Pharmacodynamics of Second-Generation Antipsychotics

Jose de Leon, MD

(12-18-15)

Learning Objectives

After completing this presentation, the participant should be able to:

1) Appreciate the relevance of second-generation antipsychotic pharmacodynamics, mainly D_2 blockade for efficacy in schizophrenia and bipolar mania, and our limited understanding of the pharmacodynamics behind the adjunctive use of these drugs in treatment-resistant depression, which may not be associated with more benefit than harm.

2) Appreciate the relevance of pharmacodynamics in the safety of second-generation antipsychotics, including central and peripheral mechanisms.

3) Be familiar with use of new D_2 partial agonists.

Abbreviations

- ADR: adverse drug reaction
- AED: antiepileptic drug
- ALP: alkaline phosphatase
- ALT: alanine transaminase (serum glutamate-pyruvate transaminase, SGPT)
- ANC: absolute neutrophil count
- AP: antipsychotic
- AST: aspartate transaminase (serum glutamic oxaloacetic transaminase, SGOT)
- CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness
- CBM: carbamazepine
- FGAP: first-generation AP
- BP: blood pressure
- DDI: drug-drug interaction
- EPS: extrapyramidal symptoms
- GGT: gamma-glutamyl transferase
- HDL: high density lipoprotein
- ID: intellectual disability
- IM: intramuscular
- IV: intravenous
- NMS: neuroleptic malignant syndrome
- SGAP: second-generation AP
- TD: tardive dyskinesia
- VPA: valproic acid
- WBC: white blood count

SGAP abbreviated names

- AMI: amisulpride (not approved in the US)
- ARI: aripiprazole
- ASE: asenapine
- BRE: brexpiprazole (marketed in the US in 2015)
- CAR: cariprazine (marketed in the US in 2015)
- CLO: clozapine
- HAL: haloperidol
- ILO: iloperidone
- LUR: lurasidone
- OLA: olanzapine
- PAL: paliperidone (or 9-hydroxyrisperidone)
- QUE: quetiapine
- RIS: risperidone
- ZIP: ziprasidone

A FGAP is used as the control on meta-analysis slides.

Statistical Abbreviations

- CI: confidence interval
- NNH: number needed to harm
- NNT: number needed to treat
- OR: odds ratio
- RCT: Randomized Clinical Trial
- SMD: standardized mean difference

The presentation "Introduction to Statistical Concepts Needed for Clinical Pharmacology" explains how to these statistical concepts.

Receptor Terminology

- **Allosteric Regulation:**
The modification of the reactivity of ENZYMES by the binding of effectors to sites (ALLOSTERIC SITES) on the enzymes other than the substrate BINDING SITES.

http://www.ncbi.nlm.nih.gov/mesh?term=allosteric%20regulation

- **Partial agonist: a drug with affinity and activity somewhat lower than that of an agonist.**
At D_2: action depends on the dopamine concentration at that site:
  □ Low concentration: agonist
  □ High concentration: antagonist

Warning

This is a long presentation (>200 slides):

1) You may need to read it more than once until you have become familiar with key aspects. The first time you read it you may want to shorten it by skipping any section not relevant for you, such as Section 3 on New Partial D_2 Agonists). Shocking facts are marked in red.

2) More importantly, you need to practice every day and review the pharmacodynamics of drugs when any of your patients is taking an SGAP and polypharmacy.

3) There is a long list of ADRs. If you think it is too long to remember, you may want to stop prescribing SGAPs. Dr. de Leon has seen deaths caused by psychiatrists who were not aware of their lack of knowledge of SGAP ADRs. Once, a psychiatrist justified his unsafe practice: "I have been doing this for many years". Dr. de Leon did not reveal what he thought, "I see; the question is how many more patients have you killed during those years."

Statistical Warning and Abbreviations

- This presentation does not explain how to interpret meta-analyses.
- These concepts were described in a prior presentation, "Introduction to Statistical Concepts Needed for Clinical Pharmacology":
  - CI: confidence interval
  - NNH: number needed to harm
  - NNT: number needed to treat
  - OR: odds ratio
  - SMD: standardized mean difference
- New concept: LHH: likelihood of being helped or harmed; LHH=NNH/NNT http://www.ncbi.nlm.nih.gov/pubmed/23574101
  - <1 means more harm than benefit.
  - >1 means more benefit than harm.
  - >10 means >10 times more benefit than harm.

Lecture Content

1. SGAP Pharmacodynamics of Efficacy

2. SGAP Pharmacodynamics of Safety

3. Update on New D$_2$ Partial Agonists

Lecture Content

1. SGAP Pharmacodynamics of Efficacy
    1.0. Clinical Efficacy
    1.1. Blockade of D_2 Receptors at Basal Ganglia and Cortex
    1.2. Unknowns in Depression
    1.3. Comment on Pharmacokinetics

2. SGAP Pharmacodynamics of Safety
    2.1. Brain
        2.1.1. EPS
        2.1.2. Hyperprolactinemia
        2.1.3. Weight Gain
        2.1.4. Sedation
        2.1.5. Memory Impairment
        2.1.6. ↓ Seizure Threshold
        2.1.7. Obsessive-Compulsive Symptoms
    2.2. Periphery (some can include brain effects):
        2.2.1. Hyperglycemia
        2.2.2. Hyperlipidemia
        2.2.3. Sexual ADRs
        2.2.4. Orthostatic Hypotension
        2.2.5. Hypertension
        2.2.6. Anticholinergic Symptoms
        2.2.7. Nausea
        2.2.8. Swallowing Impairment
        2.2.9. Prolongation of QTc
        2.2.10. Myocarditis
        2.2.11. Agranulocytosis/Neutropenia
        2.2.12. Risk for Hyponatremia
        2.2.13. Risk for Venous Thromboembolism
        2.2.14. Risk for Temperature Dysregulation
        2.2.15. ↑ Liver Enzymes and Severe Hepatic Injury
        2.2.16. Pancreatitis
        2.2.17. Cerebrovascular Accidents and Death in Demented Patients
    2.3. Comment on Pharmacokinetics

3. Update on New D_2 Partial Agonists

1. Pharmacodynamics of SGAP Efficacy

1. Pharmacodynamics of SGAP Efficacy

1.0. Clinical Efficacy

1.1. Blockade of D_2 Receptors at Basal
   Ganglia and Cortex

1.2. Unknowns in Depression

1.3. Comment on Pharmacokinetics

1.0. Clinical Efficacy

1.0. Clinical Efficacy

- Approved indications for some drugs:
  - Schizophrenia psychosis
  - Bipolar disorder (mania, relapse depression)
  - Adjunctive for treatment-resistant major depression
  - Irritability in children with autism
  - Tourette syndrome
- Off-label:
  - Dementia (psychosis and agitation)
  - Drug-induced psychosis
  - Delirium
  - Treatment-resistant OCD
  - PTSD
  - Personality disorders

1.0. Clinical Efficacy

1.0.1. Schizophrenia

1.0.2. Bipolar Disorder

1.0.3. Treatment-Resistant Major Depression

1.0.1. Efficacy: Schizophrenia

1.0.1. Efficacy: Schizophrenia

1.0.1.1. Acute

1.0.1.2. Maintenance

1.0.1.1. Efficacy in Schizophrenia: Acute Phase

1.0.1.1. Efficacy in Schizophrenia: Acute Phase

■ Acute phase versus placebo:

Leucht et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019

Overall change in symptoms; SMDs in order (95% CI)

☐ CLO: -0.88 (-1.03 to -0.73)
☐ AMI: -0.66 (-0.78 to -0.53)
☐ OLA: -0.59 (-0.65 to -0.53)
☐ RIS: -0.56 (-0.63 to -0.50)
☐ PAL: -0.50 (-0.60 to -0.39)
☐ HAL: -0.45 (-0.51 to -0.31)
☐ QUE: -0.44 (-0.52 to -0.35)
☐ ARI: -0.43 (-0.52 to -0.34)
☐ ZIP: -0.39 (-0.49 to -0.30)
☐ ASE: -0.38 (-0.51 to -0.25)
☐ LUR: -0.33 (-0.45 to -0.21)
☐ ILO: -0.33 (-0.43 to -0.22)

1.0.1.2. Efficacy in Schizophrenia: Maintenance

1.0.1.2. Efficacy in Schizophrenia: Maintenance

- Data on maintenance is very limited.
  Leucht et al. 2012: http://www.ncbi.nlm.nih.gov/pubmed/22560607
  - ☐ Data on APs versus placebo
  - ☐ No data on individual SGAPs

1.0.2. Efficacy: Bipolar Disorder

1.0.2. Efficacy: Bipolar Disorder

1.0.2.1. Mania

1.0.2.2. Bipolar Depression

1.0.2.3. Maintenance

1.0.2.1. Efficacy: Mania

1.0.2.1. Efficacy: Mania

■ Cipriani et al. 2011:
Mean change score; SMDs in order (95% CI) (drug versus placebo)
- RIS: -0.50 (-0.63 to -0.38)
- OLA: -0.43 (-0.54 to -0.32)
- QUE: -0.37 (-0.51 to -0.23)
- ARI: -0.37 (-0.51 to -0.23)
- ASE: -0.30 (-0.53 to -0.07)
- ZIP: -0.19 (-0.37 to -0.03)

Other drugs:
- HAL: -0.56 (-0.68 to -0.43)
- Lithium: -0.37 (-0.50 to -0.25)
- CBM: -0.36 (-0.60 to -0.11)
- VPA: -0.20 (-0.37 to -0.04)

