

**Aggression and Violence**  
**An Evidence-Based Medicine (EBM) Monograph for**  
**Psychosomatic Medicine Practice**  
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# **Violence and Aggression – EBM Summary**

## **INTRODUCTION**

### **Objective and methods:**

This monograph summarizes current knowledge related to the diagnosis, epidemiology, and management of aggression and violence in the general hospital. The monograph is modeled after previous guidelines provided by the Evidence-Based Medicine Sub-Committee of the Academy of Psychosomatic Medicine and the European Association of Psychosomatic Medicine (EAPM). It is based on a systematic review of clinical trials and expert opinion. The quality of the evidence discussed in this monograph is graded as 'high', 'moderate', 'low' or 'very low', following the Grading of Recommendations Assessment, Development and Evaluation' (GRADE) system, which was developed by the Cochrane Collaborative (<http://www.gradeworkinggroup.org/intro.htm>) Readers are encouraged to consult the recommended readings for more detailed information (Appendix A).

### **Definition and symptoms:**

The terms aggression and violence and the related concepts of agitation and hostility have no universally accepted definitions. Being concerned with overt behavior that might have the consequence of causing damage and harm, the terms describe complex behaviors that have dimensions with biological, psychological and social determinants. The following definitions pertaining to these overt behaviors are based on a consensus from the extant literature:

**Impulsivity:** A behavioral state characterized by diminished restraint to action in response to some stimulus.

**Agitation:** A state of emotional arousal or motor restlessness associated with purposeless activity.

**Aggression:** Physical violence toward people or objects or verbal threats and intimidation (1).

**Violence:** Overt physical aggression that has the potential consequence of physical harm to another person or object.

### **Risk Factors:**

Aggression and violence are often classified according to whether the behavior is considered to be impulsive (associated with a high degree of affective arousal) or predatory (planned and not associated with high levels of affect).

A variety of psychiatric diagnoses are associated with either repetitive or acutely elevated risk for aggression and violence. When confronted with episodes of aggression or violence within the general hospital the consultation psychiatrist may be called upon to make a specific diagnosis as a basis for understanding and intervention.

### **Prevalence and incidence:**

Violence is a major public health problem worldwide. Each year, millions of people die as the result of injuries due to violence. Many more survive their injuries, but live with permanent disabilities. Violence is a leading cause of death among people aged 15-44 years worldwide, accounting for 14% of deaths among males and 7% of deaths in females (2). The Centers for Disease Control (CDC) maintains a comprehensive surveillance system for monitoring violent deaths in the US. The National Violent Death Reporting System (NVDRS) is operative in 18 states. The CDC estimated that there were 18,500 homicides in the US in 2006 (3). While affecting individuals at each stage of life, homicide is the third leading cause of death among those ages 15-24, after accidents and suicide (4).

Workplace violence is an occupational hazard drawing increasing attention. Healthcare facilities are among the more frequent sites for violence. Between 1993 and 1999, there were 1.7 million episodes of workplace-related violence each year in the United States, and in 12% of these episodes, the victim was a health care worker (4). The occurrence rate is such that surveys in general hospitals reveal that half of surveyed employees have witnessed patient or visitor violence within the prior year, 11% within the prior week (5).

Consultation psychiatrists may be called upon to assist with recommending methods to predict or manage such events.

There are no available surveys of the incidence of aggression or violence among patients in general hospitals.

### **Diagnosis and risk factors:**

In epidemiological studies aggression is often associated with psychiatric diagnoses (6). Longitudinal data collected during the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicates that mental illness alone does not predict future violent behavior. Future violence instead is associated with various clinical factors (substance abuse and perceived threats), demographic factors (younger age, male sex, less than high school education, and lower income), historical factors (past violence, juvenile detention, physical abuse, and parental arrests), and social factors (recent divorce, unemployment, history of victimization). The strongest predictor of future violence is the co-occurrence of serious mental illness and substance abuse (7). Sheridan et al (8,9) describe that patient and staff conflicts, especially those that involve enforcement of rules, denial of requests, and involuntary admission or transfer can precipitate aggressive acts and violence.

A variety of psychiatric disorders are associated with either repetitive or acutely elevated risk for aggression and violence, such as psychosis, mania, delirium, and some personality disorders.

### **Psychotic Disorders:**

#### Schizophrenia

There is an extensive literature documenting increased risk for violent behavior among individuals diagnosed with schizophrenic disorder. Moderate quality evidence from epidemiological studies links violent episodes with the presence of some positive psychotic symptoms. There is low quality evidence suggesting that some symptoms, such as persecutory delusions (10) and command hallucinations (11) increase risk of violence. The presence of negative symptoms may decrease risk of violence (12). There is moderate quality evidence that the majority of risk for serious violence in this group is due to the frequent co-occurrence

of substance use disorders (13). Patients with high levels of hostility and low levels of insight are at greater risk for violent offending (14, 15).

### **Bipolar Disorder:**

There is low quality evidence that the presence of bipolar disorder is a predisposing factor to violence (with odds ratios reported between 2.0 to 9.0). While severity of illness or symptom profile does not predict aggressive and violent behavior the largest amount of variance is due to presence of co-occurring substance use disorder (16, 17).

