Psychosis, Agitation, and Antipsychotic Drugs

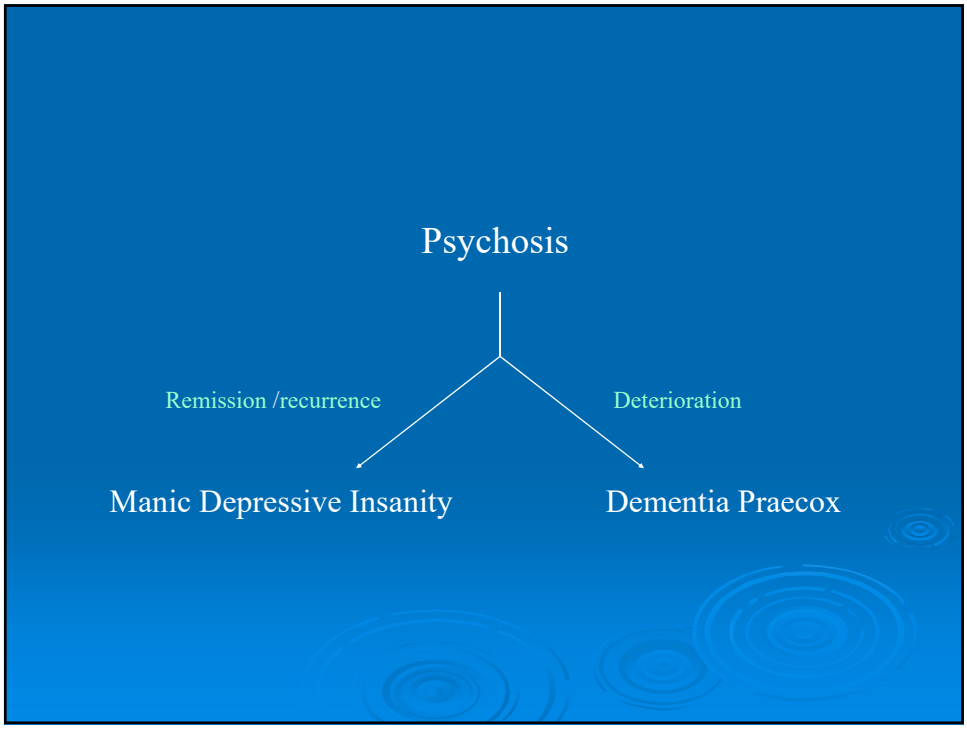
Steven L. Dubovsky, M.D.

Diagnostic Issues

Prophecy or Schizophrenia?

- I saw four living creatures….each one had four faces and each one four wings…the four of them had a man's face with a lion's face to the right…a bull's face on the left...also an eagle's face
- A voice said to me: "you must speak my words to them, regardless of whether they hear…You must lie upon your left side…for 390 days…And you must lie upon your right side…for 40 days…A day for a year [of the error of the house of Judah]…You must cut your hair and beard and divide the hair…A third you will burn…A third you will strike with the sword…and the last third you will scatter to the wind…You must take a few [hairs] and pitch them into the fire…From one a fire will go forth to all the house of Israel
- Differential diagnosis: prophecies come true

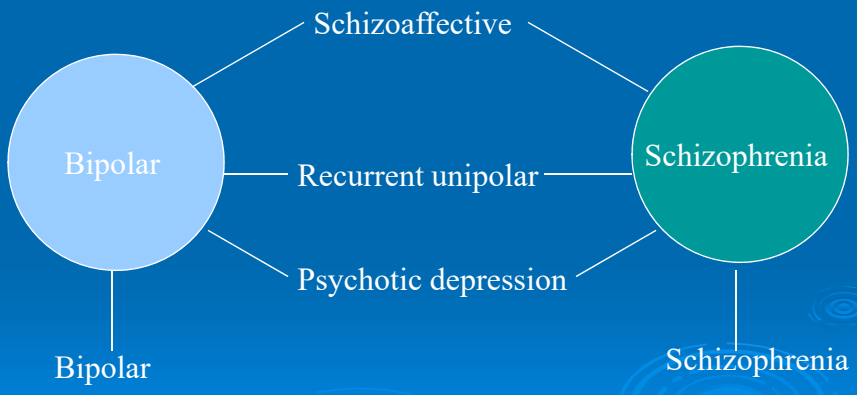
Ezekiel 1-5



It is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses [manic depressive insanity and dementia praecox], and this brings home the suspicion that our formulation of the problem may be incorrect.

Kraepelin, 1920

Familial Overlap



Structural Abnormalities in Bipolar and Schizophrenia

- Common genetically determined findings:
  - Decreased white matter volume
  - Thinner orbitofrontal cortex
  - Thinner medial temporal cortex
  - Thicker temporoparietal cortex
- Shared neurodevelopmental abnormalities suggest
  - Arrest of white matter development
  - Slowed development or increased shrinkage of orbitofrontal and medial temporal cortex
  - Impaired pruning of temporoparietal cortex
- Some common factors may be related to inherited neurodevelopmental/psychosis factor

HE Hulshoff et al: Arch Gen Psychiatry 2012;69:349

Prodromal Psychosis

- Attenuated psychotic symptoms (APS)
  - Mild delusions
  - Fleeting hallucinations
  - Bizarre thinking
  - Feeling possessed or dissolved
  - Idea that one's thoughts are not one's own
  - Mind control
- Common in general population
  - 57% of 4914 Israeli subjects over 24 years follow-up

Slide 1

N Werbeloff: Arch Gen Psychiatry 2012;69:467-475

Prodromal Psychosis

- Up to 1/3 of UHR patients convert in 3 years
  - Rate has decreased recently due to early treatment
- Higher APS scores associated with
  - 4.3 times increased risk of nonaffective psychosis
    - 5.4 times increased risk of schizophrenia
  - 2.2 times increased risk of hospitalization for other disorders
- Psychiatric hospitalization over 24 years
  - 0.5% with weak APS
  - 1.27% with strong APS
- Risk of hospitalization increased by
  - Poor social functioning
  - Anxiety disorder
- Treatment of prodromal state can decrease risk of progression
  - Antipsychotics
  - Antidepressants
  - CBT

Slide 2

N Werbeloff: Arch Gen Psychiatry 2012;69:467-475

Progression of Prodromal Features

- 723,316 Israeli males age 16-17 got comprehensive evaluation for draft registration
- Cross-referenced to national hospital database
  - 3929 hospitalized for schizophrenia average of 10 years later
- 1659 schizophrenia patients and an unaffected sibling compared with control sibling pairs
- Subjects who developed schizophrenia had
  - Decreased social activity starting 12 years before first hospitalization
  - Decreased decision making and conflict resolution in interactions starting 5 years before hospitalization
  - Deficits increased as time to hospitalization got closer
  - Work/school impairment did not start until after hospitalization
- Unaffected sibs of patients had milder impairments that did not progress
- Social impairment is an early manifestation of progressive pathophysiology
  - Inherited but does not progress in sibs

E Velthorst et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.2253

Cognitive Dysfunction a Schizophrenia Prodrome

- 689 subjects at high risk of psychosis and 279 controls
  - Baseline neuropsychological testing
  - Followed for 2 years
- High risk patients had significant cognitive impairment, especially in
  - Attention
  - Working memory
  - Declarative memory
- Greatest impairment was in high risk subjects who converted to psychosis
- High baseline verbal ability + impaired memory + unusual/delusional thought content predicted conversion to psychosis
- No difference between medicated and unmedicated subjects
  - Antipsychotic drugs did not cause or help cognitive deficits

LJ Seidman et al: JAMA Psychiatry 10.1001/jamapsychiatry.2016.2479

NIMH First Episode Psychosis Early Treatment Study (NAVIGATE)

- 404 patients age 15-40
  - Diagnoses: schizophrenia, schozoaffective, schizophreniform, brief psychotic disorder, psychosis NOS
    - 90% schizophrenia spectrum
    - Mood disorders and medical conditions excluded
  - Single psychotic episode
  - ≤6 months of lifetime antipsychotic medications
- 34 CMHC's in 21 states
  - Randomized to experimental intervention (223 patients) or TAU (181 patients)
    - 17 CMHCs in each intervention)
- 2-year follow-up

Slide 1

JM Kane et al: Am J Psychiatry doi:10.1176/appi.ajp.2015.15050632

NIMH First Episode Psychosis Early Treatment Study (NAVIGATE)

- NAVIGATE interventions
  - Personalized medication management
  - Family psychoeducation
  - Resilience-focused individual therapy
  - Supported employment and education
- NAVIGATE patients
  - Remained in treatment longer and had more extensive treatment
  - More improvement in QOL
    - School and work
    - Interpersonal relationships
    - Sense of purpose, motivation, emotional engagement
    - Engagement in activities
    - Effect size 0.31
  - Greater reduction in PANSS scores
  - No difference in hospitalization

Slide 2

JM Kane et al: Am J Psychiatry doi:10.1176/appi.ajp.2015.15050632

Intermediate Psychotic Syndromes

- Late onset paraphrenia
  - Schizophrenia with involutional onset
  - Worse prognosis than early onset schizophrenia
- Delusional disorder
  - No formal thought disorder
  - Generally poor prognosis
- Involutional paranoid state
  - Premorbid suspiciousness with gradual involutional deterioration and prominent paranoia
- Schizoaffective disorder
- Cycloid psychoses

Slide 1 of 4

Intermediate Psychotic Syndromes

- Schizoaffective disorder
  - RDC: Mood incongruent psychotic symptoms and formal thought disorder
    - Occur in 20% of bipolar patients
  - DSM-IV: Psychotic symptoms for > 2 weeks in presence of normal mood
    - Better predictor of outcome
  - Outcome intermediate between schizophrenia and mood disorders
    - Schizoaffective-depressed has outcome similar to schizophrenia
    - Schizoaffective-bipolar (schizomanic) has outcome similar to bipolar

Slide 2 of 4

Intermediate Psychotic Syndromes

- Cycloid psychoses
  - History:
    - Boffée délirante (Magnan, 1893)
    - Zykloide psychosen (Kleist, 1929)
    - Cycloid psychosis (Leonhard, 1960s)
  - Characteristics:
    - Rapid onset
    - Frequent recurrence
    - Abrupt and complete interepisode recovery
    - Strong affective coloring but not mania or hypomania
    - Affective lability
    - Confusion
    - Perplexity
    - Polymorphic psychosis
  - Lifetime prevalence: <1%

Slide 3 of 4

Intermediate Psychotic Syndromes

- Cycloid psychoses (cont)
  - Differences from schizophrenia and bipolar disorder:
    - No ventricular enlargement
    - Different patterns of P300 auditory evoked potential
    - Less deterioration than either bipolar disorder or schizophrenia
  - Subtypes
    - Motility psychosis
      - Periods of excitation and stupor, but normal content and form of thought
    - Anxiety-happiness psychosis
      - Alternation between fear of impending doom or end of the world and a transcendent sense of having a special mission to save or destroy the world
    - Confusion psychosis
      - Agitated or inhibited thought
        - Excited incoherence or perplexed thought blocking

Slide 4 of 4

Pathophysiology

Familial Factors in Schizophrenia

Relationship	% Shared Genes	% Risk
General population	0	1
Spouse of patient	0	2
2nd degree relative	25	2-6
1st degree relative	50	6-17
DZ twin	50	17
MZ twin	100	48
Risk the same whether or not proband raised with biological parent		

The Evolution of Schizophrenia Risk

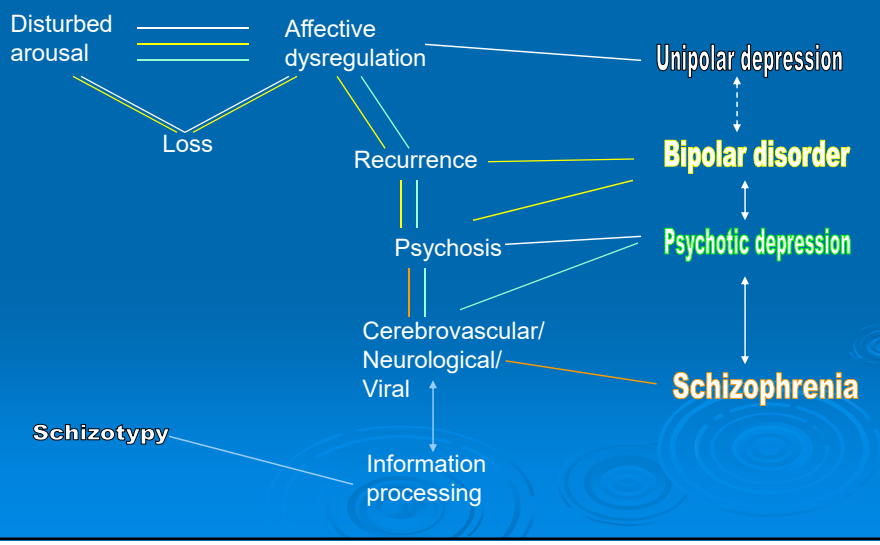
- Genes associated with schizophrenia seem to have emerged when homo sapiens diverged from Neanderthal
  - Linked to genes for abstract thought, executive function, language, creativity
  - Also appeared with development of tools, burial practices
- Genes associated with other disorders, weight, and BMI present in Neanderthal and homo sapiens
- Risk of schizophrenia may be specific to evolution of human race

Srinivasan et al: Biol Psychiatry 2015 doi:http://dx.doi.org/10.1016/j.biopsych.2015.10.009

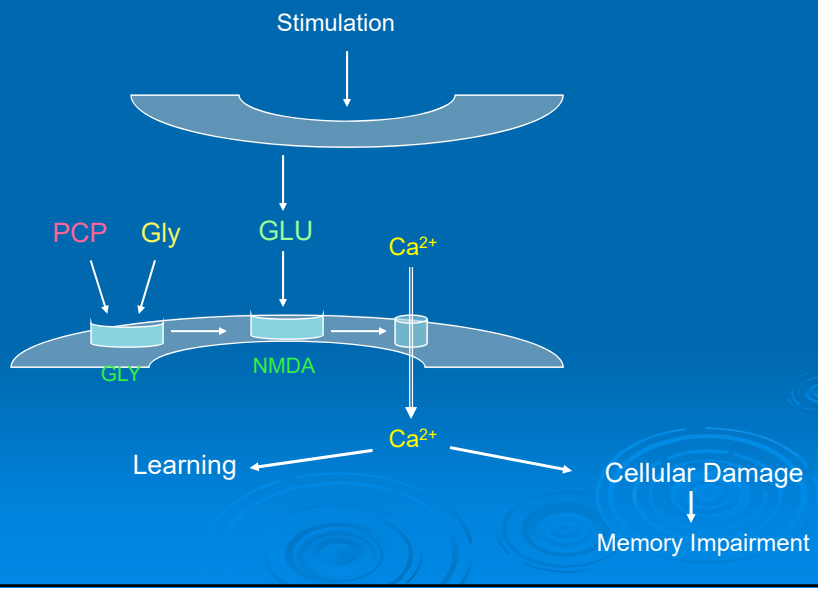
An Inherited Psychosis Factor?