1.0.2.2. Efficacy: Bipolar Depression

1.0.2.2. Efficacy: Bipolar Depression

■ SGAPs with FDA approval:
  □ OLA combined with fluoxetine
  □ LUR
  □ QUE
■ Treatment of bipolar depression is a controversial issue.
  A meta-analysis is presented in the next slide.
  Other recent meta-analyses:
  □ Selle et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/24549862
  □ Taylor et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/25283309

1.0.3. Efficacy: Bipolar Depression

■ Ketter et al. 2014: http://www.ncbi.nlm.nih.gov/pubmed/25533911

	NNT	NNH	LHH
OLA-fluoxetine	4	6 weight gain	1.5
QUE	6	5 sedation	0.8
LUR monotherapy	5	15 akathisia	3
LUR adjunctive	7	17 nausea	2.4

1.0.3. Efficacy: Bipolar Depression

- As LUR may have a good profile, it is briefly reviewed:
  - ☐ Pharmacokinetics:
    - Metabolized by CYP3A4
    - Do not combine with CBM (potent inducer).
    - Administer with food.
    - (see presentation on SGAP pharmacokinetics for details)
  - ☐ Safety comparison with other SGAPs:
    - High EPS risk (similar to RIS)
    - Average on prolactin ↑
    - Low weight gain (similar to placebo in RCTs)
    - Moderate sedation (similar to RIS)
    - (see meta-analysis slides in this presentation)
  - ☐ Initial dose: 20 mg given once daily
    - (monotherapy or adjunctive therapy with lithium or VPA)
    - This dose may be effective.
  - ☐ Maximum daily dose: 120 mg

1.0.2.3. Efficacy: Bipolar Maintenance

1.0.2.3. Efficacy: Bipolar Maintenance

■ Unfortunately: very few RCTs and
even less with SGAPs
  □ No SGAP has FDA approval for
maintenance in bipolar disorder.
■ Meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/21733231
  □ Some data on QUE monotherapy and
in combination

1.0.3. Efficacy: Adjunctive For Treatment-Resistant Depression

1.0.3. Efficacy: Treatment-Resistant Depression

■ Spielmans et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/23554581

OR response rates in order (95% CI)
- ☐ ARI: 2.07 (1.58 to 2.72.)   NNT= 7
- ☐ RIS: 1.83 (1.16 to 2.88)   NNT= 8
- ☐ QUE: 1.53 (1.17 to 2.00)   NNT= 10
- ☐ Olanzapine/fluoxetine combination was not significant:
       1.30 (0.87 to 1.93)

1.1. Blockade of D$_2$ Receptors at Basal Ganglia and Cortex

1.1. Blockade of D_2 Receptors at Basal Ganglia and Cortex

- **Main pharmacodynamic mechanism:**
  - ☐ Antipsychotics rather than anti-schizophrenia drugs
  - ☐ Dopamine hypothesis: blocking D_2 receptors
    - ● Most of them: D_2 antagonists
    - ● ARI, BRE and CAR: D_2 partial agonists
      In situations of high dopamine: antagonists
      Antagonists at nigrostriatal-cortex receptors
      In case reports: ARI has been associated with worsening of psychosis.

1.1. Blockade of D_2 Receptors at Basal Ganglia and Cortex

- The FDA requires that the efficacy of each classified drug must be proven.
- Physicians tend to consider all drugs within the class as alternatives. For example, all APs have antagonistic properties at D_2 receptors (antagonists or partial agonists) and are likely to use the same pharmacodynamic mechanism. All APs have NOT been approved for mania, but it is likely that most or all are anti-manic agents.

1.1. Blockade of D$_2$ Receptors at Basal Ganglia and Cortex

■ It is unclear which pharmacodynamic mechanisms explain efficacy in other diagnoses.
  □ The dopamine hypothesis is usually assumed for efficacy in most indications.
  □ Not all SGAPs appear to have efficacy in depression. Are other receptors important for efficacy in depression?

1.2. Unknown Pharmacodynamic Mechanisms in Depression

1.2. Pharmacodynamic Mechanisms in Depression

1.2.1. Bipolar Depression

1.2.2. Treatment-Resistant Major Depression

1.2.1. Pharmacodynamic Mechanisms in Bipolar Depression

■ Approved for monotherapy:
  □ LUR
  □ QUE

■ Hypotheses:
  □ High ratio for 5-HT$_{2A}$/D$_2$ receptors
  □ Role for 5-HT$_{2A}$ or α$_2$ blockade

1.2.2. Pharmacodynamic Mechanisms in Treatment-Resistant Major Depression

1.2.2. Pharmacodynamic Mechanisms in Treatment-Resistant Major Depression

- Approved for adjunctive therapy of treatment-resistant depression:
  - ARI
  - BRE
  - OLA combined with fluoxetine
  - QUE
- Hypotheses:
  - 5-HT_{2A} blockade (shared by approved SGAPs)
  - 5-HT_{1A} partial agonism for ARI and norquetiapine
  - 5-HT2_C antagonist and inhibition of noradrenaline transporter by norquetiapine, the main active QUE metabolite.

1.2.2. Pharmacodynamic Mechanisms in Treatment-Resistant Major Depression

- Complexity of predictions based on pharmacodynamics:
  - □ ZIP in clinical doses blocks reuptake of serotonin, noradrenaline and dopamine, which may suggest potential for antidepressant properties.
  - □ The only ZIP RCT in bipolar depression indicated this compound had no more efficacy than placebo.

1.3. Efficacy:

Comment on Pharmacokinetics

1.3. Interaction of Efficacy with Pharmacokinetics and Pharmacodynamics

- Pharmacokinetics facilitates pharmacodynamics: Sufficient drug concentration is needed for efficacy.

- Pharmacodynamics determines efficacy when there is sufficient drug concentration.

2. Pharmacodynamics of SGAP Safety

2. Pharmacodynamics of SGAP Safety

2.0. Clinical Safety

2.1. Brain

2.2. Periphery (with/without brain)

2.3. Comment on Pharmacokinetics

2.0. Clinical Safety

2.0.1. Schizophrenia

2.0.2. Mania

2.0.3. Treatment-Resistant Major Depression

2.0.1. Safety: Schizophrenia

2.0.1. Safety: Schizophrenia

■ Leucht et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019
All-cause discontinuation ORs in order (95% CI)
(drug versus placebo)
- AMI: 0.43 (0.32 to 0.57)
- OLA: 0.46 (0.41 to 0.52)
- CLO: 0.46 (0.32 to 0.65)
- PAL: 0.48 (0.39 to 0.58)
- RIS: 0.53 (0.46 to 0.60)
- ARI: 0.61 (0.51 to 0.72)
- QUE: 0.61 (0.52 to 0.71)
- ASE: 0.69 (0.54 to 0.86)
- ILO: 0.69 (0.56 to 0.84)
- ZIP: 0.72 (0.59 to 0.86)
- LUR: 0.77 (0.61 to 0.96)

2.0.2. Safety: Mania

2.0.2. Safety: Mania

■ Cipriani et al. 2011: http://www.ncbi.nlm.nih.gov/pubmed/21851976
Dropout rates; ORs in order (95% CI) (drug versus placebo)
□ OLA: 0.57 (0.44 to 0.74)
□ RIS: 0.61 (0.44 to 0.83)
□ QUE: 0.64 (0.45 to 0.91)
□ ARI: 0.76 (0.55 to 1.06); no different from placebo
□ ZIP: 0.91 (0.61 to 1.34); no different from placebo
□ ASE: 0.98 (0.57 to 1.71); no different from placebo
Other drugs:
□ CBM: 0.73 (0.42 to 1.28); no different from placebo
□ VPA: 0.73 (0.51 to 1.05); no different from placebo: -
□ HAL: 0.82 (0.62 to 1.15); no different from placebo
□ Lithium: 1.05 (0.78 to 1.43); no different from placebo

2.0.3. Safety: Adjunctive for Treatment-Resistant Depression

2.0.3. Safety: Treatment-Resistant Depression

■ Spielmans et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/23554581

	NNT (CI) response	NNH (CI) most frequent ADRs	LHH[1]
ARI	7 (5-12)	4 (3-6) akathisia	0.6
QUE	10 (6-26)	3 (2-3) sedation	0.3

[1]LLH=NNH/NNT; calculated by Dr. de Leon

-Olanzapine/fluoxetine combination was definitely harmful with sedation NNH 5 (3-12) but not significant efficacy NNT=7

-RIS provided no NNH data; NNT=8 (5-33)

■ Citrome 2013: http://www.ncbi.nlm.nih.gov/pubmed/23554581

	NNT	NNH akathisia	LHH[1]
ARI	7	5	0.7
BRE	11	15	1.4

[1]LLH=NNH/NNT

■ Very troubling data:

☐ More harm than benefit (LLH<1)

- ARI
- OLA + fluoxetine
- QUE

☐ Little benefit vs harm

- BRE: LLH=1.4 (1.4 times more benefit)

2.1. The Brain: Pharmacodynamics of SGAP Safety

2.1. The Brain:
Pharmacodynamics of SGAP Safety

2.1.1. EPS

2.1.2. Hyperprolactinemia

2.1.3. Weight Gain

2.1.4. Sedation

2.1.5. Memory Impairment

2.1.6. ↓ Seizure Threshold

2.1.7. Obsessive-Compulsive Symptoms

2.1.1. EPS

2.1.1. EPS

2.1.1.1. Meta-Analysis

2.1.1.2. Reversible EPS

2.1.1.3. TD

2.1.1.4. Neuroleptic Malignant Syndrome

2.1.1.1. EPS Meta-Analysis

2.1.1.1. EPS: ORs in Meta-Analysis

■ Leucht et al., 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019

ORs in order (95% CI) (drug versus placebo)

