MEDICATION FOR IMPULSIVE AGGRESSION
Publications


Metoprolol for intermittent explosive disorder (1985)  *American Journal of Psychiatry*

Psychopharmacology of temper outbursts: A review (1986)  *Journal of Nervous and Mental Disease*

Propranolol for adults with temper outbursts and residual attention deficit disorder (1986)  *Journal of Clinical Psychopharmacology*

Comparative effectiveness of carbamazepine and propranolol for rage outbursts (1990)  *Journal of Neuropsychiatry and Clinical Neurosciences*

Valproic Acid for Nonaffective Aggression in the Mentally Retarded (1992)  *Journal of Nervous and Mental Disease*

Oxcarbazepine in Patients with Impulsive Aggression (2005)  *Journal of Clinical Psychopharmacology*

Levetiracetam in Patients with Impulsive Aggression (2008)  *Journal of Clinical Psychiatry*
Other emotions are treated with medications:

Depression

Mania

Fearfulness (Anxiety)

Why not anger?

Why hasn’t anger been studied as much as depression?

Maybe because it’s considered “bad”, not an illness (similar to alcoholism)
Types of Aggression in Animals

Predatory Aggression
Territorial Aggression
Spontaneous Aggression between Males
Fear Induced Aggression – Self Defense
Pain Induced Aggression
Mouse-Killing (Muricide) by Rats
Aggression Induced by Brain Lesions or Drugs
Affective Aggression
A MAJOR CLINICAL QUESTION:

Is aggression manipulative or due to lose of control?

If it is manipulative, to obtain a goal, the solution is to change the contingencies, i.e., so the person can’t get what he wants by being aggressive
Relationship to Other Psychiatric Diagnoses with Standard Treatment?

Mania
Schizophrenia
Depression
OCD
Alcohol/Drug Abuse

The other diagnosis should almost always be treated first.
Other Psychiatric Diagnoses Associated with Impulsive Aggression

ADHD
Personality Disorders (Antisocial, Borderline, etc.)
Impulse Control Disorder, NOS
Intermittent Explosive Disorder
• DSM-IV: Exclude if other disorder that can cause aggression, e.g., Antisocial Personality Disorder?
• DSM-V: Diagnose if aggression not better accounted for by other disorder?
Mental Retardation/Autism

No standard medication for aggressiveness in patients with these diagnoses.
Certainly many Psychological factors contribute to aggression:

1) Frequent history of being physically abused (a victim of aggression)
2) Inadequate parental support/poor role models for controlling anger
3) Culture of violence, gangs, etc.
Telemetered EEG from patient after onset of a recording of baby crying. Brain wave abnormality which occurred after patient heard the taped cry was more pronounced in posterior leads.
Neurological/Medical Causes for Aggression

Epilepsy (Russell Monroe: Episodic Dyscontrol)

Brain Lesions
  Tumor
  Trauma (Phineaus Gage)

Toxicity, e.g., lead poisoning, crack cocaine, alcohol

Genetics
RELATIONSHIP OF AGGRESSION TO NOREPINEPHRINE METABOLITE (MHPG) IN CSF

Aggression and CSF MHPG

Brown et al., 1979
RELATIONSHIP OF AGGRESSION TO SEROTONIN METABOLITE (5HIAA) IN CSF

Aggression and CSF 5HIAA
Brown et al., 1979

[Graph showing the relationship between 5HIAA concentration (ng/ml) and mean aggression score.]
RELATIONSHIP OF AGGRESSION TO CSF NEUROPEPTIDE Y

Coccaro et al., 2012
TREATMENT

Medication vs. Psychotherapy

• A psychological approach, e.g., Anger Management, is a reasonable option before medication, if no urgency.

• No medication is FDA approved specifically for the treatment of impulsive aggression.

• But there are reasons why no drugs are FDA approved, unrelated to the issue of whether drugs help:
  1) Short patent life after approval for other indication.
  2) Depakote ER was studied, with equivocal results.