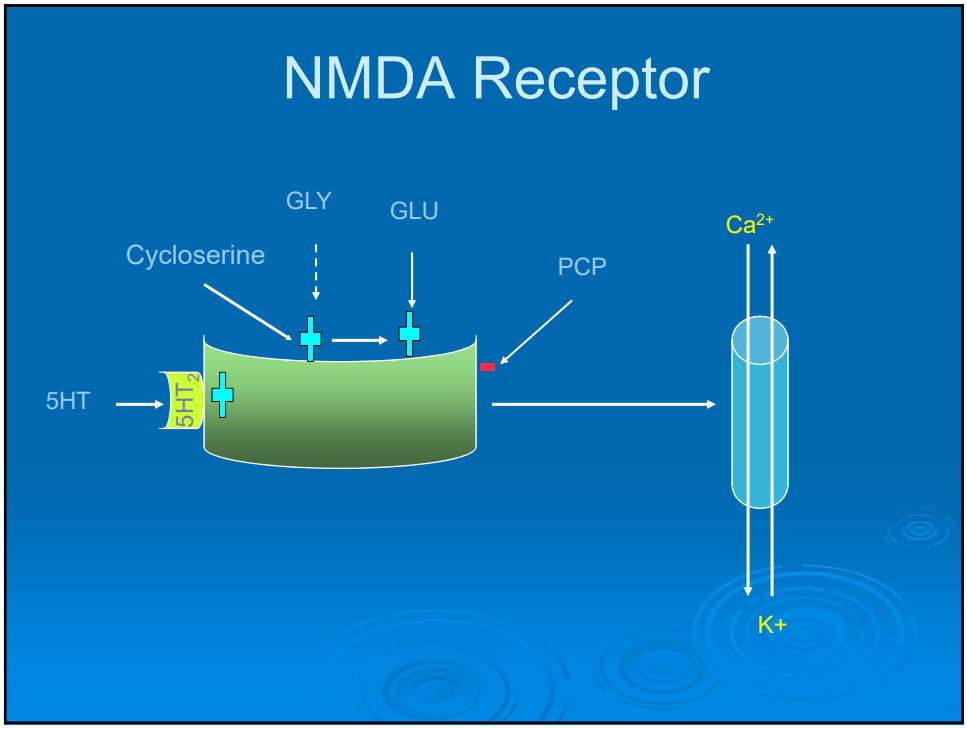
- Pseudoautosomal trait
- High rate of recombination
- Variable penetrance and expressivity
- Expression modified by affective disorder, neurological factors, infection, personality traits
- Influences development of cerebral laterality

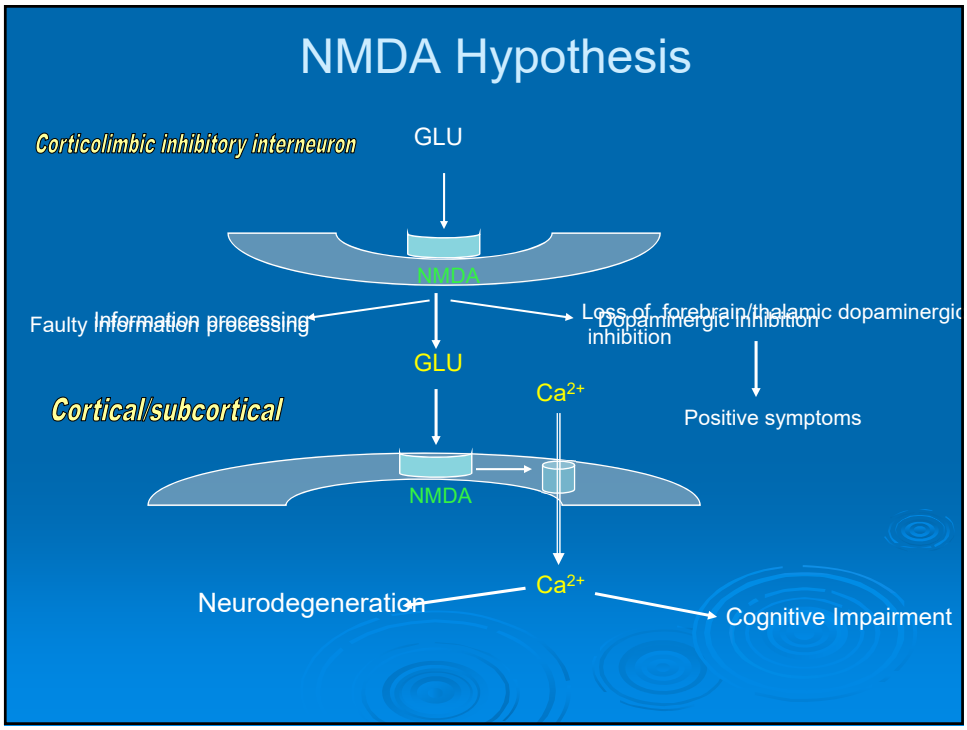
Risk Factor Interactions



Excitatory Amino Acid Transmission




NMDA Receptor
GLY
GLU
Cycloserine
PCP
Ca2+
5HT
5HT2
K+


NMDA Hypothesis
Corticolimbic inhibitory interneuron
GLU
NMDA
Faulty information processing
Loss of forebrain/thalamic dopaminergic inhibition
GLU
Ca2+
Cortical/subcortical
Positive symptoms
NMDA
Ca2+
Neurodegeneration
Cognitive Impairment

Glycine Partial Agonist Treatments for NMDA Hypofunction

- GlyR required for NMDAR function
- Clozapine is a partial glycine receptor agonist
- Other partial agonists of glycine receptor
  - Serine
  - D-cycloserine
    - D-alanine
- Augmentation of antipsychotic drugs
- Significant reduction in negative but not positive symptoms in some studies
  - Similar results with augmentation of neuroleptics and atypicals

GlyT1 Inhibitors

- Glycine-1 transporter is coexpressed with NMDA receptor
  - Inhibition could increase glycine levels
- Sarcosine
  - Glycine agonist
  - Weak GlyT1 inhibitor
  - Improved positive, negative and cognitive symptoms when added to antipsychotic drug
  - Severe side effects: respiratory depression, ataxia, sedation
- Non-sarcosine GlyT1 inhibitors more promising
  - Benzoylpiperazines

Slide 1

E Pinard: J Med. Chem. 2010;53:4603-4614; H Zhang: J Physiol 2009;13:3207-3220

GlyT1 Inhibitors

- Bitopertin
  - Selective GlyT1 inhibitor (glycine reuptake inhibitor or GRI)
  - Phase II study showed improved negative symptoms
- Three 24-week phase 3 trials of addition of study medication to ongoing antipsychotic drug other than clozapine in stable patients with negative symptoms
  - One discontinued after interim analysis showed chance of effect size ≥ 3 was 25% for 10 or 20 mg
  - Two trials completed
    - Total 1199 patients
    - Random assignment to placebo or 5, 10 or 20 mg
    - Bitopertin not > placebo for negative symptoms
    - High placebo response rate suggested patients responded well to psychosocial interventions

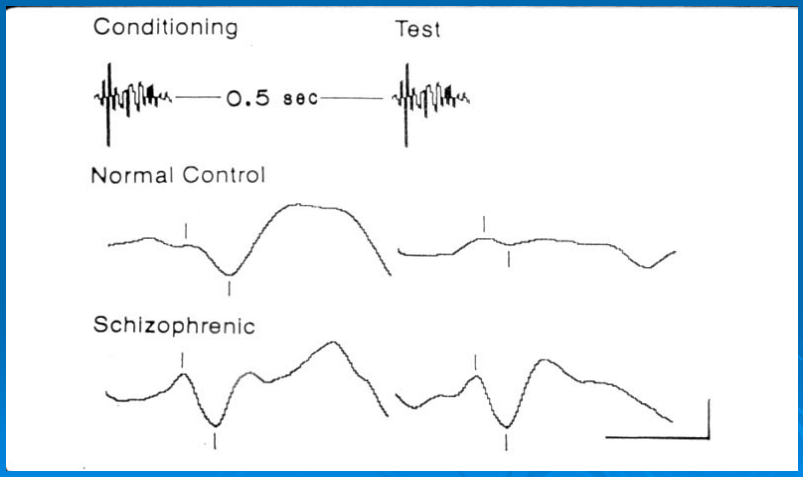
Slide 2

D Bugarski-Kirola et al: Biol Psychiatry doi:http://diagnosis.doi.org/10.1016/j.biopsych.2016.11.014

Filter Hypothesis

- Prefrontal cortex protects from information overload via cortical-striatal-pallidal-thalamic circuits
- GABAergic and glutaminergic projections to striatum reduces information flow to cortex
- Increased DA and decreased GLU decrease inhibitory effect on information processing

Many Schizophrenics Fail to Inhibit the Neuronal Response to Repeated Sounds

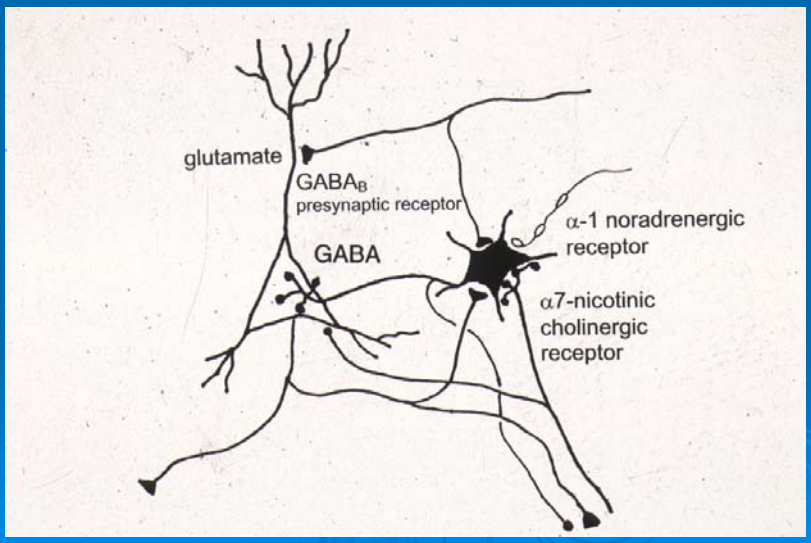


Courtesy of Dr. Robert Freedman

Impaired Sensory Gating

- Trait variable
- Seen in schizophrenia and well relatives
- Associated with impaired attention and language
- Loss of inhibitory function may be related to difficulty with information processing
- Abnormal gating linked to alpha7 nicotinic receptor gene on chromosome 15
- Similar findings in bipolar disorder

Malfunction of Nicotinic Receptors Means that the Brain's Own Acetylcholine is no Longer Sufficient to Activate Neurons that Filter Sensory Input



Courtesy of Dr. Robert Freedman

Alpha-7 Partial Agonist

- ABT-126
  - Selective partial α7 agonist
- 12- week DBPC trial in patients with stable schizophrenia
  - ABT-126 10 mg, 25 mg or placebo
  - 165 patients completed study
- On a composite cognitive score
  - No difference overall
  - In nonsmokers, ABT-25> placebo overall (ES=0.84) and for
    - Verbal memory
    - Working memory
    - Attention/vigilance

GM Haig et al; Am J Psychiatry doi: 10.1176/appi.ajp.2015.15010093

Conclusions from Information Processing Studies

- Deficits of early preattentive processing
- Under-recognition of both change and lack of change in auditory information
- Imprecise assessment of stimulus properties
- Misapprehension of social cues
- Inability to distinguish between relevant and irrelevant information
- Psychosis may represent pathological attempt to restore information processing in patients with psychosis trait; others are schizotypal

Potassium Channel Gene in Schizophrenia

- Allele of gene for K+ rectifier current (KCNH2-3.1) associated with schizophrenia risk
- KCNH2 mRNA expression lower in hippocampus and DLPFC of schizophrenia patients than controls
  - Slow information processing
  - Greater hippocampal activity with memory task
    - Indicates inefficient processing in DLPFC with executive function

Slide 1

Huffaker SJ: Nature Medicine 2009;15:509

Potassium Channel Gene in Schizophrenia

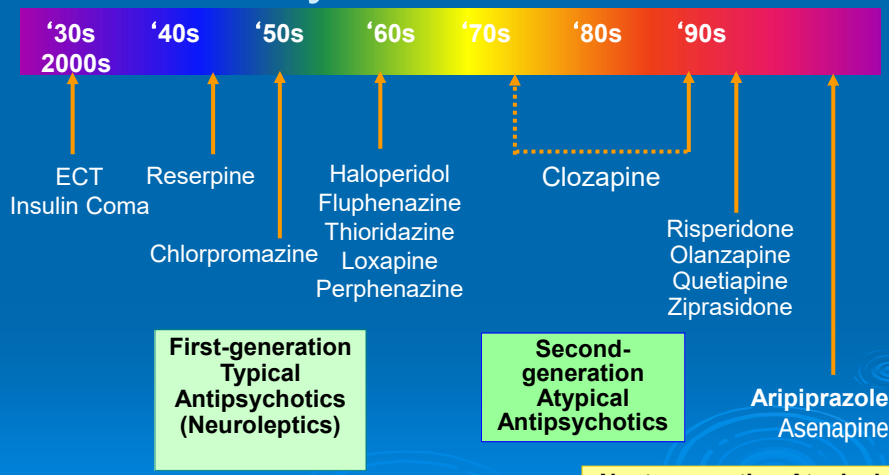
- Malfunctioning K+ current causes slow repolarization
- May lead to continued bursts of information
- Excess irrelevant information that floods deficient gating system
- KCNH2-3.1 antagonist specific to brain could improve cognition without causing QT prolongation in heart

Slide 2

Huffaker SJ: Nature Medicine 2009;15:509

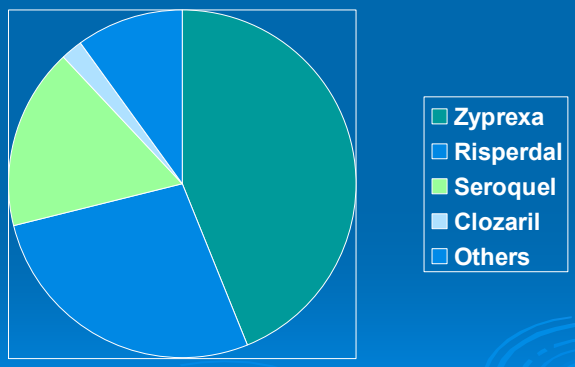
Antipsychotic Treatments

Evolution of Treatments for Psychotic Disorders



Tandon R. *Psychiat Q.* 2002;7:297-311.
Courtesy of Dr. D. Goff

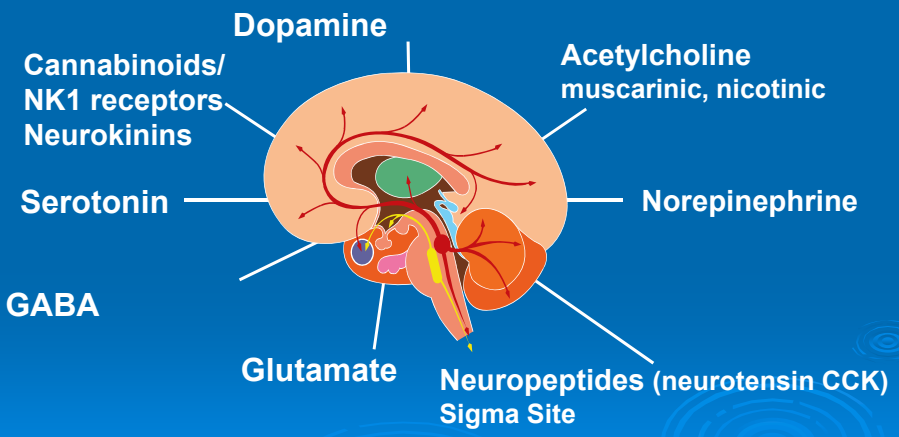
Antipsychotic Market Share, 2002



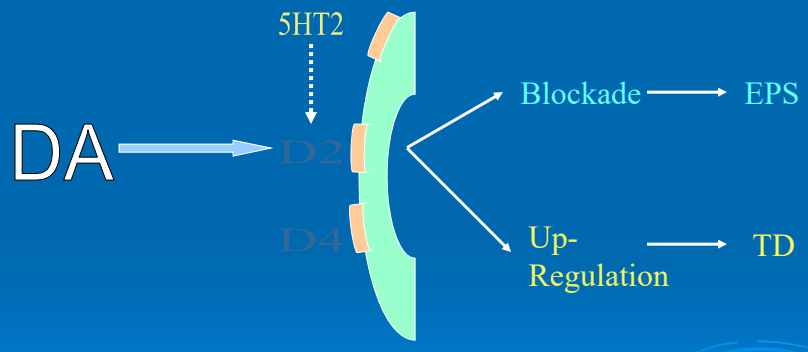
Total sales $11.7 B in 2005

1% of all outpatient health care visits (36 million)
Resulted in antipsychotic prescription 1997-2000

