The Psychopharmacology of Violence and Impulsivity

Part 2

Managing Aggressive Patients
Learning Objective

• Apply evidence-based treatment strategies to individuals with violent, impulsive, and aggressive behaviors
Poll Question

I feel competent applying evidence-based treatment strategies to individuals with violent, impulsive, and aggressive behaviors.

A. 1 (strongly disagree)
B. 2
C. 3
D. 4
E. 5 (strongly agree)
Sophia is a 31-year-old patient who was recently arrested for assaulting her father with a sledgehammer. The assault was instigated by the patient's delusion that her father is an alien, indicating only partial response to her current clozapine treatment. What are potential evidence-based treatment strategies for psychotic patients with inadequate response to clozapine?

A. Raise clozapine dose to 900 mg/day
B. Maintain plasma clozapine levels between 400 and 600 ng/mL
C. Augment with a second antipsychotic
D. A and C
E. B and C
A 42-year-old male patient with psychotic aggression is unable to take clozapine due to a history of thrombocytopenia. Which of the following is a reasonable approach to treatment-resistant psychosis when clozapine is not an option?

A. Dose olanzapine >40 mg/day
B. Dose olanzapine to achieve plasma drug levels >120 ng/mL but <700-800 ng/mL
C. Dose quetiapine to 1800 mg/day
D. Dose ziprasidone to 320 mg/day
E. All of the above
F. None of the above
Top-Down: Willpower When Provoked

Don't hit that guy

1. Top-Down: When Provoked
   - Amygdala
   - OFC
   - VMPFC
   - DLPFC
   - PFC

2. Hypoactivation
   - VTA

overactivation
normal
baseline
hypoactivation

Copyright © 2012 Neuroscience Education Institute. All rights reserved.
Treating the Top-Down System

- **Boosting acetylcholine in cognitive disorders**
  - Acetylcholinesterase inhibitors
  - Reducing/discontinuing anticholinergics

- **Tuning dopamine and norepinephrine in cortex**
  - Stimulants
  - Alpha 2 agonists
  - Norepinephrine reuptake inhibitors

- **Enhancing GABA in impulsive and psychotic disorders**
  - Benzodiazepines

- **Enhancing glutamate in impulsive and unstable mood disorders**
  - NMDA antagonists
  - Dextromethorphan/quinidine
Bottom-Up: Temptation With Impulsive Action

1. anticipation of threat
2. impulsive choice
3. threat sensitivity
4. protection
5. lack of cognitive flexibility

OFC VMPFC DLPFC

amygdala

Hit that guy

overactivation
normal
baseline
hypoactivation
Treating the Bottom-Up System

• Boosting 5HT in non-psychotic disorders
  – SSRIs/SNRIs targeting the amygdala and PFC

• Blocking DA (extensively in psychotic and impulsive disorders)
  – D2 antagonists targeting mesolimbic dopamine systems
That guy disrespected me; I want more cigarettes, drugs, and respect – a cell phone would be nice, too; good thing the rules don't apply to me.

Unemotional planning and execution; no fear of carrying this out or of the consequences.

I don't need to do anything that is frustrating to me.

Can I get away with it? Callous disregard for others.

Hit that guy when he is not expecting it and when I can get away with it.

Suppress the action until it is time.

1. OFC → VMPFC → DLPFC
2. PFC
3. amygdala
4. Unemotional planning and execution; no fear of carrying this out or of the consequences
5. Hit that guy when he is not expecting it and when I can get away with it

Overactivation
Normal
Baseline
Hypoactivation
Psychopharmacological Treatment of Instrumental Aggression

• Is there any?

• Transplant a conscience into the patient's brain?

• Rule out and treat any comorbid conditions that may contribute psychotic or impulsive dimensions to the instrumental violence
  – Psychotic and especially impulsive violence can masquerade as instrumental violence

• Send to a prison where behaviors will be detected or to isolation, where chances of interaction with others will possibly lessen these behaviors
Impulsive Aggression: Bottom-Up Out of Control

1. Staff is telling me to change my behavior and is refusing my request.

2. Act first, think later – ADHD, psychosis, cognitive dysfunction, substance abuse, child abuse.

3. Do I really need to hit somebody to get my way?

4. Remember, I got in trouble the last time.

- OFC
- VMPFC
- DLPFC
- PFC
- NA
- amygdala
- VTA

**Legend:**
- **Red**: overactivation
- **Purple**: normal baseline
- **Light Blue**: hypoactivation

Copyright © 2012 Neuroscience Education Institute. All rights reserved.
Psychopharmacological Treatment of Impulsive Aggression

• Improvement in hostility, violence, aggression, and assaultiveness is not necessarily correlated with improvement in positive symptoms if patient is psychotic

• However, improving psychosis with antipsychotics may "lengthen the fuse"

• So might treating manic/mood symptoms with mood stabilizers or even dextromethorphan/quinidine

• Also, stimulants, atomoxetine, or guanfacine, even in combination with antipsychotics may be effective

• Combining pharmacological treatment with psychotherapy may provide the best outcomes
Psychotic Aggression: Bottom-Up Out of Control

① That guy is going to hurt me – paranoid threat generated internally by psychosis (schizophrenia, bipolar, drug abuse)

② Go for it!

