Psychopharmacology for medical students

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Thanks to Fergus Law, Anne Lingford Hughes, David Best, David Nutt and others for some of the slides

Scope of today
- Quick overview
- Flying visit to year 2 (receptors, PK/PD)
- Nitty gritty of the receptor systems
- Marrying the nitty-gritty to the real world

Why doesn't it make sense?
- “...the practice of polypharmacy in psychiatric therapy is a common and debatable practice: rational when we carry it out, but irrational in the hands of our colleagues.”
- “Most diagnostic categories in psychiatry have not been shown to be valid because they are not discrete entities with natural boundaries that separate them from other disorders.”

Why doesn’t it make sense?
- Top Level – Behaviour (DSM-V, ICD-10) e.g. Schizophrenia, Severe Depression
- Intermediate Level – Neurochemistry (DA, 5-HT, NA, GABA, Glu etc.)
  - Genetics
- Wiring Level – Neuroanatomy & circuitry (Cortico-Thalamic loops, DLPFC)
  - Added Complexity Level - Epigenetics

Why doesn’t it make sense? II
Why doesn't it make sense? III

What do I need from psychopharmacology?
- Prescribe an ADD + backup
- Prescribe a benzo (when/how long/issues)
- Drugs in cognition / dementia
- Don’t be scared of opiates
- Acute psychosis / Mania

Why is it studied during psychiatry?
- The vast majority of people with psychiatric syndromes benefit from medication
- Medication has very large prophylactic effect in schizophrenia, bipolar affective disorder, recurrent major depressive disorder and chronic anxiety disorders
- NB Psychiatric disorders are the largest cause of morbidity and loss of earnings worldwide
- NB this may be last time you get any teaching on this in your life
- many of the 'more conceptual aspects will relate to medicines of the future

What is psychopharmacology?
- Psychopharmacology is the study of the effects of endogenous or exogenous chemical manipulation on brain function
- Clinical psychopharmacology restricts itself to medicines and drugs used in clinical psychopharmacology and society
- This knowledge is useful for the whole of clinical psychopharmacology and surgery and for discussion in your community

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What is the brain?
- The brain is an organ at the 'centre' of the nervous system that allows rapid adaptation by the organism to changing environments following genetically determined and environmentally learnt schemes
- The human brain is made of about 20 billion neurons each of which has up to 10000 connections, so that each cubic millimetre of cortex has about 1 billion connections
- These interact following the principles of functional segregation and spatial connectivity
- Glial (supporting) cells are also likely to be of importance in various diseases and in health, but there has been little focus on them so far
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What about the diseased brain?

Addiction syndrome

(remarkably similar between drugs of abuse)

- Salience
- Mood modification
- Tolerance
- Withdrawal
- Conflict
- Relapse

- Similarity of relapse rates between drugs
- Refining of mode of delivery to increase rate of drug delivery to the brain

Why Can’t Addicts Just Quit?

Non-Addicted Brain

- Control
- Drive

Addicted Brain

- Salience
- Memory

Because Addiction Changes Brain Circuits

Adapted from Volkow et al., Neuropsychopharmacology, 2004.

Neurocircuitry of Addiction Koob and Volkow Neuropsychopharmacology 2010
The Many Uses in One Day of A Single Drug of Abuse

• Effects from a standard dose:
  – To get going in the morning
  – To enjoy the drug effects (numbing or self medicating)
  – To “top-off” a pleasant experience
  – To cope with stressful experience
  – To cope with anger or self-hate
  – To cope with boredom or loneliness
  – To promote sleep at night

• Effects from a higher dose:
  – To get euphoria/buzz/high/rush
  – To get sedation, gauch, warm comforting feeling

Pharmacokinetics

• Absorption
  – eg stomach surgery, IM, IV
  – Delivery important eg smoking, intranasal spray, IV
  – Alcohol strength and duodenal absorption

• Distribution
  – Eg Alcohol toxicity in women
  – Dosing different sizes

• Metabolism
  – CYP 450 variation, inhibition and induction
  – Liver disease

• Excretion
  – Lithium

Pharmacokinetics

“Chasing the rush”

• Faster onset of drug effect = “better rush”

