What every C-L psychiatrist should know about psychopharmacology

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Principles for drug selection

1. Effect on the clinical problem
2. Effect on the underlying disease
3. Implications of side-effect profile
4. Interactions with "somatic" drugs
5. Oral or parenteral treatment
6. Liver / kidney function and dosage
7. Biological tailoring?
1: Evidence based treatment guidelines?

- Limited systematic research in C-L settings
  
  www.cochranelibrary.com
  www.clinicalevidence.com
  www.acpjc.org
  http://ebmh.bmjjournals.com
  www.tripdatabase.com

Reminder:
Psychopharmacology has partly different effects than psychotherapy and vice versa.
Changes in regional glucose metabolism (fluorine-18–labeled deoxyglucose PET) in CBT responders (top) and paroxetine responders (bottom) following treatment. Metabolic **increases** are shown in orange and **decreases in blue**.

(Goldapple et al. Arch Gen Psychiatry 2004; 61:34-41)
Relationships among regions mediating cognitive behavior therapy (CBT) and drug response

(Goldapple et al. Arch Gen Psychiatry 2004; 61:34-41)
Choosing treatments in C-L psychiatry

- Meta-analyses have limited validity
- Psychotherapies and drugs are effective, but have modest effect sizes (No panacea!!!)
- Insufficient evidence to conclude regarding psychotherapy vs drug treatment for most disorders
- However, psychotropic drugs and psychotherapy have partly different effects
- When to add drug - and which type of drug - is the question: Choose horses for courses!
Principles for drug selection

2. Biological effect on the underlying disease

3. Implications of side-effect profile

i.e. Pharmacodynamics
(the drug’s effect on the body)
Serotonin receptor stimulation

Receptor:

5-HT\textsubscript{1A}  
Anti-depressive, Anti-anxiety, anti-obsession; anti-bulimia. (Down regulation of emotions and impulses)

5-HT\textsubscript{2A}  
Behavioral activation, insomnia, anxiety, sexual dysf

5-HT\textsubscript{2C}  
Irritability, decreased appetite

5-HT\textsubscript{3}  
Nausea, headache and emesis
Serotonin receptor antagonism

Receptor:

- $5-HT_{2A}$: Reduces behavioral activation, improves sleep, reduces sexual sexual dysfunction
- $5-HT_{2C}$: Reduces irritability and appetite; reduces cortisol?
- $5-HT_3$: Reduces nausea, headache and emesis
Other receptor stimulation

Receptor:

- Alfa-1 → Hypertension, increased vitality, reduced fatigue
- Muscarine₁ → Improved cognition
- Histamine₁ → Pain
- Dopamine → Motivation (reward), emesis
Other receptor antagonisms

Receptor:

- **Alfa-1**: Ortostatic hypotension, dizziness, reflex tachycardia, priapism
- **Muscarnine**\(_1\)**: Accomodation problems, dry mouth, unspecific sedation, obstipation / urine retention, sinustachycardia, impaired cognition
- **Histamine**\(_1\)**: Sedation, weight increase, reduced attention
- **Dopamine**\(_2\)**: Antipsychotic, anti-emetic
Antidepressant profiles

- Inhibition of presynaptic mono-amine reuptake (serotonin, noradrenaline, dopamine)
- Antagonism of serotonin-2-receptors combined with ....
- Inhibition of mono-amino-oxidase
- GABA & glutamate antagonists
- Others
Neuroleptic profiles

- All drugs effect D2 receptors
- Additional effects on other receptors differentiates the drugs
- In comparable doses, the clinical effects are similar
- Small doses may interfere with receptors and be useful in C-L settings and psychosomatic medicine
Choosing horses for courses (1):
Wanted receptor profile effects

• **Depressed & detrusor instability:**
  5HT & NA-reuptake blocking (e.g. duloxetine, milnacipran (?) or venlafaxine (??))

