PSYCHOPHARMACOLOGY ESSENTIAL PSYCHOPHARMACOLOGY: 2011 TREATMENT OF SCHIZOPHRENIA

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WHAT IS AN ATYPICAL ANTIPSYCHOTIC DRUG?

• All antipsychotic drugs block D₂ postsynaptic receptors
  – Conventional antipsychotics do not have significant effect on serotonin 5HT₂A/₂C receptors;
  – Blockade of postsynaptic 5HT₂A/₂C is greater than blockade of D₂ for atypicals but not for conventional antipsychotics

• Blockade of 5HT₂A/₂C receptors enhances presynaptic dopamine release in the striatum
ARE THERE THERAPEUTIC DIFFERENCES AMONG ANTIPSYCHOTIC DRUGS?

• Leucht meta-analysis: Olanzapine > risperidone = aripiprazole > quetiapine, ziprasidone, but only for positive symptoms
  – Clozapine not different from olanzapine, quetiapine risperidone or ziprasidone

• Cochrane meta-analysis: no significant difference among 2nd generation antipsychotics

Leucht 2009; AJP 166:152; (Kane, 1990; Wahlbeck, 1999; Chakos, 2001; Kane 2001)(Bollini, 1994; Geddes, 2000)
OTHER DIFFERENCES: ELIMINATION HALF-LIFE

- Asenapine: 24 hours
- Aripiprazole: 72
- Clozapine: 16
- Haloperidol: 20
- Olanzapine: 30
- Perphenazine: 8-12
- Quetiapine: 7
- Risperidone: 3
- Ziprasidone: 7
CATIE: CONCLUSIONS

• Phase I: olanzapine advantage in longer time to discontinuation partially (but not completely) offset by frequency of metabolic syndrome:

• Phase II:
  – Clozapine had clear advantage over all others in longer time to discontinuation
  – Ziprasidone had advantage in not producing metabolic syndrome
  – Risperdal was best tolerated overall

Citrome, 2006
CUtLASS STUDY

- British multi-site study of chronic patients over 1 year
- Compared FGAs and SGAs at therapeutic doses
- Primary outcome: Quality of Life Scale scores
- Results confirmed CATIE conclusions
Differences in Quality of Life Scale (QLS) scores at 1 year between patients taking first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs)

Differences Between FGAs and SGAs in Quality of Life at 1 Year

Estimate of Difference in QLS After Imputation of Missing Data, With 95% CI for Difference

Hypothesis of 5-Point Advantage for SGAs Excluded

Observed

Favors FGAs --- Equivalence --- Favors SGAs

Difference in QLS Scores

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CONCLUSIONS ABOUT CLOZAPINE

• Probably the most effective antipsychotic (but not by much)
• Probably takes months for significant response to emerge
• Metabolized by CYP450 1A2 and 2D6
  – Polymorphisms of 1A2 increase blood levels of parent compound and desmethyl metabolite and increase risk of elevated lipids and insulin resistance
FIRST GENERATION VS. SECOND GENERATION ANTIPSYCHOTICS FOR FIRST-EPISODE SCHIZOPHRENIA

• No difference between haloperidol and risperidone for:
  – Therapeutic effect
  – Drop out rate
  – Quality of life

• Slightly more EPS with haloperidol

IS ARIPIPRAZOLE DIFFERENT?

• Is a partial dopamine D$_2$ agonist:
  – Acts as an antagonist in hyperdopaminergic states
  – Acts as an agonist in hypodopaminergic states

• Unlike other atypicals, it has a low 5-HT$_2$ : D$_2$ affinity ratio and a high D$_2$ affinity
  – Produce 80-90% D$_2$ occupancy without producing EPS
  – Suggests it produces a much lower level of functional antagonism of D$_2$ than full antagonists

• Partial agonism at 5-HT$_{1A}$ may also contribute to low EPS
CATIE RESULTS-IX, SIDE EFFECTS

- Weight gain greatest in olanzapine group
- Larger proportion (30%) of patients in olanzapine group gained 7% or more of their baseline body weight than the other groups (7-16%).
- Risperidone associated with increased prolactin levels
- No widening of QT interval or development of cataracts
- EPS rates the same in all groups
CATIE STUDY: METABOLIC SYNDROME

• 42.7% of the CATIE sample had the metabolic syndrome at baseline which is nearly twice the prevalence in the general population ages 40-49 years.
• 11% had diabetes and 45.3% of these were not receiving treatment;
• Of the 32% of patients with hyperlipidemia, 89.4% were not receiving a statin;
• Of the 38% of patients with hypertension, 62.4% were not receiving any antihypertensive
Mechanisms of Weight Gain

• Receptor affinity may be associated with weight gain: 5-HT$_{2c}$, H$_1$, α$_1$
  - 5HT$_{2c}$ polymorphism may increase vulnerability to developing the metabolic syndrome

• Compounds that antagonize these receptors greater than their affinity for D2 are linked with increased weight

• Histamine receptors increase weight; H2 antagonists (cimetidine) decrease weight
TREATMENT FOR METABOLIC SYNDROME?