Neuroreceptor Targets for Antipsychotic Drugs



D_2 Receptors



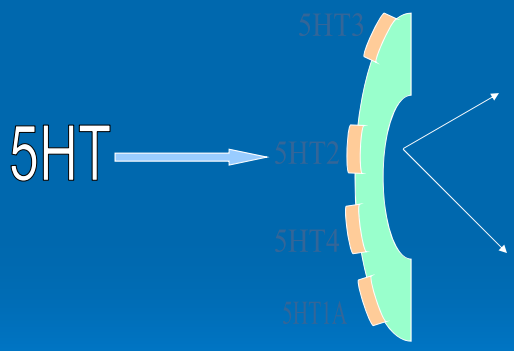
D_2 Receptor Occupancy

60-70% >80%

Antipsychotic Effect | Negative subjective experience | EPS

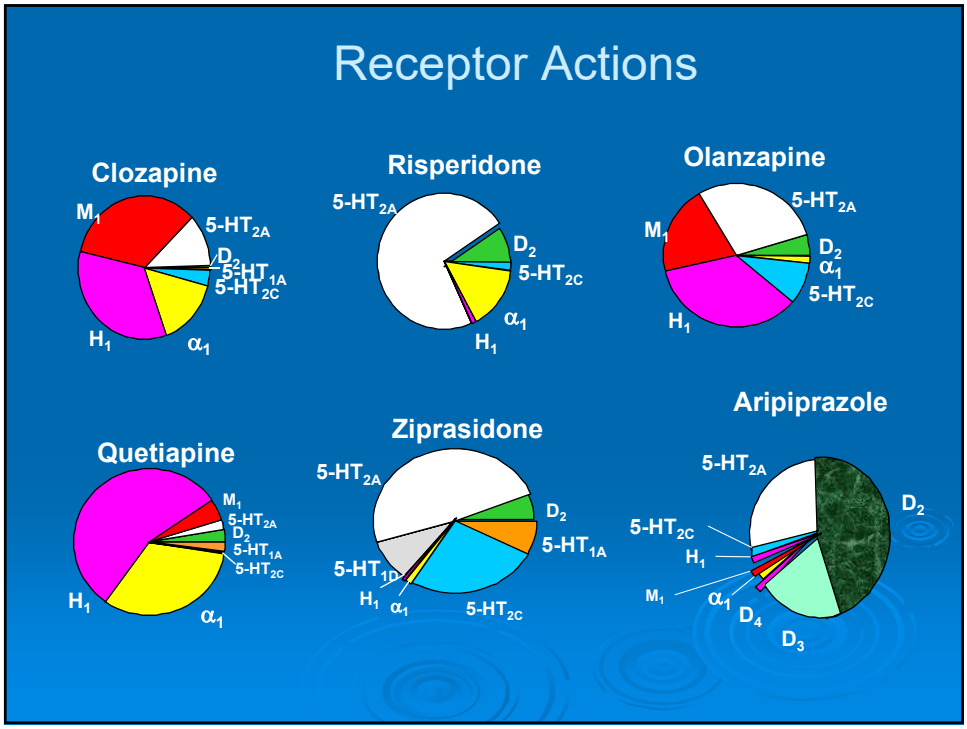
Clozapine | **Other atypicals** | **Neuroleptics**

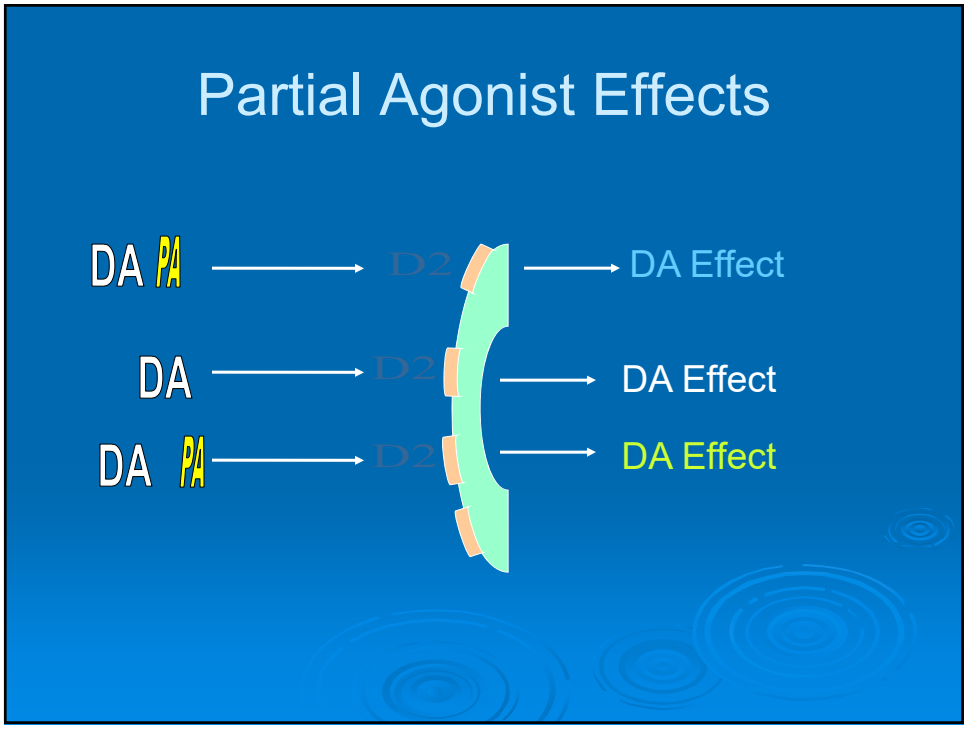
$5HT_2$ Receptors



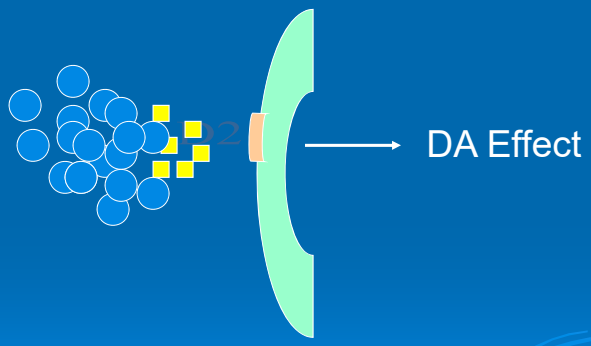
Psychosis
Anxiety
Depression
Sleep
Vasomotor Tone

Up-regulation of D_2 receptors

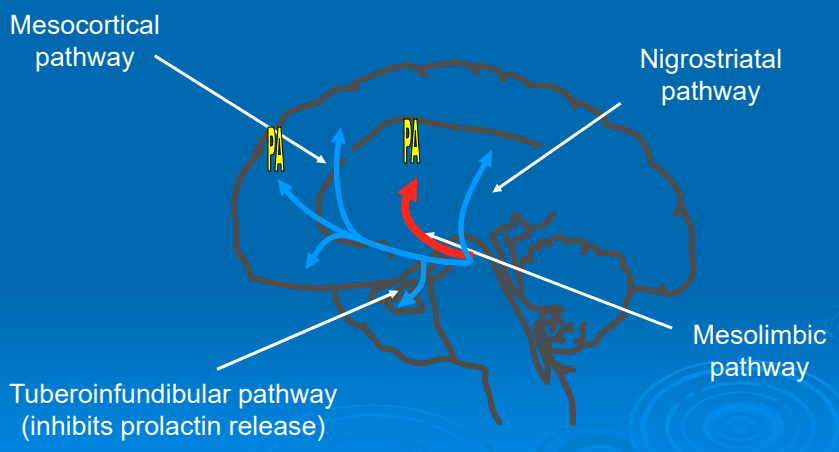

Receptor Actions
Clozapine
M1
5-HT2A
D2
5-HT1A
5-HT2C
H1
α1
Risperidone
5-HT2A
D2
5-HT2C
α1
H1
Olanzapine
5-HT2A
M1
D2
α1
5-HT2C
H1
Quetiapine
M1
5-HT2A
D2
5-HT1A
5-HT2C
H1
α1
Ziprasidone
5-HT2A
D2
5-HT1A
5-HT1D
H1
α1
5-HT2C
Aripiprazole
5-HT2A
D2
5-HT2C
H1
M1
α1
D4
D3


Partial Agonist Effects
DA PA
D2
DA Effect
DA
D2
DA Effect
DA PA
D2
DA Effect

Partial Agonist Actions Depend on Agonist Availability



Partial Agonist Actions



Adapted from Inoue and Nakata. *Jpn J Pharmacol.* 2001;86:376.

Known Gene Regulation by Antipsychotic Drugs

- Number of genes regulated in animal striatum, frontal cortex and hippocampus
  - Haloperidol: 140-153
  - Olanzapine: 102-120
- Induction of neurotensin, CRF binding protein, dopamine transporter, enkephalin, acetylcholinesterase, GluR2
- Induction of 27-31 transcription factors: Zinc finger, homeobox, basic helix-loop-helix, kruppel-associated box

Slide 1

MJ Girgenti: J. Neurochemistry 2010;113:175-187

Known Gene Regulation by Antipsychotic Drugs

- Induction of genes of retinoic acid signaling cascade
- Activation of Wnt signaling cascade via regulation of genes for Wnt 7, Frizzled 1, Disheveled 1 and 2, ILGF, fibroblast growth factor
  - Trophic proteins for cell proliferation, structural plasticity and neuronal resilience
- Down-regulation of somatostatin receptors
- Induction of proteins for cellular assembly, nervous system development and presynsaptic function

Slide 2

MJ Girgenti: J. Neurochemistry 2010;113:175-187; D Ma et al: J Proteome Res 2009;8:3284

Efficacy of Atypical Antipsychotics

- Problems with antipsychotic comparisons
  - Studies biased toward neuroleptic nonresponders
    - Patients who tolerate/respond to neuroleptics not likely to enroll
    - Previous responders to atypicals not excluded
    - Previous atypical nonresponders are excluded
  - Haloperidol usual comparator
    - Haloperidol levels not measured
    - Doses often too high
  - Large N to demonstrate efficacy suggests small effect size
  - Duration of treatment variable
  - Multiple comparisons sometimes evaluated with inappropriate statistical tests
  - Statistically significant findings may not be clinically significant
- Atypicals appear better tolerated
  - Benefits outweigh risks

Davis et al 2003

Meta Analysis of Schizophrenia Efficacy Studies

- Haloperidol effect size > placebo: 0.60
  - Corresponds to decrease of 13 points on PANSS or 8 points on BPRS
- Effect sizes >haloperidol
  - Clozapine: 0.49
  - Risperidone: 0.25
    - Corresponds to reduction of 4-6 points on PANSS or 3-4 points on BPRS
  - Olanzapine: 0.21
- Superiority of clozapine to haloperidol almost as great as superiority of haloperidol to placebo
- Olanzapine and risperidone superiority to haloperidol half that of clozapine
- Quetiapine, ziprasidone, aripiprazole about as effective as neuroleptics but fewer side effects

Davis et al 2003

CATIE* Trial

- 1493 schizophrenia patients
  - Data available on 1432
- 18 month follow-up
- Primary outcome measure: time to study discontinuation
- Randomly assigned to (doses adjusted clinically)
  - Perphenazine 21 mg/day
  - Olanzapine 20 mg/day
  - Risperidone 4 mg/day
  - Quetiapine 543 mg/day
  - Ziprasidone 113 mg/day
- 74% discontinued medication
  - 64% olanzapine-82% quetiapine
    - No difference between olanzapine and perphenazine or ziprasidone when correction made for multiple comparisons
  - Discontinuation for lack of efficacy 15% olanzapine versus 25-28% for other medications
    - Difference from 24% not statistically significant (ziprasidone)

Slide 1

*Clinical Antipsychotic Trial of Intervention Effectiveness

Lieberman et al NEJM 2005;353:1209

CATIE Trial

- No difference in discontinuation rates because of patient preference or EPS
- No differences in symptom change
- 30% on olanzapine versus 10-15% on other medications gained >7% of body weight
  - 9.4 lbs versus 1.1 lbs weight gain-2 lbs weight loss
- Conclusions
  - Most schizophrenia patients discontinue antipsychotic drugs
  - Patients stay on olanzapine slightly longer but are more likely to have clinically important weight gain
  - Effectiveness of atypicals against negative symptoms not as great as originally reported
  - No EPS difference when low neuroleptic doses are used
  - No atypical antipsychotic is dramatically superior
  - Still first line treatments

Slide 2

Lieberman et al 2005

CATIE Phase II

- Open study
- Patients who were unresponsive to an atypical switched to another one
- After switch, clozapine>olanzapine, quetiapine, risperidone

McEvoy JP et al: Am J Psychiatry 2006;163:600-610

CUtLASS* I

- 227 chronic schizophrenia patients randomized to neuroleptic or atypical for 1 year
- Primary outcome measure comprehensive QOL/social-psychological-occupational functioning scale score
- No between group differences in
  - QOL
  - Positive symptoms
  - Negative symptoms
  - EPS
  - Depression
  - Total cost of care

Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study

Jones PB: Arch Gen Psychiatry 2006;63:1079

EUFEST

- Funded by AstraZeneca, Pfizer and Sanofi-Aventis
- Multicenter 12-month open study
- Random assignment of 498 patients with first episode schizophrenia, schizophreniform or schizoaffective disorder (mostly inpatients) to
  - Haloperidol 1-4 mg
  - Amisulpride 200-800 mg
  - Quetiapine 200-750 mg
  - Ziprasidone 40-160 mg
- Other medications allowed

Slide 1

Kahn RS et al: Lancet 2008;371:1085-1087

EUFEST

- Suicidality at baseline: 10-15%
- Substance dependence/abuse: 15-28%
- Discontinuation for any cause (months to d/c):
  - Haloperidol: 72% (0.5)
  - Amisulpride: 40% (5.3)
  - Olanzapine: 33% (6.3)
  - Quetiapine: 53% (1.2)
  - Ziprasidone 45% (1.1)
- Compared with haloperidol, H.R. for discontinuation:
  - Amisulpride: 0.37
  - Olanzapine: 0.28
  - Quetiapine: 0.52
  - Ziprasidone: 0.51

Slide 2

Kahn RS et al: Lancet 2008;371:1085-1087

EUFEST

- Akathisia: Ziprasidone>haloperidol>amisulpride=olanzapine>quetiapine
- Parkinsonism: haloperidol>ziprasidone=amisulpride=quetiapine=olanzapine
- No differences in
  - PANSS scores (average 60% reduction with all)
  - Quality of life
  - Hospitalizations
  - Medication adherence
  - SAEs
  - Dystonia
  - TD
  - Blood sugar, lipids, fasting insulin, QT prolongation

Slide 3

Kahn RS et al: Lancet 2008;371:1085-1087

Off-Label Studies

- 162 efficacy studies and 231 observational studies
- Dementia: 38 trials
  - Mean sample size 238
  - Aripiprazole, olanzapine, quetiapine, risperidone
    - Effect size 0.12-0.20
      - Only risperidone significantly > placebo for psychosis
        - Effect size 0.20
    - 95% CI significant only for aripiprazole due to 1 study
  - No superiority of one atypical over another in direct comparisons
  - Use in agitation discussed later

Slide 1

AR Maher et al: JAMA 2012;306:1359

Off-Label Studies

- GAD
  - Quetiapine: effect size 0.30
    - Quetiapine=paroxetine and escitalopram in two 8-week studies
  - Other atypicals: no significant effect compared with placebo
- OCD
  - Risperidone augmentation improves response rate
    - NNT=5
    - Effect size 1.14
    - Dose 0.5-2.25 mg
  - Two studies suggest quetiapine augmentation>placebo
- Eating disorders
  - No benefit
- PTSD
  - Risperidone augmentation may be helpful
- Substance abuse
  - No benefit

Slide 2

AR Maher et al: JAMA 2012;306:1359

New Clozapine Data: Believable?

