



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 par enteral 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.bmjournals.com>

www.tripdatabase.com

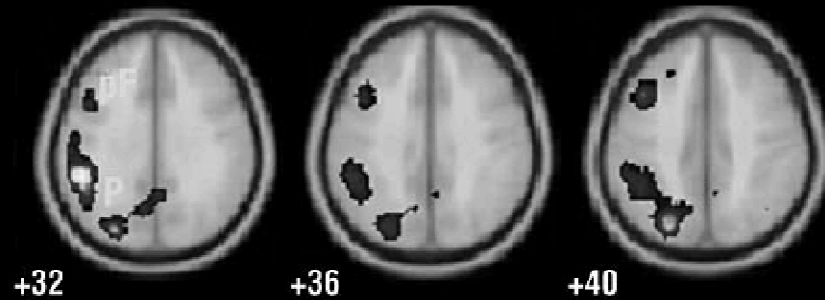
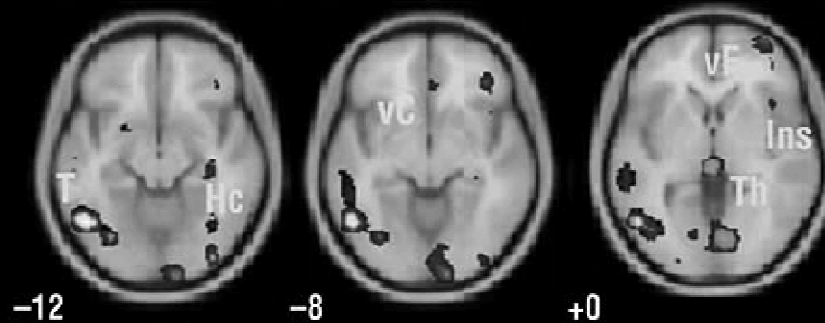
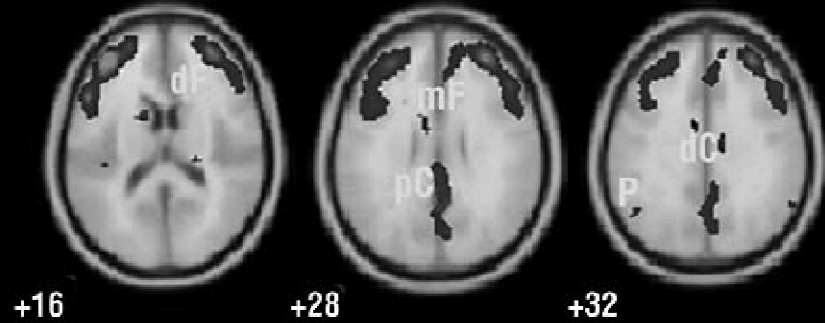
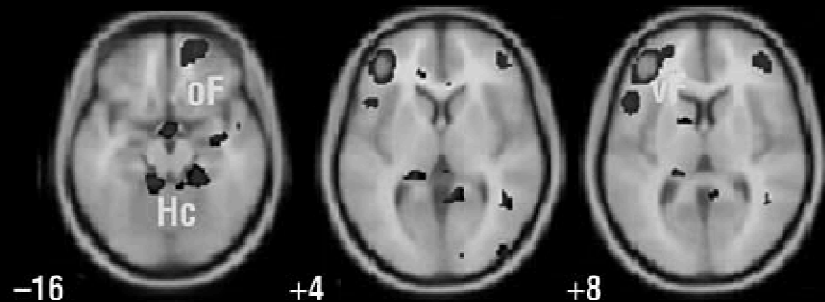
Ruddy R, House A: Meta-review of high quality systematic reviews of interventions in key areas of liaison psychiatry. Br J Psychiatry 2005; 187 (August): 109-120.



Reminder:
**Psychopharmacology has
partly different effects
than psychotherapy and
vice versa**



Cognitive
Behavior
Therapy



z-4  z+4

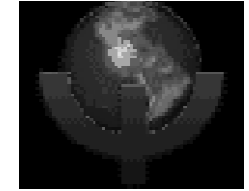


Changes in regional glucose metabolism (fluorine-18–labeled deoxyglucose PET) in CBT responders (top) and paroxetine responders (bottom) following treatment. Metabolic **increases** are shown in orange and **decreases** in blue.

