

Atypical Antipsychotics

Practical tips to compare agents

Colette Raymond, Pharm D



Objectives



- ◆ Define atypical antipsychotic
- ◆ Review mechanism action
- ◆ Review pharmacology of atypical agents
- ◆ Review comparative efficacy
- ◆ Review adverse effects
 - Movement disorders, Cardiovascular, Anticholinergic, Sexual, Weight gain, Hyperglycemia, TD, NMS
- ◆ Review unique features of each atypical agent
- ◆ Discuss when to use one agent over another

Uses for atypical antipsychotics

- ◆ Schizophrenia
- ◆ Shizoaffective disorder
- ◆ Mood disorder with psychosis
- ◆ Dementia with psychosis / aggression
- ◆ Delerium
- ◆ Delusional disorder
- ◆ Psychosis secondary to a medical condition
- ◆ Developmental disability with psychosis
- ◆ Tourette's
- ◆ Intractable hiccups
- ◆ Bipolar mania
- ◆ Augmentation in major depression

Atypical Antipsychotic

– the ideal agent

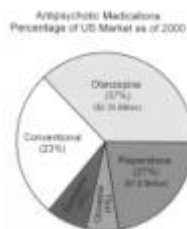
- ◆ 5HT 2A and D2 antagonist
- ◆ Minimal EPS
- ◆ No TD
- ◆ Minimal prolactin elevation
- ◆ Treat negative symptoms
- ◆ Treat refractory symptoms

Clozapine is the only agent that meets these criteria!

Atypical Antipsychotics



- ◆ Clozapine
- ◆ Risperidone
- ◆ Olanzapine
- ◆ Quetiapine
- ◆ Ziprasidone



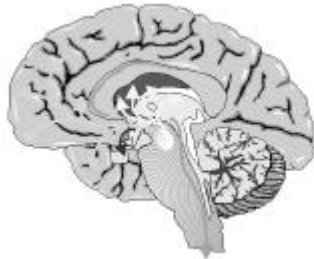
Mechanism of action of atypicals

- ◆ Dopamine blockade
 - Less D2 blockade than typicals, more D4
 - Movement disorders
 - Prolactin elevation
- ◆ Serotonin blockade
 - Increases dopamine in areas where deficient
 - Unique to atypicals
 - Decrease negative symptoms?



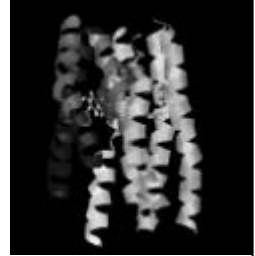
Dopamine pathways

- ◆ Mesolimbic
 - Overactivity + sx
- ◆ Mesocortical
 - Decreased activity - sx
 - Atypicals ↑ dopamine
- ◆ Nigrostriatal
 - Movement
 - Atypicals ↑ dopamine
- ◆ Tubuloinfundibular
 - Prolactin secretion

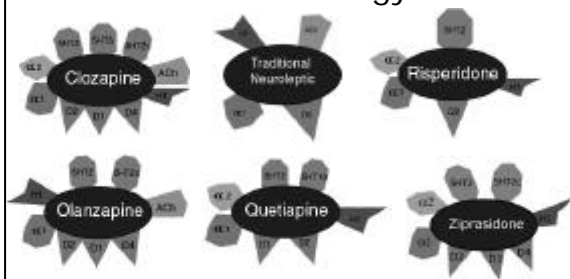


Mechanism of action of atypicals

- ◆ Histamine blockade
 - Sedation
 - Weight gain
- ◆ Muscarinic blockade
 - Constipation
 - Dry mouth, blurred vision
 - Delirium
- ◆ Alpha blockade
 - Hypotension, tachycardia
 - Dizziness



Pharmacology



<http://www.gcwweb.com/PsychosisDSS/clinical/pharar.html>

Efficacy of atypicals

- ◆ Efficacy
 - What is measured in clinical trials
 - Ideal circumstances
 - Non refractory patients
- ◆ Effectiveness
 - What happens in real life
- ◆ RCTs provide us with the best evidence of the effectiveness of interventions, but:
 - Cross trial comparisons DIFFICULT
 - HIGH dropout rates (50%) in psychiatry



How do atypical agents compare to placebo and traditional agents?

