ANTIPSYCHOTICS: Traditional Drugs (p.1)

1. **Introduction**

antipsychotic drugs = "major tranquilizers", "neuroleptics"
these drugs have revolutionized the tx of schizophrenia since 1950s
do not cure schizophrenia (or mania or Tourettes), but do significantly
reduce their symptoms
allow clearer thought, less agitation
without marked sedation, dependence, addition, or tolerance (to the beneficial effects)

there are **two broad categories** of antipsychotic drugs:
a. 1st generation or **traditional** (phenothiazines & butyrophenomes)
b. 2nd generation or **atypicals** (dual action drugs)

history of their development:
French surgeon (**Henri Laborit**), 1950, searching for a drug to reduce surgical shock (fear, anxiety, high ANS arousal, high muscle tension)
started with a phenothiazine molecule (which was like histamine)
--- no effect on ANS, but did calm pts while they were still awake

French chemist (**Paul Carpentier**) experimented with phenothiazine, added Cl- atom --- chlor promazine (Thorazine)!
Laborit persuaded MD colleague to try it on his patients (1952)
significantly improved manic, agitated, hallucinating pts., enabled them to live as out-pts, without physical restraints

in **1955 Thorazine** was approved for use in USA --- immediate reduction in #s of hospitalized pts.
and for the first time interest in the **neural basis** of "mental" illness began, suggested a **biological cause** (vs. learned)

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2. **Neural Basis of Schizophrenia** (summary)
   . Sxs significantly worsen in early 20s (as **frontal lobes** become fully active – damaged)
   . large overlap with depression (**limbic system** damaged)
   . sources of neural damage: **pathological genetic** expression, **acquired damage** (viral, CNS stimulant abuse, prenatal fever)
   . damage to **DA, glutamate, 5HT, & GABA** systems
   . **widespread damage** (multi NT systems, many symptoms): perceptual distortions (esp. auditory), language (disorganized speech), poor inferential thinking (delusions), poor social skills (blunted affect, distorted emotions), poor motor skills, anhedonia, poor cognitive/ executive function skills (poor focus, concentration, memory)
   . implies widespread, basic damage (in synaptogenesis, synaptic "pruning", apoptosis, neural migration, muelination, neural meitosis)
   . Sxs associated with both "soft" and "hard" neurological signs

3. So-called **"positive" and "negative" Sxs** of schizophrenia
   + Sxs: delusions, hallucinations, bizarre behaviors/postures
   dissociated/fragmented thoughts, illogical thinking
   incoherent speech, impaired executive functioning
   most likely due to **overly active DA system**

   - Sxs: blunted affect, odd/reduced emotional reactions, apathy
   no initiative, no motivation, no interests, no goals
   social withdrawal
   lack of spontaneous speech
   likely due to **underactive glutamate/NMDA system**, perhaps secondary to **abnormalities in 5HT system**

   drugs used to treat psychosis affect many RSs:
   DA2, AChMuscarinic, 5HT1A, 5HT2, H1, NE alpha#1&2, & more

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4. **<u>Traditional Antipsychotics</u>**

are especially good at reducing the + Sxs (do not reduce – Sxs)

major SEs – **EPSEs** (extrapyramidal side effects), **TD** (tardive dyskinesia)

major affect on NS is to block DA2 postsynaptic RSs --- up-regulation?

DA2 RSs are found in **4 systems** in the CNS:

mesocortical **hypothalamic-pituitary**

mesolimbic **nigrostriatal-basal ganglia**

also block several other NTs: **ACh, NE, 5HT, H** (are "**dirty drugs**")

as + Sxs decrease, S becomes more aware of improvement

all neuroleptics are about equal in decreasing the + Sxs

but different pts. respond better to different drugs…implies that there are **individual differences in exact underlying NTs/neural systems**

must also combine pharmacotherapy with **supportive environment and cog.-behavioral therapy**

S can live as out-pt now…but increases stress of needing to cope with "real world" and increased risk for medication non-compliance

general approach:

treat S initially with higher doses, enough to reduce + Sxs

when S stabilizes, the begin to reduce dose to lowest possible dose to still block + Sxs & yet has fewest SEs possible

use only one drug at a time if possible

use no/minimal other drugs to control SEs

do not recommend "drug holidays", may actually worsen SEs

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4. **<u>Traditional Antipsychotics</u>** (cont.)

there are high and low potency neuroleptics:

high potency drugs - strongly block DA2 RS, weak antiACh effects

lots of EPSEs, higher risk for TD

fewer antiACh effects, but greater risk for NMS (neuroleptic malignant syndrome)

less sedation, less orthostatic hypotension

e.g. haloperidol **(Haldol)** fluphenazine **(Prolixin,Permitil)**
trifluoperazine **(Stelazine)** thiothixene **(Navane)**
molindone **(Moban)** perphenazine **(Trilafon)**
pimozide **(Orap)** loxapine **(Loxitane)**

low potency drugs – weakly block DA2 RSs, strong antiACh effects

fewer EPSEs, less risk for TD

severe antiACh effects (constipation, poor memory/concentration, dry mouth, urinary retention, worsened glaucoma, orthostatic hypotension; at higher doses --- delirium, tachycardia, bradycardia, blurred vision)

more sedation, more orthostatic hypotension

esp. in elderly *Ss*

e.g. thioridazine **(Mellaril)** chlorpromazine **(Thorazine)**
mesoridazine **(Serentil)**

which drug is given to which pt. is mostly a matter of which set of SEs *S* will tolerate better

like the antidepressants, may have to do trial&error approach

fortunately, there is a **large therapeutic index** for all these meds

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5. **SE: Motor Disturbances**

found in 70-85% of all pts. on neuroleptics

blockage of DA2 RSs in basal ganglia

note: NC pts. develop Parkinson's Disease when >80% of DA neurons have died

these motor disturbances are often called EPSEs or "Parkinson-like"

a. **Parkinsonian effects** (40% of all pts.)

