Schizophrenia

HISTORY AND MENTAL STATE EXAMINATION OF PSYCHOSIS

Who's been stealing your thoughts?...

CHARACTERISTIC SYMPTOMS: at least 2, through the duration of a month

- **DELUSIONS** – bizarre or illogical false beliefs that are not culturally congruent, or false interpretation of normal perception
  - **PARANOID, RELIGIOUS, GRANDIOSE, PERSECUTORY….**
  - **- these beliefs will be contradictory. Reasoning with them will usually yield no result.**
  - **- CHALLENGE the delusions: ask them "is it possible that this might NOT be the case?"**
  - **- A DELUSION which is amenable to reason is more like an overvalued idea.**
  - Its not that logical processes are totally disrupted; it just seems that the idea or notion becomes somehow exempt from the normal processes of logical validation.
  - **A BATTERY OF QUESTIONS: not limited to this petty array below; ask in detail**
    - **Feel like you have special powers?**
    - **Been reading people's thoughts?**
    - **People been reading your thoughts?**
    - **Someone putting thoughts inside your head?**
    - **Receiving messages from someone?**
      - **Throught the TV? Newspapers? Radio? Its usually the mass media…**
- **HALLUCINATIONS** – seeing things which aren't there. Separated from illusions by virtue of that fact. Illusions are perceptual distortions of something that actually does exist.
  - **AUDITORY: most common; usually voices., sometimes commanding or taunting**
  - **VISUAL or TACTILE hallucinations = strongly suggest ORGANIC CAUSE**
- **Disorganised Speech:**
  - **INCOHERENCE—a breakdown of the relationships between words within a sentence**
  - **DERAILMENT—wandering off the point during the free flow of conversation**
  - **TANGENTIALITY—answers to questions that are off the point**
  - **LOSS OF GOAL—failure to reach a conclusion or achieve a point.**
  - **METONYMS—unusual uses of words (e.g. hand-shoe instead of glove)**
  - **NEOLOGISMS—new words invented by the patient.**
- **Grossly Disorganised or Catatonic Behaviour**
- **NEGATIVE FEATURES: tend to persist longer than positive features**
  - **POVERTY OF SPEECH- the rate of speech production is reduced**
  - **POVERTY OF CONTENT- the amount of information conveyed is relatively little in proportion to the number of words uttered.**
  - **SOCIAL WITHDRAWAL- no longer interested in the world outside**
  - **POOR JUDGEMENT and INSIGHT – unable to effectively manage one's daily affairs**
  - **COGNITIVE IMPAIRMENT- normally not so bright; now even duller.**
- **MOOD COMPONENT**
  - **INVESTIGATE: was it present before the onset of psychotic symptoms?**
  - Could this be a psychotic mania or a psychotic depression?

    Otherwise, if features of schizophrenia exist for at least 2 weeks without a mood disturbance at any stage during this mood-disturbance-coloured-psychosis, it's a SCHIZOAFFECTIVE DISORDER . so you need a glimpse of pure schizophrenia somewhere to call it schizoaffective, rather than a mood disorder with psychotic features.

OTHER IMPORTANT HISTORY of a psychotic episode

- **Pre-morbid personality: is there a definite PRODROMAL PERIOD?**
  Or is this psychosis just out of the blue? Prodrome is more closely associated with long-term psychiatric illness; sudden onset suggests organic causes, and especially drugs. Usually onset is over weeks.

