

#CHAIR2017

10TH ANNUAL
CHAIR SUMMIT

neuroscience CME

Master Class for Neuroscience Professional Development

November 16 - 18, 2017 | Hotel Monteleone | New Orleans, LA

Provided by
CME
Outfitters



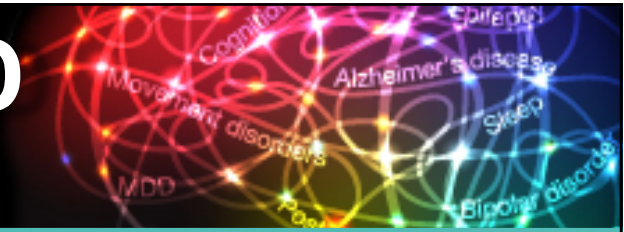
Assessment and Management of Aggression in Psychiatric Patients

John W. Thompson, Jr., MD
Tulane University School of
Medicine
New Orleans, LA



John W. Thompson, Jr., MD

Disclosures



- Dr. Thompson has nothing to disclose.

Learning Objective 1

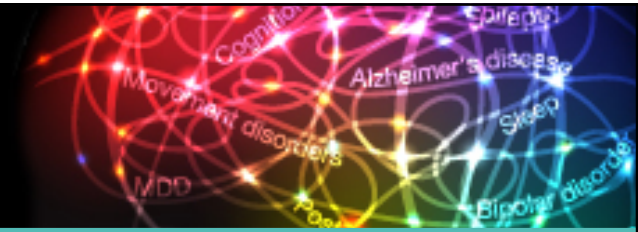
Integrate strategies into your practice to assess aggression in patients with mental illness.



Learning Objective 2

Evaluate best practice strategies to manage aggression in psychiatric patients.

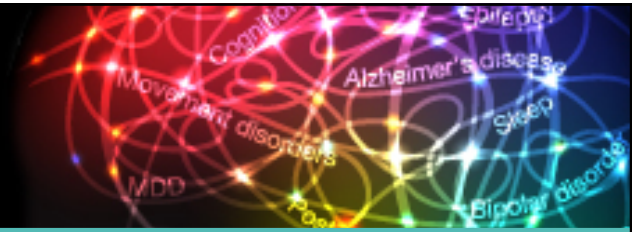




This presentation will include the off-label discussion of agents for the management of aggression.

Currently, there are no FDA-approved agents specifically for the management of aggression.

Definition of Aggression



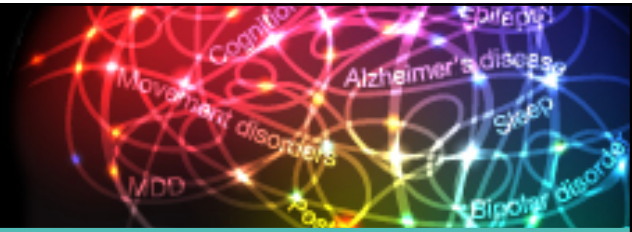
- Overt behavior
- May be physical or verbal aggression
- Not self-injurious or self-mutilating
- Complicated by definitions of violence and hostility
- Complicated by criminal behavior

Models of Aggression/Violence



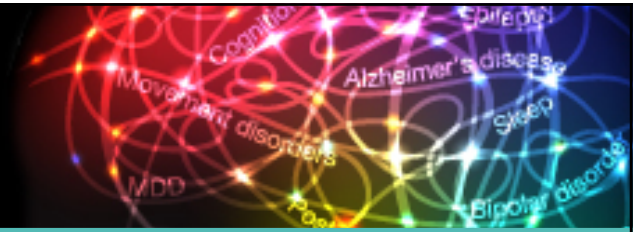
- Nature or Nurture Model
- Nature interacts with Nurture Model
 - Chi Square Analysis
- Transactional Model

Factors Influencing Aggression Overview



- **Neurochemical:** 5-HIAA, dopamine, etc.
- **Neurological:** Frontal, temporal lesions
- **Congenital:** Family, twin, adoption studies
- **Developmental:** Physical abuse literature
- **Environmental:** Watching violence = violence
- **Psychiatric diagnosis:** Antisocial personality disorder (ASPD), schizophrenic chronic paranoid type (SCPT), mania, substance abuse

Aggression in Animals

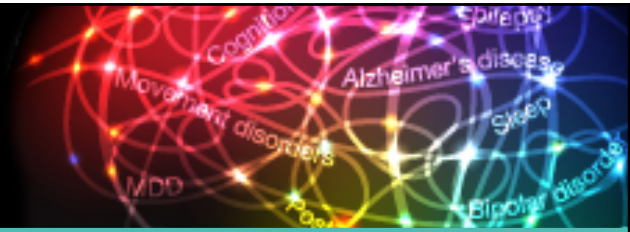


- Predatory aggression
- Inter-male aggression
- Fight or flight aggression
- Maternal aggression
- Irritable aggression
- Sex-related aggression
- Instrumental (experimental) aggression

