ANTIPSYCHOTICS: Atypical Drugs (p.1)

1. **Introduction**

the "atypical" antipsychotic drugs are defined as atypical because:
both dopamine & serotonin antagonists
low incidence of extrapyramidal symptoms (EPSEs)
good efficacy for treating the negative Sxs of psychosis

there were initially (in the 1960s) antipsychotics developed that were somewhat different from haloperidol (Haldol):
molindone (Moban)
loxapine (Loxitane)
pimozide (Orap) (introduced 1996)
introduced in the 1970s, but less widely used now
are chemically closer to the traditional antipsychotics than they are to the now named "atypicals"
but were noteworthy because interacted with 5HT systems as well as DA systems…had a "dual action" aspect

2. **True "Atypicals" (dual action antipsychotics)**

all were developed since 1989, starting with clozapine

a. clozapine (Clozaril)
introduced 1989
most closely resembles loxapine (Loxitane)
is more effective than the traditional antipsychotics
can be used to treat treatment-resistant *Ss*
effective in treating both + and – Sxs,
very few EPSEs
has less of a negative effect on cognitive abilities/executive functions than do traditional antipsychotics
esp. good for tx. of "disorganized schizophrenics"

so…why is it not used now more widely?
can --- **agranulocytosis** (reversible when D/C drug)

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2. **True "Atypicals"** (cont.)
   a. **clozapine (Clozaril)** (cont.)

pharmacokinetics:
taken PO, well absorbed
metabolized by the liver, 2 fairly inactive metabolites
½ life = 9-30 hours
SEs – sedation, wt. gain, constipation, urinary incontinence,

hypotension, esophagitis, seizures, drooling, and **NMS (**rare)

therapeutic window: 200-350 nanograms/milliLiter

dependence/withdrawal:
unpleasant w/d Sxs, so **must gradually taper off Clozaril or immediately substitute olanzapine (Zyprexa)**

delusion, hallucinations, hostility, paranoid reaction
nausea, vomiting, diarrhea
headache
restlessness, agitation, confusion
sweating

mechanisms of action:
low rate of DA2 binding (blockage)
higher rate of 5HT2 blockage
also decreases glutamate RS mRNA (via affecting a 2nd messenger system)

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2. **<u>True Atypicals</u>** (cont.)

b. **<u>risperidone (Risperdal)</u>**
introduced in 1993
is highly plasma protein bound
has an active metabolite
½ life of parent molecule = 3 hours; of active metabolite = 22 hours
is a **potent blocker of both DA2 and 5HT2 RSs**

end result of its actions is to **normalize GABA & NMDA systems in frontal lobes**

is as effective as clozapine/Clozaril at decreasing – Sxs
is not as effective as " / " at decreasing + Sxs

can be used to tx **autistics, pervasive developmental disorder**
can be used to tx **conduct disorder (decreases aggression, rage)**
can be used to tx **Tourette's Syndrome**

SEs: sedation, somnolence
agitation, anxiety, insomnia
headache
nausea
some wt. gain (not as bad as clozapine or olanzapine)
EPSEs (esp. a doses > 8mg/day; still < traditional antipsychotics)
NMS (rare)

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2. **True Atypicals** (cont.)

c. **olanzapine (Zyprexa)**

introduced in 1996
structurally similar to clozapine
blocks several RSs, including DA2 and5HT2
blocks DA2 RS as much as risperidone, but **few EPSEs**

good for treating both + and – Sxs

pharmacokinetics:
PO, well absorbed
metabolized by liver
½ life = 27-38 hours

effective in treating **bipolar pts, aggressive psychotic pts, & pervasive developmental disorder**

SEs: sedation, somnolence
dizziness
orthostatic hypotension
dry mouth
wt. gain (< clozapine, > riperidone)
no agranulocytosis, rare NMS

d. **sertindole/Serlect**

introduced in 1997
binds to (blocks): 5HT2 > NEalpha#1 > DA2 RSs
decreases both + and – Sxs
low incidence of EPSEs
no blocking of H1 RS --- so what SE is not seen?
½ life = 60-95 hours
serious SE: can **prolong Q-T interval** --- severe EKG arrhythmias

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2. **True Atypicals** (cont.)

e. **quetiapine (Seroquel)**

introduced 1999
½ life = 7 hours
blocks 5HT2 > DA2 (similar to clozapine)
also blocks **NMDA/glutamate RSs** (also similar to clozapine)
comparable to traditional antipsychotics in decreasing + Sxs
less consistent in decreasing – Sxs
few EPSEs

f. **ziprasidone (Zeldox)**

introduced 2000
as effective as traditional antipsychotics, esp. for tx of + Sxs
low risk of EPSEs
½ life = 6 hours
unique effects: blocks 5HT2 & DA2
agonist at 5HT1A RS (similar to buspirone/BuSpar)
little wt. gain
metabolized to inactive forms
can be used to tx Tourette's Syndrome

g. **amisulpride (Solian)**

introduced 2001
is a "dual action" drug that **blocks two separate DA RSs**
blocks DA2 postsynaptic RS in limbic system but not in basal ganglia! implications…
does so only at **higher** doses
effective for tx of **psychosis** (decreases both + and – Sxs)

also blocks the DA3 presynaptic autoreceptors ---?
does so at **lower doses**
effective for tx of **dysthymia & depression**
does not bind to the 5HT2 RSs…unusual

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2. **True Atypicals** (cont.)

g. **amisulpride (Solian)** (cont.)

½ life = 12 – 16 hours (child – adult)
weakly metabolized by liver, two inactive metabolites

SEs: insomnia, anxiety, agitation (5-10%)
somnolence, constipation, nausea, vomiting, dry mouth (2%)

hypotension & sedation in elderly

NMS (rare)

can affect endocrine system -"hyperprolactinaemia"(females)
--- galactorrhoea, gynaecomastia, breast pain, amenorroea

3. **Summary**

both the "traditional" and the newer "atypical" antipsychotic drugs block the DA2 RS and are effective in decreasing + Sxs
the newer "atypical" drugs, which also block 5HT2 RS, have much less risk of EPSEs and are much more effective in decreasing – Sxs

newer "atypical" drugs also have less of a harmful effect on cognition & memory than "traditional" antipsychotics, but the former drugs do increase weight and may be sedating

for children, do not what to risk agranulocytosis…but "atypical" drugs do offer other benefits, so use them (except clozapine) to treat schizophrenia, pervasive developmental disorder (autism), and aggression/conduct disorder

for elderly, use "atypicals" because do not present much of a risk of EPSEs, including tardive dyskinesia
for sedation or "calming" use neither traditional or atypicals
use sed-hypo drugs instead (BZDs)