

Efficacy and Side Effects of Antipsychotics

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Pre-Lecture Exam

Question 1

1. Antipsychotics can be effective for which of the following indications?
 - A. Major depression with psychotic features
 - B. Psychotic disorders secondary to medical conditions
 - C. Mania
 - D. Tourette's syndrome
 - E. All of the above

Question 2

- 2. Which of the following statements about the pharmacokinetics of antipsychotics is incorrect?**
- A.** Patients receiving an oral antipsychotic reach a peak plasma level more rapidly than those receiving an intramuscular preparation.
 - B.** Patients reach a peak plasma concentration 1-4 hours after receiving an oral dose.
 - C.** Patients receiving an oral antipsychotic reach steady state in 3-5 days.
 - D.** Antipsychotics are well-absorbed when administered orally.

Question 3

- 3. Which of the following statements about the time course of antipsychotic response is correct?**
- A.** Patients usually improve in agitation and excitement after psychosis improves.
 - B.** Delusions commonly improve before thought disorder.
 - C.** Psychosis will commonly improve three to five weeks after starting an antipsychotic.
 - D.** If patients fail to demonstrate improvement in psychotic symptoms three days after starting an antipsychotic, they should be switched to another drug.

Question 4

4. Most antipsychotics are effective when they occupy what proportion of D₂ receptors?
- A. 10%
 - B. 30%
 - C. 70%
 - D. 95%

Question 5

- 5. Which of the following dopamine pathways is related to the neurological side effects of antipsychotics?**
- A. Nigrostriatal
 - B. Tuberoinfundibular
 - C. Mesolimbic
 - D. Mesocortical

Question 6

- 6. Which of the following is recommended by the Texas Medication Algorithm Project for refractory schizophrenia?**
- A. Trial of a second generation (atypical) antipsychotic before clozapine**
 - B. Augmentation with lithium or valproate before clozapine**
 - C. First generation (typical) antipsychotics as first line agents**

Phases of schizophrenia and goals of treatment

- Acute - Reduce acute symptoms
- Stabilization - Minimize the likelihood of relapse; enhance adaptation to community; consolidate remission
- Stable - maintain or improve level of function and quality of life; prevent relapse; monitor for adverse treatment effects.

Effectiveness of antipsychotics in schizophrenia

- Well-designed clinical trials invariably demonstrated the superiority of drug vs placebo.
- The only exception was when doses below 400 mg of chlorpromazine were prescribed.
- Early intervention with antipsychotics may reduce long-term morbidity and decrease the number of rehospitalizations.

Acute phase: Psychiatric management

- Psychosocial management: reduce overstimulating or stressful events in a structured and predictable environment
- Inform patient on the nature and management of their illness
- Initiate a relationship with family

Acute phase: Antipsychotic medication

- Indicated for nearly all acute psychotic episodes in schizophrenia
- Assess the ability of patients to participate in decisions about medication
- Administer involuntarily when appropriate

Acute treatment: Considerations in drug selection

- Prior response
- Side effect profile
- Patient preference
- Route of administration
- Cost? (Not in guidelines)

Pretreatment Evaluation

- Physical exam w/ neuro
- Basic labs including LFT's
- EKG?
- Weight

Antipsychotic dosing strategy

- Use moderate doses, eg, 10 mg haloperidol, 4 mg risperidone, 12.5 mg olanzapine, 400 mg quetiapine.
- Use a fixed dose without prn's.
- Oral benzodiazepines or short-acting intramuscular drugs (eg. haloperidol) can be used for agitation.

Acute treatment: Dose selection

- High potency conventional: 5-20 mg of haloperidol or fluphenazine
- Low potency conventional: 300 to 1000 of CPZ
- Risperidone: 4 to 6 mg
- Olanzapine: 10 to 25 mg
- Quetiapine 300 to 750 mg
- Ziprasidone 120-160 mg
- Aripiprazole 10-20 mg

Time Course of Antipsychotic Response

- Certain target symptoms may diminish in first few days.
 - Agitation.
 - Psychomotor excitement.
- Improvement in psychotic symptoms typically occurs in the following order.
 - Thought disorder.
 - Hallucinations – decreased intensity, frequency.
 - Delusions – new misinterpretations are first affected.

Time Course of Antipsychotic Response (Cont)

Evaluate antipsychotic response in 3-5 weeks.