③ Is this a real threat?

④ Remember, I got in trouble the last time

amygdala

VTA

OFC VMPFC DLPFC PFC

NA

overactivation normal baseline hypoactivation

Hit that guy
Psychopharmacological Treatment of Psychotic Aggression

• Improvement in hostility, violence, aggression, and assaultiveness is not necessarily correlated with improvement in positive symptoms

• Clozapine is the best treatment

• Other antipsychotics may also be useful

• Especially at high degrees of D2 occupancy as tolerated and if effective
  – Polypharmacy (simultaneous use of 2 antipsychotics)
  – High-dose monotherapy

• Combining pharmacological treatment with psychotherapy may provide the best outcomes
Treatment Algorithm

Atypical Antipsychotic Monotherapy
*Standard dose for adequate duration*

Atypical Antipsychotic Monotherapy
*Standard dose for adequate duration*

Atypical Antipsychotic Monotherapy
*Standard dose for adequate duration*

Conventional Antipsychotic Monotherapy
*Standard dose for adequate duration*

High-Dose Antipsychotic Monotherapy

Clozapine Monotherapy
*Standard dose for adequate duration*

Polypharmacy

Back to Antipsychotic Monotherapy
Why Do Antipsychotic Monotherapies Fail?

• Standard doses of all antipsychotics target 60-80% occupancy of D2 receptors

• Some patients do not respond in 2-6 weeks to standard doses of 1 or more antipsychotics; this lack of response may represent both pharmacokinetic and pharmacodynamic failures
  – Not achieving 60-80% D2 occupancy
  – Not responding to 60-80% D2 occupancy
Hypothetical Thresholds for Antipsychotic Drug Effects

- **D2 receptor blockade (%)**
- **Dose; plasma concentration**

**EPS threshold**

**Antipsychotic effect threshold**
Pharmacokinetic Failures (1)

• If standard dosing achieves <60% D2 receptor occupancy, standard doses may not be effective, no matter how many drugs are tried

• How does one know this without measuring therapeutic drug levels?
  – Repeated failures without side effects
Pharmacokinetic Failures (2)

• Poor absorption of standard doses
  – Gastric bypass, lap-band, ileostomy, colectomy
  – Low absorption of some drugs without food

• Low drug levels in liars
  – Drugs don't work if patients don't take them
  – May require long-term injectables to enforce adherence

• CYP450 variants, which can now be confirmed by genotyping
  • Rapid metabolizers never get adequate D2 occupancy from standard doses
  • Slow metabolizers cannot tolerate standard doses (initially, high drug levels; then, low drug levels after stopping medication)
Pharmacokinetic Failure: Below Usual Threshold at Standard Doses

Ideal pharmacokinetics

Pharmacokinetic failure

Usual EPS and hyperprolactinemia threshold

Usual antipsychotic effect threshold

D2 receptor blockade (%) vs. Dose; plasma concentration
Novel Solutions to Pharmacokinetic Failures

- Better compliance with food when dosing (ziprasidone and lurasidone)
- Sublingual administration of standard doses (asenapine)
- Long-term injectables (risperidone, paliperidone, olanzapine, soon aripiprazole)
- Sometimes such patients respond to the administration of 2 agents; each is suboptimally absorbed, but together, they reach >60% D2 occupancy
- Is this the best solution?
- High-dose monotherapy to achieve standard 60-80% occupancy of D2 receptors might be better than polypharmacy, in which each agent achieves substandard occupancy of D2 receptors
Pharmacodynamic Failures

• The downstream effects of D2 blockade take more than 2-6 weeks to become manifest
  – In such cases, can time be considered a drug?

• 60-80% D2 occupancy is apparently not enough for some patients
  – Patients with multiple failures of adequately dosed agents
  – Patients with aggression or violence

• Do patients with treatment resistance to occupancy of 60-80% of D2 receptors, especially those who are violent and aggressive, respond to 80-100% occupancy of D2 receptors?
Pharmacodynamic Failure

Violence, treatment-resistant threshold?

