The Pharmacological Management of Persistent Violence in Psychiatric Inpatients

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Disclosures

Katherine Warburton, DO (Chair)
None

Jonathan Meyer, MD
Dr. Meyer reports having received speaking or advising fees from Acadia Pharmaceuticals, Alkermes, Allergan, Forum Pharmaceuticals, Merck, Neurocrine, Otsuka America, Inc., Sunovion Pharmaceuticals and Teva Pharmaceutical Industries.

Laura Dardashti, MD
None

Michael A. Cummings, MD
None

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Agenda

1. The Problem of Persistent Aggression and the Need to Categorize Aggression into Psychotic, Impulsive and Predatory Subtypes - Katherine Warburton DO (Chair)

2. The Neurobiology of Persistent Aggression - Jonathan Meyer MD

3. The Management of Persistent Psychotic Aggression - Laura Dardashti MD

4. The Management of Persistent Impulsive Aggression in Patients with Schizophrenia, TBI and Dementia - Michael Cummings MD

5. Concluding Remarks - Katherine Warburton DO (Chair)

6. Question and Answer - Panel
Learning Objectives

• At the conclusion of this session, the participant will be able to understand the clinical value of categorizing aggression into psychotic, impulsive and predatory subtypes and how this can inform clinical decision-making

• At the conclusion of this session, the participant will be able to understand the neurobiological basis for impulsive aggression

• At the conclusion of this session, the participant will be able to utilize the evidence-based data from studies of psychotic and impulsive aggression to treat patients with schizophrenia spectrum disorders, traumatic brain injury and dementia

• At the conclusion of this session, the participant will understand the limitations of certain medications, including the absence of efficacy data for antipsychotic use in TBI patients, and the mortality risk for antipsychotics in dementia patients

The Problem of Persistent Aggression and the Need to Categorize Aggression into Psychotic, Impulsive and Predatory Subtypes
Violence and State Hospitals

- ABC 15 Investigation Exposes a Shocking' Level of Violence at the Arizona State Hospital. Arizona August 9, 2013.
- Assaults on Staff are Focus of Scathing Report at Catonsville Psychiatric Hospital. Maryland March 2, 2013.
- Danger at Mid-Hudson Psych: ‘I’m just waiting for a Staff Member to Come Out Dead’. New York
- Safety inspectors investigating violence at Hawaii State Hospital. Hawaii December 5, 2013.
- Daily attacks common at the Oregon State Hospital, some say. Oregon April. 18, 2013.
- Assaults on Staff at Western State Hospital Costing Millions. Seattle Times. November 27, 2015.
- Man pleads guilty to assaulting nurse at Montana State Hospital ...Montana Standard-Aug 11, 2016.
- Man charged with killing snoring roommate at Utah State Hospital ...Daily Herald-Aug 18, 2016.

California Dept. of State Hospitals (DSH) New Admissions and Violence

<table>
<thead>
<tr>
<th>FY</th>
<th>Violent</th>
<th>Total Admits</th>
<th>% Violent</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY10/11</td>
<td>1206</td>
<td>3388</td>
<td>35.6</td>
</tr>
<tr>
<td>FY 11/12</td>
<td>1080</td>
<td>3388</td>
<td>31.9</td>
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<tr>
<td>FY 12/13</td>
<td>972</td>
<td>3365</td>
<td>28.9</td>
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<tr>
<td>FY 13/14</td>
<td>1022</td>
<td>3733</td>
<td>27.4</td>
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<tr>
<td>FY 14/15</td>
<td>1060</td>
<td>3899</td>
<td>27.2</td>
</tr>
</tbody>
</table>

California Dept. of State Hospitals Data
When Does Violence Occur?