Genetics can explain treatment resistance

\[
\begin{array}{|c|c|}
\hline
CYP2D6 genotype & Number of patients \\
\hline
EM & 71 (87.6\%) \\
PM & 2 (2.5\%) \\
Duplication & 8 (9.9\%) \\
All & 81 (100\%) \\
\hline
\end{array}
\]

Prevalence of the CYP2D6 genotypes in 81 depressed Swedish patients refractory to treatment with CYP2D6 substrate antidepressant drugs

Kawanishi et al 2004

Pharmacokinetics of Opiates

St John’s Wort can reduce plasma drug levels

Mean concentration-time of indinavir alone (solid line) and with concomitant St John’s wort (dotted line)

St John’s Wort can reduce plasma drug levels
How does it work?

- Each neuron transmits information within the neuron via electrical impulses.
- The majority of communication is mediated by chemical signals (neurotransmitters) that affect electrical potentials or intracellular chemistry in the receiving neuron(s).
- Neurons are supported by glia.
- The brain integrates all these events and produces outputs.
- It is useful to think of its functional organisation in terms of levels: from subcellular to systems to psychosocial.

How can molecules affect its function?

- Endogenous and exogenous molecules can modulate:
  - Neurotransmitter production
  - Neurotransmitter metabolism
  - Neurotransmitter release
  - Receptor function
  - Transporter function
  - Ion channel function
  - Cellular chemistry
  - Nuclear function
  - Protein production and disposition

What are receptors?

What type of receptors do we know?

- Receptors are proteins that change configuration once molecules (ligands) bind to them thus producing either a change in channel conductance (ionotropic) or in cellular chemical signalling (metabotropic) usually via G proteins or tyrosine kinase receptors.
- Their number can be modulated in which case we talk of upregulation or downregulation.
- At synapses receptors can be post-synaptic or pre-synaptic. The latter are usually 'brakes' on the system.
- Heteroreceptors are receptors associated with a particular neurotransmitter that can modulate the release of another neurotransmitter.
- There are cytosolic, mitochondrial receptor etc.

Mirtazapine

- α2-adrenoceptor
- α2-autoreceptor
- presynaptic NA neuron
- postsynaptic NA neuron
- noradrenaline
- serotonin
- mirtazapine
### Function of receptor ligands

- Agonist
- Partial agonist
- Antagonist
- Partial Inverse Agonist
- Inverse Agonist

- Usually steep dose response over 2 Log units

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Agonist</td>
<td>Agomelatine</td>
</tr>
<tr>
<td>Partial agonist</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Antagonist</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Partial Inverse Agonist</td>
<td>Ro 15-4513</td>
</tr>
<tr>
<td>Inverse Agonist</td>
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### What are transporters?

- Transporters are proteins that use energy to move molecules across cell membranes
- In psychiatry, transporters or reuptake sites are (usually pre-synaptic) proteins that ‘clear-up’ a neurotransmitter from the synapse eg serotonin and SSRIs

### Enzyme modulation

- Blocking enzymes will reduce their function thus either increasing or decreasing the target substance. This can be competitive or non-competitive depending on whether the molecule binds at the same site as the substrate or not and reversible/irreversible.

### How do molecules affect neurotransmission

- They can increase or decrease the amount of neurotransmitter in the synapse, thus increasing or decreasing its effects eg reboxetine
- They can modulate the efficacy of a neurotransmitter eg benzodiazepines
- They can affect receptors thus blocking the effect of the neurotransmitter or stimulating receptor activity eg aripiprazole

### What are dirty drugs?

- Many medicines used in psychiatry are ‘dirty’ i.e they have an effect at a number of different sites. This may be an advantage eg Clozapine or disadvantage eg Tertiary tricyclics

### Ascending/descending modulation

- The concept of modulation of brain function by ascending fibres originating from cell bodies in the midbrain/hindbrain is important.
- Monoaminergic (dopamine, noradrenaline, serotonin) histaminergic and cholinergic systems are clear example of ascending
- Brain modulation of parasympathetic and sympathetic outputs are examples of descending modulation
Cross talk
- Many of these systems have modulatory inputs on other systems.
- For example, Mirtazapine increases raphe firing via effects on the locus ceruleus.

