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Neuropsychiatry of Aggression

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Synopsis

Aggression is a serious medical problem that can place both the patient and the health care provider at risk. Aggression can result from medical, neurologic and or psychiatric disorders. A comprehensive patient evaluation is needed. Treatment options include pharmacotherapy as well as non-pharmacologic interventions, both need to be individualized to the patient.

Keywords

Aggression; pharmacotherapy; diagnosis; neurobiology

Introduction

Before embarking on any discussion of the etiology and treatment of aggression, it is important to clearly define what is meant by aggression. Aggressive behavior is prevalent in most species, and aggressive behavior patterns may serve an adaptive function. In humans however, extreme and persistent forms of aggression are often indicative of psychopathology¹, especially when they persist across the lifetime^{2, 3}.

While several definitions have been proposed, here we will operationally define human aggression as (a) a social behavior that involves the interaction at least two people; (b) is intended to harm another person; who (c) finds this harm aversive and would act to avoid it^{4, 5}. Note that this definition includes the requirement of a social context (i.e., verbal and non-verbal interaction). Thus, aggression directed toward self (i.e., self-injury, suicide) rests outside the scope of this chapter. Importantly, provocation and retaliation are known to be critical determinants of aggression, and these factors necessarily require a social context⁶.

2. Brain regions associated with pathologic aggression

In general, data from both human and non-human studies find that subcortical brain regions, particularly the limbic system and specifically the amygdala, are associated with the

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processing of emotionally salient events, including aggression⁷. The limbic system consists of several components that interact with each other and project to areas of autonomic and somatomotor emotional control⁸. The amygdala has repeatedly been shown to mediate fear, defensive reactions, emotional learning, and motivation⁷. The amygdala and hypothalamus interact in the emotions of anger and fear⁹. Patients with damage to the amygdala show impairment in the recognition of fearful facial expressions¹⁰, and the amygdala is active in a number of human social conditioning and fear paradigms¹¹.

In addition to subcortical regions, several cortical brain regions have been associated with emotions. The dorso-lateral pre-frontal cortex (DLPFC) and the orbito-frontal cortex (OFC) receive limbic inputs from amygdala and other medial temporal areas as well as sensory inputs, and thus may integrate sensory information with affective signals¹². Damage to limbic and pre-frontal cortex (PFC) regions negatively affect cognition, memory, and emotional processes¹³. Several theories propose that (a) it is the interconnected network between the limbic (amygdala), OFC, and DLPFC regions that primarily subserve the processing of emotional and goal driven behavior (e.g., “hedonic” function), and (b) damage or dysfunction in any of these areas or this network results in problems with the regulation of emotion and subsequent difficulties with inhibitory and aggressive behavior¹⁴.

There is considerable evidence that the limbic-dorsolateral prefrontal-and orbital frontal network facilitates the activation and inhibition of aggressive behavior. Patients with brain lesions in OFC have higher aggression/violence scores compared to normal controls and patients with lesions in other brain regions¹⁵. Following frontal lobe damage, particularly injury to the ventro-medial prefrontal cortex, subjects who exhibited sociopathic behavior showed decreased autonomic skin conductance responses to emotional visual stimuli¹³. Alzheimer’s patients presenting problems with behavioral disinhibition showed decrements in OFC, DLPFC, and anterior cingulate metabolic activity that were not present in Alzheimer dementia patients without such problems¹⁶. In patients with organic mental syndromes and violent behavior, lesions in the amygdala-hippocampal region were found in brain imaging scans that were not present in non-violent organic patients¹⁷. These studies concluded that widespread damage to the amygdala (as opposed to pinpoint surgical lesions) produces behavioral disinhibition and violent behavior.