- Network meta analysis of 40 blinded studies in 5172 patients
  - Average study duration 11 weeks
  - Treatment resistance= failure to respond (≥20% symptom reduction) to 1 or 2 antipsychotics for 3 weeks
- No clear superiority of clozapine over olanzapine and risperidone
- Problems:
  - Clozapine dose too low; no blood levels
  - Patients not highly treatment resistant
  - Trials too short
  - Industry sponsored studies find no difference, but government sponsored studies (CUtLASS, CATIE) still find clozapine superior
- Bottom line: don't ignore clozapine for true treatment resistance, especially with suicidality

MT Samara et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.2955; JM Kane, CU Correll: JAMA Psychiatry Feb 3, 2016

Newer Antipsychotics

Paliperidone (Invega)

- Metabolite of risperidone
- OROS formulation designed for stimulants in ADHD
  - No rationale in schizophrenia

Paliperidone Pivotal Trial: Compare to Your Patients

Nationality	Europe, India
Diagnosis	"Acute schizophrenia"
Exclusion criteria	Substance dependence within 6 months Medical illness TD history Suicide or violence risk History of antipsychotic nonresponse
Inclusion criteria	Severe illness (PANSS 94) but able to give informed consent Able to withdraw previous medication
Number of screen fails	Not given
Compliance	65-78% taking active drug completed study

Paliperidone Results

- Best PANSS decrease: from 94 to 71
- "Response" (30% ↓ in PANSS): 56-61% paliperidone versus 30% placebo
  - 50% ↓ in 23-32% paliperidone versus 15% placebo
- Personal and social functioning score ↑ 9-12 with paliperidone versus 0.5 with placebo
  - Secondary outcome measure: study not powered for this outcome
  - No baseline given
  - Increasing by a functioning "category" not valid because a change of 1-2 points could increase to the next category

Paliperidone Adverse Effects

- EPS similar to placebo
  - Same originally reported for risperidone 6 mg
  - ↑ prolactin from 17-45 suggests significant D2 blockade
- No change in glucose or insulin in 6 weeks may not predict longer term effect

What Does it Mean?

- Paliperidone reduces symptom scores by average of about 24% in 6 weeks
- Symptom score reduction paralleled by about the same improvement in functioning
- Claim of no need for titration because of OROS technology does not make sense
  - Dose increases itself over one day, not over many days
- Claims of low EPS overly optimistic
- No evidence of applicability in refractory schizophrenia
- Probably somewhere between risperidone and aripiprazole
- Cost would probably impact medication choice

Asenapine (Saphris)

- Receptor affinity
  - $D_{3/4}$>D_2
  - $5HT_{2A}$, $5HT_{2C}$, $5\text{-}HT_6$, $5HT_7$
  - NE α_{2A}, α_{2B}, α_{2C}
- Sublingual
- No food or water within 20 minutes
- Less weight gain than some others
- Not superior to other antipsychotics

D Bishara and D Taylor: Drugs 2008;68:2269

Iloperidone (Fanapt)

- $5HT_{2A}$, D_3>D_{2A}, D_4
- Dose 8-24 mg
- Response defined as 20% decrease in PANSS
  - Positive symptoms: 72% response vs 52% with placebo
    - NNT=5
- Common side effects: weight gain, dizziness, sedation, dry mouth, prolonged QT
- No maintenance studies
- No advantage over other antipsychotics

L Citrome: Int J Clin Pract 2009;63:1237-1248; D Bishara, D Taylor: Drugs 2008; 68:2269

Lurasidone (Latuda)

- Azapirone derivative
- Receptor binding
  - D2 antagonist
  - 5HT2A, 5HT7 antagonist
  - 5HT1A partial agonist
  - NE α2C
- Lower H1 and muscarinic activity
  - Less weight gain and sedation
- Not superior to other antipsychotics
  - Effect size small

T Ishibashi et al: J Pharmacol Exp Ther 2010;33:171-181

Cariprazine (Vraylar)

- D2/D3 partial agonist
- 5HT1A partial agonist
- 5HT2A antagonist (weak)
- 5HT2B antagonist
- Binds to H1 receptors
- 5HT2C and alpha1a binding
  - Not muscarinic
- Induces its own metabolism
  - 3A4 substrate
- 3 of 4 studies > placebo for PANSS total score
- NNT 7 for mania in 2 studies
- No apparent superiority over other antipsychotics

L Citrome: CNS Drugs 2013;27:879

Brexpiprazole (Rexulti)

- Receptor effects
  - D2/D3 partial agonist
  - 5HT1A partial agonist
  - Potent 5HT2A antagonist
  - Dopamine and 5HT affinity > aripiprazole
  - α1 antagonist
- No difference between brexpiprazole, aripiprazole and placebo in phase II study
- 6-week comparison of brexpiprazole and aripiprazole (N=97)
  - Significant decrease PANSS (-22.9, -19.4)
- DBPC 6-week study (N=636) in schizophrenia
  - 4, 2, 0.25 mg and placebo
  - Treatment difference -8 on PANSS
  - 0.25 mg no > placebo
- CYP 2D6 and 3A4 substrate

Clinicaltrials.gov

Lumateperone (Caplyta)

- Known actions
  - 5HT2A antagonist
  - GluN2B receptor phosphoprotein antagonist
  - D1-dependent enhancement of NMDA and AMPA currents
    - Via mTOR pathway
  - SRI
- Superior to placebo in 2/3 RCTs for PANSS scores
- May have less weight gain and metabolic effects than risperidone

K Vanover et al: CNS Spectrums 2019;24:190

Lumateperone RCT

- Manufacturer sponsored design, conduct, interpretation and publication of results
  - Most authors had significant financial ties to sponsor
- 450 patients (mean age 42) with acute exacerbation of schizophrenia randomly assigned to
  - Lumaterone 42 mg (60 mg lumateperone tosylate)
  - Lumateperone 28 mg (40 mg tosylate)
  - Placebo
- Lumateperone effective on primary outcome measure (PANSS reduction) for 42 but not 28 mg

Slide 1

CU Correll et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2019.4379

Lumateperone RCT

- Unadjusted PANSS reduction significant (p=0.02)
  - Adjusted for multiple comparisons, p=0.05
  - ES=0.3
- Response (≥30% PANSS reduction) rate
  - 37% at 42 mg
  - 36% at 28 mg
  - 26% placebo
  - NNT=9
- Low EPS and metabolic AEs over 30 days
- Low effect size similar to brexpiprazole, lurasidone, cariprazine
- Authors' claim of improved psychosocial function comes from PANSS subscale, not actual measure of functioning
- Not an advance even in highly selected population

Slide 2

CU Correll et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2019.4379

Olanzapine Pamoate

- 150 mg/2 weeks, 300 mg/2 weeks or 405 mg/4 weeks
  - Oral equivalents 10, 15 and 20 mg
- All studies used sample enrichment
- Longest double-blind study 24 weeks
- One open-label 4-year study
  - 880 patients
  - PANSS decreased from 56.28 to 54.90 (p=0.013)

Oral Versus Long Acting Injectable (LAI) Antipsychotics in Schizophrenia

- Meta analysis of 21 RCTs involving 5176 patients
- No difference between pooled LAIs and pooled OAPs in
  - All cause discontinuation
  - Discontinuation due to AEs
  - Lack of efficacy (pooled data), but
    - Fluphenazine LAI>OAPs
    - Olanzapine LAI<OAPs
  - Hospitalization (pooled data), but
    - Fluphenazine LAI>OAPs
- LAIs preferable for nonadherent patients
- Continued debate about when to initiate LAIs

T Kishimoto et al: Schizophrenia Bull 2014;40:192

Pharmacoeconomics of Atypicals

- Clozapine cost effective for refractory schizophrenia with high hospital utilization
  - Increased cost of clozapine offset for patients with more than $60,000 in inpatient costs
    - Care is shifted to outpatient setting
    - Clozapine not likely to save money for refractory patients who are not hospitalized frequently
- Olanzapine and risperidone cost neutral but improve outcome long-term
- Savings more obvious when hospitalizations reduced
- Risperidone average cost for schizophrenia inpatients $6.42 vs $12.29 for olanzapine
  - Higher discharge rates with high dose risperidone vs any dose olanzapine*

*Kathy DL et al: Psychiatric Services 2001;52:676

Antipsychotic Polypharmacy

- 435 patients taking antipsychotic drugs for >90 days in British Columbia
- 26% took multiple antipsychotic drugs chronically
  - Schizoaffective disorder: 34%
  - Schizophrenia: 32%
  - Psychosis NOS: 20%
  - Bipolar disorder: 17%
  - MDD: 14%
- Antipsychotic doses 1.94 times as high with polypharmacy vs monotherapy

Procyshyn RM et al: J Clin Psychiatry 2010;71:566-573

Using Antipsychotic Drugs

- Schizophrenia
  - Low doses as effective as high doses but take longer
    - Fewer adverse effects
    - Better long-term compliance
  - Antipsychotic effect is not immediate
  - Supplement with benzodiazepines for agitation
  - Only clozapine clearly superior to other antipsychotics
- Psychotic depression
  - Higher doses may be necessary
- Mania
  - Use acutely
    - Transition to mood stabilizer if possible

Antipsychotics in Childhood Schizophrenia

- All atypicals have been found > placebo for PANSS reduction except ziprasidone and paliperidone
- Clozapine controlled trial, open trial and case studies: effective and safe
  - One study found clozapine > olanzapine in refractory schizophrenia
- Children more sensitive to AEs

AC Childress et al: J Child Adolesc Psychopharmacol 2009;19:351; HN Kranzler, SD Cohen: Child and Adolesc Psychiatr Clin N Amer 2013;22:727

Changes in Pediatric Antipsychotic Use

- Antipsychotic drug use has increased in children >12
- Use of antipsychotic drugs in Tennessee doubled from 1996-2001
  - >95% atypical antipsychotics
  - New use for ADHD and mood disorders increased 2.5 times
- In a chart review of adolescent inpatients, only 17% of patients taking atypical antipsychotics had a primary psychotic diagnosis
- In a chart review of 732 children and adolescents in RTCs, 273 received antipsychotic medications.
  - 43% of these had no evidence of psychosis
  - Reasons for antipsychotic prescription: ADHD, substance abuse, dangerousness, elopement, delinquency
- 57-67% of youth receiving antipsychotics had no psychiatric diagnosis in another study

Slide 1

Rawal PH et al: Journal of Behavioral Health Services & Research 2004;31:178-188; Kelly DL et al: J Child Adolesc Psychopharmacol 2004;14:75-85
Cooper WO et al: Arch Pediatr Adolesc Med 2004;158:829-830; M Olfson et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.0500

Changes in Pediatric Antipsychotic Use

- 6 atypicals approved for short-term use in childhood
  - Schizophrenia
  - Mania
  - Irritability with autism
  - Tourette's
- Most common uses
  - Aggression
  - Behavioral dyscontrol
  - ADHD
    - 19% of ADHD patients in one study were taking atypicals
    - Risperidone used most frequently
    - Usually used to treat behavior problems
  - Disruptive behavior disorders
  - Depression
- Not used as frequently for
  - Psychosis
  - Mania
  - Tourette's
  - Autism spectrum
- Concomitant medications
  - Stimulants: 45-69%
  - Antidepressants: 51-59%
  - Benzodiazepines: 12-34%
  - Mood stabilizers: 35-41%
- Only 1/3 of children and adolescents get an antipsychotic prescription from a child psychiatrist
  - <25% have any psychotherapy

Slide 2

U Christoph et al: JAMA Psychiatry 2015; M Olfson et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.0500

Adverse Effects

EPS with Atypicals

- Meta analysis of all RCTs comparing atypicals to low potency neuroleptics
  - 31 studies involving 2320 subjects
- Only clozapine had a lower risk of EPS than neuroleptics
  - Risk of EPS 15% lower
- Difference between olanzapine and neuroleptics not statistically significant
- At doses <600 mg chlorpromazine equivalent, other atypicals were not less likely to cause EPS

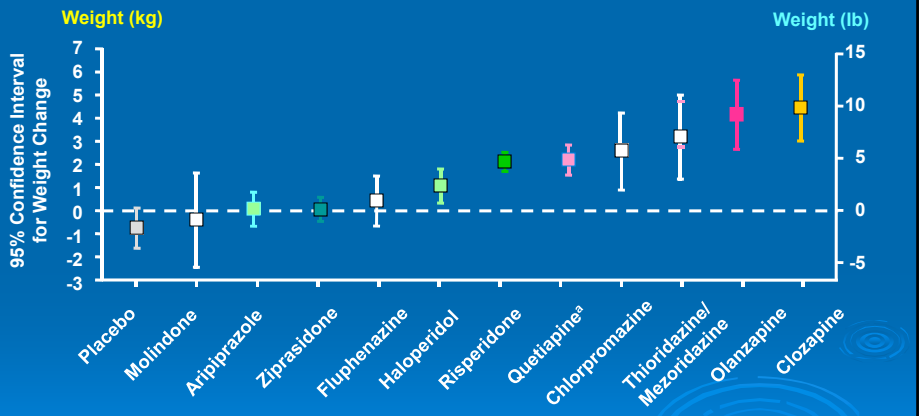
Leucht S et al. Lancet 2003;361:1581-1589

Interpreting Weight Gain

- Overweight: BMI 25-29.9
- Obesity: BMI ≥ 30
- Metabolic syndrome (syndrome X):
  - Hypertension
  - Low HDL
  - High cholesterol
  - High plasma glucose
  - Central adiposity
  - Insulin resistance
- In 12,861 noninstitutionalized people
  - 23% had metabolic syndrome
  - 60% of obese men and 50% of obese women had metabolic syndrome

Park et al 2003

Meta-analysis of Antipsychotic-related Weight Gain at 10 Weeks



[a] Quetiapine weight gain estimated at 6 weeks

[b] Quetiapine weight gain estimate at 6 weeks extrapolated to 10 weeks

Adapted from Allison et al. *Am J Psychiatry* 1999;156:1686–1696

Weight Gain with Atypical Antipsychotics

- Begins within first few weeks
- May not peak in first year
- Immediate weight gain is in lean body mass
- Most long-term weight gain is in form of fat
  - Increased visceral fat mass
  - Increased hepatic lipid content
- Most weight gain with clozapine and olanzapine
- Less weight gain with ziprasidone, aripiprazole, lurasidone
- Quetiapine and risperidone intermediate

Weight Gain in Children

- Children more prone to weight gain and metabolic changes
  - Waist circumference ≥ 90th percentile: 68%
  - Impaired fasting glucose: 19%
  - Increased B.P.: 13%
  - Elevated triglycerides: 11%
  - Metabolic syndrome: 17%
  - Weight gain 3.2 kg in first 12 weeks of risperidone for disruptive behavior
    - 2.1 kg in next six months

M Weiss et al: J Child Adolesc Psychopharmacol 2009;19:572

Weight Gain in Adolescents

- Adolescent mental health center patients treated with olanzapine, risperidone or haloperidol
- Weight gain over first 12 weeks
  - Olanzapine: 7.2 kg; >7% baseline, in 91%
  - Risperidone: 3.9 kg; >7%, in 43%
  - Haloperidol: 1.2 kg; >7%, in 12.5%
- Olanzapine significantly> other groups
- Increased caloric intake important cause

Ratzoni G et al: J Am Acad Child Adol Psychiatry 2002;41:337; Gothelf D et al: Am J Psychiatry 2002;159:1055

Glucose Intolerance and Schizophrenia

- Meta analysis of 16 case control studies
  - 731 patients and 614 controls
  - Early onset schizophrenia spectrum disorder
    - Mostly unmedicated
    - Some patients had <2 weeks antipsychotic treatment
- Patients had increased FBS, decreased glucose tolerance on GTT, increased insulin, insulin resistance
  - No difference in HgbA1c
- All findings except FBS remained significant after controlling for BMI
- When diet and exercise could be controlled, no effect on findings
- Possible causes: abnormal cellular signaling affecting metabolism and brain, maternal diet/smoking, genetic linkage
- Implement early screening for glucose dysregulation
  - GTT more reliable than FBS
  - Start lifestyle counseling early

T Pillinger et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3802

Atypicals and Diabetes

- Record review of 3115 patients treated with antipsychotics
- Patients who gained ≥7% of body weight (significant weight gain) or had new onset diabetes in first year of treatment each matched with 4 controls
- Statistically significant increased risk of weight gain with
  - Risperidone: OR 1.8
  - Olanzapine: OR 2.3
- Risk of diabetes significantly increased only for olanzapine: OR 2.65
- Weight gain not correlated with developing diabetes

Slide 1

WR Farwell: APA 2003

Atypicals and Diabetes

- 3.5 million patients in 400 British general practices
  - All cases of schizophrenia (19,637 patients) who did not already have diabetes
    - 451 of these patients were identified as having developed diabetes within 3 months of starting an antipsychotic drug
  - Each schizophrenia patient who developed diabetes was matched with six schizophrenia patients who never developed diabetes

Slide 2

Koro et al 2002

Atypicals and Diabetes

- Compared with no use of antipsychotics in schizophrenia
  - Olanzapine increased risk of diabetes 5.8 times
  - Risperidone increased risk of diabetes 2.2 times
  - Neuroleptics increased risk of diabetes 1.4 times
  - Olanzapine but not risperidone was significantly more likely than neuroleptics to be associated with development of diabetes
- Diet and severity of schizophrenia were not controlled