### **Personality Disorders:**

#### Antisocial personality disorder

There is high quality evidence for linking violent episodes to disorders associated with a lack of empathy or concern for others. Individuals with these characteristics are overrepresented in cases of purposeful and directed violence (18, 19).

#### Borderline personality disorder

The diagnostic criteria for Borderline Personality include the presence of impulsivity, affective instability, inappropriate anger or deficits in emotional regulation. Paranoid ideation and brief psychotic episodes have been described in this group of patients (20). There is moderate quality evidence that a diagnosis of BPD is a risk factor for elevated risk for violence in clinical and forensic populations. The evidence for violent predisposition in community samples is low (21).

### **Impulse Control Disorders:**

Intermittent Explosive Disorder (IED): IED is an impulse control disorder characterized by repeated episodes of serious assaultive or destructive acts out of proportion to precipitating stressors. Since DSM-IV TR includes an exclusion criterion for the co-occurrence of another disorder that would better account for this symptom picture, some have argued that this has led to under-diagnosis of this condition because of frequent co-occurrence of personality disorder (22). The DSM-5 criteria for IED does not include such exclusionary criteria. Epidemiological studies suggest that this condition appears early in life (age 14-20) and is underrepresented in treatment samples. Estimates of lifetime prevalence are 5-7% in community samples. (22). There is no equivalent diagnosis present in ICD-10.

### **Substance Use Disorders:**

Aggression and violence are frequently associated with patients who have alcohol and drug use disorders. There is moderate evidence that violent behavior attributed to serious mental illness is accounted for by the coincident presence of substance use.

#### Alcohol

There is high quality evidence supporting an association between alcohol use and violent injuries reported in many countries (23). There is moderate quality evidence linking the onset of aggressive and violent behavior to the amount of drinking preceding such events and blood alcohol levels at the time of presentation. There is high quality evidence for the relationship between alcohol use disorders and admission to general hospitals for multiple causes (24). Alcohol use has been long recognized to play a role in criminal violence (25).

### Stimulants

Use of stimulant drugs, including cocaine, is associated with a propensity for irritability, hostility and aggression, resulting in high rates of interpersonal violence, emergency department and trauma center visits, assault, weapons charges and increased public health and safety burdens. (26,27). Up to a third of such users presenting to emergency departments require sedation for agitation and aggression. High rates of aggressive behavior have been reported in community samples of amphetamine users. (28).

### CNS Depressants

There is moderate quality evidence that aggressive behavior may follow the use of benzodiazepine drugs in persons with impulse control or personality disorders (29).

### Anabolic Steroids

There is low quality evidence for development of irritability, aggression and violent behavior in individuals using anabolic steroids to enhance athletic performance or in body-building (30,31).

**Developmentally Disabled** - There is moderate quality evidence demonstrating increased prevalence of significant aggressive and challenging behavior in persons with developmental disability. Over half of this population engages in some form of aggression. Only a small number is responsible for frequent or severe acts (32). There is moderate quality evidence suggesting that half of patients are involved in overt aggressive acts. Such behavior is often directed at healthcare personnel and may lead to considerable caretaker burden in all settings (33).

**Delirium:** There is high quality evidence that the presence of the attention deficits, paranoia, illusions and hallucinations can result in reactive aggression in patients with hyperactive delirium. (34).

**Dementia (Neurocognitive Disorders – moderate and severe):** There is high quality evidence that psychotic symptoms such as hallucinations and delusions are common among those suffering with dementing illnesses with rates of 30 to 50% in those with Alzheimer's and other dementias (35). Aggressive behaviors are frequent symptoms among patients with dementia. Symptoms such as hitting, kicking, biting, pushing are very commonly associated with cognitive decline and occur more frequently (70-100%). These symptoms are particularly common in patients with moderate to severe neurocognitive disorders in inpatient settings. Aggressive symptoms are the cause of considerable caregiver burden and risk of injury to patients and staff (36).

**Brain Disorders:** Moderate evidence suggests that lesions that affect frontal lobe function including tumors, vascular disorders or traumatic injuries are associated with disinhibition resulting in aggression and violence (37).

**Traumatic Brain Injury:** While there is moderate quality evidence for agitation and aggression in the acute phase of traumatic brain injury (10-34%), it is predominantly verbal, characterized by anger and threats of violence rather than physical aggression. Violent acting-out is not common. Significant correlates for violence include impaired psychosocial functioning and new-onset major depression (38). In case studies, lesions of the hypothalamus and amygdala have been associated with rage attacks (39,40).

**Epilepsy:** While agitated and aggressive behavior has been observed among patients with seizure disorder there is low quality of evidence supporting an association between idiopathic epilepsy and elevated levels of aggression or violent behavior (41).

## TREATMENT

### Acute agitation and violence when diagnosis is unclear

Intervention in situations involving aggression and violence begins with an understanding of the nature of any provocation and a diagnostic assessment of factors that might lead to altered arousal or impaired impulse control. A detailed assessment of provocative factors that produce frustration or anger can often suggest methods of intervention. Evidence for effectiveness in reducing aggression and violence in the acute care setting has been limited by the obvious difficulty in obtaining informed consent to participate in such studies.