Aggression in Humans



Neurochemistry Overview



- Serotonin
- Norepinephrine
- Dopamine
- GABA
- Acetylcholine
- Testosterone - neuroendocrine

Neurochemistry and Aggression



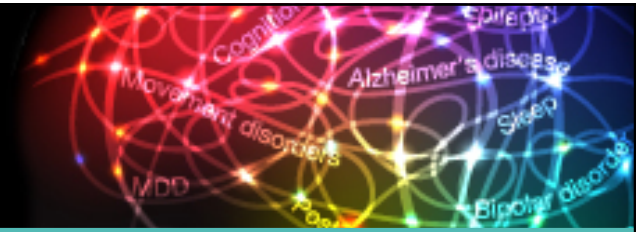
● Serotonin

- Inhibitory in a large number of animals
- CSF studies
- Tryptophan content in plasma
- Neuroendocrine challenges of central serotonin receptors
- Unspecified central dysfunction of 5HIAA is linked to impulsive behavior

5-Hydroxyindoleacetic acid

Seo D, et al. *Aggress Violent Behav.* 2008;13(5):383-395.

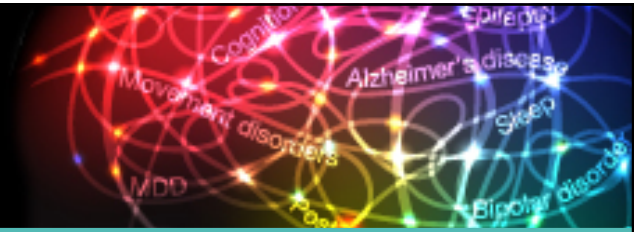
Dopamine



- D₂ receptor subtype implicated
- Central DA agonists increase aggression
- L-Dopa ↑ animal aggression
- Dopamine antagonists ↓ aggression
- Nucleus accumbens reinforcement

Narvaes R, et al. *Psychology & Neuroscience*. 2014;7(4):601-607.

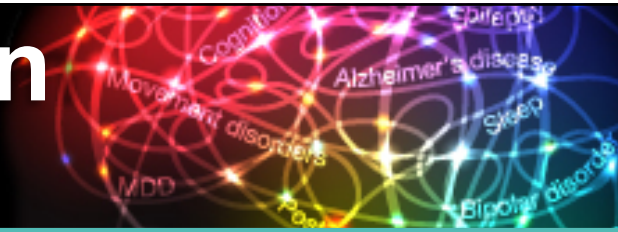
Neurochemistry



- Testosterone and Androgens
 - Many animal studies
 - Aggressive individuals have slight elevations
 - Violent sexual offenders
 - Anti-androgens also anti-aggressive

Batrinis ML. *Int J Endocrinol Metab.* 2012;10(3):563-568; Cunningham RL, et al. *Neuroendocrinology.* 2012;96(2):131-140.

Epidemiology of Violence in Schizophrenia



Reiger, 1990	10,000 patients	5.6 x higher
Swanson, 1990	Epidemiologic Catchment Area (ECA) Data	Alcohol and drug use disorder 2 x higher than those with schizophrenia
Hodgins, 1992	15,117 patients	Males: 5 x higher Females: 27 x higher
Rasanen, 1998	11,017 patients	25.2 x higher Schizophrenia + alcohol
Volavka, 1997	1,107 patients	20.6 x higher

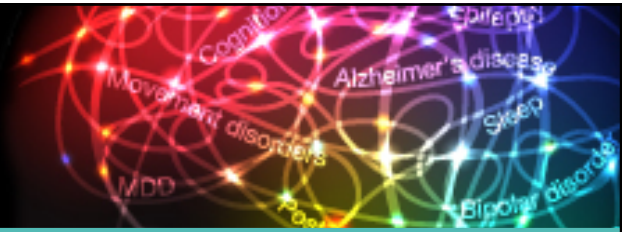
Regier DA, et al. *JAMA*. 1990;264(19):2511-2518; Swanson J, et al. *Hosp Comm Psychiatry*. 1990;41:761-770; Hodgins S, et al. *Arch Gen Psychiatry*. 1992;49:476-483; Rasanen P, et al. *Schizophr Bull*. 1998;24:437-441; Volavka J, et al. *Br J Psychiatry*. 1997;171:9-14.

Evaluation of the Violent Patient



- Chief complaint
- Present illness
- Past psychiatric history (hx), substance use, sexual hx
- Family hx
- Developmental hx, abuse hx
- Physical exam
- Labs to include imaging
- COLLATERAL DATA

MacArthur Study of Mental Disorders and Violence



Dynamic Risk Factors

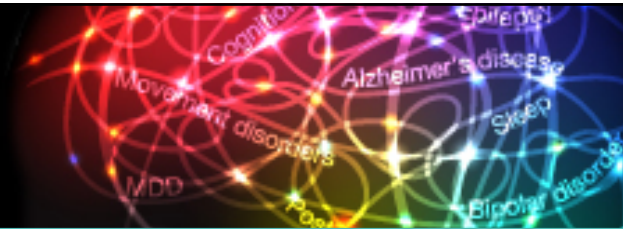
- Anger-behavior
- Schizophrenia
- Drug abuse
- Unemployment
- Alcohol abuse
- Suicide attempts

Static Risk Factors

- Number of arrests
- Father's drug use
- Legal status
- History of brain injury
- Abuse as child
- Father arrested
- Age (youth)
- Violence at admission

Monahan J, et al. Rethinking Risk Assessment: The MacArthur Study of Mental Disorder and Violence. 2001.