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Which systems are we going to explore today
- GABA
- Glutamate/aspartate/glycine
- Glucocorticoid
- Other hormones
- Cannabinoid
- Dopamine
- Serotonin
- Noradrenaline
- Acetylcholine
- Histamine
- Opiate
- Other Peptides

GABA pharmacology and anatomy
- GABAergic neurons are ubiquitous in the cerebral cortex and cerebellum providing local inhibition. GABA is the most common inhibitory neurotransmitter.
- There are at least 18 subtypes of GABA-A receptors, made of pentamers with up to 13 possible subunits, many of which are sensitive to benzodiazepines. The regional distribution is varied and distinguishable by the type of α subunit: receptors containing α1 and α2 subunits are probably important for anxiety while α6 subunits are involved in cognition. In addition there are GABA-B and GABA-C receptors.
- Benzodiazepines and other molecules that bind in the same position modulate GABA i.e. they change receptor sensitivity to GABA and have no intrinsic activity.
**GABA in clinical psychopharmacology**
- Anticonvulsants: Progabide
- Anxiolytics: Diazepam
- Hypnotics: Zolpidem
- (Muscle relaxation): Baclofen
- Relief of spasticity: Valproate
- Bipolar affective disorder: Valproate

**GABA in society/addictions**
- Alcohol: exerts some of its effects through GABA receptors
- Barbiturates: Benzodiazepines are generally safe and well tolerated. BZ abuse is limited to IV drug users
- Muscimol

**Glutamate anatomy and pharmacology**
- Glutamate is the most common excitatory neurotransmitter in man and is distributed throughout the cortex and cerebellum.
- There are 4 families of receptors: kainate and AMPA (ionotropic), mGluR (metabotropic) and NMDA (ionotropic but requires two ligands and is also voltage gated). Glutamate has a reuptake site.
- Glutamate is also a metabolic product and in high concentrations it can be neurotoxic – an effect mediated by Calcium influx in the cell.
- NMDA receptors in hippocampus important for learning.
- Glutamate pharmacology difficult and likely to evolve

**Glutamate in clinical psychopharmacology**
- Alzheimer's & dementias: Memantine
- Schizophrenia: Lamotrigine
- Stroke: Promnestic
- Alcohol and alcohol withdrawal: Acamprosate
- Possibly many others including anxiety and depression
- In general neurotoxicity
- Promnestic: Cycloserine

**Glutamate in society and addictions**
- Alcohol impairment and withdrawal
- PCP (angel dust)
- Ketamine
- Monosodium glutamate
- Caffeine via adenosine receptors

**Aspartate and glycine**
- Other two aa NTs
- Aspartate stimulates NMDA
- Glycine inhibitory in periphery. Strychnine is a glycine antagonist.
- In brain glycine is a positive allosteric modulator of NMDA receptor
- Glycine transporter 1 inhibitor (RG1678) in phase III for RX of cognitive and negative Sx in schizophrenia
Glucocorticoid pharmacology and anatomy

- Glucocorticoid receptors are cytosolic and distributed throughout the brain. Cortisol dimerizes the receptors which are transported into the nucleus and elicit a genomic response.
- GRs have low occupancy at baseline and therefore are able to respond to variations in glucocorticoid level.

Glucocorticoid in clinical psychopharmacology

- Psychiatric syndromes associated with Cushing’s and Addison’s disease.
- Steroid psychosis, mania and depression.
- High levels of cortisol are associated with treatment resistance.
- Diurnal rhythm necessary for antidepressants to affect neurogenesis.
- CRH influences fear responses.

Other hormones

- Hypothyroidism and hyperthyroidism both cause anxiety and depression.
- Thyroid hormone receptors same family as GR and widely expressed in the brain.
- T3 and T4 may be useful adjunct treatments in treatment resistant affective disorders.
- Some literature on sex hormones but no firm conclusions at this stage.

Cannabinoid pharmacology and anatomy

- Cannabinoid system in brain acts through CB1 receptors that are among the most abundant in the brain and widely distributed; other unknown receptors also present. Endogenous ligand not known.
- Inhibit GABAergic neurons pre-synaptically.