Efficacy of atypicals

	<u>vs. Placebo</u>	<u>vs. Typical</u>
Clozapine	>	>
Risperidone	>	>
Olanzapine	>	>
Quetiapine	>	=



How do these agents compare to one another?

◆ "We need more head to head trials..."

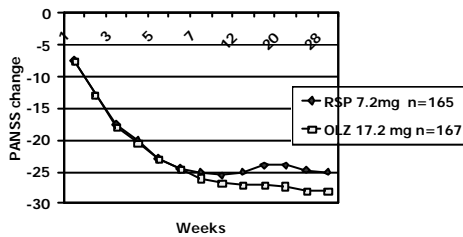
Positive and Negative Syndrome Scale

Positive Scale Max 49 pts	Negative Scale Max 49 pts	General Psychological Scale: Max 112 pts	
Delusions	Blunted affect	Somatic concern	Unusual thought content
Disorganization	Emotional withdrawal	Anxiety	Disorientation
Hallucinatory behavior	Poor rapport	Guilt feelings	Poor attention
Excitement	Social withdrawal	Tension	Lack of judgment and insight
Grandiosity	Abstract thinking	Mannerisms and posturing	Disturbance of volition
Suspiciousness	Lack of spontaneity	Depression	Impulse control
Hostility	Stereotyped thinking	Motor retardation	Preoccupation
		Uncooperative	Active social avoidance

Olanzapine vs. Risperidone

Tran, 1997

48% dropouts

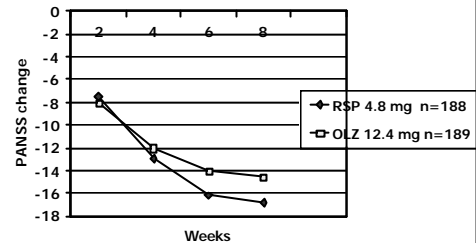


Change in PANSS total, positive, negative and general scores NSS
% pts to achieve 40% decrease in PANSS 37% O vs. 27% R (p<0.05)

Olanzapine vs. Risperidone

Conley, 2001

38% dropouts



Change in PANSS total, negative, disorganized thoughts, CGI NSS
PANSS positive symptoms RSP > OLZ p<0.05
% pts to achieve 20% decrease in PANSS NSS

Olanzapine vs. Risperidone

(Randomized controlled trials)

Study	Dose (mg/d)	Efficacy	Toxicity
Tran N=339 28 wks	O : 17.2 R : 7.2	O > R Total PANSS 7.5 pts (210 pt scale) p<0.05	R > O EPS RR 1.67 NNH 8
Thomas N=62 30 wks	O : 10-20 R : 4-8	NSS	R < O wt gain (NSS)
Purdon N=65 54 wks	O : 11 R : 6	NSS	R < O wt gain
Conley N=377 8 wks	O : 12.4 R : 4.8	R > O PANSS + and anxiety scales p<0.05	R < O wt gain R 3.4 lbs O 7.2 lbs p<0.001

Adverse Effects

	Tran, 1997 O : 17.2 R : 7.2 N=339 28 wks	Conley, 2001 O : 12.4 R : 4.8 N=377 8 wks
Weight Gain	4.1 kg OLZ, 2.3 kg RSP (p<0.05)	3.4 lbs OLZ, 7.2 lbs OLZ (p<0.05) 3.7% ↑ 12% RSP, 27% OLZ
EPS	31% RSP, 19% OLZ (p<0.05) Dystonia 6% RSP, 2% OLZ (p<0.05) PK 19% RSP, 10% OLZ (p<0.05) Rating scale RSP > OLZ (p<0.05)	24% RSP, 20% OLZ (NSS) Rating scale NSS Ach 32% RSP, 28% OLZ (NSS)
Others	Salivation, abnormal ejaculation, nausea, tachycardia RSP > OLZ (p<0.05) ↑ AST/ALT, ↓ WBC OLZ > RSP	Dry mouth: 11% RSP, 22% OLZ

Conclusions – comparative trials

- ◆ Dose matters!
- ◆ Risperidone may be better at low doses, olanzapine may be better at higher doses
- ◆ Sponsorship matters!
- ◆ Independent replication required for a tie breaker



Stahl, 1999

Adverse effects

- ◆ Movement disorders
- ◆ Cardiovascular
- ◆ Anticholinergic
- ◆ Sexual
- ◆ Weight gain
- ◆ Hyperglycemia
- ◆ *Cross-trial comparisons*
 - *Subject to flaws!*



