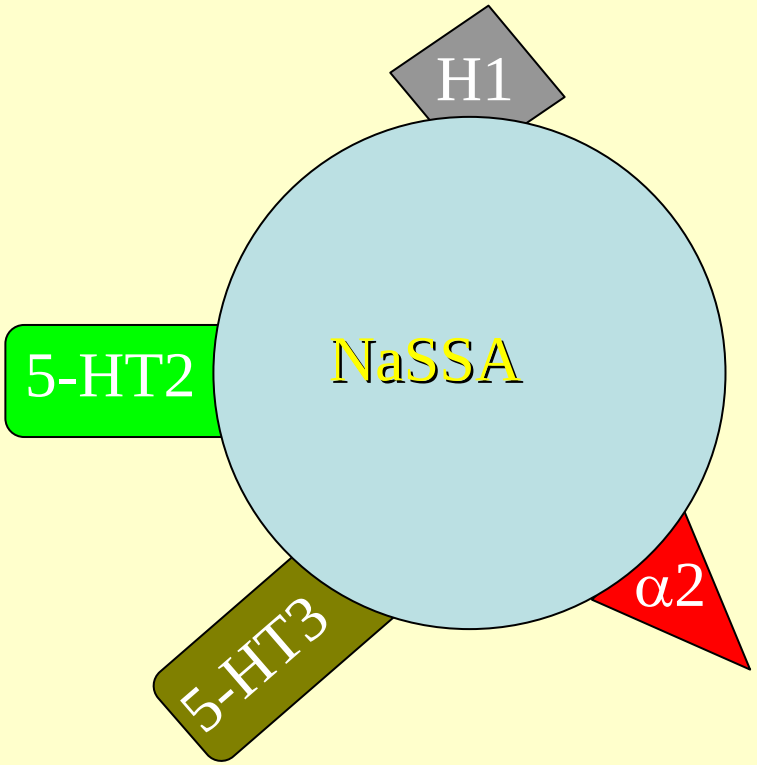
- e.g. reboxetine (lofepramine)
- Inhibit NA uptake
  - Produces therapeutic effect
  - Produces side effects
- Well tolerated
- Alternative class for patients who fail an SSRI

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)



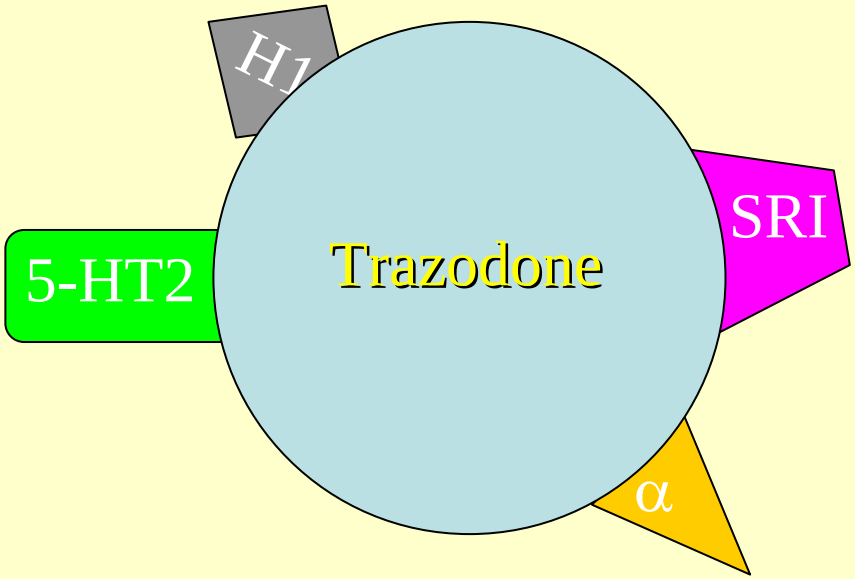
- e.g. venlafaxine, duloxetine
- Inhibit 5-HT and NA (and DA) uptake
  - Produces therapeutic effect
  - Produces side effects
    - Similar to SSRI
- Better tolerated than TCAs and ? more effective than SSRIs for severe depression therefore good second/third line treatment