☐ HAL: 4.76 (3.70 to 6.04)
☐ LUR: 2.46 (1.55 to 3.72)
☐ RIS: 2.09 (1.54 to 2.78)
☐ PAL: 1.81 (1.17 to 2.69)
☐ ASE: 1.66 (0.85 to 2.93); no different from placebo
☐ ZIP: 1.61 (1.05 to 2.37)
☐ AMI: 1.60 (0.88 to 2.65); no different from placebo
☐ ILO: 1.58 (0.55 to 3.65); no different from placebo
☐ ARI: 1.20 (0.73to 1.85); no different from placebo
☐ QUE: 1.01 (0.68 to 1.44); no different from placebo
☐ OLA: 1.00 (0.73 to 1.33); no different from placebo
☐ CLO: 0.3 (0.12 to 0.62); better than placebo

2.1.1.2. Reversible EPS

2.1.1.2. Reversible EPS

2.1.1.2.1. Symptoms

2.1.1.2.2. Mechanisms

2.1.1.2.3. Other Risk Factors

2.1.1.2.1. Reversible EPS: Symptoms

2.2.1.2.1 Reversible EPS

■ Reversible EPS:
  □ Acute dystonic reactions:
    ● FGAP: more frequent in young males
      first doses or increase
        typically in first days of treatment
    ● SGAP: rare and not well studied
        risperidone is probably worst
  □ Parkinsonian symptoms:
    ● FGAP: more frequent in older patients
        thought to be dose-related
  □ Akathisia

Case report lectures provide more information on acute dystonic reactions and akathisia.

2.1.1.2.2. Reversible EPS: Mechanisms

2.1.1.2.2. Reversible EPS: Mechanism

■ Mechanism for 3 reversible EPS:
  □ All 3 are due to D_2 blockade at nigrostriatal system in general
  □ They must have somewhat more specific different mechanisms since they have different risk factors and different timing.

2.1.1.2.2. Reversible EPS: Mechanism

- Among SGAPs:
  - Higher: LUR, PAL & RIS
  - Average: AMI, ASE, ILO, OLA & ZIP
  - Lower: QUE
  - Lowest: CLO
- Two main theories of "atypicality":
  - High ratios of 5-HT$_{2A}$/D$_2$ (Meltzer)
  - Low affinity for D$_2$ (Seeman)

2.1.1.2.2. EPS: Seeman's Theory

- CLO: a different profile with low D_2 blocking in *in vivo* studies due to low D_2 affinity.
- Dopamine displaces CLO: 25-40% of D_2 receptors are occupied by CLO while many of the rest may be occupied by dopamine.
- Low affinity and fast dissociation from D_2 receptors would explain how CLO & QUE are only "atypicals."
- They use a "hit-and-run" action toward D_2 receptors (Stahl).

2.1.1.2.2. EPS: Partial D_2 Agonists

- ARI, BRE & CAR:
  Low EPS risk except for akathisia

2.1.1.2.3. Reversible EPS: Other Risk Factors

2.1.1.2.3. Other Risk Factors

- AP polypharmacy
- No prior exposure to APs:
  Lower "neuroleptic threshold"
  Prior AP exposure is associated with some kind of ↑ tolerance
- Aging
- Dementing illness
- Parkinson disease
- Schizophrenia?: some naïve patients have EPS
- Intellectual disabilities: ↓ doses
- "Organic" brain problems
- Children? (pharmacokinetics)

2.1.1.2.3. Parkinson Disease

- Most cases: environmental (or gene-environment interaction);
  Genetic cases: rare
- Symptoms:
  loss of 80-90% of nigrostriatal dopamine
- The older the patient, the greater the loss:
  - Many are asymptomatic, indicating they have > 20% of dopamine left.
  - Imaging: transcranial sonography
- Some geriatric patients with drug-induced Parkinsonism may develop persistent Parkinson disease.

2.1.1.3. TD

2.1.1.3. TD

2.1.1.3.1. Mechanisms

2.1.1.3.2. Other Risk Factors

2.1.1.3.1. TD: Mechanism

2.2.1. EPS: TD

■ Irreversible
  □ TD (> 3 months after withdrawal)
■ Mechanism: Not well understood.
  Most quoted theory: blockade of
  D_2 at nigrostriatal system leads to
  dopamine hypersensitivity

2.2.1. EPS: TD

■ SGAPs: less risk than FGAPs;
Correll & Schenk, 2008:

http://www.ncbi.nlm.nih.gov/pubmed/18332662

	SGAP	FGAP	No APs
Annualized incidence	3.9%	5.5%	
children	0.4%		
adults	3.0%	7.7%	
elderly	5.2%	5.2%	
Prevalence in adults	13.1%	32.4%	15.6%

2.1.1.3.2. TD: Other Risk Factors

2.1.1.3.2. TD: Other Risk Factors

- FGAP risk factors (textbooks):
  - □ Old age
  - □ Female gender
  - □ AP duration
  - □ Possibly high doses
  - □ Presence of reversible EPS
  - □ Lack of teeth
  - □ Schizophrenia?
- Genetic variations http://www.ncbi.nlm.nih.gov/pubmed/17549063
- Meta-analysis in schizophrenia:
  - □ non-White ethnic group & early EPS
  - □ old age: suggestive but inconclusive

http://www.ncbi.nlm.nih.gov/pubmed/19645070

2.1.1.4. NMS

2.1.1.4. NMS

■ NMS while on SGAPs has rarely been described.
  □ Frequency is low: estimated around 0.2% (Caroff & Mann, 1993)
  □ "Atypical" presentations: especially with CLO

■ Dr. de Leon believes it is a complex area due to:
  □ low frequency
  □ complex differential diagnosis
  □ differences in definitions of NMS used

In 13 years of reviewing deaths in public state facilities covering 4 million people, Dr. de Leon has found no death associated with NMS.

2.1.2. Hyperprolactinemia

2.1.2. Hyperprolactinemia

2.1.1.2.1. Meta-Analysis

2.1.1.2.2. Symptoms

2.1.1.2.3. Mechanisms

2.1.1.2.4. Partial Agonists: ↓ Prolactin

2.1.2.1. Hyperprolactinemia: Meta-Analysis

2.1.2.1. Hyperprolactinemia: ORs in Meta-Analysis

■ Leucht et al., 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019
  SMDs in order (95% CI) (drug versus placebo)
  □ PAL: 1.30 (1.08 to 1.51)
  □ RIS: 1.23 (1.06 to 1.40)
  □ HAL: 0.70 (0.56 to 0.85)
  □ LUR: 0.34 (0.11 to 0.57)
  □ ZIP: 0.25 (0.01 to 0.49)
  □ ILO: 0.21 (-0.09 to 0.51); no different from placebo
  □ OLA: 0.14 (0.00 to 0.28)
  □ ASE: 0.12 (-0.12 to 0.37); no different from placebo
  □ QUE: -0.05 (-0.23 to 0.13); no different from placebo
  □ ARI: -0.22 (-0.46 to 0.03); no different from placebo

2.1.2.1. Hyperprolactinemia: Risk from SGAPs

- Hyperprolactinemia risk:
  - Higher: AMI, PAL & RIS
    Remember risperidone-induced gynecomastia is frequent in young boys.
  - Average: ASE, ILO, LUR, OLA & ZIP
  - Lower: QUE & CLO

- Partial D_2 agonists appear to be associated with hypoprolactinemia

2.1.2.2. Hyperprolactinemia: Symptoms

2.1.2.2. Hyperprolactinemia: Symptoms

■ ♀: □ Menstrual irregularities, or amenorrhea
□ Galactorrhea
□ Sexual ADRs (↓ libido)

■ ♂: □ Gynecomastia
□ Sexual ADRs: erectile dysfunction

■ Both: osteoporosis? (long-term AP use); not well-studied

2.1.2.3. Hyperprolactinemia: Mechanisms

2.1.2.3. Hyperprolactinemia: Mechanism

- Blockade of D_2 at tubero-infundibular system

- Females: higher prolactin levels make it easier to detect AP effects

2.1.1.2.4. Partial Agonists:

↓ Prolactin

2.1.1.2.4. Prolactin and Partial D_2 agonists

■ Partial agonists: ↓ prolactin agonists at tubero-infundibular system

■ Relevance of ↓ prolactin is unknown. ↑ Prolactin in some physiological situations: □ pregnancy
□ adolescence

We have no experience with wide prescription of other drugs that ↓ prolactin.

Using these drugs in children is an experiment with unknown results.

2.1.3. Weight Gain

2.1.3. Weight Gain

2.1.1.3.1. Meta-Analysis

2.1.1.3.2. Mechanisms

2.1.1.3.3. Other Risk Factors

2.1.3.1. Weight Gain: Meta-Analysis

2.1.3.1. Weight Gain: SGAP Summary

- Leucht et al., 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019
  SMDs in order (95% CI) (drug versus placebo)
  - □ OLA: 0.74 (0.67 to 0.81)
  - □ CLO: 0.65 (0.31 to 0.99)
  - □ ILO: 0.62 (0.49 to 0.74)
  - □ QUE: 0.43 (0.34 to 0.53)
  - □ RIS: 0.42 (0.33 to 0.50)
  - □ PAL: 0.38 (0.27 to 0.48)
  - □ ASE: 0.23 (0.07 to 0.31)
  - □ AMI: 0.20 (0.05 to 0.35)
  - □ ARI: 0.17 (0.05 to 0.28)
  - □ LUR: 0.10 (-0.02 to 0.21); no different from placebo
  - □ ZIP: 0.10 (-0.02 to 0.22); no different from placebo
  - □ HAL: 0.09 (-0.00 to 0.17)

2.1.3.1. Weight Gain: Risk from SGAPs

- Among SGAP short-term RCTs (prior slide):
  - Higher risk: OLA, CLO, & ILO
  - Average risk: AMI, ASE, PAL, QUE & RIS
  - Lower risk: ARI, LUR & ZIP

Please remember this is in short-term use.