History of Violence



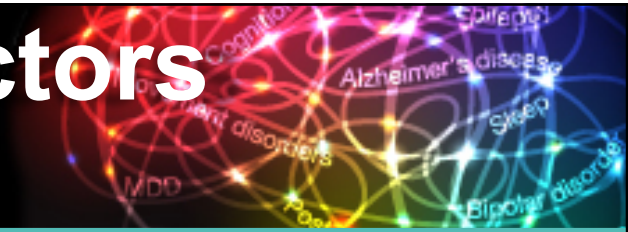
- First violent episode
- Each subsequent violent episode
- Frequency and target of violent behavior
- Recurring patterns and themes
- Symptoms before and after each episode
- Treatment history including helpful meds, therapies
- Impulsive behavior: suicide, sex, driving, fires
- Detailed criminal behavior, RAP sheet

Aggression Assessment Instruments



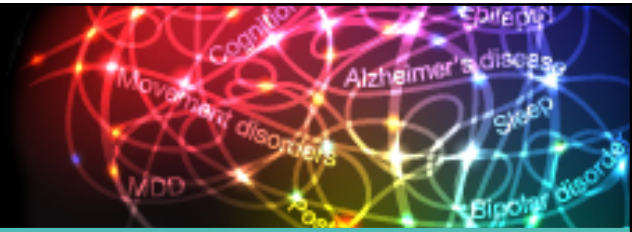
- Psychopathology Checklist–Revised (PCL-R)
- Violence Risk Appraisal Guide (VRAG)
- Sex Offender Risk Appraisal Guide (SoRAG)
- Historical Clinical Risk Management-20 (HCR-20)
- Minnesota Multiphasic Personality Inventory-2 (MMPI-2)
- Modified Overt Aggression Scale (MOAS)
- Incident reports in hospital
- Investigations in hospital

Inpatient Violence Risk Factors (The Patient)



- Criminal history – non-violent convictions or violent arrests
- First 24 hours in hospital most critical
- Behavior 2 weeks before admission is predictive
- Index behavior or reason for admission
- Conceptual disorganization, unusual thoughts or paranoia

Staff/Setting Risk Factors (The Staff and Facility)



- **Punitive staff:** staff who confront just to confront
- **Time of day:** shave, shower, dressing and meals
- Older, frail staff at risk

Patterns of Inpatient Aggression



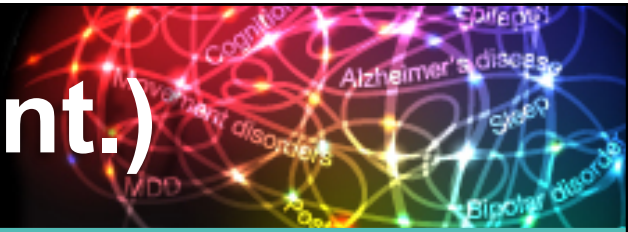
- Paranoid (core psychotic illness)
 - Early in admission
 - Responds to medication
 - Less neurological impaired
 - Over-medication vs. homeopathic medication

Patterns of Aggression (cont.)



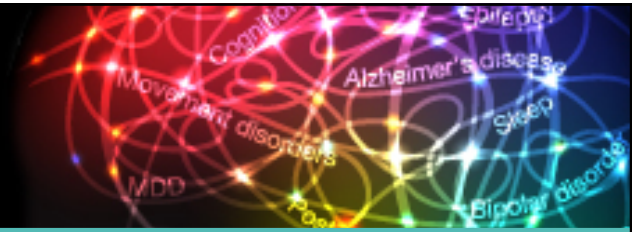
- Mental retardation or demented pattern
 - Time course not as clear
 - Multiple attacks
 - More neurologic impairment
 - Responds to atypical antipsychotic meds
 - Responds to behavior management plans

Patterns of Aggression (cont.)