Noradrenaline and Serotonin Selective Antagonist



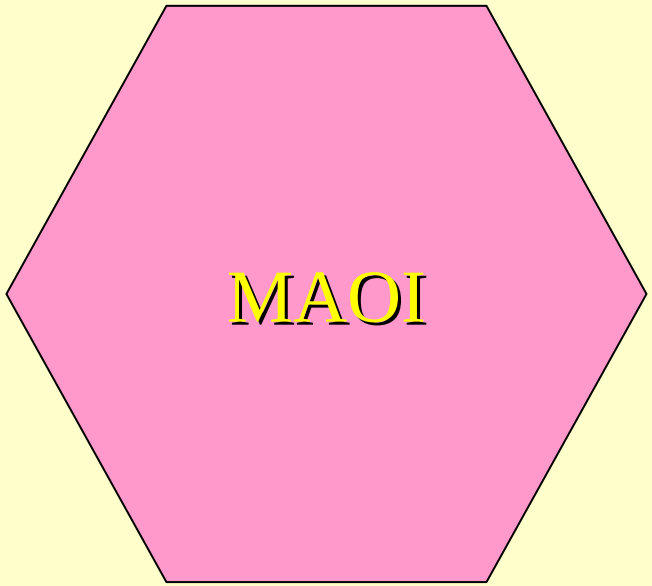
- e.g. mirtazepine
- Blocks α_2 receptors
  - Produces antidepressant effect (Increases 5-HT release)
- Blocks 5-HT_2 receptors
  - Produces decreased anxiety
- Blocks H_1 receptors
  - Produces sedation
- ? more potent than SSRIs plus lacks sexual side effects, but causes marked weight gain. Used second line

5-HT_2 antagonist



- e.g. Trazodone
- Weakly blocks 5-HT uptake
  - ? effect
- Blocks 5-HT_2 receptors
  - ? Main way produces benefit on depressive and anxiety symptoms
- Blocks H1 receptors
  - Produces sedation
- ? Potency as mainline treatment but often used to augment SSRIs or SNRIs

Monamine Oxidase Inhibitors



- Traditional
  - e.g. phenelzine, tranylcypromine
  - Food & drug interaction
- RIMA
  - e.g. moclobemide
- Increase levels of 5-HT, NA (and dopamine - traditionals)
  - produces therapeutic benefit
- Second line for atypical depression, third line treatments for severe depression

NICE Clinical Guideline 23

December 2004

NHS
National Institute for Clinical Excellence

Depression: management of depression in primary and secondary care

WWW.NICE.org.uk

NHS
National Institute for Clinical Excellence

Guidance

- Good practice points for all
- **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

- Antidepressants
  - Not recommended for initial treatment
  - Use if
    - symptoms persist after other interventions
    - depression associated with psychosocial problems
    - past history of moderate to severe depression
- Recommended interventions
  - Sleep and anxiety management
  - Watchful waiting
  - Structured exercise
  - Guided self-help

Step 3 - moderate to severe depression

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- Antidepressants
  - Antidepressants should be routinely offered
  - Address common concerns
  - Inform about potential side effects and risk of *discontinuation/withdrawal* symptoms (particularly with paroxetine and venlafaxine)
  - Inform about time delay in response
  - Continue for at least 6 months from remission
  - After 6 months review need for medication

Step 3

- Choice of antidepressant
  - SSRI in routine care
    - fluoxetine or citalopram
  - If response inadequate consider increasing dose to BNF limits
  - If not effective switch antidepressant [C]
    - Reasonable alternative to SSRIs = mirtazepine, but consider moclobemide, reboxetine, lofepramine. Venlafaxine or an older TCA for severe depression

Step 4 – Atypical, psychotic and recurrent depression

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- Atypical depression
  - Hypersomnia, increased appetite, hypersensitive
  - consider an MAOI (phenelzine)
- Psychotic depression
  - Augment with an antipsychotic
- Recurrent depression
  - Drugs
    - If 2 or more episodes consider ADs for 2 years
    - Use same dose of AD as for acute treatment
  - Psychotherapies
    - Consider CBT

Step 4 - Refractory depression

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- Failure to respond to 2 or more ADs
- Consider the following options:
  - ADs plus CBT
  - Lithium augmentation
  - Venlafaxine up to BNF limits
  - SSRI + mianserin or mirtazepine [C]
  - Consider phenelzine