Cannabinoids in clinical psychopharmacology

- Appetite promotion.
- Antiemetic.
- Spasticity.
- Pain.
- Appetite suppression Rimonabant.
- Smoking cessation.
- Δ9-THC and Cannabidiol may exert opposite effects to each other eg anxiety.
Cannabinoid in society and addiction

- Cannabis used for many centuries
- Probable higher prevalence of schizophrenia
- Different strengths - skunk
- Habit forming
- UK debate about classification confuses scientific evidence with societal expectation

Dopamine in clinical psychopharmacology

- Parkinson's disease - LDOPA
- MPTP
- Schizophrenia
- Psychoses
- ADHD
- Addictions
- Severe depression
- Smoking cessation
- Restless leg
- OCD

Dopamine pharmacology and anatomy

- Nigrostriatal, mesolimbic and mesofrontal ascending systems from substantia nigra and ventral tegmentum to basal ganglia, nucleus accumbens, anterior cingulate frontal and temporal cortex. Tuberoinfundibular regulates prolactin release in pituitary.
- Four types of receptor: D2/D3 of greatest current interest in psychiatry
- Working memory is in part regulated by dopamine influences on cingulate D1 receptors

Dopamine in society and addictions

- Addictions via dopamine reward
- Cocaine
- Amphetamine, methylamphetamine
Rewarding effects of stimulants are associated with increases in brain dopamine and occupancy of D2 receptors.

**Serotonin pharmacology and anatomy**
- Two nuclei in the pons: median and dorsal raphe
- Diffuse projections with higher density in occipital and frontal cortex, hippocampus, anterior cingulate
- Seven classes of receptors. Includes 5HT1A which are both somatodendritic and cortical postsynaptic and 5HT1B/D and 2B that are presynaptic

**Serotonergic pathways**
- Striatum
- Thalamus
- Cingulate gyrus
- Frontal cortex
- Orbitofrontal cortex
- Cerebellum
- Amygdala
- Hypothalamus
- Hippocampus
- Dorsal and medial rostral raphe nuclei
- Caudal raphe nuclei
- To spinal cord

**Serotonin in clinical psychopharmacology**
- Depression
  - Escitalopram
- Suicide
- Anxiety
- OCD
- Sleep regulation
- Antiemetics
  - Ondansetron
- Weight increase
  - Mirtazapine

**Serotonin in society and addictions**
- Psilocibin
- LSD
- MDMA

**Noradrenaline pharmacology and anatomy**
- Noradrenergic neurons originate from the locus coeruleus and adjacent area in the pons and innervate the cortex and cerebellum widely
- Alpha 2 adrenoreceptors are both post and presynaptic. The presynaptic ones are also heteroreceptors and have inhibitory effects
- Noradrenaline transporter is responsible for most dopamine clearance in the frontal cortex
Noradrenaline in clinical psychopharmacology

- Depression
- Anxiety
- Alertness
- ADHD
- Addictions

Noradrenaline in addicitions and society

- Noradrenergichyperactivity thought to be important in withdrawal syndromes
- Influenza and possibly coryza decrease noradrenergic function in brain
- Sympathomimetics in many cold remedies

Opiate pharmacology and anatomy

- There are three well-characterized families of opioid peptides produced: enkephalins, endorphins, and dynorphins.
- They act through μ, δ, κ, and nociceptin opiate receptors.
- Opiates and endorphins block pain signals by binding to the mu receptor site. The delta receptor in the brain is involved in pain relief, antidepressant effects and physical dependence. Kappa receptors in the brain and spinal cord are linked with sedation, spinal analgesia and pupil constriction.
- Mu receptors in ventral tegmental area (VTA), cerebral cortex and nucleus accumbens causing increased dopamine release and decreased GABA activity.

Opiate in clinical psychopharmacology

- Pain
- Addiction
- ?Depression

- Mu receptors agonists cause physical dependence, respiratory depression, euphoria, pupil constriction and supraspinal analgesia.
- Nociceptin receptors are involved with appetite, depression, anxiety and the development of tolerance to mu agonists.

