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: brexipiprazole (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.


- **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.”
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; $LHH = \frac{NNH}{NNT}$  

- <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 D₂ Partial Agonists
1. SGAP Pharmacodynamics of Efficacy
   1.0. Clinical Efficacy
   1.1. Blockade of D₂ 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 D₂ 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:

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.
  - 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


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:
1.0.3. Efficacy: Bipolar Depression


<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT</th>
<th>NNH</th>
<th>LHH</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLA-fluoxetine</td>
<td>4</td>
<td>6 weight gain</td>
<td>1.5</td>
</tr>
<tr>
<td>QUE</td>
<td>6</td>
<td>5 sedation</td>
<td>0.8</td>
</tr>
<tr>
<td>LUR monotherapy</td>
<td>5</td>
<td>15 akathisia</td>
<td>3</td>
</tr>
<tr>
<td>LUR adjunctive</td>
<td>7</td>
<td>17 nausea</td>
<td>2.4</td>
</tr>
</tbody>
</table>
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.
  - Some data on QUE monotherapy and in combination
1.0.3. Efficacy: Adjunctive For Treatment-Resistant Depression
1.0.3. Efficacy: Treatment-Resistant Depression


**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
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 $\alpha_2$ 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-HT$_{2C}$ 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


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


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


<table>
<thead>
<tr>
<th></th>
<th>NNT (CI)</th>
<th>NNH (CI)</th>
<th>LHH&lt;sup&gt;1&lt;/sup&gt;</th>
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<tr>
<td>response</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ARI</td>
<td>7 (5-12)</td>
<td>4 (3-6) akathisia</td>
<td>0.6</td>
</tr>
<tr>
<td>QUE</td>
<td>10 (6-26)</td>
<td>3 (2-3) sedation</td>
<td>0.3</td>
</tr>
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<sup>1</sup>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)


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<thead>
<tr>
<th></th>
<th>NNT</th>
<th>NNH akathisia</th>
<th>LHH&lt;sup&gt;1&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>ARI</td>
<td>7</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>BRE</td>
<td>11</td>
<td>15</td>
<td>1.4</td>
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</table>

<sup>1</sup>LLH=NNH/NNT
2.0.3. Safety: Treatment-Resistant Depression

■ 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 (0.73 to 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 $5\text{-HT}_{2A}/D_2$ (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 D₂ 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:


<table>
<thead>
<tr>
<th></th>
<th>SGAP</th>
<th>FGAP</th>
<th>No APs</th>
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<tbody>
<tr>
<td>Annualized incidence</td>
<td>3.9%</td>
<td>5.5%</td>
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<tr>
<td>children</td>
<td>0.4%</td>
<td></td>
<td></td>
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<tr>
<td>adults</td>
<td>3.0%</td>
<td>7.7%</td>
<td></td>
</tr>
<tr>
<td>elderly</td>
<td>5.2%</td>
<td>5.2%</td>
<td></td>
</tr>
<tr>
<td>Prevalence in adults</td>
<td>13.1%</td>
<td>32.4%</td>
<td>15.6%</td>
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</tbody>
</table>
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?


■ Meta-analysis in schizophrenia:
  □ non-White ethnic group & early EPS
  □ old age: suggestive but inconclusive
2.1.1.4. NMS
2.1.1.4. NMS

- NMS while on SGAPs has rarely been described. [http://www.ncbi.nlm.nih.gov/pubmed/19480467]
  - Frequency is low: estimated around 0.2% (Caroff & Mann, 1993) [http://www.ncbi.nlm.nih.gov/pubmed/8093494]
  - “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


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 D₂ 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 D₂ 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


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)
- $\uparrow$ 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


<table>
<thead>
<tr>
<th>Drug</th>
<th>OR (95% CI)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLO</td>
<td>8.82 (4.72 to 15.1)</td>
<td></td>
</tr>
<tr>
<td>ZIP</td>
<td>3.80 (2.58 to 5.42)</td>
<td></td>
</tr>
<tr>
<td>QUE</td>
<td>3.76 (2.68 to 5.19)</td>
<td></td>
</tr>
<tr>
<td>OLA</td>
<td>3.34 (2.46 to 4.50)</td>
<td></td>
</tr>
<tr>
<td>ASE</td>
<td>3.28 (1.37 to 6.69)</td>
<td></td>
</tr>
<tr>
<td>HAL</td>
<td>2.76 (2.04 to 3.66)</td>
<td></td>
</tr>
<tr>
<td>RIS</td>
<td>2.45 (1.76 to 3.35)</td>
<td></td>
</tr>
<tr>
<td>LUR</td>
<td>2.45 (1.31 to 4.24)</td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>1.84 (1.05 to 3.05)</td>
<td></td>
</tr>
<tr>
<td>ILO</td>
<td>1.71 (0.63 to 3.77); no different from placebo</td>
<td></td>
</tr>
<tr>
<td>PAL</td>
<td>1.40 (0.85 to 2.19); no different from placebo</td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>1.42 (0.72 to 2.51); no different from placebo</td>
<td></td>
</tr>
</tbody>
</table>
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

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.  
2.1.5.2. Memory Impairment: Mechanisms
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.