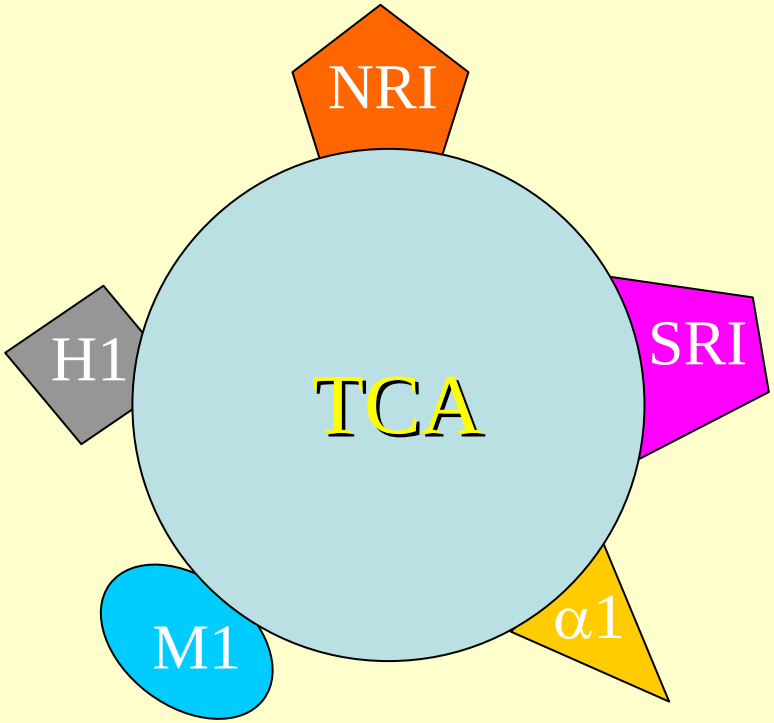
Anxiolytics/hypnotics

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

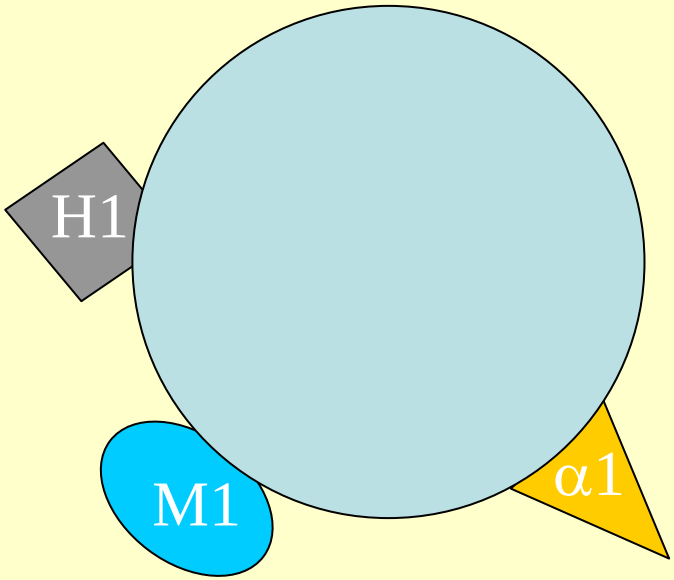
Antipsychotics

- Typicals/conventionals/first generation antipsychotics
  - e.g. chlorpromazine, haloperidol
- Atypicals/second generation antipsychotics
  - Clozapine
  - Olanzapine
  - Risperidone
  - Quetiapine
  - Aripiprazole
  - Amisulpride
  - Sulpiride