Slide 3

Koro et al 2002

Atypicals and Diabetes

- Prospective followup of all 18,023 MediCal patients <65 starting atypical antipsychotics after 12/98
- Incidence of new onset diabetes mellitus after starting antipsychotic
  - Risperidone: 3.15 times
  - Quetiapine: 3.0 times
  - Olanzapine: 4.7 times
- Compared with risperidone, risk of diabetes with olanzapine was increased 30% (OR = 1.30)
  - Greater risk with higher doses

Slide 4

AL Grogg: APA 2003

Atypicals and Diabetes

- Health plan data from 2.5 million patients
- Patients with pre-existing diabetes excluded
- Odds of developing type 2 diabetes over 12 months of treatment:
  - Risperidone: Not increased
  - Olanzapine: 3.10
  - Clozapine: 7.44
  - Low potency neuroleptics: 3.46
  - High potency neuroleptics: 2.13

Slide 5

Gianfrancesco FD et al: J Clin Psychiatry 2002;63:920-930

Diabetes Risk in Children

- Data base of 3 health plans
  - 9036 children/adolescents starting SGA
  - Compared to children taking no psychotropic and children taking an antidepressant
- Incident relative risk of diabetes in first year after starting SGA versus
  - No psychotropic: 4.24
  - Antidepressant: 1.74 (NS)
- After 11 weeks, nonrandomized trial of SGAs in children found increased
  - Weight
  - Fat mass
  - BMI
  - Greatest change with olanzapine

S. Andrade et al: Pediatrics 2011;128:1135-1141

Diabetes Risk in Adolescents

- Meta analysis of 13 studies
  - N=185,105
  - Mean age: 14
  - Mean follow-up: 1.7 years
- Risk of type 2 diabetes increased 1.5 times in psychiatric patients not taking antipsychotics
- Risk 2.1 times higher in patients taking antipsychotics than in patients not taking antipsychotics
- Increased risk with
  - Olanzapine
  - Longer follow-up
  - Not having ASD

B. Galling et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.2923

Hyperlipidemia

- Nested case control study of >18,000 patients in general practices in England and Wales
- Schizophrenia patients taking olanzapine 3.4 times as likely to develop hyperlipidemia as those taking other antipsychotic drugs
  - Clozapine not included
  - No increased risk with risperidone
- Slight increased risk of hyperlipidemia (1.4 times) with neuroleptics
- Clozapine and olanzapine associated with greatest increases in total cholesterol, LDL and triglycerides and greatest decreases in HDL

Slide 1

Koro et al Arch Gen Psychiatry 2002;59:1021-1026; American Diabetes Assn: Diabetes Care 2004;27:596-601

Hyperlipidemia

- Cross sectional study of 242 chronic schizophrenia patients taking monotherapy with
  - Olanzapine or clozapine (N=80; 72 on olanzapine)
  - Other antipsychotic drugs (N=80)
  - No medication (N=82)
- Average duration of illness 2-3.5 years
- Average duration of treatment 7-12 months
- No difference between groups in BMI
- Olanzapine/clozapine group had significantly more elevated triglycerides, low HDL

Slide 2

Birkenaes AB et al: J Clin Psychopharmacol 2008;28:132-137

American Diabetes Association / Consensus Conference Monitoring Recommendations

- Baseline weight/height (BMI), waist circumference at level of umbilicus, blood pressure, fasting lipid profile, personal and past history of obesity, diabetes, hypertension, cardiovascular disease
- Check weight every 3 months
- Check FBS and blood pressure at
  - Baseline
  - 3 months
  - Then annually
- Check lipids at baseline, 3 months, then every 5 years
- Monitor more frequently if risk factors are present
  - Obesity
  - First degree relative with diabetes
  - History of gestational diabetes or having a baby >9 pounds
  - Hypertension
  - Nonwhite ethnic status
- Treat overweight, obesity, pre-diabetes (FBS 100-125 mg.dL), diabetes (FBS ≥ 125), hypertension, dyslipidemia
- Change medication if
  - Weight increases by >5%
  - Glucose or lipids increase significantly

American Diabetes Assn, APA, Amer Assn of Clinical Endocrinologists, NA Assn for Study of Obesity: Diabetes Care 2004;27:596-601

Recommended Monitoring Frequency

Factor	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Q5 years
Personal/family history	X						
Weight (BMI)	X	X	X	X	X	X	
Waist circumference	X						
BP	X			X		X	
FBS	X			X		X	
Fasting Lipids	X			X			X

Potential Treatments for Severe Weight Gain

- Non-pharmacologic
  - Diet/exercise
    - Easier to avoid weight gain than to treat it
  - Shop in express lane
- Pharmacologic
  - Orlistat
    - GI side effects limiting
    - Cetilistat has similar weight loss (1.5-4 kg) with fewer side effects
  - Metformin
    - Discussed later
  - Topiramate
    - Weight loss 7-9.7% of baseline weight at 60 weeks
    - Limiting side effects
  - Zonisamide
  - Phentermine
    - Useful for short term treatment only

Slide 1

AG Powell et al. Clin Pharmacol Ther 2011;90:40-51

Potential Treatments for Severe Weight Gain

- Pharmacologic
  - Bupropion
    - Weight loss 2.8 kg in 1 year
  - Naltrexone/bupropion
    - 5-8 kg weight loss in 1 year
    - Not approved because of unclear cardiovascular risk
  - Zonisamide/bupropion
    - Weight loss >5% in 47-60% of patients
    - No phase 3 studies
  - Exenatide
    - Glucagon-like peptide-1 receptor agonist (GLP-1RA) used for diabetes
    - Not more effective than pleacebo for antipsychotic-induced weight loss
      - Both groups lost 2.2 kg over 3 months

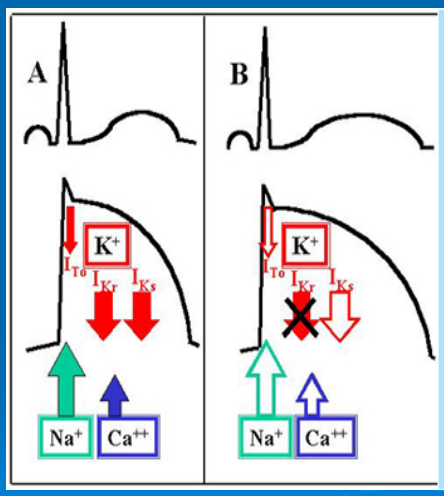
Slide 2

AG Powell et al: Clin Pharmacol Ther 2011;90:40-51

Metformin

- DBPC 16-week study of 61 ASD patients treated with atypicals
  - Average age 13
  - Mostly risperidone or aripiprazole
  - 1 normal weight, 8 overweight, 56 obese
- Random assignment to addition of metformin or placebo
- BMI decreased with metformin, increased with placebo (difference 0.95)
- Weight increased significantly less with metformin (0.07 versus 2.80 kg)
- More GI side effects with metformin
- No long-term data
  - No data on normal weight patients
- FDA: Estimated GFR must be > 45 mL/min/1.73m^2
  - Patients already on metformin and doing well may tolerate down to 30 but not lower
  - Anyone with an eGFR<20 should not take metformin

E. Anagnostou et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.1232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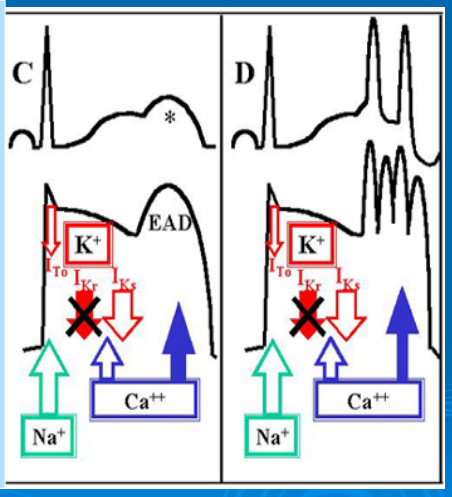
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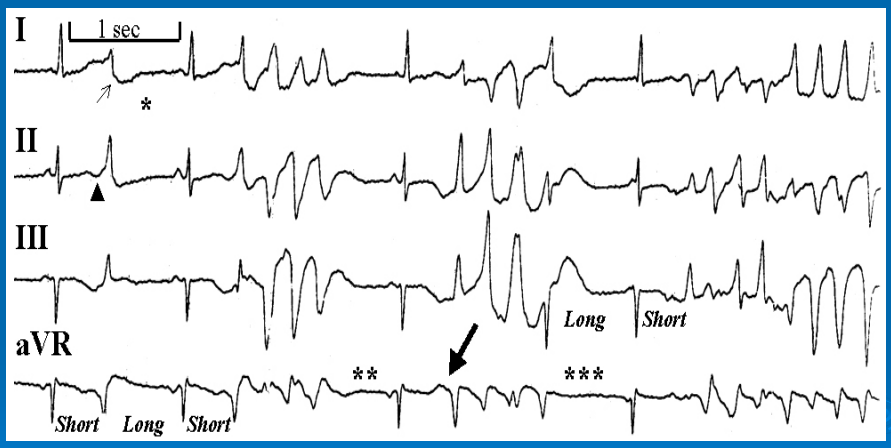


Sudden Death and Antipsychotics

- Medical records of patients in 5 psychiatric hospitals who died suddenly during a 12-year period were each compared with records of two controls matched for psychiatric illness and other relevant factors
  - 1350 patients died, 69 of them for unexplained reasons
  - Thioridazine was the only medication statistically associated with an increased risk of sudden death (OR 5.3, p = 0.004)
  - Higher doses had a greater risk
  - The most likely cause of sudden death seemed to be torsades de pointes
  - Pre-existing ischemic heart disease and hypertension increased risk of sudden death with thioridazine
  - Not enough use of atypicals to assess risk

Slide 1

Reilly et al 2002

Sudden Death and Antipsychotics

- Cohort study of data on patients with schizophrenia, psoriasis and glaucoma (controls) from 1993-1996 from 3 Medicaid programs
- Compared with patients with other illnesses, relative risk for antipsychotics was:
  - 1.7-3.2 for cardiac arrest and ventricular arrhythmia
  - 1.4-1.9 for sudden death
- Risk with high dose thioridazine > haloperidol
- Risperidone > thioridazine, but could reflect risperidone given to medically ill patients

Slide 2

Hennessy S et al: BMJ 2002;325-330

Sudden Death and Antipsychotics

- Records over 15 years of Medicaid enrollees in Tennessee age 30-74
- All people who took an antipsychotic drug
  - Each patient matched with two controls who did not take an antipsychotic drug
  - Single neuroleptic: N=44,218
  - Single atypical: N=46,089
  - Controls: N=186,600
- Secondary analysis of antipsychotic users without schizophrenia (mostly mood disorders) matched with psychiatric control not taking antipsychotic drug
  - Antipsychotic: N=67,824
  - Controls: N=116,069
- 1,042,159 person-years of follow-up
- Controlled for cardiovascular and behavioral risk factors

Slide 3

Ray WA et al: NEJM 2009;360:225-235

Sudden Death and Antipsychotics

- Demographics of antipsychotic use:
  - Number with diagnosis of schizophrenia:
    - Neuroleptic: 27%
    - Atypical: 14%
  - Number with diagnosis of bipolar disorder:
    - Neuroleptic: 12%
    - Atypical: 23%
  - Number with diagnosis of other mood disorder:
    - Neuroleptic: 36%
    - Atypical: 60%
- Rates of sudden cardiac death with antipsychotics compared with controls
  - Neuroleptic: 1.99
  - Atypical: 2.26
  - Difference between neuroleptic and atypical not significant
- Former users of antipsychotics did not have increased risk of sudden cardiac death

Slide 4

Ray WA et al: NEJM 2009;360:225-235

Sudden Death and Antipsychotics

- Significant risk of sudden cardiac death compared with controls for specific antipsychotics (adjusted for dose):
  - Haloperidol: 1.61
  - Thioridazine: 3.19
  - Clozapine: 3.67
  - Olanzapine: 2.04
  - Quetiapine: 1.88
  - Risperidone: 2.91
- Risk increased with higher dose of neuroleptic or atypical
  - Greatest risk with high dose (>300 mg) thioridazine: 5.05
- Similar findings in patients with mood disorders matched with mood disorder patients without antipsychotic:
  - Neuroleptic: 1.84
  - Atypical: 1.99
- Risk was present in patients taking antipsychotic for <1 year
  - Suggests metabolic factors did not explain risk

Slide 5

Ray WA et al: NEJM 2009;360:225-235

Cerebrovascular Risks

- FDA meta analysis of 17 RCTs of olanzapine, risperidone, aripiprazole, quetiapine in dementia
  - HR of cerebrovascular death 1.6-1.7
  - Led to black box warning in 2005
- Review of 15 RCTs of atypicals
  - RR of death 1.5
    - Only significant when results of all studies combined
- Medicaid data 1999-2002
  - OR for cerebrovascular events with atypical antipsychotics versus benzodiazepines 0.49
  - No increased risk for any atypical antipsychotic
- 10,615 demented VA patients > age 65
  - Overall mortality: 18%
  - Neuroleptics and atypicals: 29%
  - Other psychotropics: 18%
- Antipsychotics not contraindicated but careful monitoring necessary

Slide 1

Friedman JH: Neurology 2006;22:564-566; Rabins and Lyketsos JAMA 2005;294:1963-1965 ;Finkel S et al: Int Psychogeriatrics 2005;17:617-629 Kales, 2007

Cerebrovascular Risks

- Taiwanese case crossover study of 14,584 patients with incident stroke
- Mean age at stroke onset 69
- Antipsychotic drug use within 2 weeks of stroke had 1.6 fold increased risk of stroke
- No increased risk in patients with >28 days of antipsychotic use in previous year
- Atypicals had high risk
- Highest risk of stroke with
  - Higher antipsychotic dose
  - Older age
  - Dementia
- Stroke risk increased further with drugs with higher affinity for M1 muscarinic and α2 adrenergic receptors
  - No effect of binding to other receptors
- Risks independent of medical risk factors
- Implications
  - Shorter duration of antipsychotic use riskier, possibly because patients are more acutely ill
  - Use antipsychotics cautiously in older and demented patients
  - Use drugs with less alpha 2 and muscarinic affinity

Slide 2

C-S Wu et al. Biol Psychiatry 2013;73:414

Brain Shrinkage in the Iowa Longitudinal Study

- 211 patients with first episode of schizophrenia or schizoaffective disorder and minimal previous antipsychotic exposure
- Prospective 7.2-year follow-up
- Types of antipsychotic drugs
  - Clozapine: ¼
  - Non-clozapine atypicals: 2/3
  - Neuroleptics: 1/12
- Decreased brain volume in all patients over time

Slide 1

B-C Ho et al: Arch Gen Psychiatry 2011;68:128-137

Brain Shrinkage in the Iowa Longitudinal Study

- Controlled for illness severity, illness duration, substance use
- Dose related decrease with all drug classes in
  - Brain volume
  - White matter
  - Gray matter
- Enlarged lateral ventricles and putamen with all classes
- Animal studies show brain shrinkage with olanzapine and haloperidol
  - Apparent after 8 weeks
  - 10% reduction over 2 years in primates

Slide 2

B-C Ho et al: Arch Gen Psychiatry 2011;68:128-137

Cognitive Effects of Atypicals

- Atypicals>neuroleptics in improving
  - Verbal fluency
  - Fine motor coordination
  - Executive function
  - Working memory
  - Long-term memory
- Significant amount of superiority of atypicals attributable to less cognitive parkinsonism
- Only clozapine improves sensory gating

Clozapine and Smoking

- 70-80% or schizophrenic patients smoke
- Clozapine may correct same information processing deficits as nicotine
  - ?Similar spectra of action
- Clozapine was more effective in 55 refractory smokers than 15 refractory nonsmokers
- Smokers decreased smoking with clozapine but not neuroleptics
- ?Effect on nicotinic receptor