- Partial response continue for 6-12 wks
- No response switch
- Severe side effects switch

Importance of Side Effects

Decrease compliance
Decrease quality of life
Health issues

Mechanisms Of Side Effects

- EPS & hyperprolactinemia--- D₂ blockade
- Hypotension---alpha adrenergic blockade
- Sedation– histaminergic blockade
- Weight gain---histaminic and serotonergic blockade
- Anticholinergic ---muscarinic blockade
 - » Sexual side effects---serotonergic, muscarinic, noradrenergic and D₂ (via prolactin) blockade

Acute extrapyramidal symptoms (EPS)

- Akathisia- a subjective feeling of restlessness
- Acute dystonic reactions - abrupt onset muscular spasms affecting the neck, eyes, trunk, extremities
- Parkinsonism - stiffness, tremor, impaired gait

Side effects of newer antipsychotic drugs

(adapted from Jipson and Tandon)

| | DA's | CLZ | RIS | OLZ | QUE | ZIP |
|--------------|-------------|--------------|--------|---------|--------|--------|
| Agran | ± | ++ | ± | ± | ± | ± |
| Antichol | ± to +++ | +++ | ± | + to ++ | ± | ± |
| EPS | + to +++ | 0 to ± | ± to + | 0 to ± | 0 to ± | 0 to ± |
| Orth hypo | + to +++ | +++ | ++ | + | ++ | + |
| Seizures | ± to + | ++ to +++ | ± | ± | ± | ± |

Side effects of newer antipsychotic drugs (cont)

| | DA's | CLZ | RIS | OLZ | QUE | ZIP |
|-------------|-----------|-----|-----|-----|-----|-----|
| Prolac Elev | ++ to +++ | 0 | ++ | ± | ± | ± |
| Sedat | + to +++ | +++ | + | ++ | ++ | + |
| TD | +++ | 0 | ± | ± | ± | ± |
| Weight Gain | + to ++ | +++ | ++ | +++ | ++ | + |

Agraunulocytosis with clozapine

- US rate, 0.38%
- Death rate, 0.01%
- 80-85% of cases occur within the first 3 months; Only 4% occur after the first 6 months