Tricyclic Antidepressant

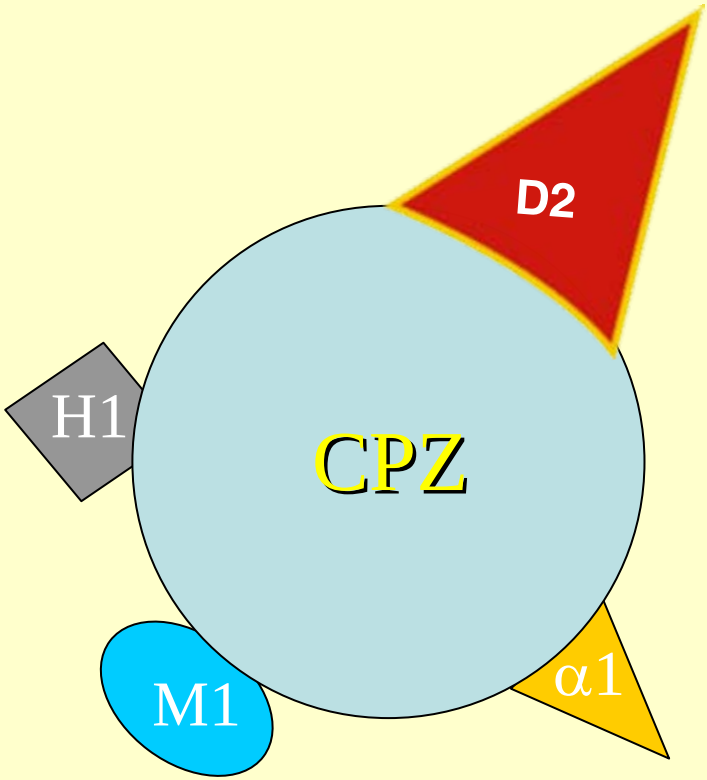


N.B. also effects on cardiac and neuronal membrane excitability



N.B. also effects on cardiac and neuronal membrane excitability

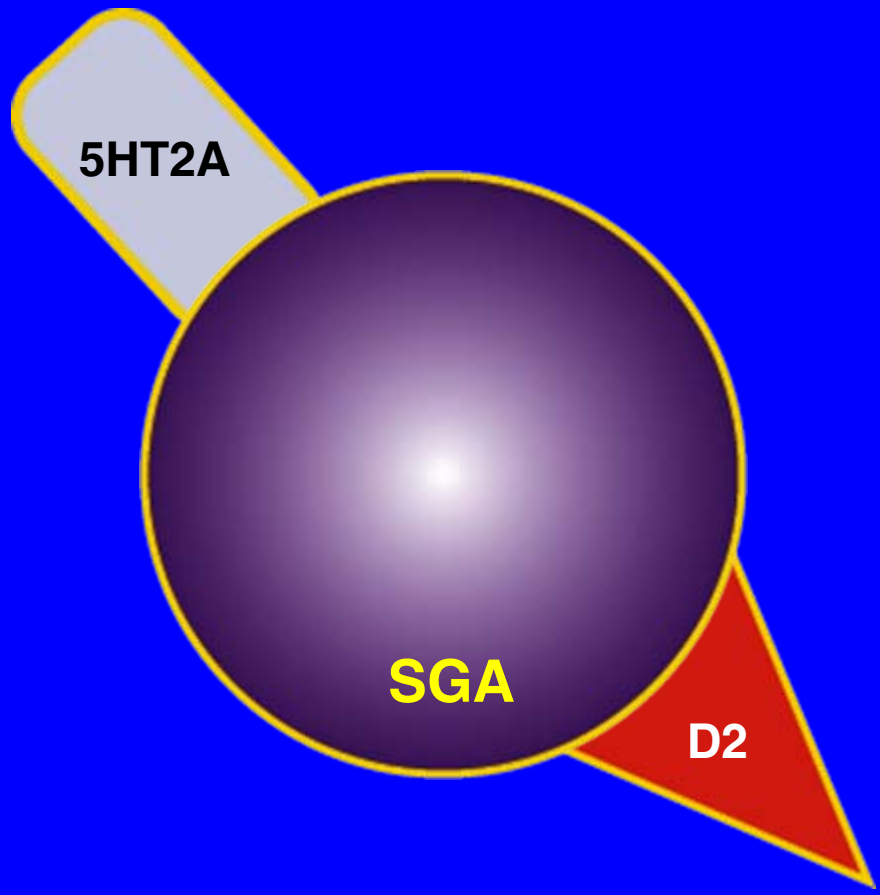
Typical antipsychotics



N.B. also effects on cardiac and neuronal membrane excitability

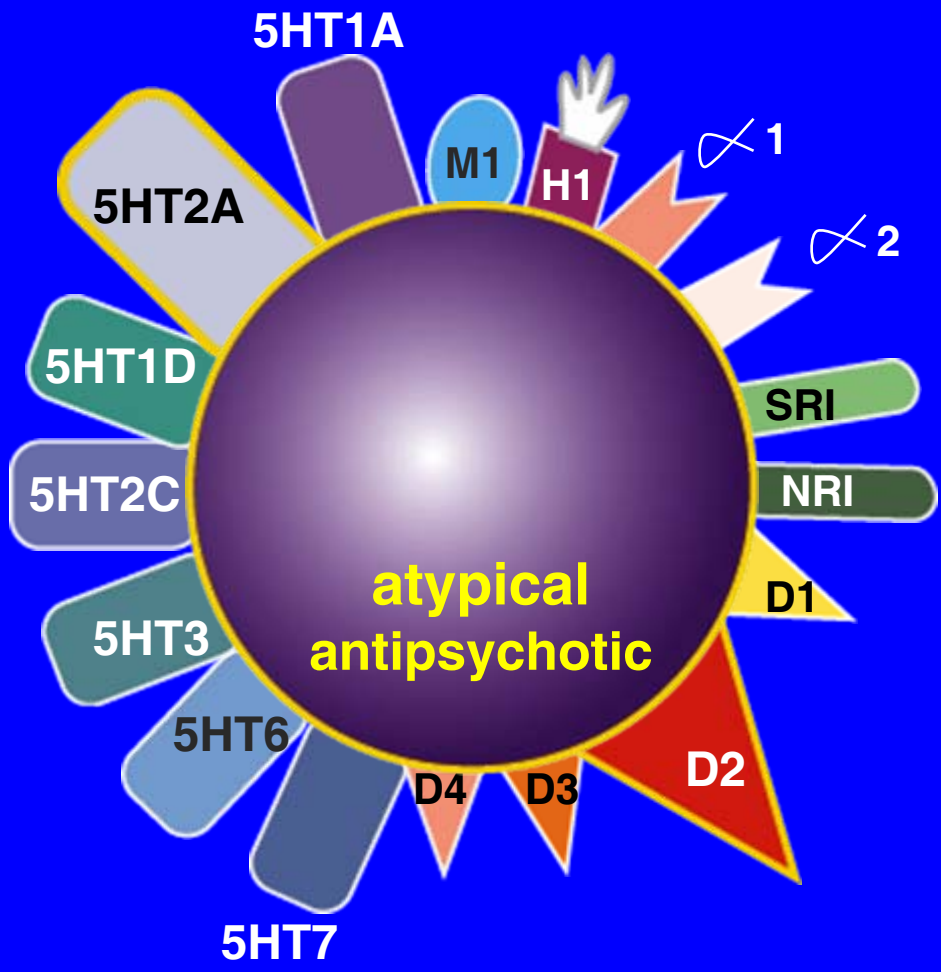
- E.g. chlorpromazine, haloperidol
- Block D_2 receptors
  - Therapeutic effects
  - EPS
- Also antagonise histamine, NA and acetylcholine receptors causing side effects
- Antipsychotic and sedative
- Used in schizophrenia, mania, psychotic depression
- NICE no longer recommend them first line