McEvoy et al: Biol Psychiatry 1999;46:125

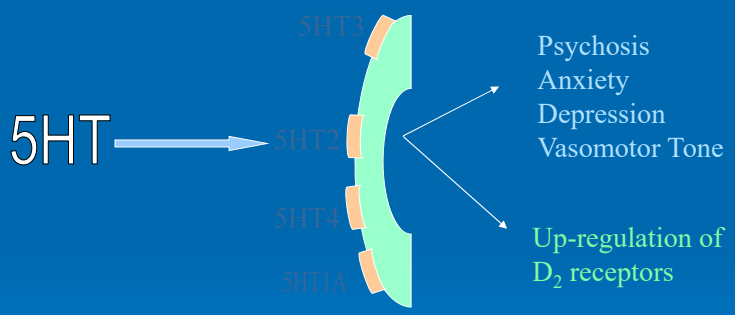
Experimental Treatments

Cholinesterase Inhibitors in Schizophrenia

- Modest improvement of some aspects of memory
- No impact on social cognition, positive symptoms or negative symptoms
- Most patients were heavy smokers
  - Nicotinic receptors may have been too down-regulated
  - Sensory gating not measured
- α7 nicotinic receptor works best with phasic stimulation

Stip E et al: Clinical Neuropharmacology 2007;30:218-229

$5HT_2$ Receptors

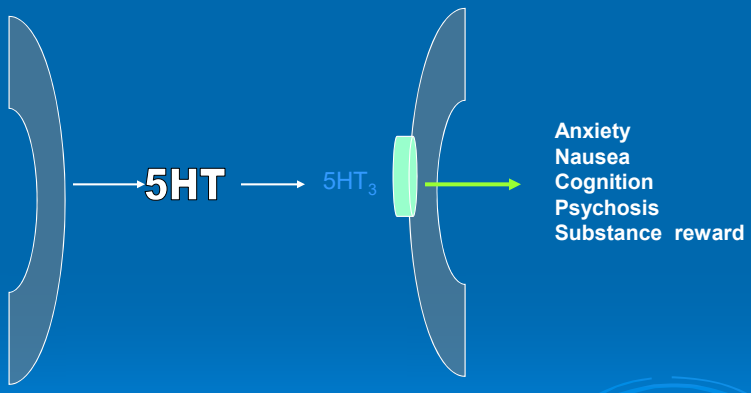


Pimavanserin (Nuplazid) and Parkinson's Psychosis

- Loss of nigrostriatal DA neurons results in up-regulation of $5HT_{2A}$ signaling
- Hallucinations in PD psychosis similar to LSD and other serotonergic psychosis
- Pimavanserin is 5HT2A inverse agonist and antagonist
- Effective for PD psychosis without sedation or significant motor side effects
  - Also improves sleep
- Clozapine effective but with sedation
- Quetiapine not effective

D Hubbard et al. Behavioural Pharmacology 2013;24:628; J Cummings, K Zhong: Clin Pharmacol Ther 2015;98:483

$5HT_3$ Receptors



$5HT_3$ Antagonists

- Ondansetron
- Granisetron
- Mirtazepine
- Zacopride

Uses of $5HT_3$ Antagonists

- Antiemetic
  - ?Treatment of cholinesterase inhibitor-induced nausea
    - Emetrol, ginger root are cheaper
- Antianxiety
- Antipsychotic
- Reduction of substance craving/withdrawal
- ?Improvement of cognition

Essential Fatty Acids

- Glycerophospholipids and cholesterol comprise cell membrane
  - Receptors
  - Signal transduction
  - Precursors of second messengers
- Degree of unsaturation (double bonds) in hydrophobic inward tail determines membrane fluidity
- Essential fatty acids must be ingested because mammals cannot insert double bonds in correct position to synthesize them

Slide 1

Essential Fatty Acids

- Alterations of membrane essential fatty acids affect
  - Ion channel function
  - Agonist binding
  - Second messengers
  - Free radical production and detoxification

Slide 2

Membrane Hypothesis of Schizophrenia

- Defective membrane fatty acid metabolism aggravated by dietary deficiency of essential fatty acid intake
- Multiple manifestations of membrane dysfunction
- Schizophrenic patients have evidence on MR spectroscopy of decreased synthesis and increased breakdown of membrane phospholipids
  - Could contribute to cognitive dysfunction

EFA Trials in Schizophrenia

- 3 of 4 double blind studies report no benefit of omega-6 when added to neuroleptics
- Most studies show improvement of PANSS and AIMS with addition of 2-10 gm/day of omega-3

Pharmacologic Management of Schizophrenia

- Use lowest possible antipsychotic dose
- Add benzodiazepine for agitation
- Add antidepressant or switch to clozapine for prominent negative symptoms
- Initiate antiparkinsonian drugs only for acute EPS
  - Less likely with low antipsychotic doses
  - Propranolol or benzodiazepine for akathisia
  - Attempt to discontinue adjunct after 1-2 months
- Treatment of TD
  - Cholinesterase inhibitor
  - CCB
  - Clozapine
  - Tetrabenazine, valbenazine

Anatomy of AVH

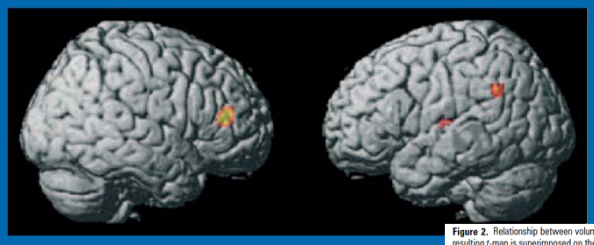


Figure 2. Relationship between volume decrease and severity of hallucinations: The resulting *t*-map is superimposed on the rendered surface of the single template brain ($P < 0.001$). Only clusters consisting of at least 55 voxels are displayed corresponding to a spatial extent threshold of $P < 0.01$. A correlation between volume decrease and severity of hallucinations was found the right prefrontal cortex (partially the region homologue to Broca's area), in the left inferior supramarginal gyrus and in the transverse temporal gyrus (Heschl's gyrus).

Figure 3. Orthogonal sections of spatial location of the findings (same thresholds used as in Fig. 2. Heschl's gyrus can be best identified by its omega-like shape in coronal and sagittal planes. Significant clusters are shown in axial, sagittal and coronal planes, superimposed on the template brain. Section coordinates conform to space of this template and refer only approximately to Talairach space: $x = -44$ mm, $y = -16$ mm, $z = 10$ mm.

(Gaser et al. 2004)

Courtesy of Dr. David Arciniegas

rTMS for Auditory Verbal Hallucinations

- 24 patients with schizophrenia or schizoaffective disorder
  - Auditory hallucinations 5 times/day
- Randomly assigned to slow (1Hz) rTMS or sham
- 9 days of treatment at 90% motor threshold
  - Left temporoparietal
- Significantly greater reduction of AVH with rTMS

RE Hoffman et al. Biol Psychiatry 2005;85:97

Direct Current Stimulation of Medial Frontal Cortex

- Prediction error signal generated in midbrain dopamine system and signaled to medial frontal cortex
  - Tells us when outcomes deviate from predictions
  - Impaired prediction error signaling in schizophrenia leads to discounting rewards and negative symptoms
  - Error-related negativity (ERN)
    - Negative potential over medial frontal cortex with prediction/outcome mismatch
      - Indicates learning prediction errors
- 35 schizophrenia patients
  - 17 had active and 18 sham transcranial direct current stimulation over medial frontal cortex
  - Active treatment produced
    - Increased ERN amplitude (better error learning possible)
    - Improved learning from mistakes on behavioral test
    - Patients' performance improved to normal levels
    - Independent of practice effect
    - Less improvement in patients with more negative symptoms
      - Poor internal representation of motivational information

RMG Reinhart et al: J Neurosci 2015;35:12232-12240

Transcranial Direct Current Stimulation (tDTS) for Negative Symptoms

- Negative symptoms associated with decreased PFC activity
- tDTC administers weak DC current through scalp electrods
  - Anode (excitatory) over left PFC
  - Cathode (inhibitory) over left temporo-parietal junction
- 95 stable, medicated schizophrenia patients with prominent negative symptoms
  - Active or sham tDCS
  - 2 treatments/day for 5 days

Slide 1

L Valiengo et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2019.3199

Transcranial Direct Current Stimulation (tDTS) for Negative Symptoms

- Active significantly > sham for reducing negative symptoms
- Benefit maintained at 12 weeks follow-up
  - Changes in excitability increase over time
- Active tDCS had 9.5 times as many patients as sham with ≥20% reduction in negative symptoms
- Clozapine and high haloperidol dose interfered with benefit of tDCS

Slide 2

L Valiengo et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2019.3199

Transcranial Direct Current Stimulation for Cognitive Dysfunction

- Meta analysis of 9 studies of 270 schizophrenia patients
  - Assigned to active or sham multi session prefrontal tDCS
- Significant improvement of working memory but not other cognitive domains
- Could improve functional outcomes over time

Z Narita et al: Schizophrenia Res 2019 doi:https://doi.org/10.1016/j.schres.2019.11.011

Deep rTMS for Negative Symptoms

- Retrospective review of 16 schizophrenia patients
  - Positive symptoms controlled
  - Prominent negative symptoms
- 5 weeks bilateral high frequency (15 Hz) rTMS to PFC
  - No control
  - Open label
- Negative symptoms decreased by 37-48%
- Positive symptoms decreased by 25%
- Depressive symptoms decreased by 70%
- Similar improvement of negative symptoms in 11 depressed and 5 non-depressed patients
  - Could still be related to an antidepressant effect
  - Antidepressants can improve negative symptoms

S Linsambarth et al: J ECT 2019;35:e46

Psychotherapy

CBT for Psychosis (CBTp)

- Goals
  - Identify appraisal biases and cognitive distortions
  - Develop alternative explanations of events
  - Cope with distress caused by psychosis
- Develop individual problem list with patient
- Handouts and homework assignments
- Patient identifies problems that interfere with functioning or cause distress

DI Velligan: Schizophrenia Bull 2015;41:597-603

Cognitive Adaptation Training (CAT)

- Manualized therapy
- Office and home visits 30-60 minutes/week
- Significant others help to place cues (e.g., mirrors, signs) in home
- Compensates for deficits in information processing
- Analysis of where patient lies on spectrum of
  - Apathy versus disinhibition
  - Impairment of executive function (ability to plan and carry out goal directed activities)
  - Attention/memory/coordination

Slide 1

Cognitive Adaptation Training (CAT)

- Compensating for apathy
  - Prompts and cues to initiate sequential tasks
    - Job site checklist of steps for making an item
    - Signs outlining steps for daily care (e.g., brushing teeth)
- Compensating for disinhibition
  - Remove distracting stimuli (e.g., telephone) and behavioral triggers
  - Redirection
    - Put entire outfit for the day into individual box for that day to reduce wearing multiple layers of clothing
- Compensating for inattention/fine motor dysfunction
  - Use different colors on posters to capture attention
  - Velcro instead of buttons
- Focus on medication adherence

Slide 2

Cognitive Adaptation Training (CAT)

- Controlled study
  - Chronic schizophrenia patients living in community at least 3 months
  - 9 month study
  - Controls:
    - Home visits on same schedule as CAT with novel items therapists chose from a list in home
    - Follow-up only
  - Patients preferred the nonspecific home visits at outset of study
  - Patients receiving CAT had better adaptive functioning and quality of life and fewer positive symptoms than both control groups

Slide 3

Velligan et al: Schizophrenia Bull 2002;28:283-292

CAT versus CBTp

- 142 schizophrenia or SA patients all taking antipsychotics and randomly assigned to
  - CAT
  - CBTp
  - CAT+CBTp (Mcog)
  - TAU (case management)
- 9 months weekly treatment
- Results
  - CAT with or without CBTp
    - Reduced hallucinations: ES 0.36 (small)

Slide 1 DI Velligan: Schizophrenia Bull 2015;41:597-603

CAT versus CBTp

- Results (cont)
  - CAT with or without CBTp
    - Delusions: No benefit
    - Improved functioning: ES 0.41 (small-moderate)
  - CBTp: no significant benefit
  - CAT+CBTp no > CAT alone
- CAT may have had better results because
  - Patients were not seeking additional treatment and therefore were less motivated
    - CAT provides more structure for such patients
  - Patients had < HS education and did not do as well with CBT
  - CAT focuses on medication adherence

Slide 2 DI Velligan: Schizophrenia Bull 2015;41:597-603

Social Cognition and Interaction Training

- Addresses 3 domains
  - Correct identification of affect expressed by others
    - Focus on irrelevant aspects of social context
  - Causal explanations for positive and negative outcomes (attributional style)
    - Cognitive rigidity
    - Tendency to jump to conclusions
    - Personalizing
  - Ability to understand others' intentions or perspectives
    - Intolerance of ambiguity

Slide 1

Penn DL et al: Psychiatric Services 2007;58:449-451

Social Cognition and Interaction Training

- Phases of treatment
  - Emotion training
    - Teach patients how to recognize emotions
      - Computer based program
  - Figuring out situations
    - Improve cognitive flexibility in social situations
    - Distinguish between social facts and social guesswork
    - Ask patients to generate facts based on photos of people interacting and compare to others' guesses
    - Play 20 questions about social situations and penalize for early guesses to reduce jumping to conclusions
  - Integration
    - Discuss actual experiences and go through identify the other person's affect, differentiate facts and guesses, avoid jumping to conclusions and coming up with solution
    - Role playing
- Improved social functioning in open studies

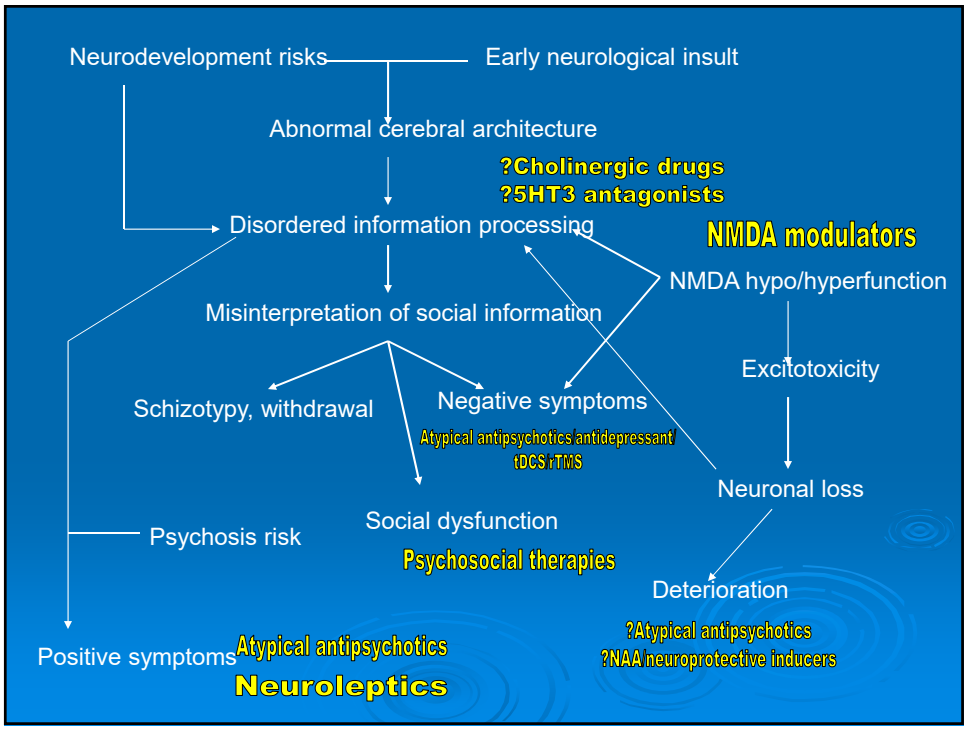
Slide 2

Penn DL et al: Psychiatric Services 2007;58:449-451

Cognitive Remediation Therapy

- Targets:
  - Shifting cognitive sets
  - Working memory
  - Planning
- RCT of 35 schizophrenia patients to CRT or social skills training
  - CRT improved executive function, verbal memory, nonverbal memory
  - Normalization of connections between central executive network and DMN
    - Increased white matter integrity in genu of corpus callosum
    - Less intrusion of internal stimuli into external perception

R. Penades et al: Biol Psychiatry 2013;73:1015



Treatment of Agitation

Violence/Aggression in Schizophrenia

- Review of 8 RCTs from 2000-2010
- O.R. of violence with antipsychotic non-adherence 2.0
- LAI may result in less violence
  - Less nonadherence
- No difference between atypicals and neuroleptics in reducing violence
  - Clozapine superior in two RCTs
- Inconsistent results with valproate augmentation
  - Topiramate helped aggression in one study but increased psychosis
- Best data for propranolol
- Treatment of comorbid substance abuse decreases violence

A Topiwala, S Fazel: Expert Rev Neurother 2011;11:53-63

Treatment of Acute Psychotic Agitation

- De-escalation
  - Limit setting without power struggles
  - Reduce interpersonal stimulation
- Offer oral medication first
- IM ziprasidone, olanzapine, aripiprazole, haloperidol
  - Might or might not add lorazepam or midazolam
- Midazolam alone
- Antipsychotic drugs worsen agitation caused by PCP

IM Aripiprazole Study: Compare to Your Patients

Nationality	Europe, India
Diagnosis	"Acute schizophrenia"
Exclusion criteria	Substance dependence within 6 months Medical illness TD history Suicide or violence risk History of antipsychotic nonresponse
Inclusion criteria	Severe illness (PANSS 94) but able to give informed consent Able to withdraw previous medication
Number of screen fails	Not given
Compliance	65-78% taking active drug completed study

Results

- Improvement of agitation score average 7 with aripiprazole versus 5 with placebo
  - Final score 19-7=12
  - Improvement within 1 hour
- Response (40% improvement): 55% with aripiprazole versus 36% with placebo
- Improvement not a function of "oversedation" (stuporous or unconscious)
  - No test of correlation with sedation

What Does it Mean?

