THE PHARMACOTHERAPY OF VIOLENCE

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Pre-Lecture Exam

For Questions 1-7:

A: 1,2,3
B: 1,3
C: 2,4
E: All of the above

Question 1

1. **Aggression or violence may be categorized by which of the following subtypes?**
   1. Affective
   2. Hallucinatory
   3. Predatory
   4. Impulsive

Question 2

2. **The affective subtype of violence is characterized by which of the following?**
   1. Impulsivity
   2. Irritability
   3. Intense autonomic activation
   4. Numerous drugs approved for treatment.

Question 3

3. **The predatory subtype of violence is characterized by which of the following?**
   1. Secrecy
   2. Planning
   3. Low autonomic activation
   4. Mild to moderate responsiveness to psychoeducational and group treatments

Question 4

4. **Which of the following hypotheses provide frameworks for the study of violent behavior?**

   1. Serotonin hypothesis
   2. Dopamine hypothesis
   3. Topographic hypothesis
   4. Lunar hypothesis

Question 5

5. The topographic hypothesis of violent behavior is characterized by which of the following?

1. The prevalence of violence in persons with brain injury
2. Finding of low CSF serotonin in violent criminals.
3. Correlations with changes in the amygdala
4. The success of neuroleptics in treating the violence of schizophrenia

Question 6

6. Which of the following treatment guidelines obtain in the pharmacotherapy of violence?

1. Target the specific disorder underlying violent behavior
2. Distinguish acute from chronic patterns
3. Be alert to the presence of substance abuse
4. Adjust the pre-treatment work-up to the underlying disorder

Question 7

7. Which of the following is true regarding use of neuroleptics for aggressive behavior?

1. Neuroleptics are useful in the violence of schizophrenia, brain injury, and mental retardation.
2. Anti-psychotic effects are immediate.
3. Low-potency neuroleptics may cause orthostatic hypotension and cognitive difficulty.
4. Atypical neuroleptics have not been adequately studied in the treatment of violence.

Question 8

8. Which statement is *untrue* regarding use of benzodiazepines in the treatment of violence?

A. Benzodiazepines may be more effective than neuroleptics in acute episodes.

B. They can decrease the amount of neuroleptic necessary to control agitation.

C. Chronic use for prevention of violence is strongly supported by the literature.

D. Short-acting forms can be useful in episodic dyscontrol.

Question 9

9. Beta-blockers are useful for which of the following reasons:

A. They diminish arousal in general.

B. They exhibit membrane-stabilizing effects.

C. They exert effects on brain catecholamines.

D. All of the above.

Question 10

10. Which of the following is true regarding beta-blockers:

A. They have minimal effects on renal and thyroid disease.

B. They may increase serum anticonvulsant levels.

C. They have few effects on neuroleptic side-effects.

D. Doses must generally be kept below 20 mgs per day.

The Many Forms of Violence

- Behavioral dyscontrol
- Behavioral disturbance
- Aggression
- Uncontrolled rage
- Temper outbursts
- Anger attacks

“Affective” Subtype

- Impulsivity
- Irritability
- Intense autonomic activation
- Responsive to pharmacotherapy, although no drug specifically approved by FDA

“Predatory” Subtype

- Secrecy
- Planning
- Low autonomic activation
- Rarely responsive to pharmacotherapy
- Somewhat responsive to psycho-educational and group therapies

Pathophysiology

Serotonin (5-HT) Hypothesis

- Low CSF 5-HT in violent criminals and suicidal depessed patients
- Some success of serotonergic drugs in these groups

Pathophysiology

Dopamine Hypothesis

- Specific D-1 antagonism can curb aggression
- Success of neuroleptics in violence of schizophrenia

Pathophysiology

Topographic Hypothesis

- Prevalence of violence in brain injury and dementia
- Correlation with hypofrontality and amygdaloid changes

Psychopharmacology Treatment Issues

- Target specific disorder underlying violence
- Distinguish acute from chronic pattern
- Be alert to high prevalence of substance abuse
- Adjust pre-treatment work-up to underlying disorder (e.g., depression, dementia, alcohol abuse)

Neuroleptics

- First-line treatment for acute aggression and psychosis-induced violence
- Acutely sedating
- Anti-psychotic effects emerge only over time
- Useful in schizophrenia, brain injury, mental retardation, and conduct-disordered children and adolescents ± psychiatric illness