Atypical – core pharmacology



Stahl S M, Essential Psychopharmacology (2000)

Atypical – "rich" pharmacology



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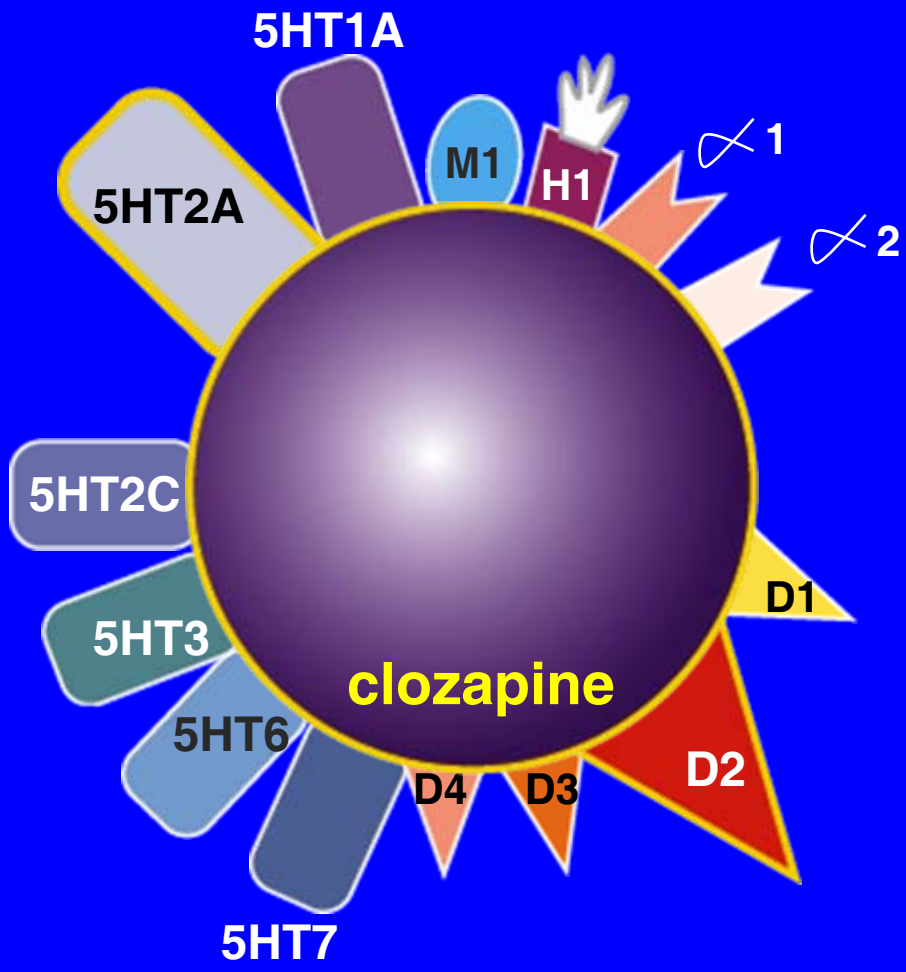
Clozapine – the archetypal atypical