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 $\alpha_1$
  - 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


- 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

  - 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.

  - Hyperglycemia (no control for effect of weight gain): OLA: > AMI, ARI, QUE, RIS & ZIP; no difference with CLO

  - 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 [source](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.
2.2.1.4. Ketoacidosis
2.2.2.4. Ketoacidosis


- **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

  - Total cholesterol:
    - **OLA > ARI, RIS & ZIP:** no different than AMI, CLO & QUE
    - **QUE > RIS & ZIP**

  - 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 ≤ 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
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.

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
  - female: • ↓ libido
  - others

  - male: • erectile dysfunction
  - problems with orgasm
  - ↓ libido
2.2.3.2. Sexual ADRs: Meta-Analysis
2.2.3.1. Sexual ADRs: Meta-Analysis

  - 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 $\alpha_1$, M & H$_1$
2.2.3.4. Priapism
2.2.3.4. Priapism

- It is rare but does occur.


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

- Mechanism: blockade of $\alpha_1$ (& $\alpha_2$) 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: Definition

  - ↓ of systolic BP ≥ 20 mm Hg or
  - ↓ diastolic BP ≥ 10 mm Hg within 3 minutes of standing.

  - 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

  - High risk: CLO
  - Moderate risk: RIS, QUE
  - Low risk: ARI, OLA & ZYP

  - 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 $\alpha_1$
- 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.

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.


- Other APs may rarely contribute to hypertension.

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

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, norcloclozapine, 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) [link](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: [link](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
  - 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.


- An AP systematic review on the risk of pneumonia:


  □ ↑ 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


**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


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:

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

- Review of RIS case reports:

  - 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


  **HAL**
2.2.10. Myocarditis
2.2.10. Myocarditis

  - 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](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)

  - Early titration: type I immune phenomenon or IgE-mediated acute hypersensitivity, or
  - Maintenance: a type III allergic reaction or direct CLO cardiotoxicity.

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

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
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
  - Jordanians
- Other non-Caucasian ethnic groups with darker skin.

To start CLO: ANC ≥ 1000/μL

ANC during CLO:
- If ANC = 500-999/μL: 3 ANCs/weekly until normalized
- If ANC ≤ 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

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.

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:

- 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
2.2.13.1. Venous Thromboembolism: Meta-Analysis

Barbui et al. 2014 [1]

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.
  

- 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
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.

  - within the first 3 weeks of treatment,
  - minor increases of 1 or 2 degrees F, and
  - resolves spontaneously with continuation of treatment

  It is associated with ↑ CRP.
2.2.14.2.2. CLO-Induced Benign Hyperthermia: Mechanism
2.2.14.2.2. CLO-Induced Benign Hyperthermia: Mechanism

  
  ↑ cytokines: same mechanism as myocarditis

  
  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:


- On rare occasions SGAPs can cause hypothermia: human body core temperature $< 35^\circ C$
- 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


- **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


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:
  
  [Link](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

  
  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 hypertriglycerideridemia.
2.2.17. Cerebrovascular Accidents and Death in Demented Patients
2.2.17. Cerebrovascular Accidents & Death in Demented Patients

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


- 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 D₂ Agonists: Efficacy & Safety Comparison


<table>
<thead>
<tr>
<th></th>
<th>Akathisia</th>
<th>Weight gain ≥7%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNT</td>
<td>NNH</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>BRE</td>
<td>7</td>
<td>112</td>
</tr>
<tr>
<td>CAR</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Bipolar mania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>CAR</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>BRE</td>
<td>11</td>
<td>15</td>
</tr>
</tbody>
</table>

- 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 D₂ Agonists: 
Pharmacokinetic Comparison

(Better described in the presentation titled “Pharmacokinetics of Oral Second-Generation Antipsychotics”)
3.5.5.3. Partial D₂ 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\textsubscript{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.

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
<th>Weeks</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI</td>
<td>up to 16</td>
<td>&gt;2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>BRE</td>
<td>up to 19</td>
<td>&gt;2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CAR</td>
<td>70-105</td>
<td>10-15</td>
<td>2.5-4</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>DOSE</th>
<th>Schizophrenia</th>
<th>Bipolar Mania</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting</strong></td>
<td>10-15</td>
<td>10-15</td>
<td>2-5</td>
</tr>
<tr>
<td><strong>Recommended</strong></td>
<td>10-15</td>
<td>15</td>
<td>5-10</td>
</tr>
<tr>
<td><strong>Maximum</strong></td>
<td>30</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>

**Doses:**
- **Schizophrenia:**
  - **Starting:** 10-15 mg/day
  - **Recommended:** 10-15 mg/day
  - **Maximum:** 30 mg/day

- **Bipolar Mania:**
  - **Starting:** 10-15 mg/day
  - **Recommended:** 15 mg/day
  - **Maximum:** 30 mg/day

- **Major Depressive Disorder:**
  - **Starting:** 0.5-1 mg/day
  - **Recommended:** 5-10 mg/day
  - **Maximum:** 15 mg/day
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

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