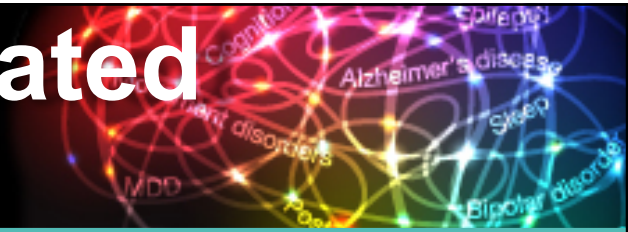
- Antisocial or predatory
 - May or may not have core psych illness
 - High risk when person not getting what they want
 - Any time in admission, passes high risk
 - May not respond to medication
 - Behavioral interventions preferred

Psychiatric Disorders Associated with Violence



- Substance abuse
- Antisocial personality disorder
- Schizophrenia
- Bipolar manic
- Mental retardation
- Borderline personality disorder
- Dementia

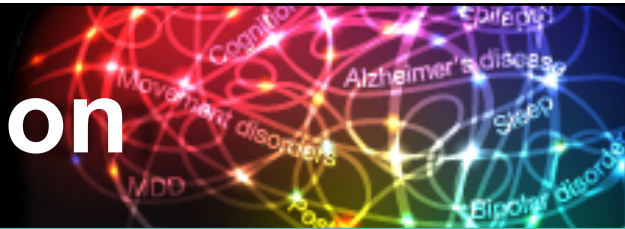
Medical Conditions Associated with Aggression



- Intracranial pathology
 - Stroke, bleed, tumor, seizure, Huntington's, infections, autoimmune disorders, toxic states
- Metabolic conditions
 - Diabetes, electrolyte abnormalities
- Withdrawal states and level of intoxication

Tilov B, et al. *J Eval Clin Pract.* 2016;22(3):421-422; Strenziok M, et al. *Soc Cogn Affect Neurosci.* 2011;6(1):2-11; Smith PH, et al. *Drug Alcohol Depend.* 2013;132(1-2):63-68.

Inpatient Violence Prevention

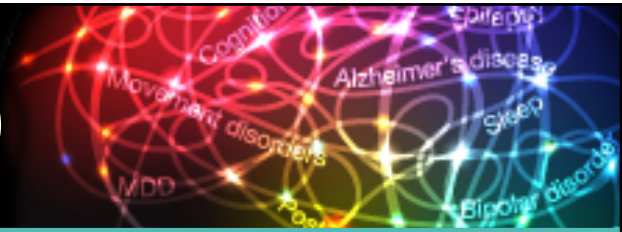


● STAFF

- Caring staff
- Reasonable limit setting
- Non-punitive
- Communicate with each other
- Prevention and management of aggressive behavior training

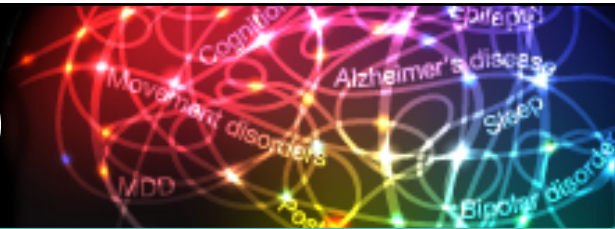
Masters KJ, et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41(2 Suppl):4S-25S.

Violence Prevention (cont.)



- Recognize warning signs and risks
 - Specific to PATIENT
 - Specific to DIAGNOSIS
 - Specific to ENVIRONMENT
 - Transference
 - Counter transference and boundary issues

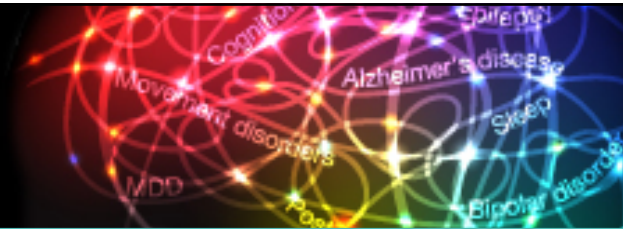
Violence Prevention (cont.)



- Seclusion and Restraint
 - The Joint Commission (JC)/Centers for Medicaid and Medicare Services (CMS) guidelines
 - Patient comfort/treatment
 - Avoid decisions based on staff convenience
 - Remove patient ASAP
 - Staff consistency

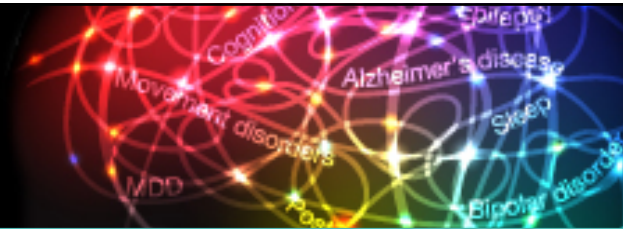
Masters, KJ. *Psychiatric Annals*. 47(1):52-55; Joint Commission Standards on Restraint and Seclusion. Available at <https://www.crisisprevention.com/CPI/media/Media/Resources/alignments/Joint-Commission-Restraint-Seclusion-Alignment-2011.pdf>; CMS website. Available at <https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R37SOMA.pdf>.