#### *Non-pharmacological treatment*

Recommendations provided here are based on expert consensus in the management of acute agitation (42).

De-escalation of agitated patients – Clinicians who have worked with patients who present with agitation to emergency departments have developed the following principles published as guidelines for management of patients recognized at risk for aggressive or violent acting out.

- Ensure the safety of patients, staff and others in the area.
- Assist the patient in managing emotional arousal and distress while helping to regain control of behavior.
- Avoid use of coercion or restraint that tend to escalate agitation.

If such approaches fail to reduce agitation and threat then the following are suggested:

- Offer of pharmacologic assistance
- Offer of a “quiet room” if available
- Show of force (show of concern)

Coercive interventions – There is moderate quality evidence that application of the above methods can result in dramatic reductions in the use of seclusion and restraints within inpatient hospital settings. If trial of these methods fails to result in return of behavioral control coercive methods such as seclusion and restraint may become necessary to prevent harm to patients, staff and others. There is no evidence to support any coercive intervention having advantage over any other.

#### *Pharmacological symptomatic treatment:*

The aim of pharmacologic treatment is to calm a patient to allow complete evaluation of the causes of a behavioral disturbance. Efficacy for use of agents to achieve “rapid tranquilization” is supported by low quality evidence. This should be undertaken only after

consideration of risks of such intervention balanced against risk of harm to patients and others in attendance (43).

Three categories of drugs have been customarily used and studied for control of agitation and aggression in these circumstances.

#### First-Generation Antipsychotics

Haloperidol is a highly potent antagonist of the D2 receptor approved in oral and intramuscular forms for treatment of schizophrenia. Haloperidol has a long record of efficacy and safety, though the quality of evidence for its use in treating acute agitation or aggression is low (44,45,46). The FDA has issued a safety alert highlighting the risk of prolonged QTc interval associated with the aggressive use of haloperidol in parenteral formulations. There have been case reports of development of Torsade de Pointes, some with cardiac arrest. While these cases have generally involved intravenous use clinicians should be aware of the risk of potentially fatal arrhythmias when parenteral haloperidol is used. Cardiac monitoring and assessment of electrolyte status may reduce risk. Haloperidol should be used with greater caution in patients with QTc greater than 450 milliseconds (47).

#### Second generation antipsychotics

Moderate quality evidence supports the view that efficacy of the second generation antipsychotics is equal to Haloperidol in the treatment of acute agitation (48). Antipsychotic agents should be used with caution in situations where a psychotic diagnosis has not been established.

#### Benzodiazepines

There is moderate quality evidence that benzodiazepines such as diazepam, lorazepam and clonazepam are effective in calming the agitated patient. Risks include central nervous system depression. These drugs are often used together with the first or second-generation antipsychotics though the quality of evidence for enhanced efficacy in combination is low (49, 50)

### Agitation and violence where a psychotic diagnosis (schizophrenia, mania) has been established

When patients present with acute agitation or threatening or violent behavior when a diagnosis of psychotic illness has been established the goal of treatment is twofold. These include the calming of the patient to allow complete evaluation of the causative factors and amelioration of the underlying psychotic process.

When severe agitation, threatening or menacing behaviors occur in patients known to have a diagnosis of schizophrenia or mania initial pharmacological interventions should include antipsychotic agents. There is no evidence that first generation antipsychotics are any less effective than second generation agents in managing agitated behaviors. Increasingly second-generation agents such as ziprasidone or olanzapine are being utilized in this context (51)