- IM aripiprazole probably as effective as IM haloperidol for moderately agitated psychotic patients
  - Average 32% improvement
  - 2.5 points > placebo
- No evidence that improvement is not a function of sedation
  - If sedation is a factor, primarily sedating medication may be best initial choice
- Probably better tolerated than IM haloperidol
- No comparisons of IM atypicals; all seem effective
- Remember placebo response rate

Inhaled Loxapine (Adasuve)

- C_{max} within 2 minutes
  - Onset of action in 10 minutes
- 2 randomized trials in agitation
  - 1 in schizophrenia
    - ES 0.45 (5 mg)-0.6 (10 mg)
  - 1 in bipolar disorder
    - ES 0.73 (5 mg)-0.94 (10 mg)
  - ES similar to IM antipsychotics
- Dangerous for patients with respiratory disease
- Loxapine is metabolized to amoxapine
- If patient inhales medication correctly, can agitation be severe?

L Citrome: Int J Clin Practice 2012;66:318

Adjunctive Mood Stabilizers for Agitation in Schizophrenia

- Addition of mood stabilizer to antipsychotic drug increased from 22%-86% from 2002-2009
  - Quetiapine most frequently used antipsychotic with mood stabilizer
- Frequency of use
  - Valproate>lithium>lamotrigine>gabapentin >topiramate>oxcarbazepine>carbamazepine
    - Valproate more frequent for suicide attempts
    - Lamotrigine more frequent for comorbid anxiety or personality disorder
- No benefit of adding mood stabilizer
  - Duration of hospitalization longer by 18%

A Ventriglio et al: Int Clin Psychopharmacol 2011;26:88-95

Nonpsychotic Agitation

TREC* Study

- Conducted in India and Brazil
- Multiple studies
- Consecutive psychiatric ER patients needing I.M. sedation for agitation, aggression or violence (N=221; 200 randomized)
  - Most patients manic
- Patients randomized to
  - I.M. haloperidol (10 mg) + promethazine (Phenergan; 25 or 50 mg) in same syringe
    - 96/100 got 50 mg promethazine
  - I.M. lorazepam (4 mg)

*Tranzuilizaccao Rapida-Ensaio Clinic Collaborative Group

Slide 1

J. Alexander Br J Psychiatry 2004;185:63-60

TREC Study

Outcome	HAL/PRO	LOR	P	RR	NNT
Asleep at 15 min	89	78	0.04	1.1 (1.01-1.29)	9
Asleep at 60 min	98	90	0.04	1.1 (1.01-1.17)	13
CGI 1 or 2 at 15 min	61	30	<0.01	2.0 (1.45-2.85)	2.5
CGI 1 or 2 at 60 min	80	60	<0.01	1.3 (1.11-1.61)	5

Slide 2

J. Alexander Br J Psychiatry 2004;185:63-60

TREC Study

- Mean CGI* at
  - 15 min
    - HAL/PRO 2.48
    - LOR 2.97
  - 60 min
    - HAL/PRO 2.09
    - LOR 2.42
  - 1 hour
    - HAL/PRO 2.09
    - LOR 2.42
- No difference in
  - Need for physical restraint
  - Additional medications
  - Further episodes of agitation or violence
  - Admitted or discharged
  - Taking oral medication 2 weeks later

Slide 3

*No longer significant after controlling for differential sedation

Limitations of TREC

- No correction for multiple statistical tests
- Most significant 95% CIs are barely > 1
- Most of benefit consists of patient asleep
- Benefit only evident for the first few minutes
- CGI differences small and probably not clinically important
- Two sedating medications are more sedating than one sedating medication

Haloperidol + Promethazine

- Haloperidol/promethazine vs midazolam (N=301) and vs lorazepam (N=200)
  - All intramuscular
  - Midazolam worked faster
  - Combination > lorazepam for patient asleep immediately but not after 2 hours
  - No difference in need for additional interventions or restraints

Cochrane Reviews 2006 vol 4

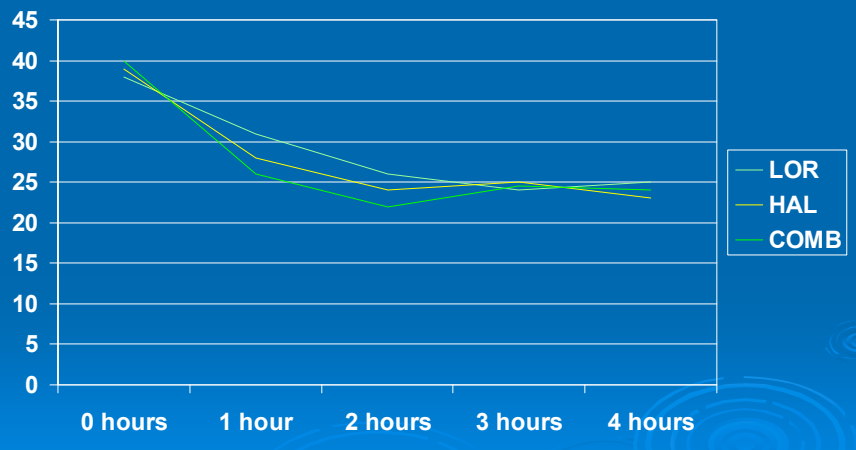
IM Haloperidol/Benzodiazepine ED Study

- Supported by Wyeth
- Primary outcome measures modified BPRS, agitation scale and CGI
- 98 ED patients
  - Agitated, restless, aggressive or assaultive
  - Any two of: hallucinations, delusions, incoherence or loose association, catatonic or disorganized behavior, flat or inappropriate affect
  - Any diagnosis except substance related
- Randomly assigned to IM haloperidol (5 mg), lorazepam (2 mg), or both
- Blind ratings
- Combination had significantly more reduction of agitation than lorazepam alone but not haloperidol alone in agitation rating scale score at one hour
  - Score 26 versus 29
    - Beginning score 40
    - Final score at 12 hours 20 for all groups
- BPRS, anxiety and psychosis scores lower for combination than either drug alone at 2 and 3 hours only
- Patients receiving combination spent more time asleep over 12 hours
  - No control for effect of sedation in comparisons of other outcomes
- No correction for multiple statistical tests
- Assertion that combination patients more cooperative not supported by data
  - No measures of this outcome

Battaglia J et al: Am J Emerg Med 1997;15:335-340

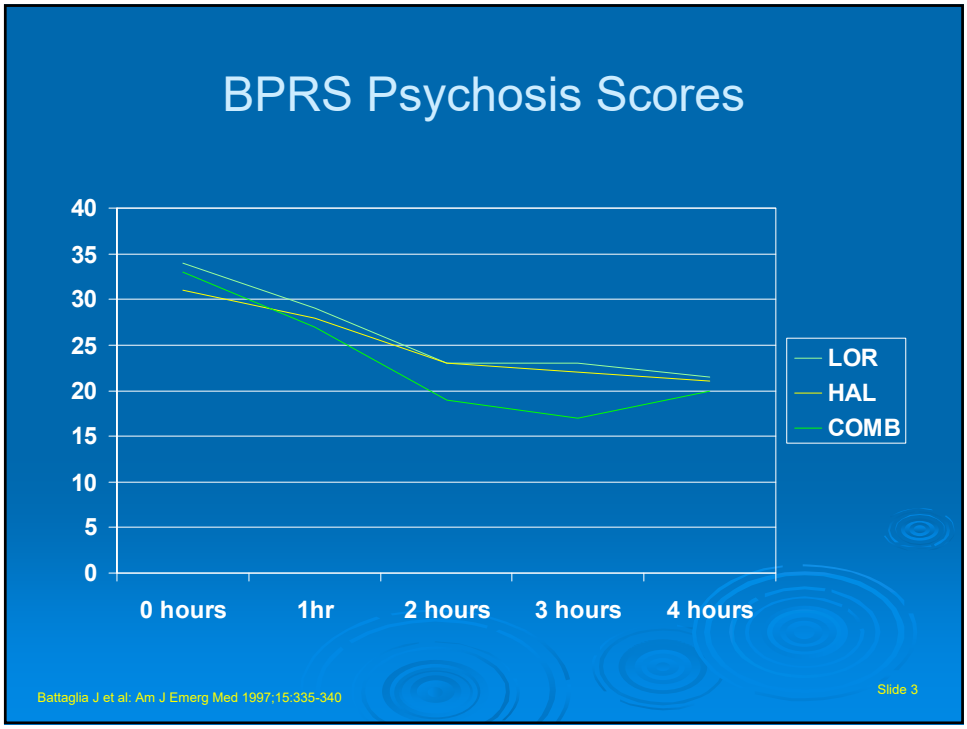
Slide 1

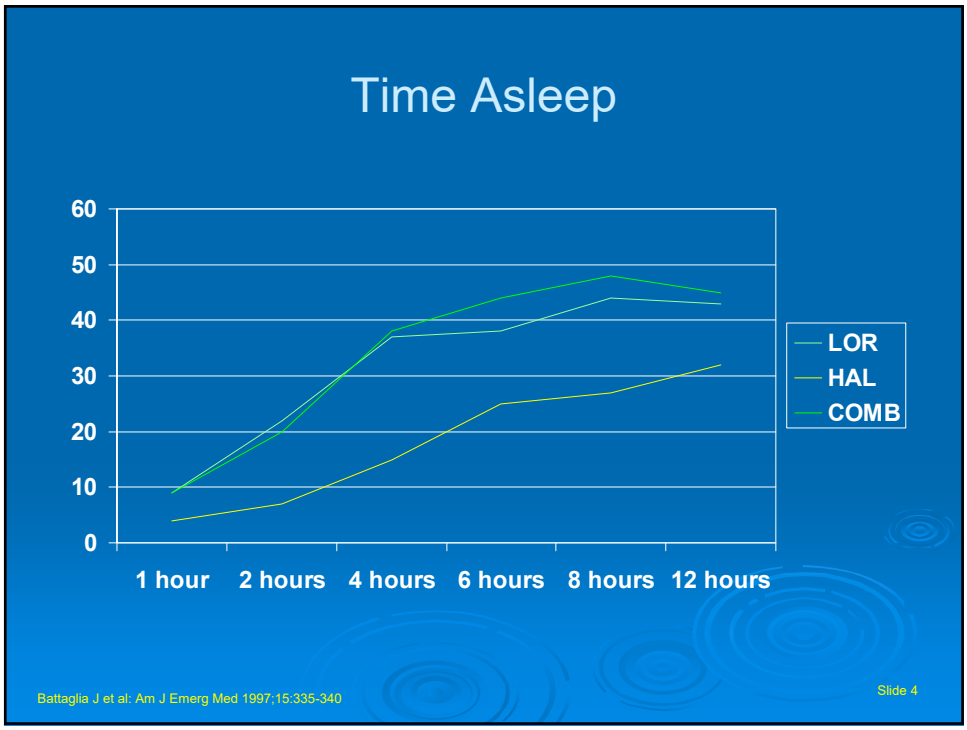
Agitation Scores



Battaglia J et al: Am J Emerg Med 1997;15:335-340

Slide 2


BPRS Psychosis Scores
40
35
30
25
20
15
10
5
0
0 hours
1hr
2 hours
3 hours
4 hours
LOR
HAL
COMB
Battaglia J et al: Am J Emerg Med 1997;15:335-340
Slide 3


Time Asleep
60
50
40
30
20
10
0
1 hour
2 hours
4 hours
6 hours
8 hours
12 hours
LOR
HAL
COMB
Battaglia J et al: Am J Emerg Med 1997;15:335-340
Slide 4

IM Haloperidol/Benzodiazepine

- 111 ER patients with severe agitation randomly assigned to haloperidol (5 mg), lorazepam (2 mg) or midazolam (5 mg)
  - All intramuscular
  - Double-blind method
  - Similar efficacy
  - Midazolam had shorter time to onset of action and recovery from sedation
- 20 psychiatric emergency patients blindly assigned to IM lorazepam (2 mg) or IM haloperidol (5 mg) + 2 mg lorazepam
  - Combination more effective after one hour but not subsequently

F. Nobay: Academic Emergency Medicine 2004;11:734; S.A. Bieniek: Pharmacotherapy 1998;18:57; J Battaglia: Am J Emerg Med 1997;15:335

Antipsychotic-Lorazepam Combinations

- 30 ER patients with acute agitation and/or psychosis randomly assigned to
  - Oral risperidone 2 mg + IM lorazepam 2 mg
  - Oral haloperidol 5 mg +IM lorazepam 2 mg
  - Oral placebo + IM lorazepam 2 mg
  - No difference between treatments

Vesser F: J Psychiatric Practice 2006;12:103

Intramuscular Ziprasidone

- Randomized comparison of IM ziprasidone and haloperidol
  - 60% of patients in both groups got adjunctive lorazepam
  - Discontinuation rates 9% for ziprasidone and 19% for haloperidol
  - Ziprasidone had greater improvement of BRPS and agitation
  - QTc prolongation 2.14 ms with ziprasidone versus 2.22 ms with haloperidol
- IM ziprasidone dosing
  - 10 mg initially, then 5-10 mg q. 4-6 hours
  - Maximum dose 80 mg/4 doses/24 hours

Brook 2000

Intramuscular Olanzapine

- 4 studies compared IM olanzapine to IM placebo (N=769)
  - All industry sponsored
  - Olanzapine > placebo for "important response" and no need for repeat injection
    - RR 0.49 (95% CI 0.42-0.59)
    - NNT 4
- 2 studies compared IM olanzapine to IM haloperidol (N=482)
  - No difference in response or need for repeat injection
  - More EPS with haloperidol
- 2 studies compared IM olanzapine to IM lorazepam (n=355)
  - No difference in response but more lorazepam patients needed repeat injection

Cochrane reviews vol 4, 2006

ACEP Practice Guidelines

- Method:
  - Literature reviews
  - Comments from leaders in psychiatry, emergency medicine, emergency nursing
- Classification of studies
  - Class I: Interventional studies, well designed RCTs, prospective cohort studies, meta analyses of RCTs
  - Class II: Observational studies, case controlled studies, other meta analyses
  - Class III: Cross sectional studies, case series, consensus panels
- Classification of recommendations
  - Level A: High degree of clinical certainty based on interventional studies (RCTs) and high quality meta analyses of RCTs or overwhelming evidence from observational studies
  - Level B: Strategires with moderate clinicl certainty based on observational studies, decision analysis or strong consensus
  - Level C: Strategies based on consensus in the absence of data or preliminary, inconclusive or conflicting evidence