Neuroleptics

Low-Potency Neuroleptics
(e.g., Chlorpromazine, Thioridazine)

- Acutely sedating
- Risks include orthostatic hypotension and cognitive difficulty
- Risks limit usefulness in medically ill or elderly

Neuroleptics

High-Potency Neuroleptics

(e.g., Haloperidol, Fluphenazine)

- More useful acutely; sedating
- Risks include dystonia and, over time, dyskinesia
- Chronically, use for underlying psychosis at common doses
- Extended use may exacerbate violence

Neuroleptics

Atypical Neuroleptics: Antagonize 5-HT_2 Receptors

- Clozapine, 300-500 mg/d
  - Useful in chronic violence of schizophrenia and brain injury
  - Titrate by usual protocol
  - Watch for agranulocytosis, usually in 1st month; and seizures, usually with large single doses or abrupt dose changes
- Risperidone, 2-3 mg/d
  - Useful in conduct disordered children ± psychiatric illness
  - Useful in treatment-resistant patients or patients with negative symptoms (up to 6 mg/d)
- Olanzapine, 5-20 mg - ?

Neuroleptics

Risks of Chronic Use

- Exacerbation of violence reported
- Tardive dyskinesia
- Masking of a medical illness causing delirium
- Elderly very vulnerable to dyskinesia, confusion, and anticholinergic side effects
- Use with care in patients using drugs with anticholinergic properties

Benzodiazepines

- Can be more effective than neuroleptics in acute episodes (e.g., 2 mg lorazepam IM > 5 mg haloperidol IM)
- Can lower amount of neuroleptic needed to control agitation, thus lowering risks for EPS
- Short acting forms effective, esp. in episodic dyscontrol and incipient rage episodes
- Chronic use for prevention unsupported by controlled trials; may cause disinhibition

Benzodiazepines

Specific Disorders

- Panic
  - Violence, aggression, and suicidality associated with panic attacks and anxiety are responsive to BZs (e.g., alprazolam 1-5 mg/d)
  - Dementia
  - Behavioral disturbance responsive to:
    - Oxazepam, 20-90 mg/d
    - Diazepam, 7.5 mg/d (average dose)
    - Chlordiazepoxide, 10-50 mg/d
  - Latter two can accumulate in tissues and oversedate
  - Shorter-acting BZs preferable in elderly

Benzodiazepines

Buspirone (Non-Benzo Anxiolytic)

- Uncontrolled studies in small groups of patients (15-60 mg/d)
- Effective in:
  - Developmentally disabled or
  - Mentally retarded pts. With various psychiatric dxs;
  - Head injured and
  - Dementia patients with aggression

Antidepressant

Fluoxetine

- Personality disorder with impulsive aggression (20-60 mg/d)
- Depression with anger attacks (20 mg/d)
- No increased risk of aggressive behaviors vs. placebo

Antidepressant

Other Agents with 5-HT Activity

- Trazodone (indirect 5-HT1 activity)
  - Organic disorders with aggression
  - Dementia with aggression
  - 75-400 mg/d
- Citalopram
  - Schizophrenia with aggression
  - Dementia with emotional disturbance
- Hydroxtryptophan (5-HT precursor)
- Eltoprazine, amperozide (experimental 5-HT2 antagonists)
- Serenics (experimental 5-HT1 specific agents)

Antidepressants

Tricyclics

- Open trials and case reports
- Amitriptyline (50 mg qhs) in brain injury
- Amitriptyline (75-200 mg/d) in agitated depression
- Imipramine (37.5-300 mg/d) in agitated depression
- Clomipramine 930-35 mg qhs) in anger attacks
- Desipramine (200 mg qhs) in anger attacks
- Nortriptyline (usual serum levels) in post-stroke depression

Antidepressants

Stimulants

- Methylphenidate (20-60 mg/d)
- Controlled studies
- Brain injury
- Aggressive delinquents and children with mild aggression
- Some efficacy in conduct disorder with ADHD
- Stimulants may cause aggression

Beta-Blockers

Mechanisms

- Diminish arousal in general
- Membrane-stabilizing effects
- Effects on brain catecholamines

Beta-Blockers

Propranolol (Lipophilic Agent)