- Best treatment is prevention
  - Dietary and exercise recommendations
  - Low doses of SGAs when possible
- Switch to aripiprazole* or ziprasidone
- Switch to FGA: molindone** (associated with weight loss)*
- Minimize use of other weight-gaining medications (e.g. valproate)

TREATING WEIGHT GAIN

- Add aripiprazole\(^1\)
  - May decrease weight gain with olanzapine
- Add topiramate\(^2\)
  - Small weight gains reported
- Add metformin\(^3\)
  - May prevent weight gain
- Switch to orally disintegrating olanzapine?
  - May reverse olanzapine weight gain from oral preparations

METFORMIN FOR ANTIPSYCHOTIC WEIGHT GAIN

- Attenuates olanzapine weight gain
- Comparison of treatments (12 weeks):
  - Life style change alone: 3 lb weight loss
  - Metformin alone: 7 lb weight loss
  - Metformin + life style change: 10 lb loss
  - Placebo: 7 lb weight gain
- Side effects:
  - Decreased absorption of B_{12} and folic acid
  - Lactic acidosis (rare)

Wu; AJP 2008; 165:352
OTHER SERIOUS CONSEQUENCES OF ATYPICAL ANTIPSYCHOTICS

- Myocarditis (clozapine)
- Interstitial nephritis (clozapine)
- Pancreatitis (olanzapine)
- Somnambulism (olanzapine)
- Periodic leg movements and restless legs (olanzapine)
ANTIPSYCHOTICS AND VENOUS EMBOLISISM

• Antipsychotics may increase the risk of venous thromboembolism
  – Over 2 year period, there was a 32% increased risk compared with non-users
  – Doubling of risk during first 3 months of treatment with antipsychotics
  – Second generation antipsychotics were associated with greater risk than first generation drugs.

• Overall risk, however, is low (4/100,000)

  Parker 2010; BMJ 341:4245
DO ANTIPSYCHOTICS DECREASE BRAIN VOLUME?

- All antipsychotics decrease gray and white matter (total brain volumes) over 2 years or more
- Mechanism is not clear; this is an association, not a clear cause/effect
- Conclusion: use lowest doses necessary to control symptoms

Ho 2011; Arch Gen Psychiat 68:128
Atypical Neuroleptics and Prolactin

- Prolactin increase due to $D_2$ receptor blockade
- 9-OH metabolite of risperidone has high affinity for $D_2$ receptor
- Increased prolactin occurs when risperidone added to clozapine
2nd GENERATION ANTIPSYCHOTICS: CARDIAC RISKS

• Cardiac side effects:
  – Risk for coronary heart disease is increased with olanzapine and quetiapine
  – Risk for coronary heart disease is decreased with risperidone, ziprasidone (and perphenazine)

Daumit 2008; SchizRes 105:175
Figure 4. Study 054: Mean Change in QTc From Baseline to Steady State

Data from the FDA Psychopharmacological Drugs Advisory Committee.12
OLANZAPINE BLOOD LEVELS

• Are threshold levels:
  – Optimum therapeutic range is 20-39ng/ml
• 2/3 of patients require more than a daily dose of 20 mg to enter this therapeutic range
• In general, women and individuals under age 18 require lower doses to reach the therapeutic plasma level range

Patel, 2011; J Clin Psychopharm
OLANZAPINE PAMOATE

- Effective long-acting olanzapine
- Injected q 2-4 weeks into buttock
- Can cause post-injection delerium

Citrome; IntJ ClinPract; 2008
USING CONSTA

- Administer 25-50 mg every 2 weeks
  - 25 mg = 2 mg orally
  - 25 mg may not be sufficiently therapeutic
- Gluteal injection (caution about patient misinterpreting injection as sexual or homosexual attack)
  - Injection sometimes hurts; patient should be warned
- Takes 4-6 weeks to reach steady-state blood levels after last injection
- Elimination complete after 7-8 weeks after last injection
- Continue oral antipsychotic for 3-4 weeks when starting Consta
- Recent report of case of priapism