Slide 1

TW Lukens et al: Ann Emerg Med 2006;47:79-99

ACEP Practice Guidelines

- Evidence on treatment of agitation
  - Benzodiazepines
    - No class I studies
    - Multiple class II studies show equivalence of 2-4 mg lorazepam to 5 mg haloperidol
    - Clonazepam and flunitrazepam shown to be equivalent to haloperidol
    - Study of haloperidol/promethazine versus lorazepam considered class III
    - Midazolam 5 mg I.M. shorter time to sedation (18 minutes) than lorazepam (32 minutes) or haloperidol (28 minutes): Class II study
      - Class III studies find 2.5-3 mg midazolam effective
    - TREC group case series found midazolam 15 mg > haloperidol 5 mg + promethazine 50 mg for rapid sedation and sleep
    - Battaglia study of haloperidol/lorazepam plus monotherapy considered class II
    - Other studies showing haloperidol/lorazepam > monotherapy are level III and do not use equivalent doses of the single drug in the combination
  - Neuroleptics
    - Droperidol > haloperidol (5 mg of each) in a class II study
    - No clear benefit of adding haloperidol to a benzodiazepine

Slide 2

TW Lukens et al: Ann Emerg Med 2006;47:79-99

ACEP Practice Guidelines

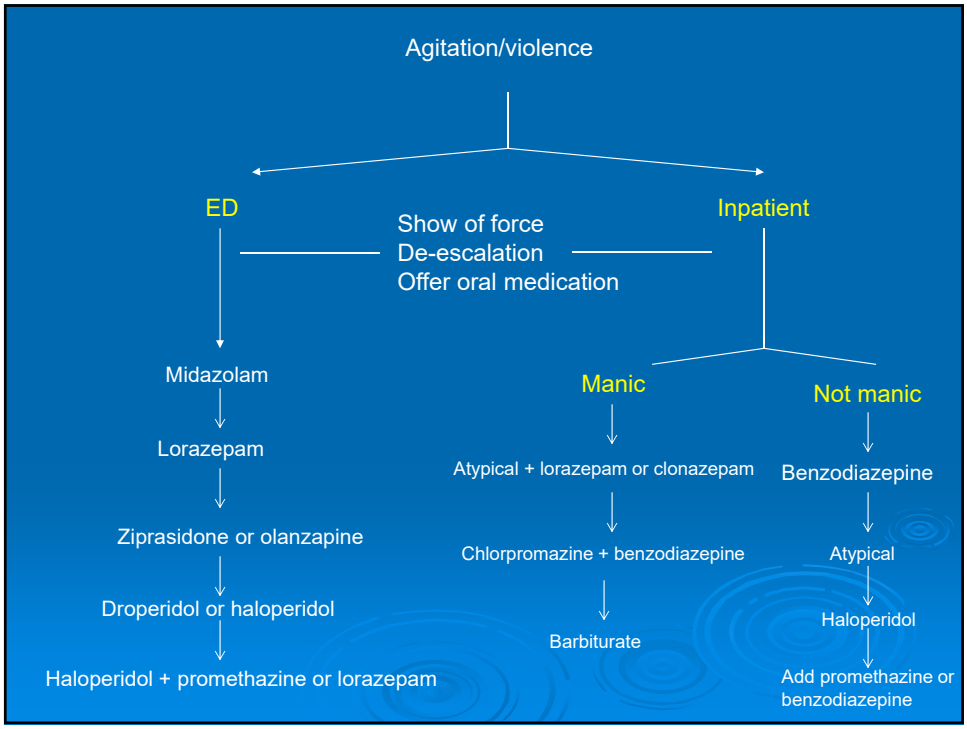
- Evidence on treatment of agitation
  - I.M. atypical antipsychotics
    - I.M. ziprasidone > placebo in class II studies
      - 20 mg > 30 mg
      - I.M. ziprasidone > I.M. haloperidol in a class III study
    - Olanzapine = haloperidol in 2 class III studies
      - Olanzapine 10 mg > lorazepam 2 mg in mania at 2 hours but not later
        - Doses not equivalent
  - Oral risperidone 2 mg + lorazepam 2 mg = I.M. haloperidol 5 mg + lorazepam 2 mg in class II study
- Recommendations
  - Level A: none
  - Level B:
    - Lorazepam, midazolam, droperidol or haloperidol monotherapy
    - For rapid sedation, use droperidol before haloperidol
    - Typical or atypical antipsychotic monotherapy as initial treatment if antipsychotic indicated because of psychosis
    - Combine oral lorazepam and oral risperidone in cooperative agitated patients
  - Level C: Combined parenteral benzodiazepine + haloperidol may produce more rapid sedation over first 1-2 hours

Slide 3

TW Lukens et al: Ann Emerg Med 2006;47:79-99

Clinical Implications

- If you believe a medication will help, it is more likely to help
- Current practices are not evidence based
  - No well designed trials
  - Statistically significant results are not necessarily clinically meaningful
  - Putting patient to sleep may not be ideal outcome
  - Aggressive treatment with neuroleptics linked to long-term nonadherence
- Superiority of haloperidol/lorazepam to haloperidol alone not clearly proven
  - Midazolam > HAL/PRO in TREC-Rio study
  - Promethazine more logical choice than lorazepam to combine with haloperidol
- Droperidol may be superior to haloperidol
  - QTc prolongation has not been associated with cardiac events in >12,000 patients
- Current data suggest that benzodiazepines probably equivalent to neuroleptics and possibly atypicals for nonpsychotic agitation
- Parenteral atypicals better tolerated than haloperidol
- Parenteral benzodiazepines less risky
- Cost and storage affect medication choice



Causes of Agitation in Brain Damaged Patients

- Delirium
- Intercurrent illness
- Minor physiologic change
  - Fever
  - Dehydration
- Paradoxical reaction to CNS depressants
- Any new medication
- Change in environment
  - Room, roommate, etc.
- Concurrent mood disorder
  - Depression
  - Mania

Treatment of Delirium

- Correct underlying illness
- Withdraw unnecessary medications
- Orient patient frequently
- Morning bright light for reversal of sleep-wake cycle
- Minimize changes in environment
- IV midazolam, droperidol, haloperidol
- ECT

Types of Chronic Nonpsychotic Agitation

- Unpredictable aggressive behavior
- Wandering
- Pacing
- Grabbing
- Biting
- Spitting
- Restlessness
- Shouting
- Profanity
- Disinhibition

Treatment of Chronic Agitation

- Correct all medical factors
- Discontinue all unnecessary medications
- Avoid sleeping pills and other CNS depressants
- Minimize changes in environment and caretaker
- Avoid power struggles
- Clock, calendar, lights at night
- Morning bright light for reversed sleep-wake cycle
- Avoid power struggles
- Medications are later choice

Medications for Chronic Nonpsychotic Agitation

- SSRIs
  - 30 mg citalopram effective but associated with cognitive decline and QT prolongation
- Beta blockers
  - Propranolol best studied
    - 80-320 mg; higher doses may be necessary
  - Improvement takes 1-2 months
- Buspirone
  - High doses
- Anticonvulsants
  - Valproate used most commonly despite lack of controlled data
    - See next slides
- Lithium
  - Neuroprotective but can have cognitive side effects
- Trazodone
  - Inadequate data

Pollock BG et al: Am J Ger Psychiatry 2007;15:942-952; Walther S et al: Psychopharmacology 2006;185:524-528; J Cummings, K Zhong: Clin Pharmacol Ther 2015;98:483

Medications for Chronic Nonpsychotic Agitation in Demented Patients

- Cholinesterase inhibitors can decrease agitation in Alzheimer's disease
- Delta-9-tetrahydrocannabinol decreases nighttime wandering
- Neuroleptics no > placebo
- Atypical antipsychotics
  - Not effective in CATIE trial
  - Cerebrovascular risks in older patients
- Withdrawing antipsychotics does not lead to behavioral deterioration in nursing home patients
- Consider propranolol, buspirone, SSRIs

Slide 2

J Cohen-Mansfield Arch Intern Med 1999;159:1733

Valproate for Prevention of Agitation and Psychosis in Alzheimer's Disease

- 313 patients with mild-moderate Alzheimer's disease
  - 2-year trial
  - Random assignment to valproate or placebo
    - Modal dose 250 mg
    - Mean level 43
    - Higher doses not tolerated
- No difference in
  - Dropouts
  - Psychosis
  - Agitation
  - Cognition
  - Functioning
  - Quality of life
  - Global outcomes

Slide 1

PN Tariot et al: Arch Gen Psychiatry 2011;68:853-861

Valproate for Prevention of Agitation and Psychosis in Alzheimer's Disease

- Placebo>valproate at 12 and 18 months for
  - Cognition
  - ADLs
- Subset of 88 patients had MRI at baseline and 1 year
  - Valproate had
    - Greater decrease in volume of hippocampus bilaterally
    - More loss of whole brain volume
    - Faster ventricular expansion
    - Lower MMSE scores
- Valproate caused more sedation and other typical side effects
- Likelihood of valproate improving agitation or psychosis once they occur not high since equal numbers became agitated and/or psychotic while taking it
- Little justification for using valproate for agitation or psychosis in Alzheimer's disease

Slide 2

PN Tariot et al: Arch Gen Psychiatry 2011;68:853-861

Dextromethorphan-Quinidine (Nuedexta)

- Actions of dextromethorphan
  - Serotonergic
  - Uncompetitive NMDA antagonist
  - Alpha-1 antagonist
  - SNRI
  - Nicotinic alpha3beta4 antagonist
- Quinidine inhibits dextromethorphan metabolism
- Multicenter, industry-sponsored RCT in Alzheimer's disease
- 2 consecutive 5-week stages
  - Increased likelihood of positive result if robust placebo response
  - Stage 1: DM/Q increased to 30/10 BID
  - Stage 2: Patients receiving placebo in stage 1 randomized to DM/Q or placebo

Slide 1

JL Cummings et al: JAMA 2015;314:1242-1254

Dextromethorphan-Quinidine

- 218 patients in intent to treat
  - 194 completed study
  - 152 received DM/Q considering both stages
  - 127 got placebo
- Primary end point: reduction in NPI agitation/aggression score
  - NPI rates frequency X severity score of 1-12
  - Stage 1 DM/Q: 7.1-3.8
  - Stage 1 placebo: 7.0-5.3
  - Least squares mean difference -1.5
  - Stage 2 DM/Q: 5.8-3.8
  - Stage 2 placebo: 6.7-5.8
  - Least squares mean difference -1.6
  - % decrease over 10 weeks
    - Only DM/Q: 51%
    - Only placebo: 26%
- Secondary measures
  - Significant improvement in CGI, total NPI, caregiver distress
  - No difference in QOL, MMSE, ADAS-Cog

Slide 2

JL Cummings et al: JAMA 2015;314:1242-1254

Meta Analysis of 15 Antipsychotic Dementia RCTs

- All but one industry sponsored
- Risperidone, olanzapine, aripiprazole, quetiapine, haloperidol
- 3353 patients on active drug, 1757 on placebo
- Overall improvement compared to placebo
  - Aripiprazole and risperidone effective
  - Olanzapine not effective overall
  - Not enough data on quetiapine
- Decreases compared to placebo
  - BPRS: 2.5/21-30
  - NPI: 3.6/34-43
  - BEHAVE AD: 1.5/16-19
- OR for cerebrovascular AEs:
  - Overall: 2.13
  - Risperidone: 3.43

Schneider LS et al: Am J Geriatr Psychiatry 2006; 14:191–210

CATIE Dementia Study

- 421 Alheimer's disease patients with psychosis, agitation or aggression
- Randomly assigned for 6 months to
  - Olanzapine (mean dose 5.5 mg)
  - Risperidone (1 mg)
  - Quetiapine (57 mg)
  - Placebo
- 80% discontinued initial medication within 5-8 weeks
  - No difference in time to discontinuation
  - Time to discontinuation because of lack of response
    - Risperidone (27 weeks) and olanzapine (22 weeks)> quetiapine (9 weeks) and placebo (9 weeks)
- Rates of global improvement same for all groups, including placebo (21-32%)
- Significantly more EPS and confusion with olanzapine and risperidone

Schneider LS et al: NEJM 2006;355:1525

Antipsychotic Risks in Cognitive Disorders

- Dementia
  - O.R. for death 1.54; NNH=87
    - Greatest with haloperidol
  - Risperidone: O.R. for stroke 3.12
    - Not with olanzapine, aripiprazole, quetiapine
  - Increased appetite and weight: olanzapine (O.R. 4.70), risperidone (O.R. 3.40)
  - Anticholinergic side effects: olanzapine (O.R. 3.30; NNH=6)
  - Increased cognitive decline compared with placebo: olanzapine, quetiapine, risperidone
- Nonelderly adults with cognitive dysfunction
  - Increased risk of sudden cardiac death with any antipsychotic
    - Dose related
  - Weight gain: olanzapine (O.R. 4.02-11.3; NNH=3)
  - Urinary tract syndromes
- Reputed benefits:
  - Behavioral syndromes with dementia: aripiprazole, olanzapine, risperidone
    - Benefit small but statistically significant
  - GAD: Quetiapine
  - OCD: Risperidone augmentation
  - No benefit in substance abuse or eating disorders
  - "The use of atypical antipsychotic medications for any of these conditions cannot be justified as evidence-based" (p. 1366)

AR Maher et al: JAMA 2012;306:1359; HC Kales et al: Am J Psychiatry 2012;169:71-79

Agitation in Children

- No controlled data
- Holding environment preferable to pharmacologic intervention
- Involve familiar caretaker if possible
- Benzodiazepine preferable to antipsychotic drug

Aggression in Children

- Antipsychotics improve tantrums, aggression and self-injury in autism
  - Also improvement in repetitive, stereotyped behavior
  - No improvement of social interaction and communication
- Consider beta blocker, buspirone, SSRI
- No data on very young children

Slide 1

DF Connor et al: J Emotional Behavioral Disord 2003;11:157; CJ McDougle et al: Am J Psychiatry 2005;162:1142-1148

Aggression in Children

- Lithium and valproate in disruptive behavior disorders
  - 3 positive RCTs for lithium
    - One negative RCT had small N and just 2 week trial
  - One positive RCT for valproate
    - Patients also had mood swings and explosive temper
- Antipsychotic drugs in disruptive behavior disorders
  - Most data with risperidone
    - Final dose 1-3 mg
  - Two RCTs of risperidone + stimulant in comorbid ADHD and disruptive behavior disorders
    - Patients age 5-12
    - IQ 36-84
    - Constant dose of stimulant + risperidone or placebo
    - Addition of risperidone decreased aggression, destructive behavior, aggression and hyperactivity more than stimulant alone
  - Small open studies of quetiapine and aripiprazole
  - Two randomized trials show efficacy of haloperidol, molindone and thioridazine in decreasing aggression and conduct disorder symptoms
- Are risks of long-term treatment in brain damaged children similar to risks in treatment of dementia in adults?

Slide 2

DH Barzman, RL Findling: Int Rev Psychiatry 2008;20:151

Aggression in Children

- Always try psychosocial and behavioral interventions first
- Treat underlying disorder before nonspecific pharmacotherapy
- Stimulants may improve other ADHD symptoms without reduction of pathological aggression
  - 44% of patients in MTA study had continued aggression after 14 months of optimized stimulant treatment
- Methylphenidate improved aggression in conduct disorder
  - 2/3 had comorbid ADHD
  - Disruptive behavior improved independent of change in ADHD
  - Most patients still had disruptive behavior
- Antipsychotic drugs first choice for psychotic agitation
  - Antipsychotic effect is not immediate

Slide 3

DH Barzman, RL Findling: Int Rev Psychiatry 2008;20:151

Atypical Antipsychotics ARE

- Better tolerated acutely than neuroleptics
- Not clearly more effective in schizophrenia
- Probably more desirable than haloperidol in emergency treatment of agitation
- Less likely to interfere with cognition
- Effective for mania
  - Neuroleptics, benzodiazepines, barbiturates also effective
- Sometimes helpful chronically in bipolar disorder
  - Especially clozapine

Atypical Antipsychotics are NOT

- Effective for core cognitive disorder of schizophrenia
  - Clozapine probably superior for sensory gating
- Likely to cure schizophrenia
  - Usual criterion 20-30% improvement
  - Combination treatment usually necessary
- Free of adverse effects
  - NMS and TD reported with all atypicals
  - Sedative and cognitive side effects
  - Metabolic effects more of a concern than cardiac effects
- Proven mood stabilizers
  - The only long-term study enriched the sample and selected patients with few recurrences
- Effective or safe for long-term treatment of agitation in demented patients