- Controlled studies
- Effective in:
  - Organic brain syndrome
  - Dementia
  - Brain injury
- Dose titrated to 500 mg/d
- Response > 4 weeks

Beta-Blockers

Propranolol

- Open trials
- Effective in:
  - Autism
  - Mental retardation
  - Elderly with agitation
  - Brain damage with rage outbursts
- Dose titrated to 60-480 mg/d
- Permits reduction of neuroleptic dosages
- Some effect in aggressive children with various psychiatric diagnoses

Beta-Blockers

Pindolol (Partial Agonist)

- Controlled study
- Effective in organic brain syndrome
- Dose 40-60 mg/d
- Response in 2 weeks
- More effective in more severely ill patients

Beta-Blockers

Nadolol (Hydrophilic Agent)

- Controlled study
- Effective in chronic patients
- Dose 120 mg/d
- Suggests peripheral as well as CNS effects of this class

Beta-Blockers

Caveats

- Use judiciously in asthma, COPD, IDDM, cardiac disease, PVD, renal disease, thyroid disease
- Monitor BP, HR
- Monitor serum anticonvulsant levels
- Monitor neuroleptic side effects

Mood Stabilizers

- Phenytoin (at anticonvulsant serum levels)
  - Effective in:
    - Aggressive outpatients
    - Prisoners
- Carbamazepine (at anticonvulsant serum levels)
  - Effective in:
    - Seizure patients with aggression, Alzheimer's disease, mania, temporal lobe, EEG abnormal, schizophrenia ± EEG abnormality
  - Requires close monitoring of the serum level
  - Risks of liver dysfunction and granulocytopenia

Mood Stabilizers

Lithium

- Controlled studies
- Effective in:
  - Nonpsychotic, nonbrain-damaged patients
  - Prisoners
  - Aggressive children with explosive affective aggression
- Open trials
- Effective in:
  - Children with mental retardation and other psychiatric disorders

Mood Stabilizers

- Lithium (cont.)
  - Case reports
  - Effective in PTSD, MR, brain damage with manic symptoms, stroke with temper outbursts
  - Equivocal results in dementia
- Valproate
  - Case reports
  - Adult with violent episodic dyscontrol
  - Dose: 1,500 mg/d
  - Serum levels: 50-75 _g/ml

Other Medications

Opiate Antagonists

- Hypothesis of opiatergic dysregulation
- Naloxone
- Naltrexone
  - Longer action
  - Oral administration
  - Greater potency
- Tested in nonsuicidal, self injurious behavior

Other Medications

Methadone

- Case reports
- Psychotic rage in opiate addicts
- Dose: 20 mg BID

Other Medications

- Antihistamines
  - Diphenhydramine
- Sedatives
  - Chloral hydrate
- Effective for general sedation in inpatient settings
- Can decrease cognitive function with paradoxical worsening

Preliminary Conclusions

- Few well-controlled studies
- Target underlying diagnosis when possible
- Four major drug classes to use
- Future emphasis on expanding pharmacopia and integrating behavior strategies

Model Algorithm

Glancy GD & Knott TF
CPA Bulletin 2003; 35(1): 13-18

- Criteria: intervention ranked by strength of research

- Based on S. McElroy's model for recognition and Rx of Intermittent Explosive D/o (IED) (JClinPsych1999; 60:S12)

Glancy Model Algorithm

If no functional mental illness

- If +EEG findings: CBM, VPA 1st
- In dementia, brain injury, MR: mood stabilizer 1st, then β-blockers, trazodone, buspirone, atypical anti-psychotics (APs)

If Schizophrenia/Schizoaffective

- conventional APs (with bz only acutely)
- clozapine
- 2d line: adjunct mood stabilizer, β-blockers, buspirone

Glancy Model Algorithm (cont.)

If Affective d/o

- Depression: SRIs ± buspirone or β-blocker
- Bipolar: Mood stabilizers ± atypical APs

Other (antisocial, borderline pd; IED; ADHD)

- Consider CBT
- Substance abuse Rx
- Use SRIs among 1st meds
- Then: b-blockers, mood stabilizers, buspirone, trazodone

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Answers to Pre & Post Competency Exams

1. B
2. A
3. E
4. A
5. B
6. E
7. B
8. C
9. D
10. B