rigidity & tremors (resting)

poverty of movement

difficulty initiating a movement/ending a movement

no (emotional) facial movements or gestures, stiff

slowness of movement (bradykinesia)

jerky handwriting

short, rotating head movements

become rigid & immobile as Sxs worsen ("frozen") except for stiff, shaking limbs

secondary to imbalance in DA & ACh (DA < ACh)

. give pt.an antiACh drug as well (Artane, Cogentin, Symmetrel)

. use an antipsychotic that blocks both DA & ACh

e.g. thioridazine (Mellaril)

. use a DA agonist(e.g.amantadine/Symmetrel,selegiline/Deprenyl)

esp. a problem in elderly pts. who have already lost some DA neurons

b. **Akathesia** (20% of all pts.)

compulsive restlessness, repetitive & purposeless movements

can look like anxiety but isn't

esp. in younger *Ss*

tx. w/ DA agonists or w/ ACh antagonists…why?

sometimes tx. with propranolol/Inderol (beta-blocker)

very unpleasant SE

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5. **SEs: Motor Disturbances** (cont.)

c. **Dystonias** (67% of all pts.)
sudden, jerky movements
usually seen shortly after start use of drug (w/i 4 days) or shortly after drug's dose is increased
continuous, involuntary writhings caused by widespread and sustained muscle contractions, spasms

e.g. "oculogyric crisis"

e.g. mouth puckers, tongue protrusion, inability to swallow, disrupted breathing movements (spasms in diaphragm), profuse sweating

also tx. with DA agonists or antiACh drugs
esp. in young males

d. **Akinesia**
reduced movements
tremors, shuffling gait/steps, stiff posture
muscle rigidity --- "catatonic" posture, "waxy flexibility"
socially withdrawn, appear "depressed" – makes difficult to Dx pt. truly depressed psychotic or "iatrogenic" effects from meds?
esp. w/ potent, low antiACh neuroleptics
e.g. haloperidol (Haldol), thiothixene (Navane)
is a reversible effect (when increase DA or decrease ACh or D/C antipsychotic…but psychotic Sxs return…

e. **Tardive Dyskinesia** (25% of adults, 12.5% of adolescents)
"late-appearing" Dyskinesia (>6 months after start of meds)
poorly coordinated movements
insidious onset of Sxs

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5. **SEs: Motor Disturbances** (cont.)

e. **Tardive Dyskinesia** (cont.)

"worm-like" movements of tongue, tongue thrusting/protrusion
darting tongue movements
puffing out of cheeks
eyelids flutter, upper lip trembles ("rabbiting")
head arches backward or turns to side
rocking, pelvic thrusting
fling or flail arms

esp. in older (> 50 – 70 years), and female pts.
more severe in pts. w/ - Sxs of schizophrenia

gets worse after antipsychotic drug is D/Cd, at least initially…why?
gets better if drug dose is increased…why?
what is underlying mechanism?... "**denervation supersensitivity**"

How to help with TD?

use lower doses to traditional antipsychotics
do not use these drugs, esp. in elderly females
use newer antipsychotics
D/C traditional antipsychotics at the very first sign of TD Sxs
may still be reversible early on

7. **SEs: Autonomic NS & Hormonal Imbalances**

occur because of blockage of DA2 RSs in hypothalamus
e.g. weight gain, constipation
e.g. faulty temperature regulation (including NMS)
e.g. sexual disturbances (esp. thioridazine/Mellaril)

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7. **SEs: Autonomic NS & Hormonal Imbalances** (cont.)

NMS = neuroleptic malignant syndrome

1 – 2.4% of pts. on neuroleptics, 14-30% of these die (renal failure)
high fever (108 degrees F.), sweating
confusion, muscle rigidity, tremors, depressed respiration, ANS hyper-reactivity, stupor, hypertension, increased heart rate
esp. w/ high potency neuroleptics (e.g. Prolixin)
esp. young adult males & non-schizophrenics

8. **SEs: AntiACh Effects**

typical anticholinergic syndrome
dry mouth, blurred vision (dilated pupils), constipation
decreased memory
increased intraocular pressure (worsens glaucoma)
urinary retention
esp. chlorpromazine/Thorazine

9. **SEs: AntiNE Effects**

typical antiadrenergic effects
lowered blood pressure, orthostatic hypotension (esp. in elderly)

10. **SEs: AntiH Effects**

antihistaminergic effects
sedation, weight gain, antiemetic effects

11. **Other SEs**

agranulocytosis (35% of these pts. die)
hepatitis and liver damage (esp. chlorpromazine/Thorazine)
photosensitivity (skin "sunburn", "night blindness")

note: **patient non-compliance with medication is almost entirely due to inability to tolerate the negative SEs of traditional antipsychotics**

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12. **<u>Other Uses of Traditional Antipsychotics</u>**

to reduce Sxs of **Tourette's Syndrome**
to reduce **nausea & vomiting** (e.g. in pt. on chemotherapy for cancer)
to reduce severe, continuous **hiccups**
to **sedate** pt. before surgery, or in an agitated pt.
to **delay ejaculation** (premature ejaculator)
to relieve severe **itching**
to reduce severe **manic symptoms** (while waiting for Li effects to start)
to reduce **withdrawal effects** (esp. hallucinations) & delirium tremens
to reduce **psychedelic hallucinations**

all of the above have been successfully treated by use of traditional phenothiazines