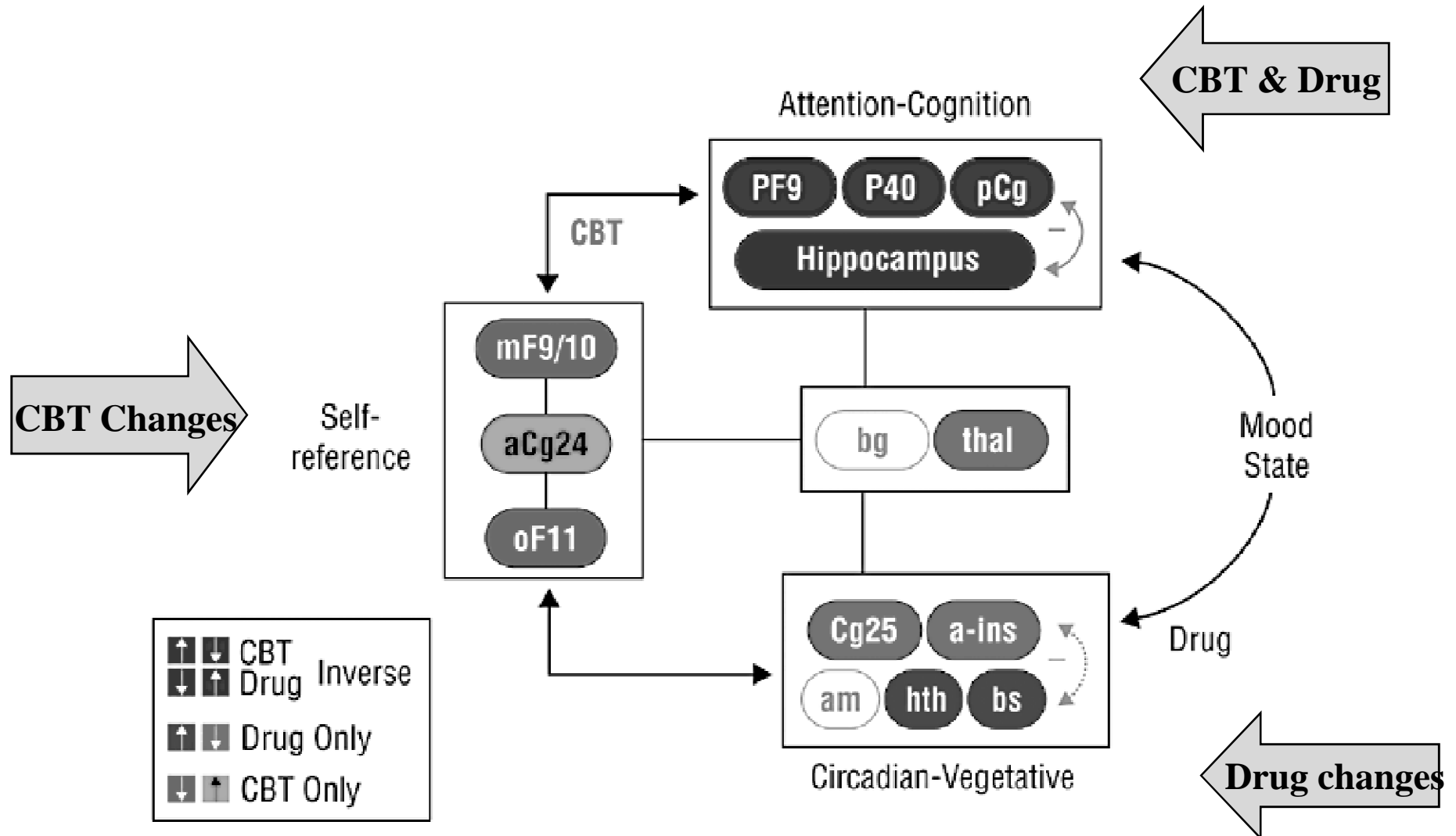
(Goldapple et al.
Arch Gen Psychiatry 2004; 61:34-41)



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**

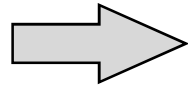
(the drug's effect on the body)

Serotonin receptor stimulation



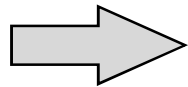
Receptor:

5-HT_{1A}



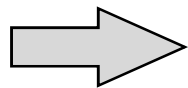
Anti-depressive, Anti-anxiety, anti- obsession; anti-bulimia. (Down regulation of emotions and impulses)

5-HT_{2A}



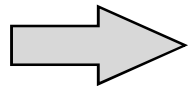
Behavioral activation, insomnia, anxiety, sexual dysf

5-HT_{2c}



Irritability, decreased appetite

5-HT₃



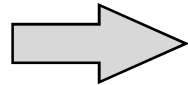
Nausea, headache and emesis

Serotonin receptor antagonism



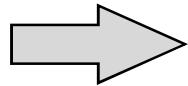
Receptor:

5-HT_{2A}



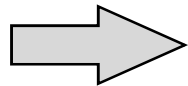
Reduces behavioral activation, improves sleep, reduces sexual dysfunction

5-HT_{2c}



Reduces irritability and appetite; reduces cortisol?