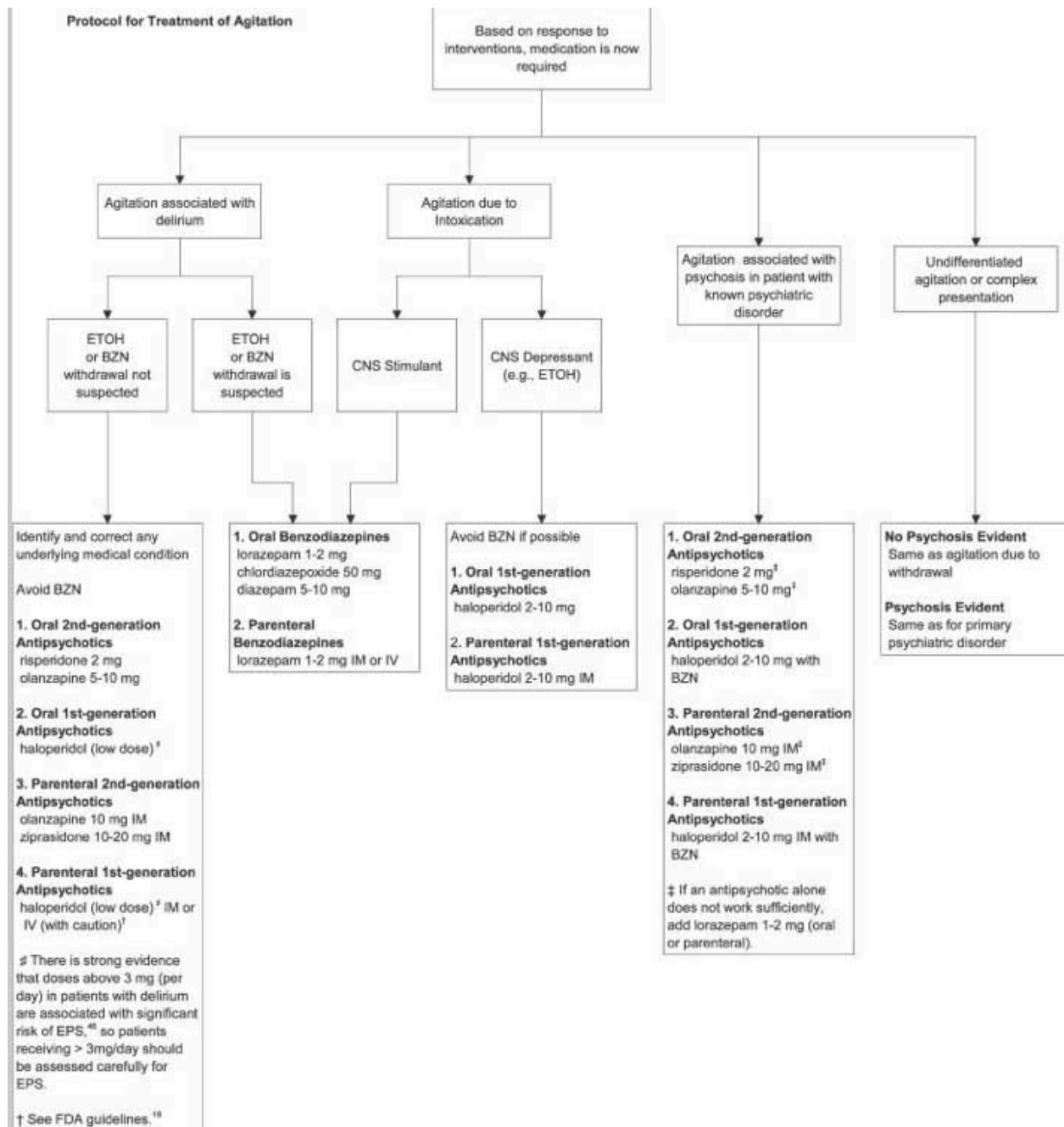


Figure 1 Protocol for Treatment of Agitation – Reproduced with permission

Agitation and violence where a psychotic diagnosis (schizophrenia, mania) has been established

## Prevention and Extended Treatment

### Psychotic Disorders – Schizophrenia

Antipsychotics are the mainstay of treatment for schizophrenia. High quality evidence supports offering clozapine to patients with schizophrenia who present with persistent symptoms of hostility and/or display persistent violent behaviors. Clozapine has anti-aggressive properties that go beyond its efficacy for psychotic symptoms. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) cohort, second generation



antipsychotics (not including clozapine) were not superior to perphenazine with regards to reducing violence over 6 months (52). In the European First Episode Schizophrenia Trial (EUFEST), olanzapine was superior in reducing hostility in early course schizophrenia compared to haloperidol, quetiapine, or amisulpride (53)

### **Bipolar Disorder**

There is low quality evidence in support of use of quetiapine to control agitated and aggressive behavior in bipolar manic and mixed states (54).

### **Personality Disorders**

There is low quality evidence suggesting a role for atypical antipsychotics and mood-stabilizing agents in patients with borderline personality disorder who demonstrate repeated aggressive or violent behavior (55).

### **Intellectually Disabled**

Evidence is lacking for the effectiveness of antipsychotic medication in reducing repetitive aggression and challenging behavior in those with intellectual impairment despite their common use. (56). A small series utilizing placebo lead-in provides low quality evidence that buspirone may reduce aggressive behavior in this population (57).

### **Intermittent Explosive Disorder**

There is modest evidence for reduction in impulsive aggressive episodes following use of fluoxetine 20-60 mg per day (58).

Low quality evidence exists from multiple studies for improvement in impulsive aggression with use of several anti-epileptic agents. There is evidence for significant reductions in both frequency and severity of aggression for those taking phenytoin, lithium and carbamazepine and oxcarbazepine, but not valproate or levetiracetam. (59).

### **Substance Use Disorder**

Identification of the presence of substance use disorders can result in referral to specialty care for definitive treatment.

### **Delirium**

Recommendations for treatment of aggressive behavior due to delirium can be found in the EBM Monograph, Delirium (60). The effective treatment of delirium requires identification and management of the medical or toxic factors causing or maintaining the condition. There is expert consensus that orientation strategies are helpful in management of delirium. There is low to moderate quality evidence that antipsychotic agents are effective in the treatment of symptoms of delirium.