50% of all violent incidents occurred within the first 120 days after admission

Typology of Inpatient Aggression

- Videotaped inpatient assaults were studied at a New York psychiatric hospital
- Assailant, witnesses, and victim were interviewed separately as soon as possible after each incident

### Findings from Nolan et al.

- Three primary categories of assaultive behavior were described
  - Disordered impulse control
  - Psychopathic (planned/predatory) behavior
  - Underlying psychotic symptomatology


### Types of Aggression at Napa State Hospital

- UC Davis researchers studied 839 assaults committed by 88 persistently violent patients in an attempt to replicate the work of Nolan et al.
  - Acts of aggression were analyzed based on a review of Special Incident Reports
- Developed a classification system to categorize aggressive acts into motivation and subcategorize them into provocation

Aggression Subtypes at Napa State Hospital


Differences Between Staff and Patient Violence Categorization

<table>
<thead>
<tr>
<th>FY</th>
<th>Staff</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impulsive</td>
<td>65%</td>
<td>39%</td>
</tr>
<tr>
<td>Organized</td>
<td>18%</td>
<td>34%</td>
</tr>
<tr>
<td>Psychotic</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Unclear</td>
<td>2%</td>
<td>7%</td>
</tr>
</tbody>
</table>

UC Davis-Napa State Hospital Additional Findings

- **Impulsive aggression** occurs most frequently in individuals who exhibit combinations of psychiatric symptoms (especially anxiety and hostility) and anger
- **Psychotic aggression** was related to psychotic symptoms
- **Predatory aggression** occurs most frequently in individuals who exhibit psychopathic/antisocial characteristics and heightened affect (anger)
  - this type of aggression results in more injury and often more severe injury


**Type of Aggression by Primary Diagnosis**

Type of Aggression by Personality Disorder Diagnosis

Injury By Category of Assault

The Neurobiology of Persistent Impulsive Aggression

Non-Impulsive Aggression

• Management of aggression motivated by psychosis:
  – relates to the treatment of psychosis itself (discussed later)

• Predatory/instrumental behavior: certain neurobiological substrates are associated with increased impulsive aggression and psychopathy
  – Increased 5HT_{1B} receptor availability is associated with trait anger in violent offenders (relates to impulsive aggression)
  – Psychopathy is associated with reduced gray matter volume
  – Despite this knowledge, goal-directed antisocial or psychopathic behavior does not lend itself to pharmacological treatment


Reward-Seeking Behavior is Influenced by Multiple Areas of the Brain

Prefrontal Cortex  
Executive Control

Amygdala  
Affect/Emotions

Ventral Tegmental Area  
Incentive Motivation

Hippocampus  
Context/Environment


Normal Reward-Seeking Behavior in Response to a Salient Stimulus

Subcortical Reward Center  
Cortical Inhibitory Control

Striatum  
Goal-directed Behavior  
Stimulus-directed Behavior

Behavior  
Dopaminergic Neurons

Salient Stimulus

Abnormal Reward-Seeking Behavior in Response to a Salient Stimulus

Cortical Inhibitory Control

Subcortical Reward Center

Striatum

Behavior

Dopaminergic Neurons

Salient Stimulus

Antipsychotics and Behavioral Treatments


Devaluation of a Reward Can Switch Goal-directed Behavior into Stimulus-directed Behavior

Reward Evaluation

Favorable Outcome

Unfavorable Outcome

How beneficial is the outcome?
Is there any risk?

Engaging in the behavior would lead to a positive result
Very little to no risk is required to achieve the reward

Engaging in the behavior would lead to a negative result
A high degree of risk is required to achieve the reward

Engaging in the behavior would lead to a novel exciting palatable result

Goal-directed behavior

Action-outcome learning

Stimulus-directed behavior

Stimulus-response learning

Stahl SM. Stahl's Essential Psychopharmacology, 5th edition, in press, copyright Neuroscience Education Institute
Maladaptations of the Reward Pathway Can Shift Behavior From Normal to Impulsive to Compulsive

**NORMAL**
- Salient Stimulus
- Favorable Outcome
  - Pleasurable Reward
- Learning
  - “Liking”
    - Opioids
- “Wanting”
  - Dopamine

**IMPULSIVITY**
- Salient Stimulus
- Favorable Outcome
  - Pleasurable Reward
- Binge
- Absence
- Anticipation

**COMPULSIVITY**
- Stimulus
- Behavior
  - Habits

**Maladaptations in the Reward Circuitry that Potentially Underlie Impulsive Violence**

**Normal**
- Subcortical Reward Center
  - Goal-directed behavior
  - Stimulus-directed behavior
- Excitatory Inputs Modulating Behavior
- Cortical Inhibitory Control