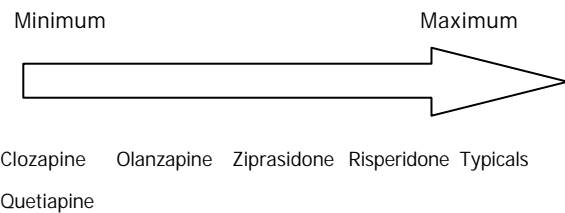
Less EPS with atypicals

- ◆ Preferential dopamine blockade in meso-cortico-limbic (not nigrostriatal) pathway
- ◆ 5HT blockade (increases dopamine)
- ◆ Ratio of 5HT to dopamine blockade high
- ◆ Low D2 blockade
- ◆ "Loose" D2 binding
- ◆ Anticholinergic effects
- ◆ Antihistaminic effects



Relative EPS

There are studies where ALL atypicals have EPS equal to placebo!



Caroff, 2002

Adverse effects - orthostatic hypotension

- ◆ Anticholinergic and alpha effects
- ◆ Common with initiation of agents and rapid titration
- ◆ Management
 - Get up slowly
 - Monitor sitting and standing BP




Relative orthostatic hypotension


- ◆ Related to dose titration
- ◆ Tolerance develops
- ◆ All agents can cause
 - 1-15% in studies
- ◆ Clozapine appears to be the worst
- ◆ No obvious difference in other agents
 - OLZ < QTP < RSP



Adverse effects - cardiac

- ◆ QTc interval prolongation
- ◆ Sertindole (off the market) 
- ◆ Cases with ziprasidone in some clinical trials (high dose)
 - FDA study zip > quet > risp > olanz > hal
 - No “black box warning” for ziprasidone
 - No cases of tdp to date
- ◆ Cases of prolonged QTc with risperidone

Adverse effects - anticholinergic

- ◆ Constipation
 - Reports of fatal bowel obstruction with clozapine
 - Awareness (pt and caregivers!)
 - Fluid, fibre, laxatives, stool softeners
 - ◆ Urinary retention
 - ◆ Blurred vision
 - ◆ Tachycardia/orthostasis
 - ◆ Delirium
 - ◆ Memory impairment
- 


Relative anticholinergic effects

- ◆ All agents can cause anticholinergic effects
 - Constipation
 - Clozapine – can be severe!
 - ◆ Risperidone > olanzapine blurred vision
 - ◆ Olanzapine > risperidone dry mouth
 - ◆ Olanzapine may be better tolerated than others (vs haloperidol)
- Stanniland, 2000


Adverse effects - sexual

- ◆ Multiple mechanisms
 - Serotonin blockade
 - Dopamine blockade (impaired erection, orgasm)
 - Norepinephrine blockade (reduced intensity)
 - Anticholinergic (impaired erection)
 - Antihistamine (impaired erection, libido)
- ◆ Reduce dose
- ◆ Switch
- ◆ Treatment:
 - Sildenafil, yohimbine

Adverse effects - sexual

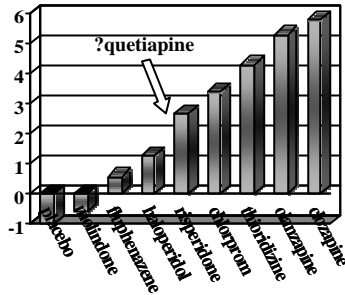
- ◆ Prolactin elevation
 - Risperidone – same elevation as typicals
 - Association b/w prolactin and gynecomastia or galactorrhea is ?????
 - Long term consequences (ex osteoporosis) not studied formally
 - ◆ Caution when switch from typical to olanzapine or quetiapine
 - Decrease prolactin may increase sexual function
 - Cases of unplanned pregnancy
- 

Adverse effects – weight gain

- ◆ Multiple mechanisms
 - Increased calorie consumption
 - Decreased calorie use
 - Genetic component
 - Dopamine blockade
 - Noradrenergic blockade
 - Histamine blockade
 - Serotonin blockade
 - Glucose and insulin dysregulation
 - ◆ Greatest increase in 1st year
- 