2.1.3.1. Comparing weight gain (Kg) after 1 year on SGAPs
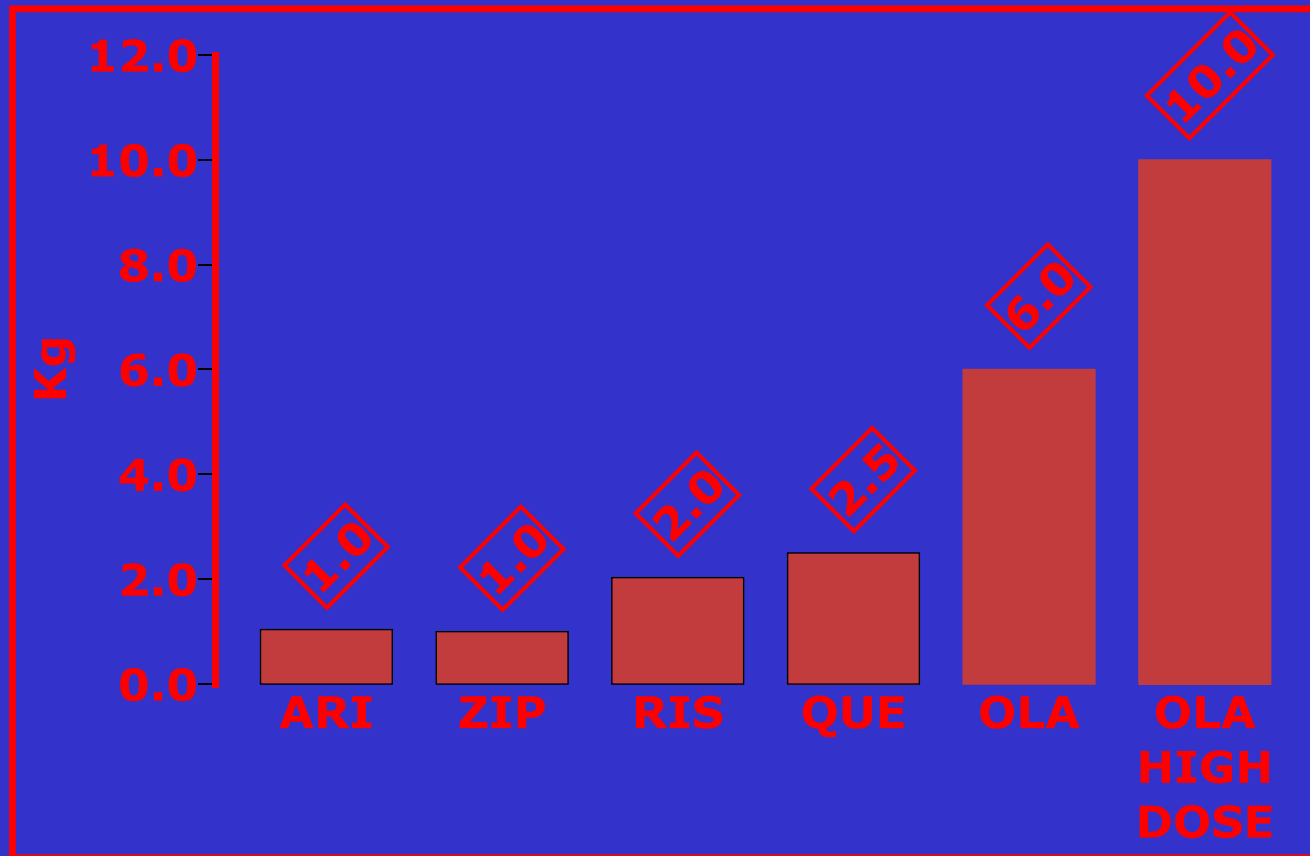
2.1.3.2. Weight Gain: Mechanism

2.2.1.3.2. Weight Gain: Mechanism

- Best predictor in APs: H_1 affinity
- Blockade of other brain receptors may be important, too ($5HT_{2C}$ and M)
- ↑ Appetite: major mediator

2.1.3.3. Weight Gain: Other Risk Factors

2.1.3.3. Weight Gain: Other Risk Factors

- Dosage-related (clear for CLO & OLA)
- Baseline weight: ↑ if underweight.
- Co-medications:
Mood stabilizers/AEDs:
  - ↑: CBM
    gabapentin and pregabalin
    lithium
    VAL
  - ↓: topiramate
    zonisamide
    (carbonic anhydrase inhibitors)

2.1.3.3. Weight Gain: Final Message

- ↑ Appetite is very important in weight gain.
- Weight gain may be dose-related but influenced by baseline weight.
- It takes weeks to > 1 year to reach a maximum weight effect.

2.1.4. Sedation

2.1.4. Sedation

2.1.1.4.1. Meta-Analysis

2.1.1.4.2. Mechanisms

2.1.1.4.3. Other Risk Factors

2.1.1.4.4. Long-Acting OLA

2.1.4.1. Sedation: Meta-Analysis

2.1.4.1. Sedation: ORs in Meta-Analysis

■ Leucht et al., 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019
ORs in order (95% CI) (drug versus placebo)
- □ CLO: 8.82 (4.72 to 15.1)
- □ ZIP: 3.80 (2.58 to 5.42)
- □ QUE: 3.76 (2.68 to 5.19)
- □ OLA: 3.34 (2.46 to 4.50)
- □ ASE: 3.28 (1.37 to 6.69)
- □ HAL: 2.76 (2.04 to 3.66)
- □ RIS: 2.45 (1.76 to 3.35)
- □ LUR: 2.45 (1.31 to 4.24)
- □ ARI: 1.84 (1.05 to 3.05)
- □ ILO: 1.71 (0.63 to 3.77); no different from placebo
- □ PAL: 1.40 (0.85 to 2.19); no different from placebo
- □ AMI: 1.42 (0.72 to 2.51); no different from placebo

2.1.4.1. Sedation: Risk from SGAPs

- Among SGAP RCTs (prior slide):
  - Higher risk: CLO
  - Then: ZIP, QUE, OLA & ASE
    (ASE: high H_1 affinity; no antimuscarinic)
  - Then: RIS, LUR & ARI
  - Then: ILO, PAL & AMI;
    no different from placebo

- Clinicians find: ARI & ZIP can cause early insomnia & activation

http://www.ncbi.nlm.nih.gov/pubmed/24330898

2.1.4.2. Sedation: Mechanism

2.2.4.2. Sedation: Mechanism

- Mechanism: blockade of brain H_1 receptors

- Dosage-related, at least at onset. Some tolerance can be expected and sedation risk ↓ by using recommended titration schedules. Pharmacological mechanism behind tolerance is not well studied: possibly mediated by epigenetic mechanisms.

2.1.4.3. Sedation: Other Risk Factors

2.2.4.3. Sedation: Other Risk Factors

- Other co-medications may be additive.
- Mood stabilizers/AEDs:
  - Sedating:
    - first-generation AEDs
    - lithium
    - topiramate
  - Non-sedating AEDs:
    - felbamate
    - lacosamide
    - lamotrigine
    - tiagabine

2.1.4.4. Sedation: Long-Acting OLA

2.1.4.4. Sedation: Long-acting OLA

- IM OLA pamoate depot
- Restricted in USA: Zyprexa Relprevv Patient Care Program:
  - ☐ Observation for 3 hours
  - ☐ Before release: healthcare professionals must confirm that the patient is alert, oriented, and absent of any signs and symptoms.
  - ☐ Patients must be accompanied to their destination.

2.1.4.4. Sedation: Long-acting OLA

■ Post-injection delirium/sedation syndrome

■ Profound sedation post-injection:

　□ 1.2% of patients, or

　□ 0.07% of injections

■ Symptoms of OLA overdose:

　□ sedation (up to coma) and/or

　□ delirium (confusion, disorientation, agitation, anxiety, and other cognitive impairment).

2.1.5. Memory Impairment

2.1.5. Memory Impairment

2.1.1.5.1. Meta-Analysis

2.1.1.5.2. Mechanisms

2.1.5.1. Memory Impairment: Meta-Analysis

2.1.5.1. Memory Impairment: Meta-Analysis

- It is difficult to assess cognitive impairment in the context of schizophrenia.

- High antimuscarinic activity was associated with worsened memory functioning in an AP meta-analysis. CLO's profile was worse than RIS or OLA. http://www.ncbi.nlm.nih.gov/pubmed/16174678

2.1.5.2. Memory Impairment: Mechanisms

- Mechanism: blockade of brain M receptors

- Blockade of M_1 and M_2 receptors has been associated with impaired learning and memory in animal studies

2.1.5.2. Memory Impairment: Mechanisms

- CLO definitely has high antimuscarinic activity and the risk of memory impairment.