### **Dementia (Neurocognitive Disorders – moderate and severe)**

Neuropsychiatric symptoms are commonly associated with Alzheimer's and other forms of dementia. Evaluation of such complaints requires consideration of precipitants, evaluation of potential painful conditions and the identification of superimposed delirium. Treatment of these conditions can reduce the severity of behavioral symptoms that are challenging. Behavioral interventions should be attempted before pharmacological treatment is considered. There are no FDA approved agents for treatment of agitation, aggression or violence in patients with dementia. While moderate quality evidence exists for modest effects of some antipsychotic agents in controlling agitation and aggression in patients with dementia there is high quality evidence for risks of use of these drugs (61,62). While there is moderate quality

evidence for modest effects in improvement of agitation and aggression with risperidone, olanzapine and quetiapine for periods of 6 weeks to 3 months there is moderate quality evidence that advantages can be offset by cognitive decline and increased morbidity associated with use of these drugs (63).

All antipsychotics carry a black box warning that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Most deaths occurring in this setting are from cardiovascular, cerebrovascular or infectious causes (64). Despite the risks associated with use of antipsychotics in this population these drugs are the only agents with evidence of effectiveness in psychotic symptoms associated with Alzheimer's dementia. US Federal regulations for nursing homes recommend a trial of discontinuation of antipsychotic drugs after three to six months. There is very limited evidence from clinical trials to support this suggestion. One study of a group of patients for whom this advice was followed point to a high risk of relapse in the months after stoppage in patients for whom discontinuation has been pursued (65).

There is low quality evidence for a modest effect in randomized control trials that memantine reduced incidence and severity of agitation in moderate to severe dementia (66).

**Recommendation:** In patients with dementia who display symptoms of severe agitation, threatening or overtly violent behavior care should be taken to establish the existence of co-existing delirium or disorders that may be producing pain. Use of antipsychotics to reduce the severity of agitation or violence should be confined to periods of up to six weeks. Regular weekly re-evaluation directed at measurement of efficacy and evaluation of side-reactions including metabolic and cardiovascular effects should be part of antipsychotic management with such patients. The majority of patients with moderate or severe neurocognitive disorders lack capacity to provide informed consent. Risks and benefits of pharmacological interventions should be explained to alternate decision makers and consent for specific interventions should be obtained and documented.

### **Traumatic Brain Injury**

There is low quality evidence that use of antipsychotics after brain injury results in declines in cognitive function and slowing of rehabilitation (67,68). Low quality evidence exists for the use of quetiapine for control of agitation that threatens progress in rehabilitation (69). Evidence that carbamazepine or valproate is effective in the management of agitation and/or aggression following brain injury is lacking.

Evidence to support pharmacological intervention to prevent or treat aggressive behavior consequent to traumatic brain injury is lacking. Moderate quality evidence supports aggressive treatment of depressive symptoms using SSRIs (70).

Over thirty studies provide moderate support for the efficacy of propranolol in reducing repetitive violent behavior in patients with a variety of chronic mental illnesses, developmental disability and organic brain disorders such as traumatic brain disorder (71).

**TABLE I – Medications used for treatment of agitation (off label) with FDA approved indications**

<b>Name</b>	<b>Dose</b>	<b>FDA Indication</b>
<b>Haloperidol (po, syrup, im, iv)</b>	<b>0.5 – 2 mg qAM, qHS</b>	Hyperactive behavior Problematic behavior in children Schizophrenia
<b>Chlorpromazine (po, syrup, im, iv, supp)</b>	<b>12.5-50mg bid/tid</b>	Behavioral syndrome Hyperactivity Schizophrenia
<b>Olanzapine (po, wafer, IM)</b>	<b>2.5 mg qHS (max 30 - 40 mg/day)</b>	Agitation in Bipolar disorder Agitation in Schizophrenia
<b>Ziprasidone (po, IM)</b>	<b>10mg im q2hr, max 40mg/day</b>	Agitation in Schizophrenia
<b>Risperidone (po, syrup, tab)</b>	<b>0.5 – 2 mg q12hrs</b>	Irritability associated with autistic disorder Behavioral Syndrome (MR)
<b>Aripiprazole (Po, syrup, IM)</b>	<b>2mg po, 9.5mg im</b>	Psychomotor agitation in autistic dsd/bipolar dsd/Schizophrenia
<b>Loxapine Inhaler</b>	<b>10mg inh/24 hours</b>	Agitation with bipolar I disorder

## **QUALITY INDICATORS**

### Organization of detection and management:

The available evidence does not allow for a recommendation of a specific model of intervention for violent and aggressive behavior.

### Specific quality indicators

The following indicators provide insight into the quality of the organizational response to potential violent acts.

The presence of an institutional protocol for response to violent and aggressive behaviors.  
Presence of documentation justifying use of antipsychotics in treatment of aggression and violence in patients without a psychotic diagnosis.