CHARACTERISTICS OF PRODROME PERIOD

-**Suspiciousness**
-**Depression**
-**Anxiety**
-**Irritability**
-**Restlessness**
-**Change in appetite**
-**Sense of alteration of self or others**
-**Social isolation or withdrawal**

Age of Onset is usually between 15 and 25 years of age

-**Pattern of INCREASING SEVERITY**
-**Marked impairment in role functioning**
-**Markedly peculiar behaviour**
-**Marked impairment in personal hygiene**
-**Blunted, flat or inappropriate affect**
-**Digressive, vague or metaphoric speech**
-**Odd or bizarre ideation**
-**Unusual perceptual experiences**

- **Drugs and Alcohol:** Notoriously psychotic episodes may be triggered by AMPHETAMINES, LSD and CANNABIS
- Previous admissions to some sort of psychiatric unit: does his always happen when they smoke pot?
- **Family history: Monozygotic twin of schizophrenic patient ----- 47% risk**
  - **Child of two schizophrenic parents ---------- 40%**
  - **Child of one schizophrenic parent ---------- 12%**
  - **Dizygotic twin of schizophrenic patient---------- 12%**
  - **Non-twin sibling of schizophrenic patient --------- 8%**
  - **General population---------- 1%**

Natural History of Psychotic Illness

3 major phases:

- **PRODROMAL PERIOD** lasting months to years;
- **ACTIVE PHASE** of irregular duration, when symptoms are prominent.
- **RESIDUAL PHASE** when some systems may persist after most have resolved.

Prognosis:

25% = complete recovery,
40% = recurrent episodes of psychosis with some degree of social disability
35% = long-term social disability.

DIFFERENTIALS: Non-psychiatric causes of psychosis

Roughly 3% of first-time psychosis is organically caused

Neurological causes

- **HIV encephalopathy**
- **Cerebrovascular disease;** late-onset
- **Brain injury;** long after the injury
- **Multiple sclerosis;** periventricular lesions
- **Huntington's disease;** psychosis in 5%- 10%
- **Epilepsy;** esp.complex partial seizures
- **Neoplasms** of the temporal lobe and cingulate gyrus
- **Brain abscesses** of all kinds
- **Amphetamine or Cannabinoid Psychosis**
- **Wilson's disease**

Endocrine, metabolic and autoimmune causes

- **Cushing's syndrome; psychosis occurs in**
- **up to 20% of patients**
- **Hyperthyroidism and hypothyroidism**
- **Hyperparathyroidism; psychosis may occur**
- **with a clear sensorium**
- **Porphyria;** acute intermittent porphyria and porphyria variegata
- **Vitamin B12 deficiency;** depression more common
- **Steroid-induced psychosis**
- **Delirium** (though that has a fluctiant course)

DIFFERENTIALS: different flavours of psychosis

- **Schizophrenia :** 6 months of ongoing disturbance (eg. long residual phase after acute episode)
- **Schizophreniform disorder** is what you call it during the first 6 months.
- **Psychotic disorder due to a medical condition** will respond to treatment of underlying condition
- **Substance-induced psychotic disorder** usually resolves uneventfully and quickly once the drugs are ceased
- **Brief psychotic disorder:** first-time psychosis, usually lasting from 1 day to 1 month
- **Major depression with psychotic features:** 2 week duration criteria
- **Bipolar disorder with psychotic features** one week duration criteria; main background = mood disturbance
- **Schizoaffective disorder** 2 weeks of non-moody psychosis among at least 1 month of mood-disturbed psychotic illness
- **Delusional disorder:** Non-bizarre delusions, and deulusion-congruent hallucinations.

INVESTIGATIONS

- **EUC**
- **ESR**
- **TFT**
- **LFT + Lipids**
- **FBC**
- **Iron studies**
- **Vitamin B12 and folate**
- **Syphilis serology**
- **EEG**
- **Urinary drug screen**
- **CT Head**
- **ESR + ANA, ANCA, etc**
- **BSL**
- **Urinary copper level**
- **HIV serology**
- **Syphilis serology**
- **Serum Cortisol**
- **Thyroid Function**

MANAGEMENT of ACUTE PSYCHOSIS

In the emergency department: remedy the immediate ills. Bleeding, burning, etc.

Risk to self or others? Severely disturbed? Need hospitalisation?
Encourage voluntary admission.

APPROPRIATE RESTRAINTS whether chemical or physical, can be used.

- **HALOPERIDOL 10mg and MIDAZOLAM 10mg**
- **CHLORPROMAZINE is an alternative**
- **OLANZAPINE is acutely sedating and thus also useful**

In the Acute Psychiatric Inpatients Unit:

Are they MENTALLY ILL or merely MENTALLY DISORDERED?