**Impulsive Trait**
- Reduced Cortical Inhibitory Control
- Risky behavior
- Inappropriate behavior
- Inability to stop actions
- Poor decision making
- Impatience

**Abnormal Compulsive Violence**
- Subcortical Reward Center
  - Goal-directed behavior
  - Stimulus-directed behavior
- Increased Excitatory Inputs Modulating Behavior


Dopaminergic Signaling to the Dorsal Striatum is Influenced by Signaling in the Nucleus Accumbens

Striato-nigro-striatal loops regulate dopaminergic activity in the striatum

The striatum shows distinct organization – ventral domains exert control over dorsal domains

Compulsive behaviors, such as drug-seeking, correlate with an increase in dopamine in the dorsal striatum

Disruption of the ventral-dorsal connection decreased drug-seeking behavior in reinforcement-trained rats

Belin D and Everitt BJ. Neuron. 2008;57:432-441.
Stahl SM. Stahl’s Essential Psychopharmacology, 5th edition, in press, copyright Neuroscience Education Institute

Frontal Cortical-Striatal Interactions Implicated in Impulsivity and Compulsivity

Lesions in the infralimbic and cingulate cortex increase impulsivity
The orbitofrontal cortex has been implicated in reward-delay behavior
The orbitofrontal cortex shows increased activity in response to food cues

The orbitofrontal cortex is important for reversal learning
Cognitive flexibility relies on both the prefrontal and orbitofrontal cortices
Compulsive habits rely on connections between the striatum and motor cortices

The Hypothesized Modulation of Compulsive Violence
By High Occupancy of D₂ Receptors Via High Dose
Antipsychotics/Polypharmacy

“The way in may not necessarily be the way out”

- May not necessarily be the “unlearning” or normalization of maladaptive behavior
- May act by restoring balance so that impulses triggered by conditioned stimuli no longer trigger habitual behavior
- May act by compensating the impulse by increasing top down inhibitory control of behavior

Stahl SM. Stahl’s Essential Psychopharmacology, 5th edition, in press, copyright Neuroscience Education Institute

Impulsive Aggression

- Improving “Top-Down” Inhibitory Control:
  - psychostimulants
  - behavioral treatments
  - antidepressants
  - antipsychotics
- Decreasing “Bottom-Up” excitatory inputs:
  - antipsychotics
  - clozapine
  - lithium
  - valproate

The Management of Persistent Psychotic Aggression

Clinical Concepts

• Psychotic aggression is the direct result of poorly controlled positive symptoms of psychosis.
• Although it is the least frequent form of aggression (15%), it is the most treatable.
• In general, treatment of psychotic aggression will follow treatment pathways for schizophrenia non-responders.
• Schizoaffective disorder, bipolar type may require antipsychotic + mood stabilizer as opposed to antipsychotic monotherapy.

Inadequate Antipsychotic Treatment Response

Question #1 - Do you have the correct diagnosis?

Question #2 – Is the aggression driven by psychosis?

Question #3 - Has the patient received an adequate trial of drug treatment?

What Works for Psychosis

1. Antipsychotics
2. Antipsychotics
3. Antipsychotics

What Doesn’t Work for Nonaffective Psychosis?

1. Lithium
2. Valproic acid
3. Lamotrigine
4. Other mood stabilizers of any shape or form
Inadequate Antipsychotic Treatment Response

Adequate Drug Trial but No Response Or Adverse Effects

Obtain a Plasma Drug Level

Inadequate Treatment Response:
The Value of Plasma Drug Levels

Plasma antipsychotic levels assist in clinical decision-making

- The decision to terminate a medication trial is best made by consideration of response and tolerability, informed by the levels.
  - Many patients are considered medication failures, but have subtherapeutic plasma antipsychotic levels. In one study, plasma levels were measured in 36 treatment-resistant schizophrenia patients. 44% showed either undetectable (19%) or subtherapeutic levels (25%).

- Many schizophrenia patients require and tolerate high plasma levels for adequate treatment response.
  - When interpreting: laboratory reference ranges are misleading and do not represent well-defined toxicity thresholds.