The connection between neuropsychiatric abnormalities and violent criminal behavior noted that “orbitofrontal injury is specifically associated with aggression” and “focal frontal lobe dysfunction is associated with aggressive dyscontrol and increased risk of violence”¹⁸. Similarly, the neurobiology of personality disorders concluded that impulsive aggression is characterized by abnormal functioning in the amygdala, OFC, DLPFC, and anterior cingulate cortex (ACC)¹⁹. Psychiatric patients with a history of repetitive purposeless violent behavior showed lower resting temporal and prefrontal metabolic activity compared to normal controls²⁰. There was a significant inverse correlation between life history of aggressive impulse difficulties and OFC regional metabolic activity²¹. Subjects who committed unplanned impulsive murders were found to have lower PFC and higher subcortical (e.g., amygdala, hippocampus) metabolic activity compared to controls²². Patients with DSM-IV personality disorders and clinically significant impulsive aggression showed an absence of activation in OFC and ACC in response to the serotonin agonist drug m-CPP²³. Individuals with a criminal history of domestic violence who also met alcohol dependence criteria had lower metabolic activity in hypothalamus, thalamus, and OFC than both non-violent alcoholics and healthy controls²⁴. Neuroimaging studies that experimentally induced anger in humans demonstrated increased activation in the DLPFC and OFC²⁵. In non-human primates, OFC and DLPFC lesions reliably produce increased aggressive behavior²⁶.

The brain neuronal circuitry underlying aggressive behavior appears quite extensive and complex. Studies in humans suggest that increased aggressive behavior may be associated with decreased functioning in orbital and dorsolateral prefrontal cortical areas, and increased functioning in medial temporal (especially amygdala) brain regions. Importantly, the relative balance of activity between dorsolateral prefrontal, orbital frontal, and limbic brain regions may be important in predisposing to violence and abnormal processing of emotional stimuli¹⁸.

3. Seizures and aggression

There have been medical legal cases in which epilepsy has been used as a defense against charges of violence. However, recent studies provide evidence that acts of aggression during seizures are simple and unsustained; they are not planned or carried out in an organized fashion, nor are they purposeful or directed. When aggression occurs in the setting of a seizure the onset is usually sudden, duration is short, and the act is generally in response to being held down or as part of a defensive motion. Seizure related aggression is usually part of an automatism which is characteristically unsustained, short lived or fragmentary.²⁷

To better understand the relation between aggression and epilepsy, an international task force from 16 epilepsy programs, selected 19 pts who were thought to have aggressive behavior during their seizure. This sample of patients was selected from a group of 5400 patients with epilepsy. The events were recorded by video-monitoring EEG and analyzed. After reviewing the clinical characteristics and their correlation with electroencephalographic (EEG) discharges, the task force made recommendations to guide the determination of causation of aggression in patients with epilepsy²⁸;

1) the diagnosis of epilepsy should be established by a neurologist with special training in epilepsy, 2) the presence of epileptic automatisms should be documented by history, closed circuit television monitoring and EEG bio telemetry, 3) presence of aggression during epileptic automatisms should be verified by videotaped recorded seizures and correlated with EEG ictal epileptiform discharges. 4) the aggressive or violent episode should be characteristic of the patient's habitual seizures at which point 5) a clinical judgment should be made by the neurologist who will then attest if in his or her opinion the act and or alleged crime was part of the seizures.²⁸

A complete history including clinical characteristics, medical, psychiatric comorbidities, social history other concomitant factors and circumstances are essential prior to making a diagnosis and before designing a necessary treatment.