• Atypicals being studied, in aggressive adolescents;
  But what will this mean, if approved?
What would Socrates think?

- Lithium and Atypicals may both work to augment antidepressants (or for aggression)
- A company spends $10 million to prove to the FDA that its atypical is better than placebo.

Conclusion???

How does the atypical compare to lithium?
Should we use the atypical before lithium, because it’s FDA approved?
Indications that Medication Might Help

1) Patient describes “loss of control”; he knows he “shouldn’t lose temper, but he does”

2) Guilt, remorse

3) Realizes problems in his life (e.g., job loss, relationship problems) are due to his temper.

4) Amnesic for episode

5) Abrupt onset and disappearance of episode
When Medication for Aggression is Not Needed

1) If aggression is goal directed, controlled, not due to loss of control

2) If aggression is due to another psychiatric illness with a standard treatment

3) If aggression can be successfully treated with Anger Management or other behavioral/psychological treatments
Patient Characteristics from Study of Inpatients with Impulsive Aggression

Sex: Percent Male 85.7%

Mean Age: 24.4 years (s.d.=8.7)

Age of onset of temper outbursts:
  - Childhood 61.3%
  - Adolescence or Adulthood 38.7%

Family History of Alcoholism, Attention Deficit Disorder, or Antisocial Personality Disorder 47.9%

Time in jail:  Ever 45.7%
  - 1-2 nights 17.3%
  - Over 3 months 12.3%

From Mattes et al., 1990, J Neuropsychiatry
### Severity of Physical Assaults

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>N</th>
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<tbody>
<tr>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>Minimal, e.g., pushing</td>
<td>4</td>
</tr>
<tr>
<td>Mild, e.g., punching or slapping but no significant bruising</td>
<td>9</td>
</tr>
<tr>
<td>Moderate, e.g., significant bruising but no hospitalization</td>
<td>39</td>
</tr>
<tr>
<td>Severe, e.g., physical injury which resulted in hospitalization or death or potential for such</td>
<td>22</td>
</tr>
</tbody>
</table>
## Severity of Destruction of Property

<table>
<thead>
<tr>
<th>Severity</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Minimal, e.g., under $10 damage, breaking a glass</td>
<td>2</td>
</tr>
<tr>
<td>Mild, e.g., under $50 damage, breaking a lamp</td>
<td>12</td>
</tr>
<tr>
<td>Moderate, e.g., under $1000 damage, smashing holes in wall</td>
<td>51</td>
</tr>
<tr>
<td>Severe, e.g., over $1000 damage, destroying a car</td>
<td>15</td>
</tr>
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</table>
## Patient Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Abnormal EEG (some with Hx Epilepsy)</td>
<td>42</td>
</tr>
<tr>
<td>Neuropsychological Testing</td>
<td></td>
</tr>
<tr>
<td>Borderline Abnormal</td>
<td>38</td>
</tr>
<tr>
<td>Abnormal</td>
<td>26</td>
</tr>
<tr>
<td>Head Trauma</td>
<td>40</td>
</tr>
<tr>
<td>CAT Abnormal – (non-specific atrophy)</td>
<td>3</td>
</tr>
</tbody>
</table>
### Specific Neurological Signs in Aggressive Adolescents

Lewis et al., 1979

<table>
<thead>
<tr>
<th></th>
<th>More Violent %</th>
<th>Less Violent %</th>
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</thead>
<tbody>
<tr>
<td>Abnormal EEG</td>
<td>29.7</td>
<td>0</td>
</tr>
<tr>
<td>Positive Babinski</td>
<td>15.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Inability to skip</td>
<td>43.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Choreiform movements</td>
<td>60.6</td>
<td>31.1</td>
</tr>
</tbody>
</table>
Medications that have been tried for Impulsive Aggression