If disordered, eg. drug induced psychoss, one may merely contain the patient and observe their behaviour (which should improve rapidly)

- USE TYPICAL ANTIPSYCHOTICS or OLANZAPINE to control behaviour
- BENZODIAZEPINES if sedation with antipychotics is insufficient

- **GOALS OF ACUTE-PHASE TREATMENT:**
  - CONTROL POSITIVE SYMPTOMS: its more satisfying because these will actually respond to drug therapy and psychotherapy. Negatve symptoms re notoriously persistent and refractory.
  - ENSURE SAFETY by controlling outrageously bizarre and dangerous behaviour
  - Try low-potency and atypical drugs first;
  - Use high-potency and typical drugs if first-line therapy fails
- **GOALS OF RESIDUAL PHASE TREATMENT:**
  - REFINE MANAGEMENT REGIMEN: use what seemed to work best in he acute phase, together with psychotherapy to teach coping skills.
  - Let the side-effects guide you
  - RESOCIALISE as best you can, hopefully to premorbid levels of functioning

In the Community: GOALS OF MAINTENANCE THERAPY:

- CONTINUE ANY NECESSARY DRUGS: usually about 2 years without relapse is the goal; after that you may try tapering down the dose
- MONITOR side-effects eg. extrapyramidal, weght gain + diabetes, etc…
- Try low-potency and atypical drugs first;
- Use high-potency and typical drugs if first-line therapy fails

- **TREATMENT-RESISTANT SCHIZOPHRENIA**
  - ECT seems to have some benefit, in select patients
  - One may add more drugs eg. carbamazepine, lithium, valproate, gabapentin, bezodiazepines, and any number of others.

PSYCHOTHERAPY FOR SCHIZOPHRENIA

- Absolutely necessary to help the patient control their symptoms
- Best commenced in the residual phase, when you can reason with them

ANTIPSYCHOTIC AGENTS

THE GOAL OF THERAPY IS TO REDRESS THE BALANCE OF D1 and D2 DOPAMINE RECEPTORS
Thus: you block the overactive mesolimbic pathway by crippling the D2 receptors, so that the defective mesocortical feedback loop can downregulate the activity of the Ventral Tegmental Area.
(Mesolimbic pathway: linking ventral tegmentum (midbrain) to the nucleus accumbens)
A little bit of theory now….

DOPAMINE RECEPTORS: can be separated into the D1 and D2 families.

The D1 family contains the receptors D1 and D5.

- D1 receptors in the brain are linked to episodic memory, emotion, and cognition.
- Schizophrenics seem to have fewer D1 receptors.

- Certain antipsychotic drugs stimulate D1 regulated pathways, which increases the D1 to D2 activity balance. in the brain. This balance can also be regained by the release of dopamine.

Not much is known about D5 due to the lack of drugs that are selective for it.

The D2 family contains the receptors D2, D3, and D4.

- D2 is the second most abundant dopamine receptor in the brain.
- D2 receptor blockade is the main target for antipsychotic drugs, because there is a higher density of D2 in schizophrenic brains. (Sedvall & Farde 1995)

This theory rests on the horribly inaccurate DOPAMINE HYPOTHESIS:

EXCESS OF DOPAMINERGIC ACTIVITY AT = POSITIVE SYMPTOMS
Eg. hallucinations, delusions
DEFICIT OF DOPAMINERGIC ACTIVITY = NEGATIVE SYMPTOMS
Eg. loss of pleasure and decrease in reward-dependent behaviour
THUS: 70% D2 blockade = antipsychotic effect;
Conversely, DOPAMINE AGONISTS INDUCE PSYCHOSIS

METABOLISM of ANTIPSYCHOTICS:
Mainly hepatic.
Steady plasma levels usually after 4 to 10 days

INTERACTION OF SEROTONIN AND DOPAMINE:
Serotonin inhibits dopamine release via 5-HT(2a) receptors
THUS: atypical antypsychotics act as 5-HT(2a) antagonists;
thus INCREASE DOPAMINE(effect is different for every pathway)

UNFORTUNATELY: dopamine receptor activity is not exclusively psychological.
Plus many other receptors are affected.