Hyperprolactinemia

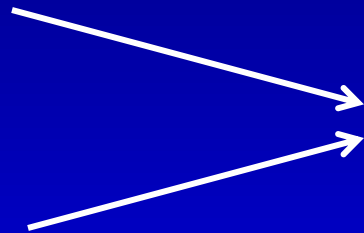
Clozapine

Quetiapine

Olanzapine

Ziprasidone

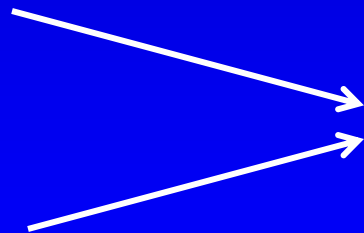
Aripiprazole



no or little sustained effect on prolactin secretion

Amisulpride

Risperidone



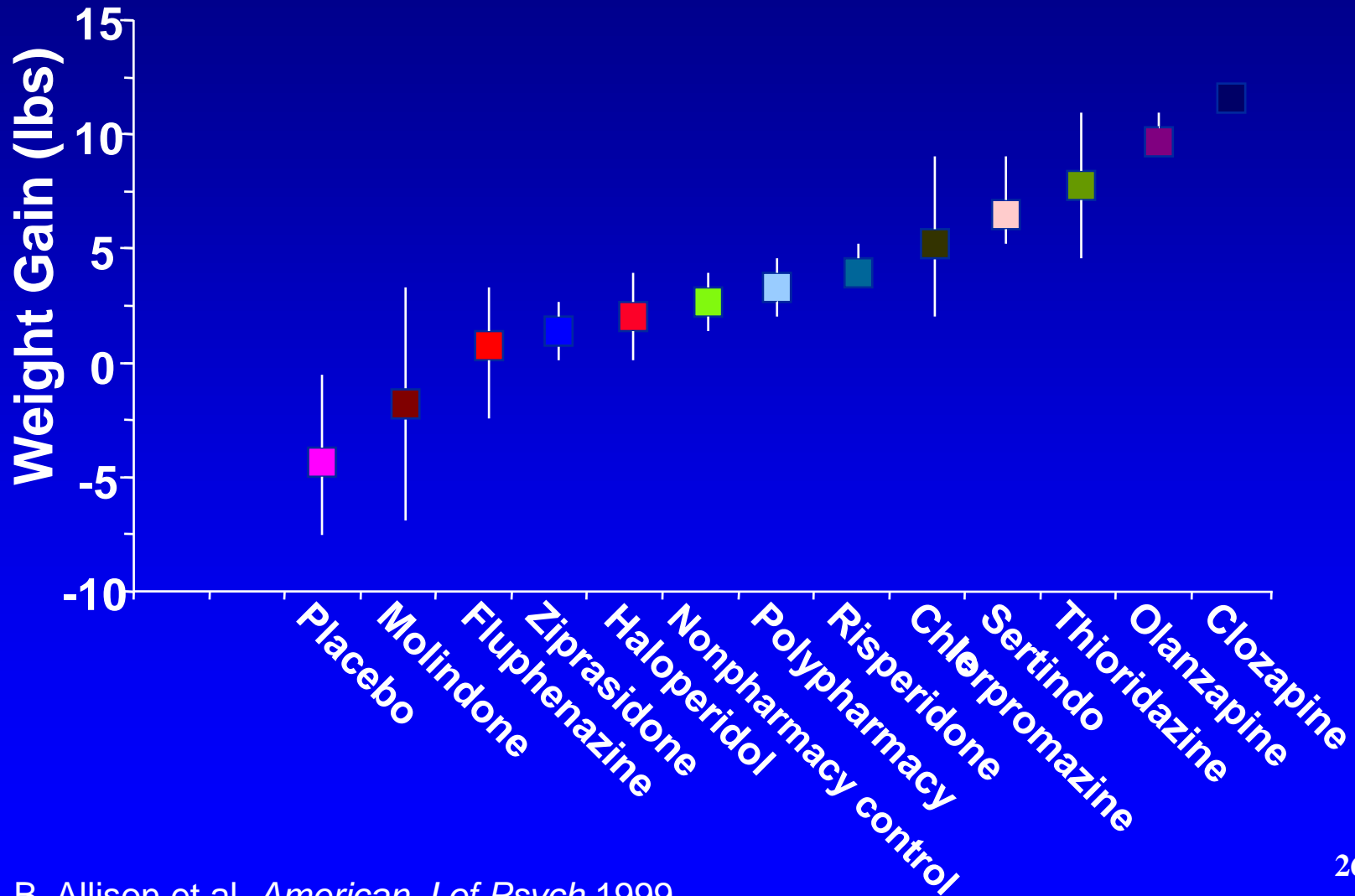
increase prolactin secretion comparable to haloperidol

Clinical Consequences of sustained hyperprolactinemia

- Sexual dysfunction
- Amenorrhea
- Gynecomastia/Galactorrhea
- Hypoestrogenism/Osteopenia?

clinical symptoms may occur with prolactin levels in the range 30-60 $\mu\text{g/l}$ and higher but are quite variable

Estimated Weight Gain at 10 Weeks on “Standard” Dose



QT_c

- This is the QT interval corrected for heart rate
- Average QT_c for general population, 400 msec

Mean (SD) change in QT_c at steady state: (msec)

| | |
|--------------|-------------|
| Ziprasidone | 20.6 (16.4) |
| Risperidone | 10.0 (11.1) |
| Olanzapine | 6.4 (13.6) |
| Quetiapine | 14.5 (12.7) |
| Thioridazine | 35.8 (13.5) |
| Haloperidol | 4.7 (16.9) |

What Should We Monitor?

- Physical Exam
 - Check weight - each visit
 - Check blood pressure - each visit
- Lab Tests
 - Hemoglobin A1c - every 3–6 months
 - Fasting blood glucose - every 3 months
 - Triglycerides - every 3 months
 - Cholesterol - every 3 months

Acute treatment: Management of poor responders

- Patients should receive an adequate dose for 4 to 6 weeks before being considered nonresponders
- Consider an antipsychotic from a different class
- Clozapine should be considered for nonresponders

Adjunctive medications

- Limited data support the addition of lithium, valproic acid, and benzodiazepines for treatment resistant patients
- These adjunctive medications may be helpful for comorbid conditions

ECT in schizophrenia

- ECT may be useful for patients with catatonic or treatment-resistant patients
- Antipsychotics should be continued during and after ECT.

Post Lecture Exam

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Answers to Pre & Post Competency Exams

1. E
2. A
3. C
4. C
5. A
6. A