Office Settings



- May be most dangerous place to practice
- Staff feel less vulnerable when they are more vulnerable
- Often lack plans for violence
- Panic button or panic codes
- Security presence
- Metal detection

Medication for Aggression



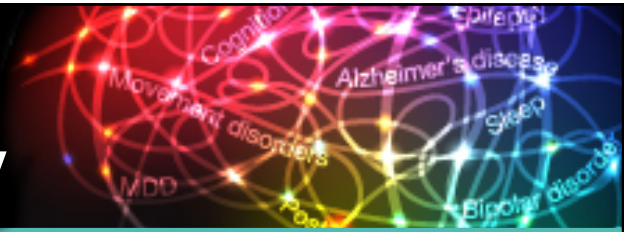
● Medication

- Anti-manic agents
- Benzodiazepines
- Beta blockers, Ca²⁺ channel blockers
- Clonidine
- Typical antipsychotics
- Atypical antipsychotics
- Antidepressants
- Naltrexone (?)

No agent is FDA approved for “aggression”

Gurnani T, et al. *J Child Adolesc Psychopharmacol*. 2016;26(1):65-73; SAMSHA. *Interventions for Disruptive Behavior Disorders: Medication Management*. 2011; Goedhard LE, et al. *J Clin Psychiatry*. 2006;67(7):1013-1024.

Medication for Aggression Long-Term and Emergency



● Long-Term

- Anticonvulsants
- Beta blockers
- Lithium
- Typical antipsychotics
- Atypical antipsychotics
- Antidepressants

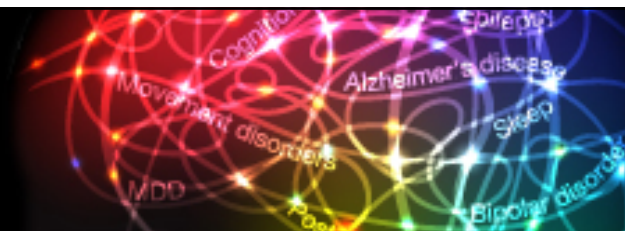
● Emergency

- Benzodiazepines
- Typical antipsychotics
- Atypical antipsychotics

No agent is FDA approved for “aggression”

Gurnani T, et al. *J Child Adolesc Psychopharmacol*. 2016;26(1):65-73; SAMSHA. *Interventions for Disruptive Behavior Disorders: Medication Management*. 2011; Goedhard LE, et al. *J Clin Psychiatry*. 2006;67(7):1013-1024.

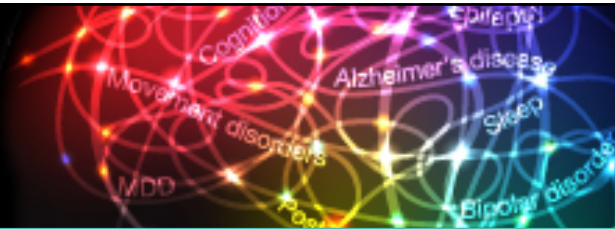
Emergency Room



- Patient cooperation and control are goals
- Calming the patient without snoring them
- Diphenhydramine hydrochloride 50mg (B-52) and rapid neuroleptic use are no longer considered acceptable practices by CMS and JC
- Use the medication that is most appropriate to the presentation, i.e. benzodiazepines for anxiety and antipsychotics for psychosis

No agent is FDA approved for “aggression”

Benzodiazepine Examples



- Diazepam: rapid onset and long half life
- Alprazolam: rapid onset but short half life
- Lorazepam: reasonable onset and half life, major advantage in intramuscular (IM) predictable delivery and predictable metabolism
- Clonazepam: may be useful in traumatic brain injury (TBI) cases with other neurologic conditions, seizure, restless legs, tics, etc.

No agent is FDA approved for “aggression”

[Package Inserts]. Drugs@FDA Website; Yudofsky SC, et al. *Management of Adults with Traumatic Brain Injury*. 2013.

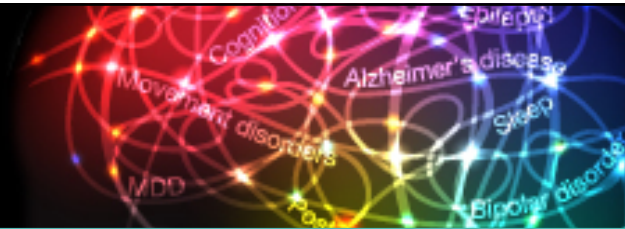
Efficacy Benzodiazepines (Alone or in Combination with Antipsychotics) in Management of Aggression

- Meta-analysis of 21 randomized clinical trials with a total of 1968 participants with acute psychosis
- Results:
 - Benzodiazepines as effective as antipsychotics in reducing aggression and agitation associated with mental illness
 - Some evidence that benzodiazepine + antipsychotic superior to either drug alone in reducing symptoms
 - Side effects such as weight gain, shaking, tremors, and slurred speech significantly higher in patients receiving antipsychotics

No agent is FDA approved for “aggression”