- OLA and high QUE doses may also be associated with clinically relevant antimuscarinic activity.

http://www.ncbi.nlm.nih.gov/pubmed/16174678

2.1.6. ↓ Seizure Threshold

2.1.6. ↓ Seizure Threshold

2.1.1.6.1. SGAP Comparison

2.1.1.6.2. Mechanisms

2.1.6.1. ↓ Seizure Threshold: SGAP Comparison

2.2.6.1. ↓ Seizure Threshold: Comparison

■ Among SGAPs:
  □ Higher risk: CLO
  □ Then: OLA and QUE
  □ Then: the rest
■ CLO: dose-related risk

2.1.6.2. ↓ Seizure Threshold: Mechanism

2.1.6.2. ↓ Seizure Threshold: Mechanism

- Not well-understood:
  - ☐ Blockade of brain receptors D_2, H_1 and α_1
  - ☐ At neuroesteroids
  - ☐ Pharmacological kindling

2.1.7. Obsessive-Compulsive Symptoms

2.2.7. Obsessive-Compulsive Symptoms

■ According to a recent review:
  □ CLO: 20-28% risk
  □ OLA: 11-20% risk

http://www.ncbi.nlm.nih.gov/pubmed/25256097

■ Mechanism: possible antagonism of serotonin receptors

2.2. Peripheral Pharmacodynamics of SGAP Safety

2.2. Peripheral Pharmacodynamics of SGAP Safety

2.2.1. Hyperglycemia
     2.2.2. Hyperlipidemia
     2.2.3. Sexual ADRs
     2.2.4. Orthostatic Hypotension
     2.2.5. Hypertension
     2.2.6. Anticholinergic Symptoms
     2.2.7. Nausea
     2.2.8. Swallowing Impairment
     2.2.9. Prolongation of QTc
     2.2.10. Myocarditis
     2.2.11. Agranulocytosis/Neutropenia
     2.2.12. Risk for Hyponatremia
     2.2.13. Risk for Venous Thromboembolism
     2.2.14. Risk for Temperature Dysregulation
     2.2.15. ↑ Liver Enzymes and Severe Hepatic Injury
     2.2.16. Pancreatitis
     2.2.17. Cerebrovascular Accidents & Death in Demented Patients

2.2.1. Hyperglycemia

2.2.1. Hyperglycemia

2.2.1.1. Meta-Analyses

2.2.1.2. Mechanism

2.2.1.3. Other Risk Factors

2.2.1.4. Ketoacidosis

2.2.1.1. Hyperglycemia: Meta-Analyses

2.2.1.1. Hyperglycemia: Meta-Analyses

- Newcomer & Haupt 2005: http://www.ncbi.nlm.nih.gov/pubmed/16933585
  - □ CLO and OLA present a higher risk.
  - □ No control for weight gain.
  - □ An estimated 25% of type 2 diabetes mellitus cases on SGAPs are not associated with weight gain or obesity.
- Rummel-Kluge et al. 2010: http://www.ncbi.nlm.nih.gov/pubmed/20692814
  - □ Hyperglycemia (no control for effect of weight gain): OLA: > AMI, ARI, QUE, RIS & ZIP; no difference with CLO
- De Hert et al. 2012: http://www.ncbi.nlm.nih.gov/pubmed/22900950 Focus on ASE, ILO, LUR & PAL
  - □ Hyperglycemia (RCTs may be too short):
    - ● ASE: 2 short treatment RCTs: -3.95 mg/dL, CI -7.37 to 0.53, $p < 0.05$
    - ● ILO: 1 RCT: 6.90 mg/dL, CI 2.48 to 11.32, $p < 0.01$
    - ● PAL 6 long-term RCTs: +3.39 mg/dL, CI 0.42 to 6.36, $p < 0.05$

2.2.1.2. Hyperglycemia: Mechanism

2.2.1.2. Hyperglycemia: Mechanism

- Indirect: weight-mediated
- Direct on glucose metabolism:
  - It is more clear for CLO, OLA and QUE.
  - Unknown whether it is dose-related or not.
  - SGAPs may directly ↑ insulin resistance by

http://www.ncbi.nlm.nih.gov/pubmed/17618085

- ↓ insulin-sensitive glucose transporters,
- causing an inability to stimulate microsomal glucose transporter recruitment to the plasma membrane, or
- ↑ serum free fatty acids.

2.2.1.3. Hyperglycemia: Other Risk Factors

2.2.2.3. Hyperglycemia: Other Risk Factors

- Takes weeks to months to start.
- Schizophrenia may ↑ risk for diabetes mellitus. http://www.ncbi.nlm.nih.gov/pubmed/22927670

2.2.1.4. Ketoacidosis

2.2.2.4. Ketoacidosis

■ Guenette et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/23344556
reviewed 69 cases of ketoacidosis with SGAPs:
  □ Drug: ● OLA: 29
            ● CLO: 18
            ● RIS: 9
            ● QUE: 7
            ● ARI: 6
  □ >1/3 had no weight gain or loss.
  □ The mortality rate was 7%.

■ Be watchful:
  □ It can be lethal.
  □ No SGAP may be safe.
  □ It can happen without weight changes.

2.2.2. Hyperlipidemia

2.2.2. Hyperlipidemia

2.2.2.1. Triglycerides and Cholesterol

2.2.2.2. HDL Cholesterol

2.2.2.1. Triglycerides and Total Cholesterol

2.2.2.1. Triglycerides & Total Cholesterol

2.2.2.1.1. Meta-Analyses

2.2.2.1.2. Mechanisms

2.2.2.1.1. Triglycerides & Total Cholesterol: Meta-Analyses

2.2.2.1.1. Triglycerides and Total Cholesterol: Meta-Analyses

- Rummel-Kluge et al. 2005: http://www.ncbi.nlm.nih.gov/pubmed/20692814
  - Total cholesterol:
    - OLA > ARI, RIS & ZIP;
      no different than AMI, CLO & QUE
    - QUE > RIS & ZIP
- De Hert et al. 2012: http://www.ncbi.nlm.nih.gov/pubmed/22900950
  Focus on ASE, ILO, LUR & PAL
  - ↑ cholesterol (RCTs may be too short):
    - ILO: 1 RCT: +11.60 mg/dL, CI 4.98 to 18.22, $p \leq 0.001$
    - ASE: 1 long-term RCT: +6.53 mg/dL, CI 1.17 to 11.89
      $p < 0.05$
  - ↑ triglycerides: only studied in PAL RCTs
    - short-term: 3 RCTs: +1.78 mg/dL, CI 0.40 to 3.17,
      $p < 0.01$
    - longer-term: 4 RCTs: -0.20 mg/dL, CI -0.40, to -0.01,
      $p < 0.05$ had a statistically, but not clinically,
      significant effect.

2.2.2.1.2. Triglycerides & Total Cholesterol: Mechanisms

2.2.2.1.2. Triglycerides and Total Cholesterol: Mechanisms

■ Two mechanisms:
  □ Indirect: weight-mediated
    ● for all SGAPs
  □ Direct in lipid metabolism:
    ● it may be more clear for CLO, OLA & QUE.
    ● it may not be dose-related.
    ● it occurs and disappears in weeks.
    ● more data exists on direct effects on triglycerides and possibly in total cholesterol.

http://www.ncbi.nlm.nih.gov/pubmed/18031993

2.2.2.2. HDL Cholesterol

2.2.2.2. HDL Cholesterol

■ Some studies show differential HDL effects of an AP vs. another AP, but do not control for weight gain.

■ De Hert et al. 2012:
For ASE, ILO, LUR & PAL
  □ ↑ HDL cholesterol:
    ● ILO (1 RCT: +3.6 mg/dL, CI 1.58 to 5.62, $p < 0.001$)
    ● LUR (5 RCTs: +1.50 mg/dL, CI 0.56 to 2.44, $p < 0.01$)

2.2.3. Sexual ADRs

2.2.3. Sexual ADRs

2.2.3.1. Symptoms

2.2.3.2. Meta-Analysis

2.2.3.3. Mechanisms

2.2.3.4. Priapism

2.2.3.1. Sexual ADRs: Symptoms

2.2.3.1. Sexual ADRs: Symptoms

■ Not well-studied
  □ ♀: ● ↓ libido
        ● others

  □ ♂: ● erectile dysfunction
        ● problems with orgasm
        ● ↓ libido

2.2.3.2. Sexual ADRs: Meta-Analysis

2.2.3.1. Sexual ADRs: Meta-Analysis

■ Serreti & Chiesa, 2011:http://www.ncbi.nlm.nih.gov/pubmed/21191308
  □ High rates (40-60%): CLO, RIS, & OLA
  □ Low rates (16-27%): ARI, QUE & ZIP

2.2.3.3. Sexual ADRs: Mechanisms

2.2.3.3. Sexual ADRs: Mechanism

■ Two mechanisms:
  □ Central: hyperprolactinemia
  □ Periphery: blockade of α_1, M & H_1

2.2.3.4. Priapism

2.2.3.4. Priapism

■ It is rare but does occur.

http://www.ncbi.nlm.nih.gov/pubmed/18090503

■ Most cases that Dr. de Leon has seen have been in ♂ with IDs who have difficulty in communicating.

■ Mechanism: blockade of α_1 (& α_2) in periphery

2.2.4. Orthostatic Hypotension

2.2.4. Orthostatic Hypotension

2.2.4.1. Definition

2.2.4.2. Frequency

2.2.4.3. Mechanism

2.2.4.4. Collapse/Respiratory Arrest

2.2.4.1. Orthostatic Hypotension: Definition

2.2.4.1. Orthostatic Hypotension: Defintion

■ A consensus definition: http://www.ncbi.nlm.nih.gov/pubmed/8628505

    □ ↓ of systolic BP ≥20 mm Hg or

    □ ↓ diastolic BP ≥ 10 mm Hg

  within 3 minutes of standing.