Inadequate Treatment Response: Checking Plasma Drug Levels

When checking plasma antipsychotic drug levels…

1. Does the plasma drug level correspond to the dose being administered?

2. Is the plasma level above the minimum response threshold (MRT)?

3. Is the patient experiencing dose-limiting adverse effects or has the plasma level exceeded the point of futility?

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### Oral Dose-Plasma Level Relationships

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/ml) = 0.08 x oral dose (mg/d) (nonsmokers)</th>
<th>Concentration (ng/ml) = 0.04 x oral dose (mg/d) (smokers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>22.9 mg ➞ 1.83 ± 0.94 ng/ml (nonsmokers)</td>
<td>20.4 mg ➞ 0.89 ± 0.43 ng/ml (smokers)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/ml) = 2.00 x oral dose (mg/d) (nonsmokers)</th>
<th>Concentration (ng/ml) = 1.43 x oral dose (mg/d) (smokers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>10 mg ➞ 20 ng/ml (nonsmokers)</td>
<td>14 mg ➞ 20 ng/ml (smokers)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active Moiety Concentration (ng/ml) = 7.00 x oral dose (mg/d)</th>
<th>Risp/9-OH Risp Ratio: 0.2 (range 0.1 - 0.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone + 9-OH Risperidone (active moiety)</td>
<td>2 mg/d ➞ C/D Ratio = 7.05</td>
<td>6 mg/d ➞ C/D Ratio = 7.15</td>
</tr>
<tr>
<td></td>
<td>10 mg/d ➞ C/D Ratio = 7.28</td>
<td>16 mg/d ➞ C/D Ratio = 6.95</td>
</tr>
</tbody>
</table>

Inadequate Treatment Response: Checking Plasma Drug Levels

When checking plasma antipsychotic drug levels….

1. Does the plasma drug level correspond to the dose being administered?

2. Is the plasma level above the minimum response threshold (MRT)?

3. Is the patient experiencing dose-limiting adverse effects or has the plasma level exceeded the point of futility?

Response and Tolerability Threshold Levels

<table>
<thead>
<tr>
<th></th>
<th>Response Threshold (ng/ml)</th>
<th>Tolerability threshold (ng/ml)</th>
<th>Level associated with 60% D₂ occupancy</th>
<th>Level associated with 80% D₂ occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>3 - 5</td>
<td>18 – 20</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.8 – 1.0</td>
<td>2.7 – 2.8</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Risperidone + 9-OH Risperidone</td>
<td>??</td>
<td>??</td>
<td>~ 17 ng/ml</td>
<td>45-47</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>23.2</td>
<td>176</td>
<td>~ 20 ng/ml</td>
<td>70-78</td>
</tr>
<tr>
<td>Clozapine</td>
<td>350</td>
<td>? 800-1000</td>
<td>??</td>
<td>??</td>
</tr>
</tbody>
</table>

Inadequate Treatment Response:
Low Antipsychotic Plasma Level

Plasma Drug Level **Below** MRT

- Steps to Optimize Adherence
- Possible Pharmacokinetic Failure
- High Dose Antipsychotic Monotherapy

Inadequate Treatment Response:
Antipsychotic Plasma Level Above MRT

- **✓** Plasma Drug Level Above MRT

  - Adverse effects present
    - SWITCH
  - Adverse effects absent
    - Push level to point of AEs or futility before deciding patient is a pharmacodynamic failure
The Point of Futility

- Historical Rule: Titrate antipsychotic to EPS and then reduce dose
- For a small subset of patients the EPS threshold may never be reached.
- Probably a point of futility for most antipsychotics beyond which the likelihood of response is virtually nil:
  - Haloperidol > 30 ng/mL
  - Fluphenazine > 4.0 ng/mL
  - Olanzapine > 200 ng/mL


Inadequate Treatment Response: Antipsychotic at MRT and No Adverse Effects

Options:

1. Higher dose of atypical antipsychotic with substantial D₂ blockade
2. Switch to a first generation antipsychotic for more D₂ antagonism
3. If local regulations limit maximal doses, clozapine is the next step
Treatment Resistance: Clozapine

- Antipsychotic of choice for treatment refractory schizophrenia
- Response rates up to 60%
- Minimum therapeutic threshold is a plasma level of 350 ng/mL
  - Levels up to 1000 ng/ml may be needed (if tolerated) for adequate response in some patients


High Dose Olanzapine vs. Clozapine in Treatment Resistant Schizophrenia

Double-blind 8 week crossover study of olanzapine 50 mg/day vs. clozapine 450 mg/day (option for dose reduction to 30 mg olanzapine or 300 mg clozapine), 8 weeks on olanzapine or clozapine, then switch.