4. Dementia and aggression

Patients with dementia can present with aggression and or agitation. Symptoms can be due to a superimposed delirium, and or to the nature and severity of the underlying degenerative or structural etiology. Identifying and treating the underlying etiology is key to maximizing outcome. As reviewed in Ballard²⁹, agitation and aggression are frequent symptoms in patients with dementia, which are distressing to family members and can lead to significant morbidity. In a retrospective review of patients who were diagnosed with Alzheimer's disease conducted by Jost et al. symptoms were defined in 3 groups to include agitation, mood symptoms and psychotic symptoms. The authors found that agitation occurred in the first year after the diagnosis, psychotic symptoms at the time of the diagnosis, and mood symptoms preceded the diagnosis on the average by two years. A comprehensive approach to these patients should include basic testing of cognitive functions as it might lead us an early accurate diagnosis with all the necessary implications.³⁰

5. Aggression and Psychiatric Diagnosis

Intermittent Explosive Disorder

DSM-IV-TR Diagnostic Criteria for Intermittent Explosive Disorder: A. Several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property. B. The degree of aggressiveness expressed during the episodes is grossly out of proportion to any precipitating psychosocial stressors. C. The aggressive episodes are not better accounted for by another mental disorder and are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., head trauma, Alzheimer's disease). As can be seen from the Diagnostic and Statistical Manual version IV Text Revision (DSM-IV-TR) criteria for Intermittent explosive disorder (IED) listed above, aggression is a key feature of the diagnosis³¹. An additional key feature of the diagnosis of IED is the fact that it is a diagnosis of exclusion; if the aggression is thought to be better accounted for by another psychiatric or non-psychiatric medical condition, the diagnosis of IED cannot be made. However, the determination of whether the aggression is better accounted for by another condition is left to the clinician, with little guidance on how this determination is to be made. In some cases the determination is relatively simple. In a situation where a patient who has no history of aggression prior to a head injury suddenly develops aggression after the injury the diagnosis of aggression related to the brain injury would be made to the exclusion of IED. In many cases however, the diagnosis is less clear. Many patients with aggressive behavior have minor head trauma and substance abuse and the causal relationship between these factors and the aggression can be difficult to ascertain. Obtaining information from friends and family of the patient regarding the association between aggression and other potential factors such as substance abuse or head trauma is critical in the determination of the causal relationship. As with the general evaluation of aggression regardless of the etiology, a thorough history and physical examination and neurologic examination are also important. Factors such as rapid onset of symptoms, association with neurological findings on physical examination, or frontal release signs (described in detail in the diagnostic evaluation section below) can be a reason for additional tests, such as neuropsychological testing and MR brain imaging. From a treatment perspective, unless the aggression is clearly better accounted for by another psychiatric diagnosis or non-psychiatric medical condition, the critical question is whether the aggression is primarily impulsive or planned. Impulsive aggression has been shown to respond to treatment with pharmacotherapy, while planned or premeditated aggression has not.

Aggression and psychosis

The relationship between aggression and psychotic disorders in particular schizophrenia is controversial.³² One potential reason for the conflicting results on the association between psychosis and aggression is the fact that past history of aggressive behavior related to antisocial personality disorder and substance abuse are independently associated with aggression, and thus need to be taken into account in the study of psychosis and violence. Taking these factors into account, there is some evidence that psychosis accompanied by depression or distress is associated for a increased risk of violence³².

Aggression and substance abuse

Alcohol—The epidemiological evidence linking alcohol to aggressive behavior is overwhelming. Alcohol intoxication, abuse and dependence are highly associated with violent criminal activity^{33, 34}. The non-health related costs of alcohol abuse to society, e.g., those resulting from criminal behavior, are estimated at \$13 billion annually³⁵. A substantial proportion of these crimes are of a violent nature; alcohol may be involved in 40 to 50% of all violent crimes, including homicide and assault³⁶. This pattern is present in

adolescents and young adults³⁷. There is a positive correlation between the quantity of ethanol consumed and the frequency of a wide variety of acts of violence including sexual assault, child abuse, and homicide³⁸. Individuals who engage in aggressive behavior report a greater amount of ethanol consumption than those without such a history³⁹. Additionally, alcohol consumption is greater in individuals who are more likely to commit violence, such as individuals with (Antisocial Personality Disorders) ASPD¹.