Usual antipsychotic effect threshold

Dose; plasma concentration

D2 receptor blockade (%)

Standard dose

Dose for aggression/violence?

Copyright © 2012 Neuroscience Education Institute. All rights reserved.
Novel Solution to Pharmacodynamic Failures: Polypharmacy

- Polypharmacy with standard doses of 2 drugs can push D2 receptor occupancy to more than 80%, although it is impossible to block more than 100% of D2 receptors
  - Adding unique binding properties other than D2/5HT2A may account for response to polypharmacy; this is perhaps more likely in depression than in psychosis/mania
  - However, this also adds the side effect receptors of each drug, making sedation, weight gain, and metabolic disturbances along with D2-mediated side effects particularly difficult to avoid
Antipsychotic Polypharmacy

2nd ANTIPSYCHOTIC

USUAL TOP DOSE

TIME

Antipsychotic Polypharmacy

PROS
- Increased D2 receptor occupancy
- Targeting of non-positive symptom domains

CONS
- Increased cost
- Increased risk of intolerable side effects
- Possibly increased mortality
- Complicated treatment regimen may negatively affect adherence
- Possible drug-drug interactions
- May mask the efficacy of monotherapy
Novel Solution to Pharmacodynamic Failures: High Dosing

- Time and high-dose monotherapy are potentially simpler, safer, and more effective strategies for overcoming these failures to optimize antipsychotic treatment without polypharmacy.

- High dosing of certain agents may be able to achieve more than 80% occupancy of D2 receptors; this would result in more D2-mediated therapeutic effects, but also more D2-mediated side effects.
  - May actually be more tolerable than combining 2 drugs.
High-Dose Monotherapy

TIME

VERY HIGH DOSE

USUAL TOP DOSE

## High Dosing of Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual dose range (mg/day)*</th>
<th>Considerations for High Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>300-450</td>
<td>Maximum dose is usually 900 mg/day; doses above 550 mg/day may require concomitant anticonvulsant administration to reduce the chances of a seizure</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2-8</td>
<td>FDA-approved up to 16 mg/day; very high doses usually not tolerated</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3-6</td>
<td>Maximum dose is generally 12 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10-20</td>
<td>Some forensic settings up to 90 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>400-800</td>
<td>Some forensic settings up to 1800 mg/day</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40-200</td>
<td>Must be taken with food; PET data support &gt;120 mg/day; some forensic settings up to 320 mg/day may be appropriate</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15-30</td>
<td>Higher doses usually not more effective and possibly less effective</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>12-24</td>
<td>High dosing not well studied and may be limited due to risk of orthostatic hypotension</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10-20</td>
<td>High dosing not well studied</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40-80</td>
<td>Must be taken with food; nightly administration may improve tolerability; high dosing not well studied, but some patients may benefit from doses up to 160 mg/day</td>
</tr>
</tbody>
</table>

* Based on oral formulation in adults
Tips for Using Clozapine at High Doses

• Treatment with clozapine is the best documented for improvement of aggressive symptoms

• Improvement of aggressive symptoms with clozapine correlates with neither improvement of overall psychopathology nor other symptom domains

• High dosing to achieve >80% D2 occupancy should be used with caution due to the potential for seizures, sedation, and sialorrhea

• When clozapine monotherapy fails at doses up to 550 mg/day (plasma concentrations of 400-600 mg/day), it may be better not to increase the clozapine dose further
  – Add risperidone, amisulpride, or a conventional antipsychotic
  – Augment with lamotrigine
Clozapine Augmentation With Antipsychotics

- Amisulpride
  - Favors Mono
    - (Assion 2008a)
    - (Assion 2008b)
  - Favors Combo
    - (Chang 2008)
    - (Fleischhacker 2008)
    - (Muscatello 2011)
    - (Zhang 1989)
    - (Mossaheb 2006)
    - (Friedman 2011)

- Aripiprazole
  - Favors Mono
    - (Josiassen 2005)
    - (Yagcioglu 2005)
    - (Honer 2006)
    - (Freudenreich 2007)
    - (Weiner 2010)
    - (Nielsen 2011)
    - (Shiloh 1997)

- Chlorpromazine
- Haloperidol
- Pimozide

- Risperidone
  - Favors Mono

- Sertindole

- Sulpiride
Clozapine Augmentation With Antileptics, Antidepressants, and Glutamatergics

- Lamotrigine
  - (Tiihonen 2003)
  - (Kremer 2004)
  - (Zoccali 2007)
  - (Goff 2007a)
  - (Goff 2007b)
  - (Afshar 2009)
  - (Tiihonen 2005)
  - (Muscato 2010)
  - (Potkin 1999)
  - (Evins 2000)
  - (Diaz 2005)