Opiate in society and addictions

- Adequate pain relief MUST be achieved
- Addictions think of societal costs, harm reduction and substitution therapy as well as detox and abstinence
- Social rather than personal problems with opiates more associated with earning capacity

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Acetylcholine pharmacology and anatomy

- Cholinergic neurons in basal forebrain in nucleus basalis of Meynert
- Distributed to cortex and hippocampus
- Nicotinic and muscarinic receptors
- During REM sleep high levels of acetylcholine in the hippocampus and low in the cortex
- Degeneration of this tract in Alzheimer’s disease
Acetylcholine in clinical psychopharmacology
- Alzheimer’s (Aricept)
- Other dementias
- Side effects (Amitriptyline)

Histamine pharmacology and anatomy
- Cell bodies in tuberomammillary nucleus of hypothalamus projecting to whole brain
- Active during wakefulness
- H3 receptors are mainly autoreceptors
- Also bind to NMDA
- Control of excitability and plasticity

Acetylcholine in society and addictions
- Smoking

Histamine in clinical psychopharmacology
- Travel sickness
- Increased appetite (Mirtazapine)
- Increased sleepiness (Trazodone)
- Narcolepsy (Modafinil)
- Adult ADHD

Histamine in society
- Modafinil one of the molecules at the centre of lifestyle drugs debate and their use in society
Melatonergic anatomy and pharmacology

- Secreted in darkness by pineal gland
- The MT1 subtype is present in the pars tuberalis of the pituitary gland and the suprachiasmatic nuclei of the hypothalamus

Melatonin clinical pharmacology

- Insomnia
- ?Phase shift
- ?Alzheimer’s
- depression
  - melatonin
  - agomelatine

Other

- Ion channels blockers
- Neurotrophic factors
- Pregabalin
- GDNF
- Intracellular message
- Blood brain barrier modulation
- Peptides
- Oxytocin, substance P, CCK etc
- Other hormones
- CRF etc
- Beta amyloid vaccines
- Unmapped proteins
- NB general anaesthetics

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Clinical psychopharmacology

Sources of prescribing information

- NICE
- Cochrane reviews
- British Association for Psychopharmacology (BAP)
- American Psychiatric Association (APA)
- European College of Neuropsychopharmacology (ECNP)
- Collegium Internationale Neuropsychopharmacologicum (CINP)
Schizophrenia and psychoses

- All antipsychotics block D2 receptors
- For most antipsychotics positive effects at >65% occupancy
- EPSE (dystonia, akathisia, Parkinsonism) at >85% occupancy
- Clozapine main exception AND only antipsychotic for treatment refractory schizophrenia
- Depot preparations

Dopamine pathways in brain and possible role in schizophrenia

- Mesocortical pathway
- Hypoactivity: negative symptoms, cognitive impairment
- Nigrostriatal pathway
- Hyperactivity: positive symptoms
- Mesolimbic pathway
- (inhbits prolactin release)

Neuroleptics block D2 receptors

- 11C-Raclopride PET Scan
- Coregistered MRI Scan
- 11C-Raclopride PET Scan
- Haloperidol 2 mg/day (74% occ.)

Affinity for dopamine D2 receptors and clinical potency

- Range and average clinical dose for controlling schizophrenia (mg/day)
- From Kapur, 1999 (presentation)

D2 occupancy predicts response for haloperidol at 2 weeks

- Clinical improvement (CGI-I)

D2 occupancy also predicts EPS/akathisia

- Subjects with EPS or akathisia
- No subject below 78% showed any EPS or akathisia
- From Kapur, 1998 (presentation)
Is dopamine the whole story?
- Increase release of dopamine upon challenge in schizophrenia
- Decreased baseline dopamine is correlated with poor performance on working memory tasks
- All current antipsychotics are D2 blockers
- However most effective antipsychotic has low D2 affinity and low average occupancy
- Alterations in other systems e.g. glutamate also observed

What makes an antipsychotic effective?
- Effective as an antipsychotic
  - Some dopamine D2 receptor blockade
- Minimise EPS: 2nd generation antipsychotic
  - ?different pharmacological mechanisms
    - Limbic selectivity – dopamine D2/D3 binding in medial temporal cortex
    - A2 adrenoreceptor antagonist activity → increase noradrenaline
    - Anticholinergic activity
    - 5HT2A blockade

OR Low Dose first generation???