Treatment-resistant schizophrenia criteria:
- Inpatients, poor function for 5 years
- Failure on 2 typicals at > 1000 mg/d CPZ equivalents and > 6 weeks
- Failure on prospective haloperidol trial 10 to 40 mg/d

Response Definition:
- 20% improvement in total BPRS & final BPRS < 35 OR 1 point improvement on the CGI-S

Results:

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>0%</td>
<td>46%</td>
</tr>
<tr>
<td>Clozapine</td>
<td>30%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Time to Clozapine Response**

Standardized dose escalation trial: 50 patients with refractory schizophrenia.¹

- Mean time to response: 82 ± 100 days (range = 10 - 401)
- Mean time to reach dose at which response was achieved: 60 ± 87 days
- Once the responding dose was reached, the average response time was 17 ± 14 days (range = 2 - 56).


**Electroconvulsive Therapy**

- Primarily used to augment pharmacotherapy in drug resistant schizophrenia
- Most common symptoms were:
  - Catatonia (most effective)
  - Aggression
  - Suicide

- *Lally et al*: Clozapine + ECT in treatment resistant schizophrenia
  - Overall response = 66% (95% CI: 57.5 – 74.3%; 83 out of 126)
  - Mean number of treatments to augment ECT = 11.3
  - 32% pts relapsed post-ECT cessation

¹ Pompili, M; Lester, D; Dominici, G. et al. Indications for electroconvulsive treatment in schizophrenia: a systematic review. *Schizophrenia Research*. 2013 May; 146(1-3):1-9

The Management of Persistent Impulsive Aggression in Patients with Schizophrenia, Traumatic Brain Injury and Dementia

The Problem of Impulsive Aggression or Violence

Definition: Aggressive or violent behavior occurring without due consideration of the consequences or costs of the behavior. Often associated with an aroused emotional state, e.g. excited, angry, or agitated. ¹

Problem: 54% of inpatient violence is impulsive aggression compared to 29% organized (AKA instrumental or predatory) 17% psychotically motivated. ²

The Management of Persistent Impulsive Aggression in Patients with Psychosis

**Clozapine for Violent Patients with Schizophrenia**

- **Method:** Randomized, double-blind, parallel-group, 12-week trial
  - Modified Objective Aggression Scale (MOAS) was rated by nursing staff every 30-90 minutes. Ratings reviewed with investigators after each aggressive act.
- **Sample:** Chronically assaultive male inpatients with schizophrenia or SAD in NY state psychiatric facilities
- **Demographics:**
  - Mean PANSS = 85
  - Mean prior hospitalizations = 11
  - Mean age = 34 years
  - Mean illness duration = 15 years
- Randomly assigned to clozapine (n=37), olanzapine (n=37), or haloperidol (n=36)
- **Mean doses at week 12:**
  - Clozapine: $565.5 \pm 112.7$ mg
  - Olanzapine: $24.7 \pm 6.1$ mg
  - Haloperidol: $23.3 \pm 7.1$ mg

Clozapine and Impulsive Violence in Psychosis: Results

- PANSS scores showed no significant differences across groups
- Clozapine produced significantly better reductions in:
  - MOAS verbal aggression scores
  - MOAS physical aggression scores
  - MOAS total aggression scores
- Retrospective analysis indicated that clozapine’s improvement of aggression and violence was related to improvements in executive functions (prefrontal cortex).