- Topiramate
  - (Zoccali 2004)
  - (Berk 2009)

- Glycine

Sommer et al. Schizophr Bull 2011; Epub ahead of print.
D2 Binding by Clozapine

Tips for Using Olanzapine at High Doses

• Studies up to 40 mg/day

• Plasma drug levels between 5 and 75 ng/mL may correspond to 60-80% D2 receptor occupancy in many patients

• Plasma levels higher than 120 ng/mL but lower than 700-800 ng/mL (which can be associated with QTc prolongation) may correspond to >80% D2 receptor occupancy

• In forensic units, patients with violence despite previous treatment with standard doses may tolerate and respond to 60-90 mg/day
D2 Binding by Olanzapine

D2 Receptor Occupancy as a Function of Plasma Olanzapine Concentration at 4 Weeks After Injection of 300 mg of Depot (N=14)

Tips for Using Risperidone and Paliperidone at High Doses

• Can gradually increase dosing to upper end of dosage range, but often not well tolerated; rarely useful to administer risperidone above 8 mg/day

• The best way to achieve high doses of these agents may be to augment the long-term injectable with the oral formulation of the same agent; curiously, this is often well tolerated
D2 Binding by Risperidone

Tips for Using Quetiapine at High Doses

• Studies up to 1200 mg/day do not show superiority over 600 mg/day, but do show more side effects

• However, forensic use shows that up to 1800 mg/day (increasing slowly from 800 mg/day while monitoring for hypotension and tachycardia) may be well tolerated and effective in violent patients who have had prior exposure and who tolerate but do not respond to standard doses
Dopamine Receptor Occupancy (%) vs. Quetiapine Plasma Concentration

Estimated D2 Receptor Occupancy (%) vs. Time for Quetiapine IR and XR Formulations

How Much Quetiapine Is Enough for Treatment-Resistant Violence Associated With Psychosis?

• Nord et al. calculate:
  – The dose of quetiapine XR required to occupy 50% of D2 receptors is estimated to be 638 mg (continuous once-daily dosing)
  – Clozapine has an antipsychotic effect at 20-67% D2 receptor occupancy
  – 1185 mg quetiapine XR is required for 65% D2 occupancy at peak
  – 2550 mg quetiapine XR is required for 80% D2 occupancy
How Much Quetiapine Is Enough for Treatment-Resistant Violence Associated With Psychosis?

- Is <60-80% receptor occupancy required to treat psychosis, especially positive symptoms in patients without treatment resistance or violence?

- What about patients with treatment resistance or violence? Is 80% receptor occupancy enough?

- Gives rationale for dosing quetiapine at >1200 mg/day and even augmenting this with another antipsychotic for difficult cases of pharmacodynamic failure
  - Augmenting antipsychotic should be used at lower doses and lower degrees and for shorter durations of D2 receptor blockade
Tips for Using Ziprasidone at High Doses

• Use up to 320 mg/day has been reported

• QTc prolongation is not dose related and in the standard dosage range of up to 160 mg/day, seems not to be associated with any increased cardiovascular mortality

• Many patients tolerate and respond to once-daily administration, which can be easier to take with food than twice-daily
Plasma Levels vs. Percentage of D2 Occupancy at 12 Hours Post-dose

Ziprasidone: Greater Effect With 120-160 mg/day in Acute Schizophrenia

BPRS Total Mean Change From Baseline

Effect size

- **P<0.01**
- ***P<0.001***
- *P=0.036*

N=335

N=220

40-80 mg/d

120-160 mg/d

Tips for Using Aripiprazole at High Doses

• Exception to the rule that high doses (>30 mg/day) may be more effective than standard doses due to its partial agonist properties, which limit maximum D2 blockade despite 100% occupancy of D2 receptors

• Thus, lower dosing may actually be more efficacious

• Its very high affinity for D2 receptors means that it blocks the effects of concomitantly administered antipsychotics; therefore, its addition may actually reduce the efficacy of other antipsychotics

• However, this blocking property can be useful in small doses to mitigate hyperprolactinemia and possibly other side effects of other antipsychotics
Aripiprazole D2 Receptor Occupancy and Blockade in Patients With Schizophrenia
Tips for Using Asenapine, Iloperidone, and Lurasidone at High Doses

• Generally, try other agents with more clinical experience

• Asenapine: no more than 10 mg/dose, but up to 30-40 mg/day with doses separated by at least 1 hour

• Iloperidone: hypotension limits high doses, but studies up to 36 mg/day have been done