■ Dr. de Leon recommends http://www.ncbi.nlm.nih.gov/pubmed/19084370

  measuring BP and pulse orthostatic changes after

  □ sitting for 3 minutes and

  □ standing for 2 minutes

  during the titration phase of: ● CLO,

           ● ILO,

           ● RIS,

           ● QUE, and

           ● ZIP.

2.2.4.2. Orthostatic Hypotension: Frequency

2.2.4.1. Orthostatic Hypotension: Frequency

- Leung et al. 2012: http://www.ncbi.nlm.nih.gov/pubmed/22565090
  - □ High risk: CLO
  - □ Moderate risk: RIS, QUE
  - □ Low risk: ARI, OLA & ZYP
- Gugger. 2011: http://www.ncbi.nlm.nih.gov/pubmed/21790209
  - □ CATIE: ● CLO: 12-24%
    - ● QUE: 11-27%
    - ● ZIP: 4-13%
    - ● RIS: 0-11%
    - ● OLA: 5-10%
    - ● ARI: 6%
  - □ Newer RCTs: ● ILO: 20% (vs. 8% in placebo)
    - ● LUR: <2%
    - ● ASE: <2%
  - □ IM: OLA: 2.4% (vs. 4.2% AP control)

2.2.4.2. Orthostatic Hypotension: Mechanism

2.2.4. Orthostatic Hypotension: Mechanism

- At peripheral receptors: blockade of α_1
- Tolerance is important. This is why several SGAPs require titration until the patient becomes tolerant.
- Titration is required for oral:
  - CLO
  - ILO
  - RIS
  - QUE
  - ZIP
- Orthostatic hypotension or syncope is rare for:
  - other oral SGAPs
  - IM OLA or ZIP

2.2.4.3. Collapse/Respiratory Arrest

2.2.4. Collapse/Respiratory Arrest

- Not well understood or defined. Rare but potentially lethal.

- Benzodiazepines with:
  - CLO (oral): first 48 hours
  - IM OLA with lorazepam IM

- A pharmacodynamic DDI at the GABA receptors may be possible.

http://www.ncbi.nlm.nih.gov/pubmed/8532064

2.2.5. Hypertension

2.2.5. Hypertension: CLO

- CLO:
  - The only AP consistently associated with hypertension
  - Occurs in <5% of patients
  - Typically in patients with prior hypertension history or borderline BP baseline readings.

    http://www.ncbi.nlm.nih.gov/pubmed/17618085

- Other APs may rarely contribute to hypertension.

  http://www.ncbi.nlm.nih.gov/pubmed/16945059

2.2.6. Anticholinergic Symptoms

2.2.6. Anticholinergic Symptoms

2.2.6.1. Mechanism

2.2.6.2. Paralytic Ileus

2.2.6.1. Anticholinergic Symptoms: Mechanism

2.2.6.1. Anticholinergic Symptoms: Mechanism

- Precisely: antimuscarinic symptoms
- Blockade of peripheral M receptors
- Symptoms:
  - tachycardia: M_2 heart
  - constipation: M_3 colon
  - dry mouth: M_1 and M_3 salivary glands
  - urinary retention: M_3 detrusor muscle in bladder
  - blurred vision: M_3 eye

http://www.ncbi.nlm.nih.gov/pubmed/21495973

2.2.6.1. Anticholinergic Symptoms: Mechanism

■ Risk: CLO > OLA > QUE (only high doses)

■ CLO does not cause dry mouth.
  It causes hypersalivation (typically nocturnal)
  by stimulating the salivary gland:

  □ Partial agonist: ●M_1 and
                      ● M_3 receptors

  □ Its metabolite, norclozapine, is an
    allosteric agonist of M_1.

2.2.6.2. Paralytic Ileus

2.2.6.2. Paralytic Ileus

- Untreated clozapine-induced constipation can lead to major complications and be potentially lethal.
- Palmer et al. (2008) http://www.ncbi.nlm.nih.gov/pubmed/18452342
  - □ used the term clozapine-induced GI hypomotility:
    - paralytic ileus,
    - ischemic colitis,
    - bowel perforation and
    - acquired megacolon.
  - □ 102 cases with a 28% mortality rate.
  - □ Risk factors: ● high clozapine dose/concentration,
    - anticholinergic use, or
    - intercurrent illness.
- French database: http://www.ncbi.nlm.nih.gov/pubmed/19572384
  CLO explained 7/38 ischemic colitis and necrosis.
  (31 cases: FGAPs + antimuscarinic drugs)

2.2.7. Nausea

2.2.7. Nausea: Mechanism

- APs, because of their dopaminergic blockade, are considered anti-emetic drugs.
- ARI, LUR & ZIP are definitely associated with nausea.
  CAR also appears to be associated with nausea/vomiting.
- The mechanism for nausea is unknown. Nausea usually manifests in the first weeks of treatment.

2.2.8. Swallowing Impairment

2.2.8. Swallowing Impairment

2.2.8.1. Swallowing Impairment: Mechanism

2.2.8.2. Risk for Aspiration Pneumonia

2.2.8.1. Swallowing Impairment: Mechanism

2.2.8.1. Swallowing Impairment: Mechanism

- Never well-studied.
- The mechanism is not well-understood:
  - Case reports: dysphagia associated with EPS

    http://www.ncbi.nlm.nih.gov/pubmed/17024549

  - For CLO, the contributing factors are:
    - sedation
    - nocturnal hypersalivation

2.2.8.2. Risk for Aspiration Pneumonia

2.2.8.2. Risk for Aspiration Pneumonia

■ Swallowing impairment contributes to risk of aspiration, particularly in:

□ adults with IDs

□ demented patients

A systematic review in frail older adults describes the role of APs in aspiration pneumonia, supported by case-control studies.

http://www.ncbi.nlm.nih.gov/pubmed/21450240

■ An AP systematic review on the risk of pneumonia:

http://www.ncbi.nlm.nih.gov/pubmed/26017021

□ ↑ risk for SGAPs: OR=2.0 (CI 1.7 to 2.4) but also for FGAPs.

As the pharmacokinetic presentation describes, pneumonia can lead to ↑ clozapine levels because cytokines may ↓ the metabolism of CLO (and possibly other SGAPs).

2.2.9. QTC Prolongation

2.2.9. QTc Prolongation

2.2.9.1. Meta-Analysis

2.2.9.2. Mechanism

2.2.9.3. Torsades de Pointes

2.2.9.1. QTC Prolongation: Meta-Analysis

2.2.9.1. QTc: SMDs in Meta-Analysis

■ Leucht et al., 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019
SMDs in order (95% CI) (drug versus placebo)
□ AMI: 0.66 (0.39 to 0.91)
□ ZIP: 0.41 (0.31 to 0.51)
□ ILO: 0.34 (0.22 to 0.46)
□ ASE: 0.30 (-0.04 to 0.65); no different from placebo
□ RIS: 0.25 (0.15 to 0.36)
□ OLA: 0.22 (0.11 to 0.31)
□ QUE: 0.17 (0.06 to 0.29)
□ HAL: 0.11 (0.03 to 0.19)
□ PAL: 0.05 (-0.18 to 0.26); no different from placebo
□ ARI: 0.01 (-0.13 to 0.15); no different from placebo
□ LUR: -0.10 (-0.21 to 0.01); no different from placebo

2.2.9.1. QTc: SMDs in Meta-Analysis

■ Leucht et al., 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019
Summary of RCTs (prior slide):
☐ Higher risk: AMI, ZIP & ILO
☐ Intermediate risk: ASE, RIS, OLA, & QUE
☐ Low risk and no different from placebo:
 PAL, ARI & LUR
CLO RCT did not provide QTc data.

2.2.9.2. QTC Prolongation: Mechanism

2.2.9. QTc Prolongation: Mechanism

■ Blockade of heart potassium repolarizing channels, which are encoded by the human ether-a-go-go-related gene (HERG).

■ It appears to be dose-related. Therefore, IM involves more risk (higher serum peaks).

2.2.9.3. Torsades de Pointes

2.2.9.3. Torsades de Pointes

■ Most cases of drug-induced torsades de pointes occur in the context of substantial prolongation of the QTc interval, typically (>500 msec), but QTc alone is a relatively poor predictor of arrhythmic risk in any individual patient.

2.2.9.3. Torsades de Pointes

■ A pharmacoepidemiological review:

http://www.ncbi.nlm.nih.gov/pubmed/23553446

  □ ZIP and AMI are similar to HAL in torsadogenic risk.

■ Review of RIS case reports:

http://www.ncbi.nlm.nih.gov/pubmed/23812796

  □ RIS may cause it on rare occasions.

2.2.9.3. Torsades de Pointes

- The literature on clinical cases of torsade de pointes is very complex.
  - □ Cases frequently include polypharmacy and DDI:
    - ● Pharmacodynamic component; multiple drugs with HERG channel inhibitory properties
    - ● Plus sometimes a pharmacokinetic component; an inhibitor ↑ concentrations of one or several of the drugs
  - □ Other risk factors

2.2.9.3. Torsades de Pointes

■ Other risk factors:
- □ geriatric age
- □ female gender
- □ bradycardia
- □ hypokalemia
- □ hypomagnesemia

■ Be careful prescribing SGAPs in patients with risk factors.

■ Be extremely careful prescribing SGAP-SSRI combinations in patients with risk factors.

