ANTIPSYCHOTICS: Atypical Drugs

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)
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 2\textsuperscript{nd} messenger system)
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2. True Atypicals (cont.)

b. **risperidone (Risperdal)**
   - 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 and 5HT2
   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
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.)
      \[ \frac{1}{2} \text{life} = 12 \sim 16 \text{hours (child – adult)} \]
      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, amenorrhoea

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)