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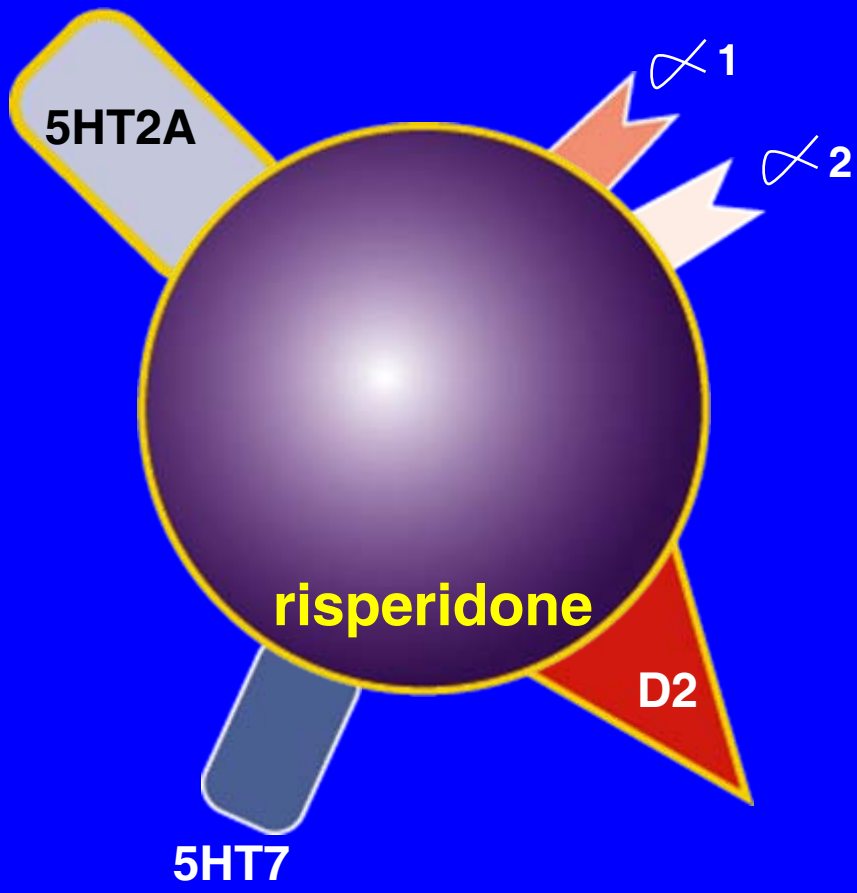
Clozapine

- Introduced in Europe in 1975 (but not UK)
- Less extrapyramidal symptoms than typicals
- Withdrawn due to cases of fatal neutropenia
- Kane et al. (1988) - large trial of ‘treatment resistant’ schizophrenic patients (300+)
  - failed at least three antipsychotics before entry
  - all given high dose haloperidol - those who failed to respond randomised to chlorpromazine or clozapine
  - 30% response to clozapine c.f. 4% to chlorpromazine
  - significant effect on ‘negative symptoms’

Newer atypicals

- More recently introduced drugs
- Some more dopamine selective
  - e.g. sulpiride, amisulpride
- Most recent dopamine partial agonist
  - e.g. aripiprazole
- Most combined 5-HT_2 and D_2 antagonists
  - e.g. risperidone, olanzapine, quetiapine
- All pharmacologically differ



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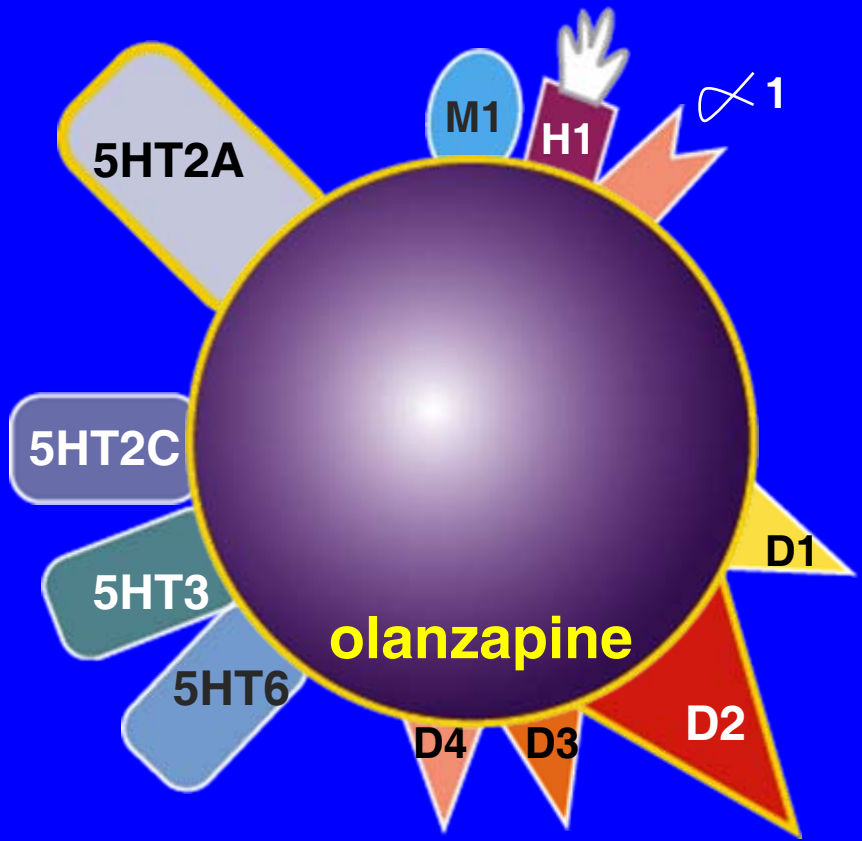