5-HT₃

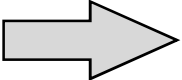
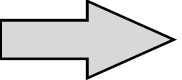
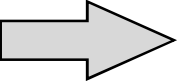
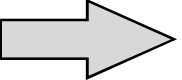


Reduces nausea, headache and emesis



Other receptor stimulation

Receptor:

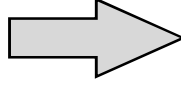
- | | | |
|------------------------|---|---|
| Alfa-1 |  | Hypertension, increased vitality, reduced fatigue |
| Muscarine ₁ |  | Improved cognition |
| Histamine ₁ |  | Pain |
| Dopamine |  | Motivation (reward), emesis |



Other receptor antagonisms

Receptor:

Alfa-1  Ortostatic hypotension, dizziness
reflex tachycardia, priapism

Muscarine₁  Accomodation problems, dry
mouth, unspecific sedation,
obstipation / urine retention,
sinustachycardia, impaired
cognition

Histamine₁  Sedation, weight increase,
reduced attention

Dopamine₂  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: α -₂ antag / H₂ 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 Sjögren'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** genetic 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.

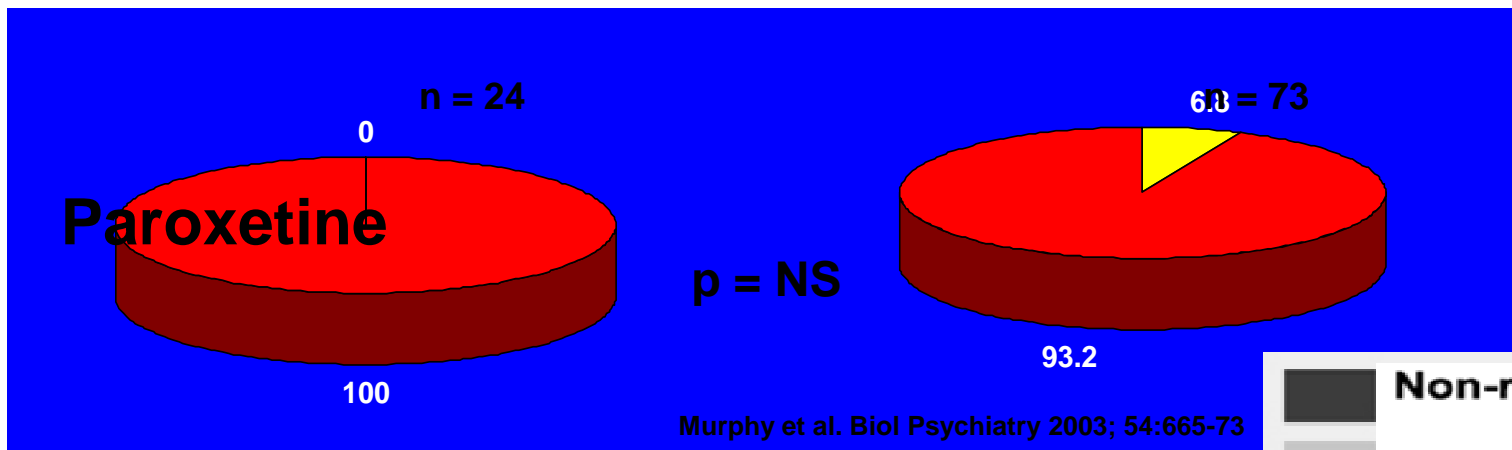
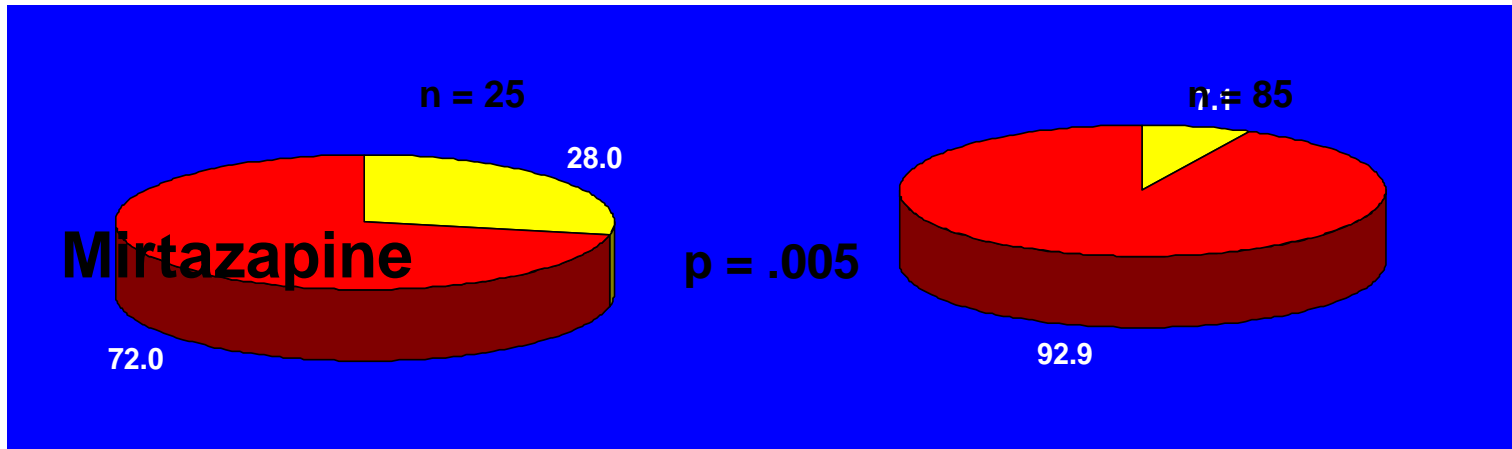
HAMD-17 Remitters