PITUITARY EFFECTS:
- Lactation (except clozapine)
- Menstrual irregularities
- Weight gain
- Impotence

NIGROSTRIATAL EFFECTS:
- Dystonia
- Masked facies
- Tremor
- shuffling gait
- Tardive Dyskinesia
- Akathisia (restessness)

MANAGING DYSTONIA:
Benztropine IV or Diphenhydramine IM, IV.

MUSCARINIC EFFECTS:
- Dry mouth
- constipation
- urinary retention
- blurred vision,
- narrow angle glaucoma

ALPHA-1 ADRENERGIC
- Orthostatic hypotension
- Lightheadedness
- tachycardia
- sedation
- sexual dysfunction.

HISTAMINE-1
- Sedation
- weight gain (also 5HT 2c)
- fatigue.

SEROTONIN 1-C
- weight gain (olanzapine)

NON-SPECIFIC SIDE EFFECTS
- Hyperthermia
- Hypothermia
- hepatitis
- photosensitivity
- lowered seizure threshold
- ARANULOCYTOSIS
- and rash.

DIVISION OF TYPICAL AGENTS BY POTENCY:
High-potency: highest affinity for D2 receptors
Low-potency: poorer affinity for D2 receptors

ATYPICAL AGENTS: also block SEROTONIN 5HT-2a receptors;
Less nigrostriatal effects: less dyskinesias

CLOZAPINE: in a class of its own; blocks the following receptors:
- 5HT-2a
- Apha-1 adrenergic
- Dopamine 1, 2and 4
- Some histamine
- Acetylcholine

DANGERS OF ANTIPSYCHOTICS:

Tardive dyskinesia: permanent effect!

Neuroleptic Malignant Syndrome: Risperidone seems to put you at greater risk.

CLOZAPINE DOES NOT CAUSE TARDIVE DYSKINESIA

ZYPREXA:
Best thing ever for very acute episodes of psychosis when the patient is AT HOME. It calms them right down, right away.

GENERAL RULES OF ANTIPSYCHOTIC THERAPY:

START LOW
GO SLOW

Continue drugs for 2 years following 1st episode, or 5 years if episodes confluent or recurrent.

- Atypical agents = first line
- CONTROLLING POSITIVE SYMPTOMS: No generaliseable difference in efficacy between typical and atypical agents
- CONTROLLING NEGATIVE SYMPTOMS: Atypicals clearly superior

THUS:

Use typical agents for acute psychosis (they sedate better)
Use atypical agents for maintenance (less long-term side effects)

CLOZAPINE is only indicated after most other antipsychotics are ineffective

See www.crazymeds.org/ for detailed discussions of psychiatric meds from a patients viewpoint

Some Atypical Antipsychotic Drugs:

Aripiprazole (Abilify), a Quinolinone: half-life is 75 hours for aripiprazole and 94hours for its active metabolite, dehydro-aripiprazole. Not very sedating, but very nausea-inducing plus anxiety, insomnia No lactation, little weight gain; BUT: this drug is very young and we don't know the long-term freaky side effects.

Clozapine (Clozaril), a: Dibenzodiazepine, one of the oldest ones. Half-life 11 hours, hepatic metabolism. Side-Effect Profile: Orthostatic hypotension (high), sedation (high), anticholinergic (high), but absolutely no extrapyramidal symptoms. Most common side effects:

On clozapine, improvement is continuous and things slowly get better over 12 to 18 months of treatment.

sedation, dizziness, hypotension, tachycardia, constipation, hyperthermia, and hypersalivation. Hypersalivation can be treated with anticholinergic agents.

! MYOCARDITIS, thus ECHO at 6 months

Clozapine has a 1-2% incidence of agranulocytosis. REGULAR FBCs!