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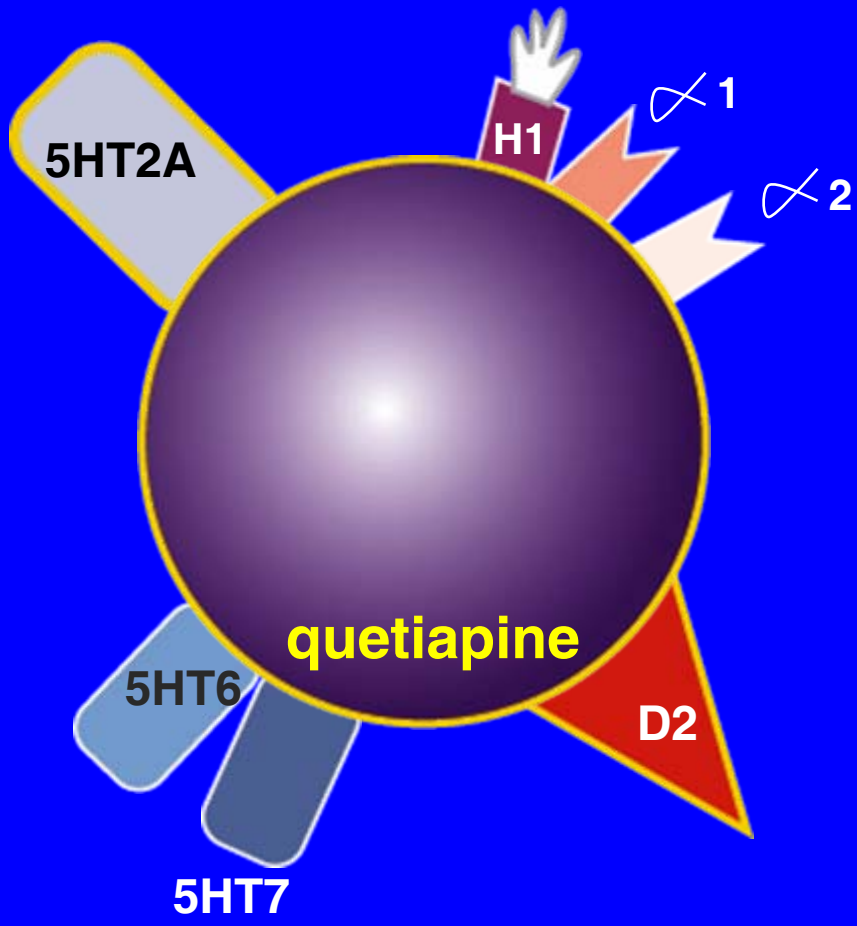

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Atypicals

- Now first line antipsychotics for schizophrenia and mania (+ other effects in bipolar disorder)
- Less EPS
  - quetiapine, olanzapine < risperidone
  - amisulpiride, sulpiride, aripiprazole < convential antipsychotics
- Less hyperprolactinaemia
  - quetiapine and olanzapine
  - Still occurs with risperidone, amisulpiride and sulpiride
- Risk of weight gain, metabolic syndrome and diabetes
  - clozapine, olzapine > quetiapine, risperidone > amisulpiride, sulpiride, aripiprazole
- ? Differences in potency
  - Clozapine used for TRS, but risk of blood disorders
  - Olanzapine and risperidone possibly more potent than quetiapine in schizophrenia
  - Quetiapine has possibly best evidence in bipolar disorder
- Depot risperidone available
- Expensive