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## Appendix (Additional Materials)

- A) Recommended Readings
- B) Annotated List of Randomized Clinical Trials
- C) Assessment and Scales
- D) Areas for Future Research

## APPENDIX A

### Recommended Readings

#### Relevant literature:

- Abraham F.P., Calabrese J.R. Evidenced-based pharmacological treatment of borderline personality disorder: a shift from SSRIs to anticonvulsants and atypical antipsychotics. *Journal of Affective Disorders*. 2008;111(1):21-30.
- Buchanan R.W., Kreyenbuhl J, Kelly D. R. et al. The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Treatment Summary. *Schizophrenia Bulletin*. 2010;36(1):71-93.
- Lieb K, Vollm B, Rucker G. Pharmacotherapy of borderline personality disorder: Cochrane systemic review of randomized control trials. *British Journal of Psychiatry*. 2010;196:4-12.
- Maytal G., Sanders K.M. Aggressive and Impulsive Patients in Handbook of General Hospital Psychiatry. 6<sup>th</sup> ed. Saunders Elsevier. Philadelphia. 2010
- Monahan J., Steadman H.J., Silver E et al. Rethinking risk assessment: The MacArthur Study of mental disorder and violence. Oxford University Press. New York. 2001.
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- Scott C.L, Quanbeck C.D., Resnick P.J. Assessment of Dangerousness in American Psychiatric Publishing Textbook of Psychiatry, 5<sup>th</sup> edition. APPI. Washington, DC. 2008.
- Simon RI, Tardiff, K ed.. Textbook of Violence Assessment and Management American Psychiatric Press Inc. Washington, DC.2008.
- Wilson M.P., Pepper D, Currier G.W. et al. The Psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *Western Journal of Emergency Medicine*. 2012;13(1):26-34.

#### Relevant websites

[http://www.cdc.gov/ViolencePrevention/data\\_stats/index.htm](http://www.cdc.gov/ViolencePrevention/data_stats/index.htm)

## APPENDIX B

### Annotated List of Randomized Pharmacological Trials

#### Schizophrenia and Bipolar Disorder

Krakowsli M.I., Czobor P., Citrome L. et al. *Archives of General Psychiatry*. 2006;63(6):622-629. *Randomized, double-blind, parallel-group, 12-week trial. Physically assaultive subjects with schizophrenia or schizoaffective disorder who were inpatients in state psychiatric facilities were randomly assigned to treatment with clozapine (n = 37), olanzapine (n = 37), or haloperidol (n = 36). Outcome measures were number and severity of physical assaults as measured by the Modified Overt Aggression Scale (MOAS) physical aggression score and the*



*number and severity of all aggressive events as measured by the MOAS overall score. Psychiatric symptoms were assessed through the Positive and Negative Syndrome Scale (PANSS).*

*Clozapine was superior to both olanzapine and haloperidol in reducing the number and severity of physical assaults as assessed by the Modified Overt Aggression Scale (MOAS). Olanzapine was superior to haloperidol on similar outcomes. There were no significant differences among the 3 medication groups in improvement of psychiatric symptoms as measured by the PANSS total score and PANSS subscales.*

*The authors concluded that clozapine shows greater efficacy than olanzapine and olanzapine greater efficacy than haloperidol in reducing aggressive behavior. This anti-aggressive effect appears to be separate from the antipsychotic and sedative action of these medications.*

Breier A., Meehan K., Birkitt M. et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Archives of General Psychiatry*. 2002;59(5):441-48.

*This study was sponsored by a pharmaceutical company and included recently hospitalized acutely agitated patients with schizophrenia (N = 270) randomized to receive 1 to 3 IM injections of olanzapine (2.5, 5.0, 7.5, or 10.0 mg), haloperidol (7.5 mg), or placebo within 24 hours. A dose-response relationship for IM olanzapine in the reduction of agitation was assessed by measuring the reduction in Positive and Negative Syndrome Scale Excited Component scores 2 hours after the first injection. Safety was assessed by recording adverse events and with extrapyramidal symptom scales and electrocardiograms at 24 hours after the first injection.*

*Olanzapine exhibited a dose-response relationship for reduction in agitation. Mean PANSS-EC reductions 2 hours after the first injection of olanzapine were superior to those with placebo but not with haloperidol. A dose of 5.0, 7.5, or 10.0 mg of olanzapine caused a greater reduction in agitation than placebo 30 minutes after the first injection. There were no differences between treatment groups for hypotension, the most frequently reported adverse event. There was also no difference in clinically relevant changes in the QTc interval. There was a greater incidence of treatment-emergent parkinsonism during treatment with IM haloperidol (16.7%) than with IM olanzapine (0%) or with placebo (0%).*

*The authors concluded that intramuscular olanzapine at a dose of 2.5 to 10.0 mg per injection exhibits a dose-response relationship in the rapid treatment of acute agitation in patients with schizophrenia and demonstrates a favorable safety profile.*

## **Dementia**

Devanand DP, Mintzer MD, Schultz SK et al. Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease. *New England Journal of Medicine*. 2012;367(16):

*1497-1506. 180 patients with psychosis or agitation with Alzheimer's Disease who received open-label of risperidone (average dose 0.97mg per day) for 16 weeks. Those who had a response were randomly assigned to three groups: continued risperidone therapy for 32 weeks, risperidone for 16 weeks followed by placebo for 16 weeks or placebo for sixteen weeks. Rates of adverse events and deaths did not differ significantly. However, relapse in the group who had discontinued active treatment relapsed at higher rates (hazard ratio 4.88).*

Sultzer D.L, Davis S.M. Tariot P.N. et al. Clinical Symptom Response to Atypical Antipsychotics: Phase I Outcomes from the CATIE-AD Effectiveness Trial. *American Journal of Psychiatry*. 2008;165(7):844-854.