2.2.9.3. Torsades de Pointes

■ As it may be associated with high plasma concentration peaks:
  □ Do not use haloperidol IV.
  □ Be careful with IM formulations
    ● ZIP http://www.ncbi.nlm.nih.gov/pubmed/25530900
    ● HAL

2.2.10. Myocarditis

2.2.10. Myocarditis

- Only with CLO: http://www.ncbi.nlm.nih.gov/pubmed/23140648
  - □ Non-Australian countries: 0.07-0.6 per 1000
  - □ Australia: 7-34 per 1000. In an Australia study, the risk factors were: http://www.ncbi.nlm.nih.gov/pubmed/23010488
    - ● rapid titration: a cumulative dose of 920 mg in the first 9 days: OR=2.31 (CI 0.98 to 5.48)
    - ● VPA: OR= 2.59 (CI 1.51 to 4.42) Probably an inhibitor of CLO metabolism
    - ● For each decade of age: OR=1.31 (1.07 to 1.60)
- Mechanism: http://www.ncbi.nlm.nih.gov/pubmed/25865876
  - □ Early titration: type I immune phenomenon or IgE-mediated acute hypersensitivity, or
  - □ Maintenance: a type III allergic reaction or direct CLO cardiotoxicity.
- Prevent by slow titration. http://www.ncbi.nlm.nih.gov/pubmed/25865620

2.2.11. Neutropenia & Agranulocytosis

2.2.11. Neutropenia & Agranulocytosis

2.2.11.1. All APs

2.2.11.2. Neutropenia During CLO Treatment

2.2.11.3. CLO-Induced Agranulocytosis

2.2.11.1. AP-Induced Neutropenia

2.2.11.1. AP-Induced Neutropenia

■ Mechanism: unknown

■ All APs may cause it in rare instances.

■ Combination QUE-VPA: may ↑ risk

http://www.ncbi.nlm.nih.gov/pubmed/19401471

2.2.11.2. Neutropenia During CLO Treatment

2.2.11.2. Neutropenia During CLO Treatment

2.2.12.2.1. Benign Ethnic Neutropenia

2.2.12.2.2. Circadian Variations

2.2.11.2.1. Benign Ethnic Neutropenia

2.2.11.2.1. Benign Ethnic Neutropenia

- Benign Ethnic Neutropenia (normal hematopoietic system and no risk of increased infections):
  No increased risk of CLO-induced agranulocytosis.
  New US guideline since October 2015

  https://www.clozapinerems.com/CpmgClozapineUI/resources.u#tabr3

- Commonly observed in men (women less frequent) of:
  - African descent (25-50%)
  - Middle Eastern ethnic groups: ● Yemenite Jews and

  http://www.ncbi.nlm.nih.gov/pubmed/16143678   ● Jordanians

  - Other non-Caucasian ethnic groups with darker skin.
- To start CLO: ANC $\geq$1000/μL
- ANC during CLO:
  - If ANC = 500-999/μL: 3 ANCs/weekly until normalized
  - If ANC $\leq$ 500/μL: ● stop CLO
                                    ● daily ANC until normalized

2.2.11.2.2. Circadian Variations

2.2.11.2.2. Circadian Variations

■ A few patients with circadian rhythm variations have been described:
  □ low ANC in the morning and
  □ normal values in the afternoon

http://www.ncbi.nlm.nih.gov/pubmed/14608591

2.2.11.3. CLO-Induced Agranulocytosis

2.2.11.3 Agranulocytosis: CLO

- Agranulocytosis = ANC<500/μL
- US frequency < 1% due to WBC monitoring.
- Risk: □ seems to peak by the 3rd month and
    - □ ↓significantly after the 6th month,
    - □ but never reaches zero
- To start CLO in normal patient: ANC ≥1500/μL
- ANC during CLO:
    - □ ANC=1000-1499 μL: 3 ANCs/weekly until normal
    - □ ANC=500-999/μL: ● stop CLO
        - ● daily ANC until normal
    - □ ANC<500/μL: ● stop CLO
        - ● daily ANC until normal
        - ● hematological consultation

2.2.11.3 Agranulocytosis: CLO

■ Mechanism: immunological

■ HLA is a risk factor. A pharmacogenetic test is not ready for clinical practice.

2.2.11.3.HLA Genotyping and Clozapine

- Individuals with HLA-DQB1 have increased risk (OR=16.9).
- Low sensitivity (true positive rate) = 22%. Many individuals who develop CLO-induced agranulocytosis have other HLAs. Therefore, the FDA requires WBCs in order to start clozapine.

http://www.ncbi.nlm.nih.gov/pubmed/24196844

2.2.12. Risk for Hyponatremia

2.2.12. Risk for Hyponatremia

■ Most cases of hyponatremia associated with APs happen in patients with polydipsia: Atsariyasing & Goldman, 2014:

http://www.ncbi.nlm.nih.gov/pubmed/24726819

  □ Diluted urine: <239 mOsm/kg is probably psychosis exacerbation with polydipsia

  □ Concentrated urine: >246 mOsm/kg means a probable AP contribution.

2.2.13. Risk for Venous Thromboembolism

2.2.13. Risk for Venous Thromboembolism

2.2.13.1. Meta-Analysis

2.2.13.2. Mechanism

2.2.13.1. Venous Thromboembolism: Meta-Analysis

■ Barbui et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/24403009

17 observational studies:

□ APs: ● ↑ risk: OR=1.54 (1.28 to 1.86); 11 studies

● risk of pulmonary embolism: OR=4.90 95% (0.77 to 30.98) not significant; only 3 studies

□ SGAPs: ● ↑ risk: OR=2.07 (1.74-2.5); 3 studies

2.2.13.2. Venous Thromboembolism: Mechanism

2.2.13.2. Venous Thromboembolism: Mechanism

■ Not well-understood mechanism:
  □ weight gain

  □ sedation

  □ ↑ platelet aggregation

  □ ↑ antiphospholipid antibodies

  □ hyperprolactinemia

  □ hyperhomocysteinemia

2.2.14. Risk for Temperature Dysregulation

2.2.14. Risk for Temperature Dysregulation

2.2.14.1. Risk for Heat Stroke

2.2.14.2. CLO-Induced Benign Hyperthermia

2.2.14.3. Risk for Hypothermia

2.2.14.1. Risk for Heat Stroke

2.2.14.1. Risk for Heat Stroke

2.2.14.1.1. Heat Stroke: Frequency

2.2.14.1.2. Heat Stroke: Mechanism

2.2.14.1.1. Heat Stroke: Frequency

2.2.14.1.1. Heat Stoke: Frequency

■ Frequency is unknown:
Most published cases for SGAPs include FGAPs, too.

http://www.ncbi.nlm.nih.gov/pubmed/18025545

■ Particularly lethal in the elderly.
■ It usually occurs after
  ☐ intense exercise and/or
  ☐ heat exposure (high temperatures in summer).

2.2.14.1.2. Heat Stroke: Mechanism

2.2.14.1.2. Heat Stroke: Mechanism

■ Mechanism:

   ☐ Dopaminergic blockade interferes with temperature regulation.

   ☐ Muscarinic blockade from APs or antiparkinsonian inhibits sweating.

■ Be careful with SGAP combinations with carbonic anhydrase inhibitors:

   ● topiramate, or

   ● zonisamide

which inhibit sweating.

2.2.14.2. CLO-Induced Benign Hyperthermia

2.2.14.2. CLO-Induced Benign Hyperthermia

2.2.14.2.1. CLO-Induced Benign Hyperthermia: Definition

2.2.14.2.2. CLO-Induced Benign Hyperthermia: Mechanism

2.2.14.2.1. CLO-Induced Benign Hyperthermia: Definition

- If fever is found during CLO-titration but no cause is found, it is usually called CLO-induced benign hyperthermia.

- Typically: http://www.ncbi.nlm.nih.gov/pubmed/1882209
  - □ within the first 3 weeks of treatment,
  - □ minor increases of 1 or 2 degrees F, and
  - □ resolves spontaneously with continuation of treatment

- Kohen et al. 2009: http://www.ncbi.nlm.nih.gov/pubmed/19126823
  It is associated with ↑ CRP.

2.2.14.2.2. CLO-Induced Benign Hyperthermia: Mechanism

- Røge et al., 2012: http://www.ncbi.nlm.nih.gov/pubmed/22831769

  ↑ cytokines: same mechanism as myocarditis
- Chung et al. 2008: http://www.ncbi.nlm.nih.gov/pubmed/19087484

  This Chinese study find the same risk factors

  as myocarditis in Australia:

  ☐ Rapid titration of 50 mg/week

     OR=18.9 (CI 5.3 to 66.7), and

  ☐ VPA OR=3.6 (CI 1.5 to 8.9).

2.2.14.3. Hypothermia

2.2.14.2.3. Hypothermia

■ Kreuzer et al. 2012:

http://www.ncbi.nlm.nih.gov/pubmed/21956608

□ On rare occasions SGAPs can cause hypothermia: human body core temperature $< 35°C$

□ mechanism: $5HT_2$ antagonism

2.2.15. ↑ Liver Enzymes and Severe Hepatic Injuries

2.2.15. ↑ Liver Enzymes and Severe Hepatic Injuries

2.2.15.1. ↑ Liver Enzymes

2.2.15.2. Severe Hepatic Injuries

2.2.15.1. ↑ Liver Enzymes

2.2.15.1. ↑ Liver Enzymes

2.2.15.1.1 ↑ Liver Enzymes: Systematic Review

2.2.15.1.2. ↑ Liver Enzymes: Mechanism

2.2.15.1.3. ↑ Liver Enzymes: Management

2.2.15.1.1. ↑ Liver Enzymes: Systematic Review

2.2.15.1. ↑ Liver Enzymes: Systematic Review

- Marwick et al. 2012:
  - □ Frequency in 10 studies:
    - Abnormal liver test: median 32% (5-78%)
    - Clinically significant: median 4% (0-15%)
      (3-fold > upper limit of normal for ALT, AST, GGT
      or 2-fold > the upper limit of normal for ALP).
  - □ Clinical course:
    - most cases: ↑ transaminases
    - were generally asymptomatic, and
    - arose within 6 weeks.
  - □ Outcome:
    - stably persistent or
    - resolved with continued treatment

2.2.15.2. ↑ Liver Enzymes: Mechanisms

2.2.15.1.2. ↑ Liver Enzymes: Mechanisms

■ Marwick et al. 2012: http://www.ncbi.nlm.nih.gov/pubmed/22986798
4 mechanisms on APs:

☐ Phenothiazines (chlorpromazine) or metabolites can impair bile secretion and lead to cholestasis. In part, it is an immune-mediated (hypersensitivity) reaction.