NICE Clinical Guideline 1
December 2002

National Institute for Clinical Excellence

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

WWW.NICE.org.uk

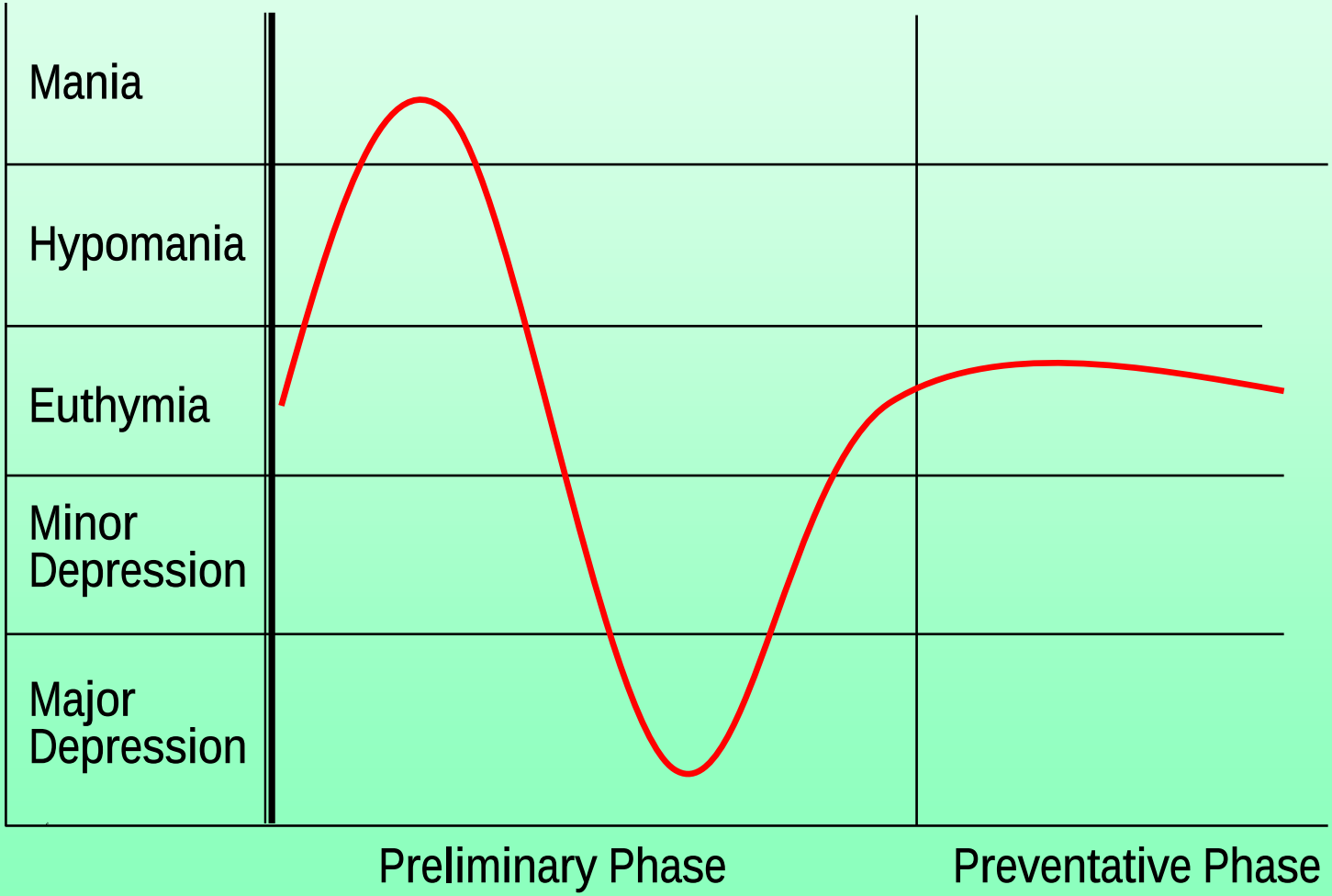
Acute Episode

- 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

What is a “Mood Stabiliser”

- Treats depression plus mania without making either pole worse and/or has prophylactic effects for both mania and depression
- Absence of a consensus definition
- NICE
  - “The guideline avoids the term ‘mood stabiliser’, because there is no agreed definition. The terms 'antimanic agent' or 'antimanic medication' are used for treatment of an acute episode, and 'prophylactic agent' or 'prophylactic medication' for long-term maintenance treatment”

The course of Bipolar Disorder



NICE Clinical Guideline 38

July 2006

NHS
National Institute for Clinical Excellence

Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care

Acute Mania

- Atypical antipsychotic (olanzapine, risperidone, quetiapine) for those with severe mania
  - If ineffective consider adding Li or valproate
- Valproate or Li if previous good response and compliance
  - Avoid valproate in women of child baring potential
  - Li only if less severe

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Acute Depression

- First line: SSRI plus antimanic agent
- If on antimanic: SSRI or quetiapine (if not on antipsychotic)
- Avoid antidepressant monotherapy
- Taper antidepressants after symptoms reduced for 8 weeks

Long-term Treatment

- First line: lithium, olanzapine or valproate
- If fails monotherapy over 6 months
  - Li + valp, Li + olanz, Valp + olanz
- If combination fails
  - Consider lamotrigine (esp. freq. depressions), carbamazepine
- NOT antidepressants routinely

Bipolar treatments: some issues

- Lithium
  - Narrow therapeutic index – monitor levels 2 monthly
  - Renal and thyroid dysfunction – renal function + TFTs 6 monthly
  - Sudden discontinuation – 50% risk of mania
  - Teratogenic – Epsteins anomaly
- Valproate
  - Not for women under 18 or of child baring potential
    - Teratogenicity (neural tube), polycystic ovary
  - Levels if ineffective, poor adherence or toxicity
- Lamotrigine
  - Risk of Stevens-Johnson syndrome
  - Slow dose titration

Clinical use of Drugs in Psychiatry

- Fundamental principles:
  - Assessment of risk/benefits
  - Consideration of costs
  - Full discussion with patient
  - Informed choice by patient
  - Repeated monitoring and re-assessment
  - Integration with other treatments

Conclusions

- Drugs are often the first line treatment in psychiatric illness
- However drugs are not the only mode of treatment
- Good evidence supports their use
- The use of psychotropics is complicated by:
  - professional perceptions of illness
  - patient perceptions of treatment
  - Complexity of their pharmacology
- “Normal” good clinical practice is essential