Improve concordance
- Be aware of issues
- Motivational interviewing
- Depot antipsychotics
  - Most injectable esters in oil preparations
  - ‘Microspheres’
  - Different kinetics- zero order
  - Beware that may continue to be active long after discontinuation

Bipolar affective disorder
- Diagnostic issues
- Lithium
- Sodium Valproate
- Lamotrigine
- Quetiapine
- Other second generation antipsychotics
  - (Other anticonvulsants including carbamazepine)
  - Haloperidol in severe mania
- Problems with prescribing antidepressants
- Thyroid hormone

Unipolar major depressive disorder
- SSRIs
- SNRIs
- NaSSAs
- Agomelatine
- NARI
- Trazodone
- TCA- secondary and tertiary
- RIMA
- MAOIs
- Second generation antipsychotics quetiapine and aripiprazole
Serotonergic synapse

**Serotonergic synapse: How SSRIs act**

No synaptic increase in 5HT until autoreceptor downregulation

The use of antidepressants

- Ascerten symptom duration
- Review 6 weekly
- Get as close as possible to symptomatic recovery
- Continue for 3-6 months after symptomatic recovery
- Minimise side effects (individualisation)
- For life or prolonged periods of time after 3 or more severe episodes in rapid succession.

Efficacy of antidepressants

**Acute treatment – very good**

Huge evidence vs placebo in registration trials = double blind, randomised, audited, independent [MHRA, EMEA]

**In prevention – outstanding**

one of strongest known effects in medicine \( p < 0.000001 \)

Geddes et al 2003 – Lancet

SSRIs (and other newer antidepressants) **preferred as first line**

= better safety, tolerability and patient acceptability

+ efficacy in related disorders especially anxiety

Patients with residual symptoms are at high risk of relapse

Adapted from Paykel
Antidepressants prevent relapse - classic study from Pittsburg

Subjects were recovered on imipramine for 3 years and then randomized to imipramine or placebo. Mean dose of imipramine at year 5, 236 mg/day

Imipramine (n=10)

Placebo (n=9)

p<0.006 by Mantel-Cox test  Adapted from Kupfer et al. Arch Gen Psychiatry 1992; 49: 769-773.

Dementias

- Acetylcholinesterase inhibitors  Aricept
- NMDA modulation  Memantine
- Cholinesterases inhibitor  Rivastigmine

- Must be careful with administration of antipsychotics especially in Lewy body
- Behavioural agitation
- Benzodiazepine
- Anticholinergics

Addictions

- Withdrawal
  - Benzodiazepines
  - Lofexidine
- Relapse prevention
  - Acamprosate
  - Disulfiram
  - Naltrexone
- Substitution
  - Methadone
  - Buprenorphine
  - Nicotine chewing gum

Generalised Anxiety Disorder

- SSRI
- SNRI
- Buspirone
- Pregabalin
- TCA
- Benzodiazepines

Panic Disorder

- SSRI
- SNRI
- NaSSA
- TCA
- High potency benzodiazepines

Imaging beta amyloid plaque in vivo
Social anxiety disorder
- SSRI
- MAOI
- SNRI
- Benzodiazepines

Obsessive compulsive disorder
- SSRI
- Clomipramine
- Second generation antipsychotic
- NB higher dose and longer to response
- NB augmenting strategies that work in depression do not in general work in OCD

PTSD
- NB Trauma focused therapies
- SSRIs
- TCAs
- Symptomatic and depressive comorbidity
- Avoid benzodiazepines
- (propranolol, steroids)

Personality disorder and Developmental disorders
- NO consensus but various studies emerging on benefits of some psychotropics

Insomnias
- NB sleep hygiene and expectations
- Zolpidem
- Zopiclone
- Zaleplon
- Benzodiazepines
- Antihistamines
- Melatonin
- 5HT2 antagonists (mirtazapine, trazodone, quetiapine)

Conclusion
- Understanding principles of psychopharmacology is useful beyond immediate prescribing and is applicable to all parts of medicine and surgery
- Societal impact of psychotropics is enormous