☐ Metabolites may sometimes have direct toxic effects; hepatocytes can adapt.

☐ Immune-mediated reactions do not reduce with exposure.

☐ Metabolic syndrome: nonalcoholic fatty liver disease

2.2.15.3. ↑ Liver Enzymes: Management

2.2.15.3. ↑ Liver Enzymes: Management

■ Marwick et al. 2012:

When to stop APs:

☐ at 3-fold > upper limit of normal for
- ALT
- AST
- GGT

or

☐ at 2-fold > the upper limit of normal for ALP.

2.2.15.1.2. Severe Hepatic Injuries

2.2.15.1.2. Severe Hepatic Injuries

■ Marwick et al. 2012:

http://www.ncbi.nlm.nih.gov/pubmed/22986798

Severe or fatal hepatic injuries:
42 case reports on SGAPs
Most frequent:
□ clozapine: 15 (3 fatal), and
□ risperidone: 13 (1 fatal).

2.2.16. Pancreatitis

2.2.16. Pancreatitis

- Koller et al. 2003:
  On rare occasions SGAPs have been associated with pancreatitis.
- Ruling out other causes is necessary.
- Mechanism:
  - □ unknown
  - □ some cases were in the context of ketoacidosis or hypertriglyceridemia.

2.2.17. Cerebrovascular Accidents and
Death in Demented Patients

■ APs compared with placebo:
↑ death in elderly demented patients.

■ Gill & Seitz, 2012: http://www.ncbi.nlm.nih.gov/pubmed/23446845
The combination of ↑ deaths is due to:
- ↑ cerebrovascular adverse events
- ↑ pneumonias and
- ↑ ventricular arrhythmias

Other causes of death associated with APs may be:
- pulmonary embolism
- aspirations
- myocardial infarcts

2.3. AP Safety:

Comment on Pharmacokinetics

2.3. AP Safety: Comment on Pharmacokinetics

■ Pharmacokinetics facilitates pharmacodynamics

☐ When ADRs are dose-related, pharmacokinetics plays a facilitator role. Sufficient concentration at the action site may be needed.

☐ When ADRs are not dose-related, pharmacokinetics may not be relevant. Small concentrations at the action site may be enough.

2.3. AP Safety: Comment on Pharmacokinetics

■ Pharmacodynamics probably determines specific ADRs in a patient when concentrations at the site of action are sufficient for "toxicity".

■ Drug concentrations that are too high (pharmacokinetics) contribute to poor safety in general. Pharmacodynamic factors probably determine whether ADRs develop or not, and which ADRs.

3. Update on
New Partial D$_2$ Agonists

3. Update on New Partial Agonists

3.1. Pharmacodynamic Comparison

3.2. Efficacy and Safety Comparison

3.3. Pharmacokinetic Comparison

3.4. Summary

3.1. Partial D$_2$ Agonists: Pharmacodynamic Comparison

3.1. Partial D_2 Agonists: Pharmacodynamic Comparison

■ In common: D_2 high affinity which explains:
  □ Efficacy (FDA approval):
    ● schizophrenia (ARI, BRE & CAR)
    ● bipolar disorder: mania (ARI & CAR)
    ● irritability in autistic disorder (ARI)
    ● Tourette's disorder (ARI)
  □ Safety:
    ● EPS profile: akathisia
    ● ↓ prolactin
■ Differences in affinity for some receptors:

http://www.ncbi.nlm.nih.gov/pubmed/26477545

  □ D_3: ● ARI & CAR: very high affinity
        ● BRE: high affinity
  □ different 5HT receptors: different affinity, and
  □ different α receptors: different affinity,
    but the clinical relevance of these differences is unclear.

3.2. Partial D$_2$ Agonists: Efficacy and Safety Comparison

3.1. Partial D$_2$ Agonists: Efficacy & Safety Comparison

Citrome, 2015   http://www.ncbi.nlm.nih.gov/pubmed/26477545

	NNT	Akathisia NNH	LLH	Weight gain ≥7% NNH	LHH
Schizophrenia					
ARI	8	25	3.1	21	2.6
BRE	7	112	16	17	2.4
CAR	10	15	1.5	34	3.4
Bipolar mania					
ARI	7	12	1.7	no difference	
CAR	5	7	1.4	no difference	
Major depressive disorder					
ARI	7	5	0.7	22	3.1
BRE	11	15	1.4	52	4.7

■ In summary, they appear similar.

■ The major difference is in major depressive disorder:

  □ ARI produces more harm than benefit (LLH akathisia = 0.7).

  □ BRE produces slightly more benefit than harm (LLH akathisia = 1.4).

3.3. Partial D$_2$ Agonists: Pharmacokinetic Comparison

(Better described in the presentation titled "Pharmacokinetics of Oral Second-Generation Antipsychotics")

3.5.5.3. Partial D_2 Agonists: Metabolism

- ARI & BRE: very similar:
  - Enzymes: CYP2D6/CYP3A4
  - Dose modifications:
    - 2 x if powerful inducer (including CBM) is present
    - 0.5 x if powerful CYP2D6 inhibitor (paroxetine) or CYP2D6 poor metabolizer is present
    - 0.25 x if fluoxetine (CYP2D6 & CYP3A4 inhibitor), or CYP2D6 poor metabolizer + CYP3A4 inhibitor is present
- CAR:
  - Enzymes: CYP3A4
  - Dose modifications:
    - Avoid using with powerful inducers (including CBM).
    - No problems with CYP2D6 inhibitors or CYP2D6 poor metabolizers
    - Avoid using with CYP3A4 powerful inhibitors.
- Combination with VPA: for ARI, modify dose x 0.75. As far as we know, no need for BRE & CAR dose changes exists.

3.3. Partial D$_2$ Agonists Need Slow Titration

■ Long half-lives:
After you ↑ dose, it will take a long time
to see full effects and reach steady state.

	Days	Weeks	Months
ARI	up to 16	>2	<1
BRE	up to 19	>2	<1
CAR	70-105	10-15	2.5-4

If you prescribe earlier increases, you may end
up with doses higher than needed.
These drugs do not appear to be good for
managing acute situations. On the other hand,
CAR efficacy and ADRs will last for months
after discontinuation.

3.5.5.3. Partial D$_2$ Agonists: Doses (mg/day)

DOSE	ARI	BRE	CAR
Schizophrenia			
Starting	10-15	1	1.5
Recommended	10-15	2-4	1.5-6
Maximum	30	4	
Bipolar Mania			
Starting	10-15		1.5
Recommended	15		3-6
Maximum	30		
Major Depressive Disorder			
Starting	2-5	0.5-1	
Recommended	5-10	2	
Maximum	15	3	

3.4. Partial D$_2$ Agonists: Summary

3.4. Partial D$_2$ Agonists: Summary

- In the US: BRE & CAR are likely to be more expensive than ARI and have not been studied as much.

- BRE & ARI
  - appear very similar regarding:
    - pharmacokinetics
    - pharmacodynamics
    - efficacy, and
    - safety.
  - Dr. de Leon finds it shocking that the FDA approved ARI for treatment-resistant major depressive disorder when the company RCTs suggest that, on average, ARI is more likely to cause akathisia than response. BRE has a little better profile, 1.4 times more likely to cause response than akathisia.

- CAR does not appear to have major benefits over ARI except that it stays in the body much longer after discontinuation, and may take 3-5 months to be eliminated. This may be beneficial in non-compliant patients with schizophrenia or mania, but also may be a problem if there are CAR-induced ADRs.

References on AP pharmacodynamics

1) 2008 article http://www.ncbi.nlm.nih.gov/pubmed/18448784 has information on RIS pharmacodynamics/kinetics (part I).

2) 2008 article http://www.ncbi.nlm.nih.gov/pubmed/18621942 has information on RIS pharmacodynamics/kinetics (part II).

3) 2012 article http://www.ncbi.nlm.nih.gov/pubmed/22332980 has tables summarizing all SGAPs and focuses on DDIs with AEDs.

4) 2014 article http://www.ncbi.nlm.nih.gov/pubmed/2449461 updates tables summarizing all SGAPs and focuses on DDIs with antidepressants.

Questions

-Please review the 10 questions in the Word document titled "Questions on the Presentation: Pharmacokinetics of Second-Generation Antipsychotics".

-You will find the answers on the last slide after the "Thank you slide". No peeking until you have answered all the questions.

-If you do not answer all the questions correctly, please review the Power Point presentation once again to reinforce the pharmacological concepts.

-List your correct answers to be given anonymously to Dr. de Leon.

Thank you

Answers

1. B

2. D

3. A

4. D

5. D

6. A

7. A

8. B

9. C

10. B