Gilles D, et al. *Cochrane Database Syst Rev.* 2013; 30(4):CD0003079

Antipsychotic Examples

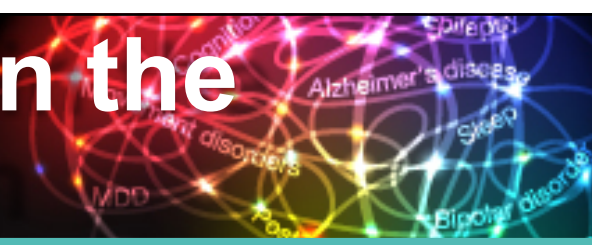


- Olanzapine: commonly used due to IM injection and sedation properties of medication
- Risperidone: commonly used due to rapid effects on positive symptoms, fewer side effects than haloperidol
- Clozapine: treatment-resistant clients

No agent is FDA approved for “aggression”

Gobbi G, et al. *Neuropsychiatr Dis Treat.* 2014;10:757-765; Gurnani T, et al. *J Child Adolesc Psychopharmacol.* 2016;26(1):65-73; Goedhard LE, et al. *J Clin Psychiatry.* 2006;67(7):1013-1024.

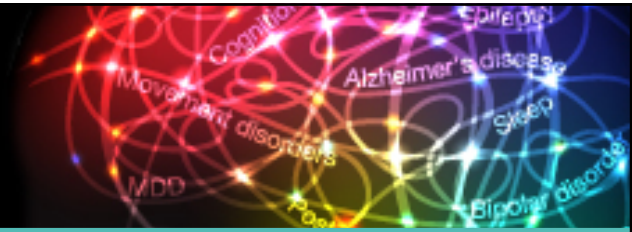
Efficacy of Antipsychotics in the Management of Aggression



Agent	Patient Sample	Result
Clozapine ¹	137 aggressive patients with schizophrenia	Over 12 month period, clozapine reduced the use of restraints ($p < .032$) and seclusion ($p < 0.001$)
Olanzapine ²	498 patients with first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder	Olanzapine significantly superior to haloperidol, quetiapine, and amisulpride in reducing hostility after 1 and 3 months
Aripiprazole (intramuscular, IM) ³	357 patients with acute agitation with schizophrenia, schizoaffective disorder, or schizophreniform disorder	9.75 mg IM aripiprazole compared to placebo reduced agitation within 45 minutes; IM haloperidol did not separate from placebo until 105 minutes
Risperidone ⁴	157 treatment-resistant hospitalized patients with schizophrenia or schizoaffective disorder	Risperidone and olanzapine effective in patients with mild aggressive symptoms; whereas clozapine effective with strong aggressive symptoms

1. Chengappa KN, et al. *Schizophr Res.* 2002;53(1-2):1-6; 2. Volavka J, et al. *J Clin Psychiatry.* 2011;72(7):955-961; 3. Tran-Johnson TK, et al. *J Clin Psychiatry.* 2007;68(1):111-119; 4. Volavka J, et al. *J Clin Psychopharmacol.* 24(2):225-228. No agent is FDA approved for "aggression"

Long-Term Aggression: Anticonvulsants



● Anticonvulsants

- Carbamazepine: controls aggression in epileptic and non-epileptic populations, developmental disabilities, mania, and schizophrenia. Limited by side effects of liver induction, careful in Asian populations due to HLA-B 1502 allele
- Valproate: controls aggression especially in combination with other meds for mania and schizophrenia. Limited by side effects as well such as weight gain, GI disturbance, liver and blood disorders

No agent is FDA approved for “aggression”

Brodie MJ, et al. *Pharmacol Rev.* 2016;68(3):563-602; Prado-Lima P. *Rev Bras Psiquiatr.* 2009;31(suppl II):S58-S65.

Efficacy of Anticonvulsants in the Management of Aggression

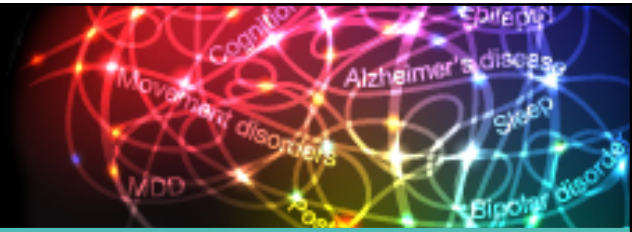


- Meta-analysis of 14 placebo-controlled clinical trials with a total of 672 participants
- Results:
 - Sodium valproate/divalproex superior to placebo for:
 - outpatient men with recurrent impulsive aggression
 - Impulsively aggressive adults
 - Youths with conduct disorder
 - Carbamazepine superior to placebo in reducing self-directed aggression in women with borderline personality disorder
 - Oxcarbazepine superior to placebo for verbal aggression and aggression against objects in adult outpatients
 - Phenytoin superior to placebo on frequency of aggressive acts in male prisoners and outpatient men with personality disorders

No agent is FDA approved for “aggression”

Huband N, et al. *Cochrane Database Syst Rev.* 2010;17(2):CD003499.