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No Significant Between Group Change in PANSS Total & Subscales

<table>
<thead>
<tr>
<th>PANSS Variable</th>
<th>Medication Group</th>
<th>Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>F (P Value)</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>Clozapine</td>
<td>2.39 ± 14.2</td>
<td>1.23 (.30)</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>4.83 ± 9.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>0.58 ± 15.2</td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>Clozapine</td>
<td>1.54 ± 5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>1.41 ± 3.6</td>
<td>2.30 (.11)</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>−0.50 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Clozapine</td>
<td>−0.56 ± 4.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>0.72 ± 3.0</td>
<td>1.65 (.20)</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>0.44 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>General psychopathology</td>
<td>Clozapine</td>
<td>1.43 ± 7.0</td>
<td>1.21 (.30)</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>2.69 ± 5.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>0.64 ± 8.2</td>
<td></td>
</tr>
</tbody>
</table>

Significant Between Group Change in MOAS Outcomes

<table>
<thead>
<tr>
<th>MOAS</th>
<th>Comparison</th>
<th>OR (95% CI) for Less Severe Violence</th>
<th>χ² (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>Clozapine vs haloperidol</td>
<td>1.69 (1.6-1.8)</td>
<td>154.7 (&lt;.001)‡</td>
</tr>
<tr>
<td></td>
<td>Clozapine vs olanzapine</td>
<td>1.30 (1.2-1.4)</td>
<td>36.2 (&lt;.001)†</td>
</tr>
<tr>
<td></td>
<td>Olanzapine vs haloperidol</td>
<td>1.30 (1.2-1.4)</td>
<td>44.9 (&lt;.001)‡</td>
</tr>
<tr>
<td>Physical aggression</td>
<td>Clozapine vs haloperidol</td>
<td>2.04 (1.8-2.3)</td>
<td>134.0 (&lt;.001)‡</td>
</tr>
<tr>
<td></td>
<td>Clozapine vs olanzapine</td>
<td>1.33 (1.2-1.5)</td>
<td>21.3 (&lt;.001)†</td>
</tr>
<tr>
<td>Aggression against property</td>
<td>Clozapine vs haloperidol</td>
<td>1.54 (1.4-1.7)</td>
<td>54.0 (&lt;.001)‡</td>
</tr>
<tr>
<td></td>
<td>Olanzapine vs haloperidol</td>
<td>1.85 (1.4-2.3)</td>
<td>18.6 (&lt;.001)‡</td>
</tr>
<tr>
<td></td>
<td>Clozapine vs olanzapine</td>
<td>1.10 (0.8-1.5)</td>
<td>0.1 (.78)</td>
</tr>
<tr>
<td>Verbal aggression</td>
<td>Clozapine vs haloperidol</td>
<td>1.67 (1.3-2.2)</td>
<td>16.4 (&lt;.001)‡</td>
</tr>
<tr>
<td></td>
<td>Olanzapine vs haloperidol</td>
<td>1.35 (1.2-1.5)</td>
<td>21.7 (&lt;.001)‡</td>
</tr>
<tr>
<td></td>
<td>Clozapine vs olanzapine</td>
<td>1.32 (1.1-1.6)</td>
<td>17.6 (&lt;.001)‡</td>
</tr>
<tr>
<td></td>
<td>Olanzapine vs haloperidol</td>
<td>1.03 (0.9-1.2)</td>
<td>0.3 (.57)</td>
</tr>
</tbody>
</table>


12 Week MOAS Totals by Baseline Composite Executive Function Scores

Additional Agents with Evidence Supporting Treatment of Impulsive Violence in Psychosis *

- Lithium (limited data in schizophrenia)
- Valproic Acid
- Centrally acting adrenergic antagonists, e.g. propranolol
- SSRI antidepressants
- Stimulants (if psychosis well controlled)

* When used as adjunctive agents along with antipsychotics in persistently aggressive and violent patients, effect sizes tend to be in the small to moderate range.


The Management of Persistent Impulsive Aggression in Patients with Traumatic Brain Injury (TBI)
Drugs with Positive Supporting Evidence for Treatment of Aggression in TBI

- Only six randomized clinical trials (Cochrane Review 2009) for aggression in TBI:
  - Four for propranolol or pindolol
  - One each for methylphenidate and amantadine
- Subsequent data permitted French consensus supporting:
  - Carbamazepine
  - Valproic acid
  - Lithium has support in intermittent explosive disorder, but not TBI.