*The CATIE-AD effectiveness study included 421 outpatients with Alzheimer's Disease and psychosis or agitation. Assigned randomly to masked flexible-dose treatment with olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks, patients could be re-randomized to a different medication treatment at the clinician's discretion This ended the Phase 1 period. Psychiatric and behavioral symptoms, functional abilities, cognition, care needs, and quality of life were measured at regular intervals.*

*There was greater improvement in patients treated with olanzapine or risperidone on the Neuropsychiatric Inventory total score, with risperidone on the Clinical Global Impression of Change, with olanzapine or risperidone on the Brief Psychiatric Rating Scale (BPRS) Hostile Suspiciousness factor, and with risperidone on the BPRS Psychosis factor at the end of phase I. There was worsening with olanzapine on the BPRS Withdrawn Depression factor.*

*In this descriptive analysis of clinical outcomes in AD outpatients in usual care settings, some clinical symptoms improved with atypical antipsychotic treatment. The authors concluded that antipsychotic medications may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas. Functional abilities, care needs, or quality of life did not appear to improve with antipsychotics.*

Vigen C.L.P. Mack W.J, Keefe R et al. Cognitive Effects of Second Generation Antipsychotic Medication in Patients with Alzheimer's Disease: Outcomes from CATIE-AD. *American Journal of Psychiatry*. 2011;168(6):831-39.

*CATIE-AD included 421 Alzheimer's disease patients with psychosis or agitated behavior, randomized to blinded flexible-dose olanzapine, quetiapine, risperidone or placebo. Based on clinician's judgment, patients could discontinue originally assigned medication and be randomized to another medication. They were followed for 36 weeks. Cognitive assessments were obtained at baseline, 12 weeks, 24 weeks and 36 weeks. Outcomes were compared among 357 patients with baseline and at least one follow-up cognitive measure obtained while on their prescribed medication or placebo for at least 2 weeks before cognitive testing.*

*Patients showed steady, significant declines over time in most cognitive areas, Patients on antipsychotics declined more than patients on placebo for multiple cognitive measures.*

## **Agitation**

Battaglia J., Moss S., Rush J et al. Haloperidol, Lorazepam or Both for Psychotic Agitation? A multi-center, prospective, double-blind emergency department study. *American Journal of Emergency Medicine*. 1997;15(4):335-340.

*Ninety-eight psychotic, agitated, and aggressive patients were prospectively enrolled during an 18-month period in emergency departments in five university or general hospitals. Patients were randomly assigned to receive intramuscular injections of lorazepam (2 mg), haloperidol (5 mg), or both in combination. Patients in each treatment group received 1 to 6 injections of the same study drug within 12 hours, based on clinical need. They were evaluated hourly after the first injection until at least 12 hours after the last. Efficacy was assessed on the Agitated Behavior Scale, a modified Brief Psychiatric Rating Scale, Clinical Global Impressions scale, and an Alertness Scale. Effective symptom reduction was achieved in each treatment group with significant ( $P < .01$ ) mean decreases from baseline at every hourly ABS evaluation. Significant ( $P < .05$ ) mean differences on the ABS (hour 1) and MBPRS (hours 2 and 3) suggest that tranquilization was most rapid in patients receiving the combination*

*treatment. Side effects incidence did not differ significantly between treatment groups, although patients receiving haloperidol alone tended to have more extrapyramidal system symptoms. The authors conclude that superior results are produced by the combination treatment and support the use of lorazepam plus haloperidol as the treatment of choice for acute psychotic agitation.*

Kwentus J. Riesenbergr RA. Marandi M. Manning RA. Allen MH. Fishman RS. Spyker DA. Kehne JH. Cassella JV. *Bipolar Disorder*. 2012;14:31-40.

Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. *Bipolar Disorders*. 2012;14(1):31-40,

*This randomized, double blind, placebo-controlled, multi-center study of 314 inpatients with agitation associated with with bipolar I disorder. Subjects were randomized to inhaled loxapine 5 mg or 10 mg, or inhaled placebo. Patients receiving Dose 1 were evaluated for 24 hours. If required, up to two additional doses of study drug and/or lorazepam rescue medication were given. The primary efficacy endpoint was change from baseline in the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score two hours after Dose 1. The secondary endpoint was the Clinical Global Impression-Improvement score two hours after Dose 1. Safety was assessed by adverse events, vital signs, physical examinations, and laboratory tests.*

*For the primary and key secondary endpoints, both doses of inhaled loxapine significantly reduced agitation compared with placebo. Reduced agitation, as reflected in PANSS-EC score, was evident 10 min after Dose 1 with both doses. Inhaled loxapine was well tolerated, and the most common adverse events were known effects of loxapine or minor oral effects common with inhaled medications.*

*The authors concluded that inhaled loxapine provided a rapid, non-injection, well-tolerated acute treatment for agitation in patients with bipolar I disorder.*

## **Impulse Control Disorders**

Coccaro, EF, Lee RJ, Kavoussi RJ. A Double Blind, Placebo Controlled Trial of Fluoxetine in Patients with Intermittent Explosive Disorder. *Journal of Clinical Psychiatry*. 2009;70(5):653-662.