Lithium (Sheard et al.)
Propranolol (Yudofsky et al., to 520 mg/day)
Anticonvulsants:
  - Valproic Acid/Divalproex
  - Carbamazepine
  - Oxcarbazepine
  - Phenytoin
SSRI’s (Cocarro et al.)
Antipsychotics
  - Typical
  - Clozapine
  - Other atypicals ____________
Stimulants (if ADHD)
Alpha 2 Agonists:
  - Clonidine, Guanfacine

being studied for adolescent aggression
EFFECT OF LITHIUM (VS. PLACEBO) ON AGGRESSIVE BEHAVIOR

Sheard et al., 1976

Infractions per Month

- - - - Lithium (N = 20)

- - - - Placebo (N = 21)

Mean Infractions Per Month

Drug Free  Medication  Drug Free

Months
Figure 1. Visit-wise and end-point scores for the fluoxetine hydrochloride- and placebo-treated personality-disordered subjects with prominent histories of impulsive aggressive behavior on the Aggression subscale of the Overt Aggression Scale—Modified for Outpatients (OAS-M). Asterisk indicates P<.05; -2, score at screen visit; and 0, score after 2 weeks of single-blind placebo treatment.
## Carbamazepine for Dyscontrol in Non-Affective, Non-Epileptic Patients

### Controlled Studies

<table>
<thead>
<tr>
<th>Research</th>
<th>Year</th>
<th>Drug</th>
<th>Population</th>
<th>Results</th>
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<tbody>
<tr>
<td>Neppe</td>
<td>1983</td>
<td>Placebo</td>
<td>11 Psychotic Patients with Abnormal EEG’s</td>
<td>8 of 11 were Better on CMZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Crossover)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardner</td>
<td>1986</td>
<td>Placebo</td>
<td>11 Borderlines with Dyscontrol</td>
<td>10 of 11 Improved</td>
</tr>
<tr>
<td>Placidi</td>
<td>1986</td>
<td>Lithium</td>
<td>17 Schizoaffectives</td>
<td>Lithium &amp; CMZ Equally Effective</td>
</tr>
</tbody>
</table>
TOPIRAMATE VS. PLACEBO
ON RATING OF ANGER

Figure 1. State Trait Anger Expression Inventory: Anger Out scale.
Are There Subtypes that Respond Better to one Medication than to Other Medications?

• In Propranolol vs. Carbamazepine study, patients with ADHD tended to do better on propranolol.

• It seems some characteristics, e.g., EEG, a biological measure, diagnosis, signs of organicity, etc., should predict differential response.

• But are no clear predictors of benefit: Similar to other psychiatric conditions and medications.
Advantages of Anticonvulsants:

1) Generally easier to use than lithium or propranolol
2) Generally less severe side effects than antipsychotics
3) Less risk of mania than with SSRI’s
Advantages of CMZ/Oxcarbazepine

1) More effect on Temporal lobe/Limbic systems, parts of brain more related to aggression

2) Somewhat, perhaps, more evidence of efficacy than Depakote or Dilantin

3) Oxcarbazepine less likely to cause liver or hematologic effects than carbamazepine
Medications that have been tried for Impulsive Aggression

Lithium (Sheard et al.)
Propranolol (Yudofsky et al., to 520 mg/day) – Studied mainly in patient with organicity
Anticonvulsants:
   Valproic Acid/Divalproex
   Carbamazepine
   Oxcarbazepine
   Phenytoin – studied in prison
SSRI’s (Cocarro et al.)
Antipsychotics
   Typical
     Clozapine (? best in aggressive schizophrenics)
   Other atypicals ———
Stimulants (if ADHD)
Alpha 2 Agonists: Clonidine, Guanfacine (? best for ADHD and aggressiveness)
CHANGES IN AGGRESSION BEFORE AND AFTER USE OF CRANIAL ELECTROTHERAPY STIMULATION (CES) (N=48)

Conclusions

For patients
1) with impulsive aggression (loss of control),
2) whose other psychiatric/medical diagnoses are being properly medicated
3) who do not respond to behavioral/psychological management

Medication might be helpful
There are many options, with little basis for choosing. May be best to decide based on concomitant symptoms, and safety.