Long-Term Aggression 2: Beta Blockers



● Beta Blockers

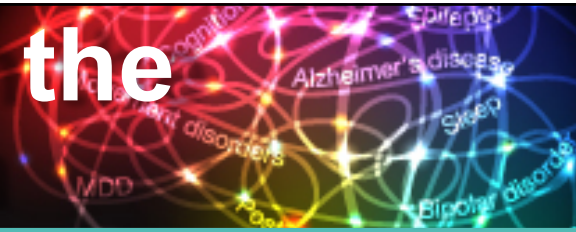
- Most researched group of meds for long-term aggression (over 25 studies since 1977)
- Best studied with reference to TBI related aggression
- Most patients were unsuccessfully treated prior to enrollment
- Doses up to 640 mg of propranolol; nadolol and pindolol also studied
- Start at 60mg and gradually go up every 2-3 days

No agent is FDA approved for “aggression”

Prado-Lima P. *Rev Bras Psiquiatr.* 2009;31(suppl II):S58-S65;

Silver JM, et al. *J Neuropsychiatry Clin Neurosci.* 1999;11(3):328-335.

Efficacy of Beta Blockers in the Management of Aggression



Agent	Patient Sample	Result
Pindolol ¹	30 male inpatients with schizophrenia involved in ≥ 4 aggressive incidents	Scores on Overt Aggression Scale (OAS) were significantly reduced for number aggressive incidents ($p < .02$) and severity of incidents ($p < .0001$) with pindolol
Nadolol ²	34 male acutely aggressive patients with schizophrenia	After first week of treatment, patients taking nadolol showed significant improved compared to placebo; no separation between nadolol and placebo at 2 weeks
Propranolol ³	6 RCTs of patients with acquired brain injury	2 RCTs found propranolol to be effective in managing aggression and agitation

No agent is FDA approved for “aggression”

1. Casper N, et al. *Int Clin Psychopharmacol*. 2001;16(2):111-115; 2. Allan ER, et al. *J Clin Psychiatry*. 1996;57(10):455-459. 3. Fleming S, et al. *Cochrane Database Syst Rev*. 2006;Oct 18;(4):CD003299.

Long-Term Aggression 3: Lithium

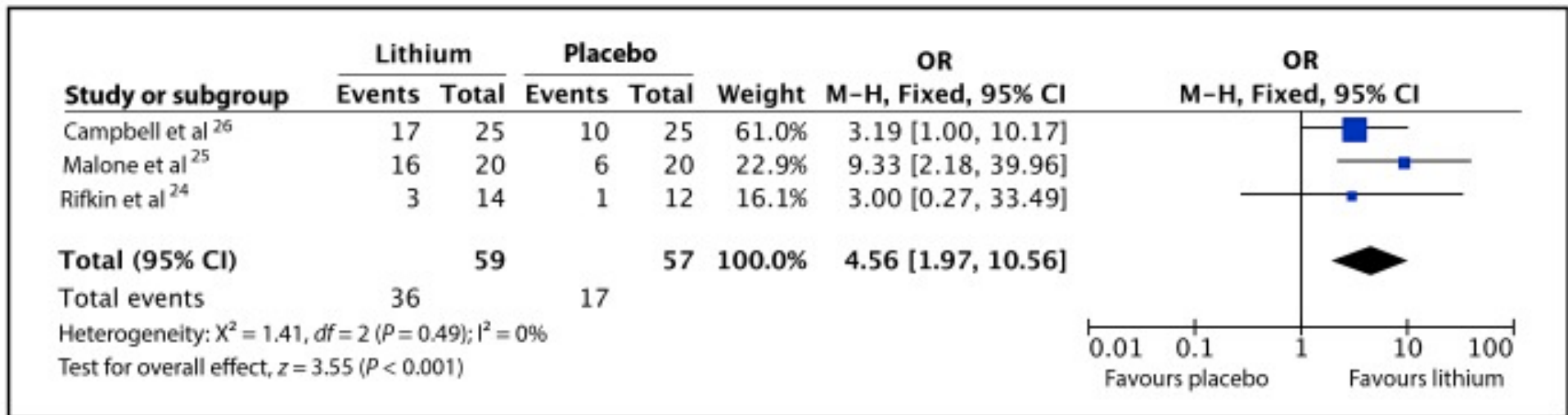


● Lithium

- Mood stabilizer in mania; still the most effective medication for Bipolar I
- Challenge: Lithium toxicity levels required
- 1.0 to 1.5 mEq/L acute levels
- 0.6 to 1.2 mEq/L for maintenance
- Toxicity starts at 1.5 mEq/L and ends 3.0 mEq/L to 3.5 mEq/L in death (dehydration, NSAIDS, infection can cause increased levels)

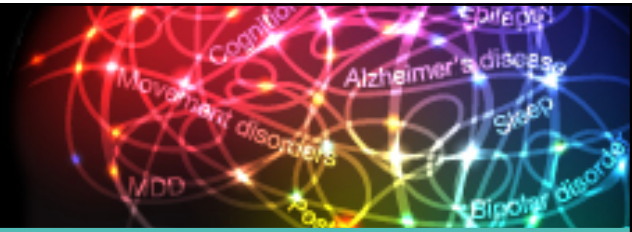
Comai S, et al. *J Clin Psychopharmacol*. 2010;32(3):237-260. Prado-Lima P. *Rev Bras Psiquiatr*. 2009;31(suppl II):S58-S65; Lithium carbonate. Drugs@FDA Website. No agent is FDA approved for “aggression”

Efficacy of Lithium in Managing Aggression in Youths with Conduct Disorder



No agent is FDA approved for “aggression”
 Pringsheim T, et al. *Can J Psychiatry*. 2015;60(2):52-61.