*A double-blind, randomized, placebo-controlled trial of fluoxetine conducted in 100 individuals with Intermittent Explosive Disorder (research diagnostic criteria) and current histories of impulsive aggressive behavior. The primary measure of efficacy was the aggression score from the Overt Aggression Scale-Modified (OAS-M) for Outpatient Use. Secondary efficacy measures included the irritability score from the OAS-M and the Clinical Global Impressions-Improvement scale (CGI-I) score. The study took place between July 1990 and July 1999.*

*Fluoxetine treatment resulted in a sustained reduction in OAS-M aggression, and OAS-M irritability scores, apparent as early as week 2 ( $p < .01$  for aggression and  $p < .001$  for irritability at endpoint). Fluoxetine was also superior to placebo in the proportion of responders on the CGI-I ( $p < .001$ ). Closer examination of the data revealed that full or partial remission of impulsive aggressive behaviors occurred in 46% of fluoxetine-treated subjects. Fluoxetine did not exert an antidepressant or antianxiety effect, and its effects on*

*impulsive aggression were not influenced by presence of current symptoms of depression or anxiety. Fluoxetine can reduce aggressive behaviors in those diagnosed with intermittent explosive disorder.*

## APPENDIX C

### **Assessment and Scales**

Several Scales have been developed to measure the propensity for and severity of violent and aggressive behavior.

The scales listed below are the best in terms use in prospective studies.

#### For psychiatric clinicians:

Overt Aggression Scale

Overt Aggression Scale – Modified

#### For nurses and other staff:

Staff Observation of Aggression Scale

Staff Observation of Aggression Scale - Revised

The Excited Component from the Positive and Negative Syndrome Scale (PANSS-EC) is a validated scale to assess agitated patients. The PANSS-EC consists of 5 items taken from the PANSS that clinicians can quickly and routinely assess: excitement, tension, hostility, uncooperativeness, and poor impulse control. The 5 items are rated from 1 (not present) to 7 (extremely severe) with scores ranging from 5 to 35 (scores  $\geq 20$  correspond to severe agitation).

Violence Risk Assessment Tools – Otto RK, Douglas KS. Handbook of Violence Risk Assessment. Routledge. New York, 2010.

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Palmstierna T., Wistedt B. Staff Observation Aggression Scale, SOAS: Presentation and Evaluation. *Acta Psychiatrica Scandanavica*. 1987;76(6):657-663.

Nijman H. Palmstierna T. Measuring Aggression with Staff Observation. *Acta Psychiatrica Scandanavica*. 2002;412:101-102.

Yudofsky S.C., Slivler J.M., Jackson W et al. The Overt Aggression Scale for Objective Rating of Verbal and Physical Aggression. *American Journal of Psychiatry*. 1986;143:35-39.

Knoedler D. W. The Modified Overt Aggression Scale. *American Journal of Psychiatry*. 1989;146(8):1081.

## APPENDIX D

### **Areas for Future Research**

Establishing the effectiveness of various interventions among patients prone to violence and aggression has been limited by ethical constraints. In situations involving acute, frequently unanticipated, events obtaining informed consent for participation is frequently not practical.

Reliance on prospective observational trials has been helpful in a limited number of studies. More of such studies are needed to establish an evidence base for use of many long accepted interventions for treatment of agitation, aggression and violence. Further studies in special populations such as personality disorders, intellectually disabled, traumatic brain injured and demented patients are needed to assure that benefits of treatment outweigh iatrogenic morbidity and mortality.

## APPENDIX E

### **Multiple choice questions**

While there is widespread public perception the patients with schizophrenia are prone to violent acts epidemiological studies have repeatedly demonstrated a strong relationship between aggressive behaviors and:

- A. Personality disorders
- B. Substance Use Disorders
- C. Financial Stresses
- D. Social Isolation

(Correct answer: B.)

The best evidence for violent behavior among patients with brain disease is for disorder involving?

- A. Frontal Lobe
- B. Temporal Lobe
- C. Parietal Lobe
- D. Corpus Striatum
- E. Limbic System

(Correct answer: A)

In approaching the patient with agitation without clear etiology which of these should be utilized first?

- A. Voluntary use of oral benzodiazepines
- B. First-generation antipsychotics with promethazine
- C. Second-generation antipsychotics intramuscularly
- D. Confrontation
- E. Verbal De-escalation

(Correct answer: E)

Evidence exists for aggressive behavior following the use of these addictive substances except?

- A. Methamphetamines
- B. Cocaine

- C. alcohol
- D. synthetic cathinones
- E. Hallucinogens

(Correct answer: E)

Among patients with the diagnosis of Intermittent Explosive Disorder which of the following pharmacological agents has shown efficacy in randomized control trials:

- A. Olanzapine
- B. Benztropine
- C. Fluoxetine
- D. Alprazolam
- E. Methylphenidate

(Correct Answer: C)