There is an extensive history of laboratory investigation regarding alcohol effects on aggression^{40, 41}. Reviews of laboratory-based studies have consistently concluded that alcohol increases aggressive responding^{38, 41}. More than any other drug, alcohol is known to increase the probability of aggression under laboratory conditions⁴¹.

Other Abused Drugs—Historically, a number of benzodiazepines have been used effectively to manage aggression in psychiatric patient populations⁴². However, previous reports have noted an association between benzodiazepine use and aggressive/violent behavior⁴³. Past reviews have documented increased risk of criminal behavior following extended use⁴⁴ and loss of self-control and violence in patient populations prescribed benzodiazepines⁴⁵. From the extant data, it is unknown if these increases were observed primarily in individuals with a history of violent behavior or underlying personality disorder. Recreational use of flunitrazepam (Rohypnol) increased the odds of involvement in physical assault, sexual assault, and motor vehicle accidents⁴⁶. A survey of Mexico City drug users an association between flunitrazepam abuse and street fights, robbery, and rape⁴⁷. In forensic studies psychiatric patients and juvenile offenders who abused flunitrazepam were more commonly involved in offenses involving robbery, weapons, and drugs⁴⁸, acts of impulsive violence, and serious violent criminal offenses⁴⁹. Thus, like alcohol, abuse of certain benzodiazepines may be related to aggression. This may be due to shared pharmacological mechanisms of action at GABA receptors, and concomitant loss of inhibitory control. However, because benzodiazepines have also been shown to be clinically effective in mitigating agitation and aggressive behavior, it appears likely that there is a subset of individuals for whom heavy use or abuse of benzodiazepines may facilitate aggressive behavior. History of criminal violence and/or personality disorders may be contributing factors.

One previous literature review concluded that there was little evidence suggesting that marijuana use was directly associated with aggressive behavior⁵⁰. However, more recent data suggest that marijuana use may be related to increased likelihood of violence, with particularly relevance to use during adolescence. Studies show increased likelihood of weapons offenses and attempted homicide in inner city low-SES youth⁵¹; a link between marijuana use during early adolescence and violence experiences in later adolescence in Columbian youth⁵²; heavy use and abuse of marijuana was predictive of violent crimes (vs. property crimes) in delinquent adolescents⁵³; and violent behavior during adolescence was associated marijuana use and dependence in early adulthood⁵⁴. The complexity of this relationship cannot be underemphasized. Developmental factors and comorbid conduct/behavior disorders highlight the difficulty of understanding direction and causality in the relationship between marijuana use and aggression. Further complexity is added by studies suggesting that aggressive behavior may increase during periods of marijuana withdrawal⁵⁵.

Several studies suggest a relationship between aggressive behavior and the use of CNS stimulants. Day to day substance use in males was related to violence toward female partners, with cocaine and/or alcohol use associated with increases in physical aggression⁵⁶. Denison et al.,⁵⁷ reported that violent behavior increased during periods of cocaine and/or cocaine-alcohol use, and that the severity of violence was altered once cocaine use escalated into cocaine dependence. Dysregulation of the limbic system following chronic has been

suggested as a mechanism by which cocaine use may lead to heightened aggression^{58, 59}. In support, Moeller et al.,⁶⁰ found that, compared to controls, cocaine dependent subjects were more aggressive than control subjects on both psychometric and laboratory measures of aggression; and further showed a significant correlation between measures of aggression and growth hormone response to a buspirone challenge, which was not observed in controls. However, a subsequent study Moeller et al.,⁶¹ suggested that the relationship between cocaine-use variables (e.g., craving, withdrawal) and aggression is mediated primarily by the presence of antisocial personality disorder. In addition to cocaine, aggressive behavior patterns may be associated with the abuse of other CNS stimulants including methamphetamine⁶² and 3,4-methylenedioxy-methamphetamine (MDMA or “Ecstasy”)⁶³.