• Lurasidone: approved at 40 and 80 mg/day, but studies at 120 and 160 mg/day have shown more efficacy in some patients
Tips for Using Conventional Antipsychotics at High Doses

• Can gradually increase dosing beyond the upper limit of dosing range and beyond the usual plasma drug levels

• Often surprisingly well tolerated

• Risk of TD and elevated prolactin are part of the risk:benefit calculation

• Haloperidol and fluphenazine may be preferable, as their blood levels are better understood and as they have depots available
# D2 Receptor Occupancy Induced by Clinical Doses of Antipsychotic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>D2 Receptor Occupancy (%)</th>
<th>EPS</th>
<th>No EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol decanoate 50 / 28 d.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flupentixol decanoate 40 / 7 d.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuclopentixol decanoate 200 / 24 d.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine 200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulpiride 800</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine enanthate 100 / 7 d.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol decanoate 70 / 28 d.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remoxipride 400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flupentixol 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melperone 250</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malarone 300</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flupentixol 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Doses in mg/day

- **EPS**
- **No EPS**

Courtesy of L. Farde.
D2 Binding by Haloperidol

Plasma Haloperidol and the Probability of Disabling Side Effects

## Data on 10 Subjects Receiving Individualized Doses of Trifluoperazine


<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Length of hosp. (yrs)</th>
<th>Max daily dose</th>
<th>Degree of improvement-psychiatric rating</th>
<th>Max neur. rating</th>
<th>Weight change</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>35</td>
<td>16</td>
<td>30 mg.</td>
<td>0</td>
<td>3.0</td>
<td>-5</td>
</tr>
<tr>
<td>02</td>
<td>52</td>
<td>31</td>
<td>150 mg.</td>
<td>0</td>
<td>1.2</td>
<td>+5</td>
</tr>
<tr>
<td>03</td>
<td>52</td>
<td>27</td>
<td>100 mg.</td>
<td>0</td>
<td>1.5</td>
<td>-3</td>
</tr>
<tr>
<td>04</td>
<td>23</td>
<td>6</td>
<td>*220 mg.</td>
<td>+</td>
<td>1.1</td>
<td>+25</td>
</tr>
<tr>
<td>05</td>
<td>30</td>
<td>11</td>
<td>*480 mg.</td>
<td>+</td>
<td>0.4</td>
<td>+30</td>
</tr>
<tr>
<td>06</td>
<td>41</td>
<td>23</td>
<td>100 mg.</td>
<td>+</td>
<td>1.1</td>
<td>+10</td>
</tr>
<tr>
<td>07</td>
<td>51</td>
<td>14</td>
<td>20 mg.</td>
<td>+</td>
<td>3.1</td>
<td>+10</td>
</tr>
<tr>
<td>08</td>
<td>57</td>
<td>16</td>
<td>30 mg.</td>
<td>+++</td>
<td>2.0</td>
<td>+12</td>
</tr>
<tr>
<td>09</td>
<td>42</td>
<td>11</td>
<td>40 mg.</td>
<td>+</td>
<td>2.0</td>
<td>+12</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>32</td>
<td>60 mg.</td>
<td>+</td>
<td>2.0</td>
<td>+6</td>
</tr>
<tr>
<td>Mean</td>
<td>43.8</td>
<td>18.7</td>
<td>123 mg.</td>
<td>1.74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 : no improvement or worse

0 : no improvement

+ : mild improvement

± : mild improvement with later worsening

++ : moderate improvement

+++ : marked improvement
Plasma Fluphenazine Level at 9 Months as a Predictor of Unexacerbation in the Following Year

Relationship Between Plasma Fluphenazine Concentration and Estimated Probabilities of Improvement and Disabling Side Effects

Risk/Benefit Probability Curve Obtained by Combining the 2 Logistic Regression Functions in the Previous Slide

Estimated probability of improvement without disabling side effects

Plasma fluphenazine (ng/mL)

Summary

• Although standard doses of all antipsychotics target 60-80% occupancy of D2 receptors, this may not be sufficient to quell violence and aggression in all patients.

• Pharmacokinetic treatment failures occur when D2 receptors are inadequately occupied; such failures may be managed by high dosing, novel routes of administration, or the administration of some antipsychotics with food.

• Pharmacodynamic treatment failures occur when patients do not respond despite achieving 80% D2 receptor occupancy; such failures can be managed by high dosing, very long treatment duration, or polypharmacy.

• Clozapine, polypharmacy, or high-dose antipsychotic monotherapy may be justified in individual cases, especially if effective in reducing assaults and if side effects are carefully monitored.