Discontinue the drug if the WBC drops below 3,000/mcL,
…or 50% of patient's normal count,
…or if granulocyte count drops below1,500/mcL.

How regular? ..Varies.
Hospital policy protocol will guide you. Guidelines for FBC regularity seem to be based on medicolegal considerations

Risperidone (Risperdal), a Benzisoxazole. Half-life is 3-20 hours. Hepatic metabolism to an active metabolite. Side-Effect Profile: Orthostatic hypotension and reflex tachycardia (alpha 1 receptor mediated, minimized with slow upward titration), insomnia, and agitation are the most frequent. I May cause weight gain and increase prolactin levels (usually not clinically significant). May prolong QT interval.

Olanzapine (Zyprexa, Zydis), a Thienobenzodiazepine. half-life 21-50 hours. Hepatic metabolism to inactive metabolites. Side-Effect Profile: Most common side effects are drowsiness, dry mouth, akathisia, and insomnia. Less frequent are orthostatic hypotension, lightheadedness, nausea, and tremor. Weight gain is common with olanzapine. Increases in lipids and blood glucose are also observed. There are reports of new onset diabetes and diabetic ketoacidosis.

Quetiapine (Seroquel), Dibenzothiazepine. Half-life is 6 hours, hepatic metabolism, no active metabolites. Side-Effect Profile: Orthostatic hypotension may occur during initial dose titration due to alpha-blockade.Somnolence and weight gain may occur due to H 1blockade. Dyspepsia, abdominal pain, and dry mouth may also occur. There are reports of new onset diabetes or diabetic ketoacidosis.

Minimal weight gain.
No anticholinergic side effects.
No sustained elevation of prolactin.

Ziprasidone (Geodon), a Benzisothiazolyl piperazine. Inactive metabolites, half-life 4 hours. Low potential for drug interactions. Side-Effect Profile: Dizziness, nausea, and postural hypotension are the most common side effects. Prolactin elevation can occur. Sedation is more common with the IM preparation.

Very low incidence of extrapyramidal symptoms.
Minimal incidence of cardiovascular problems.
Prolactin elevation is minimal.
The lowest incidence of weight gain, dyslipidaemia, and glucose intolerance.

TYPICAL ANTIPSYCHOTICS

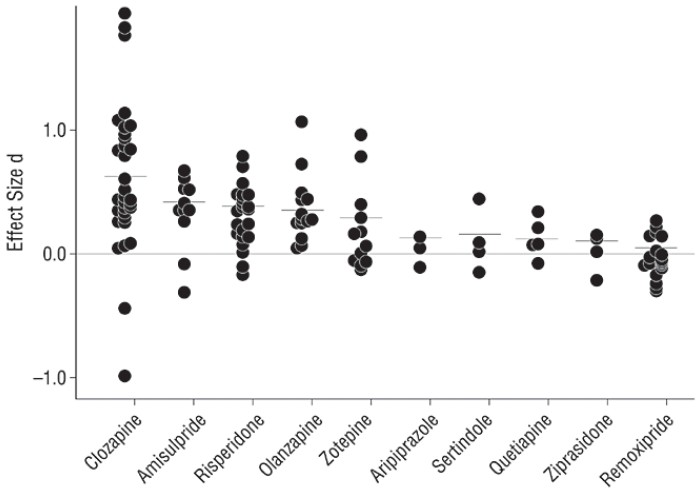
Haloperidol (Haldol) Hepatic metabolism to active metabolite. Half-life 10–20 hours. Duration of action of decanoate is approximately 4 weeks.: High incidence of extrapyramidal symptoms. May possibly lower seizure threshold in patients with a history of seizures. The normal bouquet of side-effects apart from that.

Chlorpromazine (Thorazine) : Hepatic metabolism to many metabolites;
Not recommended in elderly due to orthostatic hypotension.
Major Safety Concerns: Higher risk than most other typical antipsychotics for seizure, jaundice, hotosensitivity, skin discoloration (bluish), and granular deposits in lens and cornea. Prolongation of QT and PR intervals, blunting of T-waves, ST segment depression can occur. Associated with a high incidence of hypotensive and anticholinergic side effects. Chlorpromazine has high lethality in overdose.