• **IBS and stress:**
  + neuroticism: 5HT-reuptake blocking (e.g. SSRI)
  + no neuroticism/major psychopath: alfa-2 antag / H$_2$ antag (e.g. mianserin or mirtazapin)

• **Late stage cancer & low motivation / anergic depression:**
  DA-stimulation (e.g. methylphenidate (or bupropion??))
Choosing horses for courses(2):
Unwanted receptor profile effects

• **Depression and Sjøgren’s syndrome:**
  - avoid NA-reuptake blocking drugs (e.g. atomoxetine, reboxetine) and Ach-antag drugs (e.g. paroxetine, TCA)

• **Severe depression in an elderly with cognitive impairment:**
  - avoid drugs with Ach-antag effects (e.g. paroxetine and TCAs)
Choosing horses for courses(3):
Other unwanted side effects

- **Confusion and concurrent hypotension:**
  - avoid drugs with alfa-1-antag effects (e.g. risperidone, quetiapine)

- **Psychotic and diabetes:**
  - avoid drugs with diabetic potential (e.g. olanzapine)

- **Behavioural problems in the elderly with brain damage:**
  - avoid olanzapine and risperidone; is amisulpiride, aripiprazole, quetiapine or ziprasidone safer??; best choice to start with a SSRI??
Principles for drug selection

1+3. Effect and side-effects
4. Interactions with "somatic" drugs

i.e. pharmacodynamics and Pharmacokinetics
(the body’s effect on the drug)
Pharmacokinetics

- Absorption
- Distribution/ Plasma protein binding
- **Biotransformation** (most important in clinical practice)
- Elimination
Drug metabolism

- **Phase I:**
  - 50% metabolized (gut, liver)
  - oxidation, CYP mediated reduction and hydrolysis
CYP-enzymes: Clinical importance

- **1A2** (induceable, ex. tobacco)
- **2C9** genetic polymorphism (+ induceable, example ethanol)
- **2C19** gentic polymorphism: 3% no enzyme (15% among Chinese)
- **2D6** genetic polymorphism: 6% no; 3% LARGE quantities
- **3A3/4**-large individual variation. *Inducable* (e.g. karbamazepine)

http://medicine.iupui.edu/flockhart/clinlist.htm
Drug metabolism

• **Phase II:**
  glucuronide conjugation, sulphate and mercapturic acid conjugates
  UGT-enzymes etc activity
  water soluble metabolites (urine)

  induced by **smoking**; inhibited by **alcohol**

  Assessment of phase II enzymes not available in clinical practice
Clinical implications:
No effect or side-effects?

20 (!) times variation in serum concentration of a drug between pts given the same dosage

Compliance???
Tayloring drugs?

- **Pharmacogenomics** refers to the general study of all of the many different genes that determine drug behavior.

- **Pharmacogenetics** refers to the study of inherited differences (variation) in drug metabolism and response.

- The distinction between the two terms is considered arbitrary, however, and now the two terms are used interchangeably.
**HAMD-17 Remitters**

**Day 14**

E4 non carriers  
E4 carriers

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**Mirtazapine**

- E4 non carriers: 28.0%
- E4 carriers: 92.9%
- p = .005

**Paroxetin**

- E4 non carriers: 0%
- E4 carriers: 93.2%
- p = NS

**Remitters = Subjects with HDRS-17 <= 7**

Cochran-Mantel-Haenszel analysis

Murphy et al. Biol Psychiatry 2003; 54:665-73

Murphy Lab
Survival curves showing discontinuations due to adverse events for paroxetine and mirtazapine, stratified by Serotonin Transporter Gene Promoter Polymorphism type

S: short form; L: long form

% pts discontinuing treatment

Pharmacogenomics

Antipsychotic drug studies: polymorphisms within the serotonin 2A and dopamine receptor 2 genes may influence drug efficacy in schizophrenia.

A number of independent studies point to a significant effect of a dopamine D(3) receptor polymorphism on susceptibility to tardive dyskinesia.

The future

• A single microarray can now be used to screen 100,000 SNPs found in a patient's genome in a matter of hours. As DNA microarray technology is developed further, SNP screening in the doctor's office to determine a patient's response to a drug, prior to drug prescription, will be commonplace.
References


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- Cardiac drug-psychotropic drug 2002; 24: 283-289.
- Neurologic – psychotropic drug 2002; 24: 290-310