Dopamine Agonists for Treatment of Persisting Impulsive Violence and Aggression in TBI

- Stimulants, e.g. methylphenidate:
  - No RCT data available
  - Uncontrolled data mixed
- Amantadine 100 mg b.i.d. data:
  - One positive study (N = 76)
  - One negative replication study (N = 168)
Atypical Antipsychotics Lack Efficacy in Treatment of Persisting Violence and Aggression in TBI

Data for atypical antipsychotic efficacy:
- No efficacy for impulsive violence and aggression in TBI

Adverse effects of treatment:
- Sedation
- Worsened cognitive performance
- EPS
- Metabolic syndrome


The Management of Persistent Impulsive Aggression in the Context of Neurocognitive Disorders (Dementia)
Characteristics of Pharmacological Studies of Treatment of Aggression or Violence in Neurocognitive Disorders

• Studies focused on:
  – Alzheimer’s disease
  – Vascular dementias

• Studies limited by safety concerns regarding some pharmacological agents, e.g. antipsychotics


Second-generation Antipsychotics for Treatment of Persisting Aggression or Violence in Neuropsychiatric Disorders

• Meta-analyses positive for some agents

• Randomized controlled trials negative

• Increased mortality observed in naturalistic studies
  – RR ranged from 3.2 to 12.3 over 1880 days
  – NNH ranged from 8 to 31

Antiepileptic Mood Stabilizers for Treatment of Persisting Aggression or Violence in Neuropsychiatric Disorders

- Valproic Acid or Divalproex:
  - Positive open-label trials
  - Negative randomized controlled trials
- Carbamazepine:
  - Mixed efficacy data
  - Problematic pharmacokinetics (hepatic induction)
- Lamotrigine:
  - Single positive open-label study

Cholinesterase Inhibitors and Memantine for Treatment of Persisting Aggression or Violence in Neuropsychiatric Disorders

- Cholinesterase inhibitors:
  - Reduce agitation in mild to moderate dementia
  - Failure of one does not predict response to others
- Memantine:
  - Reduces agitation in moderate to severe dementia
  - Often combined with a cholinesterase inhibitor

References:
- Gallagher D, et al. Antiepileptic Drugs for the Treatment of Agitation and Aggression in Dementia: Do They have a Place in Therapy? Drugs 2014; 74: 1747-55
- Cummings J, et al. Role of Donepezil in the Management of Neuropsychiatric Symptoms in Alzheimer’s Disease and Dementia with Lewy Bodies. CNS Neurosci Ther 2016; 22: 159-66
SRI Antidepressants and Trazodone for Treatment of Persisting Aggression or Violence in Neuropsychiatric Disorders

- **Design:** Retrospective meta-analysis (Cochrane database)
- **Results:**
  - Only small number of studies available
  - Citalopram effective (two RCT)
  - Sertraline effective
  - Trazodone effective


Citalopram: Secondary Analysis for Neuropsychiatric Symptoms in Alzheimer’s Disease (CitAD Study)

- **Design:** Planned secondary analysis of Neuropsychiatric Inventory (NPI) data from prior 9 week study
- **Significant Results:**
  - OR 0.40 Delusions
  - OR 0.43 Anxiety
  - OR 0.38 Irritability/lability
  - A nonsignificant trend toward reduced hallucinations also was found.

**Comment:** The authors noted dosing constraints due to QT prolongation concerns, suggesting that in some patients sertraline might be a safer choice.

Take-Home Points

1. Among forensically hospitalized patients impulsive aggression is the most diverse and common form of persisting aggression
   - Psychotically driven violence is managed by treating the underlying schizophrenia spectrum disorder
   - Predatory/instrumental violence is not amenable to pharmacological strategies

2. **Clozapine** exerts a specific effect on persisting impulsive aggression independent of its effects on psychotic symptoms, likely via improvement in executive functions.

3. There is evidence to support use of carbamazepine, divalproex, centrally acting adrenergic blockers, and dopamine agonists in the treatment of persisting impulsive aggression or violence in TBI, **but no evidence to support use of antipsychotics.**

4. Data support use of cholinesterase inhibitors, memantine, SRI antidepressants, and trazodone as first-line treatments for persisting aggression or violence in neurocognitive disorders, while antipsychotics become second-line treatments due to elevated mortality risk among the elderly demented.