Day 14



E4 non carriers

E4 carriers



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



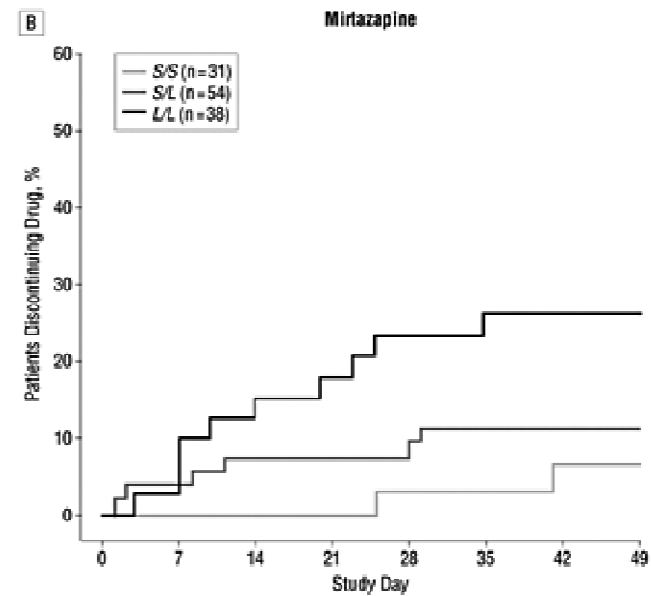
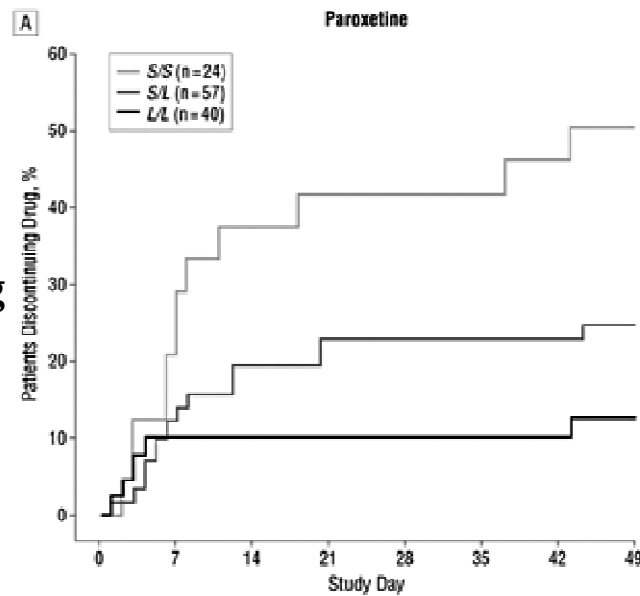
Remitters = Subjects with HDRS-17 \leq 7
Cochran-Mantel-Haenszel analysis

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
dis-
continuing
treatment



Murphy, G. M. et al. Arch Gen Psychiatry 2004;61:1163-1169.

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.

Malhotra et al. Am J Psychiatry 2004; 161:780-96



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

Davis et al. Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia: Lippincott Williams & Wilkins, 2002.

Malt UF, Lloyd G. Pharmacological treatment in liaison psychiatry. In: Handbook of Liaison Psychiatry. Editors: Geoffrey Lloyd & Elspeth A. Guthrie (to appear in 2006).

Stephen M. Stahl. Essential psychopharmacology. The prescribers guide. Cambridge Univ Press 2004

James Strain et als update series in General Hospital Psychiatry:

- Psychotropic drug versus psychotropic drug 2004; 26: 87-105
- Cardiac drug-psychotropic drug 2002; 24: 283-289.
- Neurologic – psychotropic drug 2002; 24: 290-310

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