Taylor D Acta Psychiatr Scand 2006;114:1
PALIPERIDONE

• 9-OH metabolite of risperidone
• Low lipid solubility: low bioavailability
• Dose: starting dose: 6mg in am
  – 3 mg dose increases/week
  – Maximum dose: 12mg/d
• Side effects: tachycardia, headache, somnolence, EPS, increased QTc interval
USING PALIPERIDONE ER

• Daily Dose: 3-12 mg
• Effective for positive and negative symptoms
• Effective for acute, severe symptoms
• Most common adverse events:
  – Headache, agitation, insomnia
NORQUETIAPINE

• Is the major active metabolite of quetiapine
  – Quetiapine is metabolized by CYP 450 3A4
• Blocks norepinephrine uptake transporter protein: increases synaptic norepinephrine
• Efficacy in schizophrenia, mania, bipolar depression, major depression
HIGH DOSES FOR TREATMENT RESISTANT SCHIZOPHRENIA

• 6-month, double blind study:
  – Clozapine mean dose 564mg/d
  – Olanzapine mean dose 34 mg/d
• Both produced significant reduction in symptoms; both equally effective
• Greater weight gain and increased BMI for olanzapine group
• Clozapine has lower discontinuation rate than other SGA’s

Meltzer: J Clin Psychiat 2008;69:274
Taylor: ibid:240
RATE OF RESPONSE TO ANTIPSYCHOTIC DRUGS

- Response may be seen earlier than previously believed:
  - Response may appear within the first week of treatment
  - Improvement at weeks 1 and 2 predict treatment response at week 6
  - Early non-improvement at weeks 1 and 2 is predictive of later non-response
GENETIC INFORMATION WITH POTENTIAL CLINICAL USEFULNESS

• Catechol-o-Methyltransferase polymorphism may predict drug response:
  – Met-met allele predicts better negative symptoms response
  – Met-met allele predicts better cognitive improvement with SGAs

• Polymorphisms of D₃ receptor may predict tardive dyskinesia and EPS

• Polymorphism of 5HT₂c may predict weight gain with antipsychotics

  Weinberger; Bartolino 2007; Kennedy, 2007
NEW GLUTAMATE APPROACHES TO TREATMENT: AMPA

• AMPA is activated which opens NMDA ionophore;
  – Presumably this enhances glutamate neurotransmission in the prefrontal cortex and would benefit schizophrenia

• AMPAkines have been disappointing as therapeutic enhancement of NMDA receptor function in schizophrenia
NEW GLUTAMATE APPROACHES TO TREATMENT: METABOTROPIC RECEPTORS

- Altering function of metabotropic glutamate receptors may have therapeutic properties:
  - mGlu2/3 decrease presynaptic release of glutamate at NMDA synapse;
  - mGlu5 (pre- and postsynaptic) may also influence NMDA function

Mutel, 2005
CHOLINESTERASE INHIBITORS

• Aricept; Razadyne:

• Given to enhance cognitive function
  – No sustained or significant benefit for cognitive deficits in schizophrenia
ANTIPSYCHOTIC DRUG TREATMENT

POLYPHARMACY

• Multiple antipsychotics are now commonly used for treatment resistant and recurrent schizophrenia
  – May be useful to use sedating drug at bed time and non-sedating drug in morning
  – Otherwise, no evidence that 2 drugs are more therapeutic than one drug
    • Side effects are increased
ANTIPSYCHOTIC DRUG TREATMENT POLYPHARMACY-II

• Addition of aripiprazole to clozapine (or olanzapine) may decrease weight gain and development of metabolic syndrome
  – May improve therapeutic outcome modestly
  – May cause agitation and manic-like symptoms
COMBINING ATYPICALS

• Most (but not all) evidence suggests that 2 atypicals are not better than one
• Combination produces more side effects
• Combination is more expensive

Honer, 2006
Baseline mean (SE) PANSS total scores: adjunctive placebo, 75.9 (1.0); adjunctive aripiprazole, 74.3 (1.0).

Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.
COMBINING 2 ATYPICALS IS NOT MORE EFFECTIVE THAN ONE DRUG

Honer, 2006
COMBINING ATYPICALS WITH CONVENTIONAL ANTIPSYCHOTICS

• Theory: adding a strong D₂ blocking drug to an atypical will improve positive symptoms;
• In most cases, more EPS side effects result
• Some patients with predominant positive symptoms do better on conventional antipsychotic monotherapy
COMBINING ANTIPSYCHOTICS WITH OTHER DRUGS

• Lamotrigine:
  – 5 studies: no significant differences in outcome
  – Improvement in PANSS scores “not robust”;
  – May reduce alcohol craving in patients with schizophrenia

• Antidepressants for negative symptoms:
  – Suggestion that negative symptoms benefit

• Cognitive enhancers not reliably effective

Cochrane Database Syst Rev
2006; Kalyoncu A: J Psychopharm 2005:
19:301; Rummel C; 2005; 80:85
SWITCHING ANTIPSYCHOTICS?