Trifluoperazine (Stelazine) Hepatic metabolism. Half-life 10–20 hours.

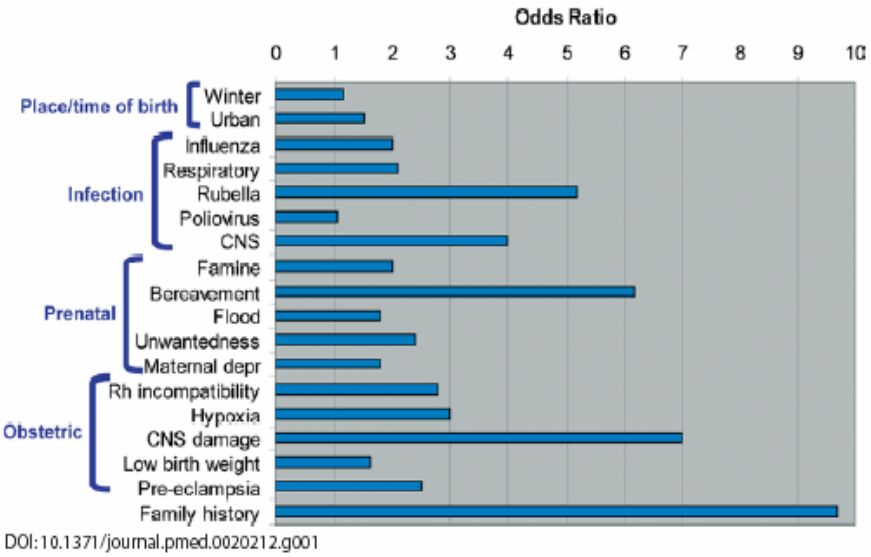
Loxapine (Loxitane) Class: Dibenzoxapine. Hepatic metabolism to active metabolite. Half-life 5-15 hours.
Loxapine may be associated with a higher risk of seizure than other high- and mid-potency agents.

Comparative effects



BORING SCIENCE and MISCELLANEOUS TOPICS

Risk Factors for Schizophrenia



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WILL CANNABIS MAKE ME CRAZY?

Honest answer: maybe.
I don't know.

Twice the risk of the general population; BUT:

- risk is dose-related;
- people who are predisposed to psychosis are also predisposed to using cannabis …?
- Predisposition to psychosis also means a greater susceptibility to cannabis-induced psychosis and cognitive impairment

Plenty of people out there, smoking cannabis. Some of them are predisposed to psychosis but never experience it because they don't smoke enough pot. A few will experience psychosis and be hospitalised, managed, rehabilitated, studied and talked about by doctors.

POSSIBLE GENETIC CULPRITS

Gene	Cytogenic band	Genome, Linkage & Association studies	mRNA in PFC	Mechanism
DISC1 Disruption in Sz	1q42.2	Yes	+	Microtubule fx, cell migration, membrane trafficking of receptors, Modulates neurite outgrowth
DTNNBP1 Dystrobrevin binding protein 1	6p22.3	Yes	++	Tethering postsynaptic receptors Unknown presynaptic fx
NRG1 Neuroregulin	8p12	Yes	+	CNS dev. Cell signalling Transmembrane proteins
RGS4 Regulator of G protein signalling 4	1q23.2	Yes	++	Modulate signalling of G-protein linked receptors

COMPLIANCE / ADHERENCE

Usually extremely poor. The more disorganised and isolated the patient, the less likely they are to take their crazy meds.

How to deal with this:

- **Educate re. necessity** (its worth a try)
- **Simplify regimen** eg. there are now preparations of antidepressant together with olanzapine; one pill only.
- **Address side effects** – major limitation of typicals
- **DEPOT medication** if that doesn't work; or
- **Engage the FAMILY to administer**