Adverse effects – weight gain

Mean wt gain after 10 wks



Allison, 1999

Weight gain – alternatives

- ◆ Lifestyle, lifestyle, lifestyle!
- ◆ Topiramate
 - Little published data
 - CNS side effects
- ◆ Stimulants some effect
 - Risk of psychosis
- ◆ Amantadine
- ◆ Antihistamine
 - Ex. Nizatadine 300 mg bid
- ◆ Many agents (ex. fluoxetine) not effective
- ◆ Newer agents (ziprasidone) minimal wt gain



Adverse effects - hyperglycemia

- ◆ Increased risk of DM in schizophrenia
- ◆ Cases of DM, DKA:
 - Clozapine
 - Olanzapine (Koro, 2002)
 - Other atypicals
- ◆ Hyperglycemia
 - Cases with all atypicals
- ◆ Mechanism unknown
 - Insulin resistance?
 - Decreased insulin sensitivity?
 - Weight gain?



Lindenmayer, 2001

Adverse effects TD

- ◆ Less TD than typicals
 - Suppressive effect
 - Passive improvement - removal of offending drug
 - 1 yr risk TD hal = 7.4%, olanz 0.52% (Beasley, 1999)
- ◆ Cases of all atypicals (even clozapine!) causing TD (0 data ziprasidone)
- ◆ Clozapine used to Rx TD
- ◆ Cases of olanzapine to Rx TD

Caroff, 2002



Adverse Effects NMS

- ◆ Neuroleptic malignant syndrome
 - Administration of neuroleptic
 - Hyperthermia (> 38°C)
 - Muscle rigidity
 - Five of the following: mental status change, tremor, tachycardia, incontinence, labile blood pressure, metabolic acidosis, tachypnea/hypoxia, CPK elevation, diaphoresis/sialorrhea leukocytosis
 - Exclusion of other central and systemic causes of hyperthermia
- ◆ Case reports with atypical neuroleptics
- ◆ Medical emergency
- ◆ Treatment: d/c antipsychotics, supportive care, dopamine agonists (bromocriptine, amantadine, dantrolene)

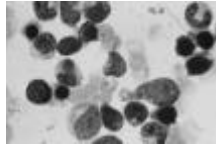


Cost comparison

Drug	Dose	1 month
Clozapine	400 mg/d	\$460
Olanzapine	15 mg/d	\$313
Risperidone	6 mg/d	\$160
Quetiapine	300 mg bid	\$240

Clozapine

- ◆ Sedation – start low, go slow!
- ◆ Anticholinergic effects
 - Orthostasis
 - Constipation!
- ◆ Hypersalivation
 - Not related to salivary flow
 - Towel, anticholinergic
- ◆ WBC monitoring 0.3% agranulocytosis
- ◆ Seizure risk
 - Dose related 4.4% > 600 mg/d
- ◆ Reserved for refractory patients



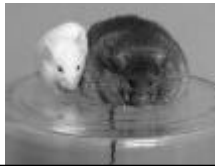
Risperidone

- ◆ Well established efficacy and safety
- ◆ Most EPS (> 6 mg/d)
- ◆ Favourable weight gain
- ◆ Elevates prolactin
 - significance?
- ◆ Cheapest
- ◆ Formulation
 - Liquid
 - Long acting (4 wk) depot coming soon



Olanzapine

- ◆ Well established efficacy/safety
- ◆ Weight gain
 - 50% gained >5 kg or more (Jones, 2001)
- ◆ Some sedation
- ◆ Transient prolactin increase
- ◆ Diabetes cases, DKA
- ◆ Formulation
 - Wafer
 - IM coming soon
 - Splitting tablets...caution



Quetiapine

- ◆ Least efficacy data
 - No long term studies
 - Some studies < haloperidol
 - ??? prn use peak blood level 90 min (sedation)
- ◆ Few side effects
 - More wt gain than RSP
 - No EPS
 - No prolactin elevation
- ◆ Formulation
 - bid dosing
 - 25 mg, 100 mg, 200 mg, 300 mg tabs
- ◆ Rare adverse effects:
 - Increase LFTs, hypothyroidism, cataracts (dogs)



So when to choose one over the

other?

Scenario	Agent of choice	Less Favourable
History of EPS	Quetiapine Olanzapine	Risperidone
Non-compliance	Risp liquid Olanzapine wafer	Quetiapine Ziprasidone (bid)
Elevated prolactin	Olanzapine Quetiapine	Risperidone
Obesity	Ziprasidone Quetiapine	Olanzapine Clozapine
Diabetes	Risperidone Ziprasidone Quetiapine	Olanzapine

Risperidone