• Switching antipsychotics to improve therapeutic outcome usually does not work

• Switching antipsychotics to improve side effects is important and effective
  – Decrease risk of metabolic syndrome (e.g. by switching to aripiprazole)
    • Start with low dose and gradually increase
    • Slowly discontinue previous antipsychotic over 1 month period at same time

Stroup 2011; Am J Psychiat 168:947
NEW DRUGS

• Asenapine
  – Antipsychotic with serotonin and noradrenergic properties (like clozapine)
  – No anticholinergic properties
  – Strong blocker of $5\text{HT}_{2A/2C}$

• Iloperidone
  – low weight gain, no diabetes, low extrapyramidal symptoms, no hyperprolactinemia;
  – prolongs QTc interval
ASENAPINE (SAPHRIS)

- **Sublingual** administration only
  - Is immediate release
  - Therapeutic plasma levels reached in 20-30 minutes
  - Best daily dose: 5mg BID

- **Side effects** like other atypical antipsychotics
  - May have less metabolic syndrome
  - No effect on QT<sub>C</sub> interval
  - Mild oral hypoesthesia (2%)
ASENAPINE FOR SCHIZOPHRENIA
ILOPERIDONE (FANAPT)

- Atypical antipsychotic
  - $D_2/5HT_{2A}$ antagonist
  - $5HT_{2C}$ antagonist (weight gain, metabolic syndrome)
  - $\alpha_1$ antagonist (orthostatic hypotension)
  - Prolongs QTc
  - Raises prolactin

- Common side effects
  - Insomnia, anxiety, dizziness, nasal congestion
  - May aggravate schizophrenia
LURASIDONE (Latuda)

- New atypical antipsychotic with profile like other atypicals
  - Similar side effect profile
    - Low weight gain, EPS
    - Can cause dizziness ($\alpha_1$ antagonist)
- Antagonizes 5HT$_7$ receptors
  - May improve cognition
  - May have antidepressant properties
- Metabolized by CYP 450 3A/4
- Dose: 40-80mg/d with food, once daily
LURASIDONE (LATUDA)-II

- Effective for positive and negative symptoms of schizophrenia
- Causes akathisia
- Mild metabolic syndrome
- Sedating
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ROLE OF ANTIDEPRESSANTS IN TREATING SCHIZOPHRENIA

• Early use of TCA’s added to first-generation antipsychotics:
  – Unreliable and modest improvement in affective symptoms; no improvement in schizophrenia

• Antidepressants given to adolescents in pre-psychotic phase may prevent appearance of full syndrome

1Siris:
AUGMENTATION FOR SCHIZOPHRENIA- I

• Lithium:
  – Traditionally added to neuroleptics: modest augmentation efficacy but no monotherapy effect\(^1\)

• Carbamazepine:
  – Modest efficacy\(^2\)

• Oxcarbazepine augmentation of neuroleptics decreased agitation and paranoia\(^3\)

• Valproate:
  – Augments haloperidol

\(^1\) Shopsin, 1971, \(^2\) Mueller 1984; Gonsalves 1985 \(^3\) Velikonja, 1984
AUGMENTATION FOR SCHIZOPHRENIA - II

• Lamotrigine:
  – Significantly reduces ketamine-induced positive and negative symptoms\(^1\)

• Inhibits excess glutamate release\(^1\)
  – Suggests that glutamate hyperfunction in schizophrenia may have presynaptic basis
  – Augments clozapine: significant decrease in BPRS after 4 weeks; all patients show a dramatic reduction in BPRS by week 24\(^2\)

• Increases Clozapine blood levels\(^3\)

\(^1\)Anand, 2000  \(^2\)Dersun, 1999,2000  \(^3\)Kossen, 2001
ω-3 FATTY ACIDS FOR PSYCHOSIS

• 12 month study
  – Study of patients at high risk of becoming psychotic (subthreshold psychosis in adolescents and young adults)
  – 1.2 g/d ω-3 fatty PUFA or placebo

• Treated subjects had fewer transitions to psychosis:
  – Reduced positive symptoms
  – Improved overall functioning

Amminger 2010, Arch Gen Psychiatry 67:146