Long-Term Aggression 5: Antipsychotics

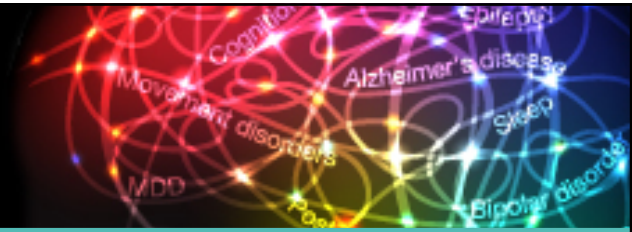


● Antipsychotics

- Too many to count and the number is still rising
- Studies of aggression have focused on olanzapine and risperidone
- Haloperidol and chlorpromazine studied in past and have great efficacy when primary target symptoms is psychosis / schizophrenia
- Use caution in young and elderly populations given recent guidelines by CMS

Gobbi G, et al. *Neuropsychiatr Dis Treat.* 2014;10:757-765; Gurnani T, et al. *J Child Adolesc Psychopharmacol.* 2016;26(1):65-73; Goedhard LE, et al. *J Clin Psychiatry.* 2006;67(7):1013-1024. No agent is FDA approved for “aggression”

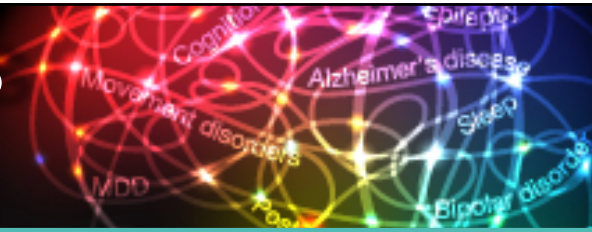
Long-Term Aggression 6: Antidepressants



- Antidepressants: more commonly used in depression with psychotic features
- Can be used in other conditions such as aggression associated with deviant sexual behavior or obsessive and compulsive aggression

No agent is FDA approved for “aggression”
Rothschild AJ. *Schizophr Bull.* 2013;39(4):787-796.

Efficacy of Antidepressants on Aggression



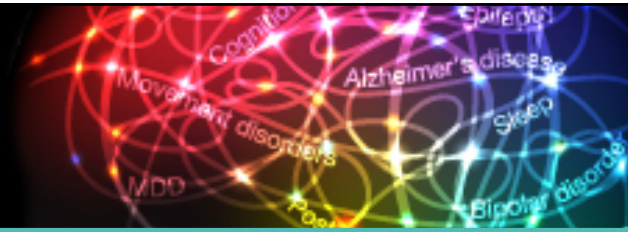
Agent	Patient Sample	Result
Fluvoxamine ¹	38 patients with borderline personality disorders	Significant improvement only on mood shifts
Paroxetine ²	12 males with criminal records	Decreased aggressive and impulsive responding
Citalopram ³	186 patients with Alzheimer's disease and clinically significant agitation	Citalopram was more effective in patients with mild agitation and little cognitive impairment

No agent is FDA approved for “aggression”

Rhinne T, et al. *Am J Psychiatry*. 2002;159:1048-2054.; 2. Cherek DR, et al. 2002.

Psychopharmacology;159:266-274; 3. Schneider LS, et al. *Am J Psychiatry*. 2016;173(5):465-472.

Aggression Summary



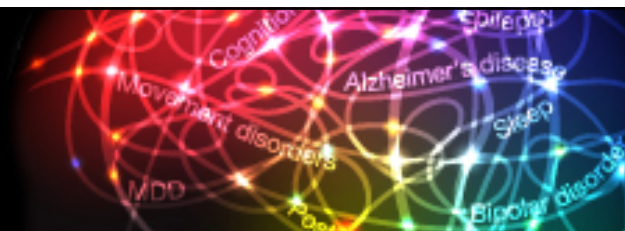
Presentation/drug

- Acute/Severe agitation
 - High potency antipsychotic
 - Benzodiazepine
- Chronic agitation
 - Atypical antipsychotic
 - Valproate, carbamazepine
 - SSRI, SNRI
 - Beta blockers

Primary Indication

- Aggression/short
- Aggression/long
 - Psychosis
 - Seizure disorder
 - Psychotic depression
 - Aggression without clear diagnosis or failure of clinically indicated forms of treatment

Call to Action



- Increase your recognition of aggression in children, adolescents, and adults
- Develop and apply best practices for the management of acute and chronic aggression

Questions & Answers



Don't forget to fill out your evaluations to collect your credit.