Epidemiological data indicate that, generally, the presence of a psychiatric disorder increases risk for violent behavior, but this risk is greatly increased by the presence of substance abuse symptoms⁶⁴. Most prominent is the finding that comorbid substance use disorders and Axis-II personality disorders (particularly conduct, antisocial personality, and borderline personality disorders) increase the risk for violent behavior above either disorder alone; by one account on the order 15–20:1 compared to community-matched base rates⁶⁴. Adolescent drug users were more prone to fighting and assault than non-drug users, and were more likely to be victims of violent behavior⁶⁵. The collective implication of such data is that, at least in natural settings, rather than a direct pharmacological effect of abused drugs on aggressive behavior, there are important interactions with concomitant factors such as history of aggressive behavior and presence of psychiatric disorders that must be understood.

Diagnostic evaluation of aggression

History and Presentation

Aggression is a behavioral finding of many etiologies, necessitating a detailed history and physical exam in establishing the cause and potential treatments. A comprehensive approach to include premorbid function, prior psychiatric and medical comorbidities, history of alcohol and or substance abuse, concomitant medications, presence of absence of social support, and coping mechanisms is imperative as identifying and treating the underlying etiology is key to maximizing outcome.

Specific questions in the history about aggression may help characterize illness and inform clinicians about the potential for future aggressive acts. Legal history including reason for, number and length of incarcerations, history of abuse toward spouse, child or other person or animals should be obtained as well as ownership and carrying pattern of firearms. Developmental components relating to patterns of abuse and childhood environment as well as developmental delays, childhood legal history, diagnosis with conduct disorder or oppositional defiant disorder may also help to further characterize presentation of aggression.

Physical Examination

In general, a basic evaluation for aggressive behavior should include a complete medical, neurological and psychiatric evaluation. Laboratory tests should include a CBC, metabolic panel, thyroid functions, urine drug screen, and urinalysis. In addition, although of lower yield, B12, and folate levels may be helpful. Brain imaging and EEG may be indicated based on the history and physical exam findings as described below.

Physical findings in individuals with aggressive behavior of psychiatric origin, while generally nonspecific may be helpful at understanding underlying causes of aggression. Likewise, as mentioned previously, a diagnosis of intermittent explosive disorder is made by

exclusion of non-psychiatric medical causes of aggression. Hence, this diagnosis can only be made after a thorough medical evaluation.

Abnormal vital signs and or acute change in mental status may suggest delirium and should be investigated. In institutionalized patients with dementia, urinalysis and chest-x rays may be particularly helpful in determining the cause of delirium.

Sudden change in behavior or focal neurologic findings suggest focal brain pathology that should be evaluated by MRI or CT scans. Gradual decline in cognitive functioning concomitant with aggression suggests dementia, which would necessitate a thorough workup for causes of dementia, including brain imaging, neuropsychological testing, and EEG.

Additional findings on physical exam may include signs of past physical altercations, including healed signs of fracture, contusion, laceration, gunshot wound and other signs of violence. Frontal release signs may direct the history and evaluations towards a diagnosis of dementia, skull injuries may suggest a traumatic etiology.

Treatment of aggression

Pharmacotherapy for aggression can be separated into acute and chronic phases. The goal for the treatment of acute aggressive behavior, which is generally initiated in the emergency Department or on an inpatient unit, is elimination of the aggressive behavior for the safety of the patient and staff. In the pharmacotherapy of acute aggression, sedation is accepted and even sought after, while it is considered an unacceptable side effect in the treatment of chronic aggression. With these factors in mind, medications are used for the treatment of acute aggression tend to not have specific effects on aggression but to have substantial sedative effects. A common practice is the use of injectable benzodiazepines and antipsychotic medication, alone or in combination. In a recent Cochrane meta-analysis of studies on the use of benzodiazepines for the treatment of acute aggression, Gillies et al.,⁶⁶ concluded that the benzodiazepine lorazepam reduced excitement after 24 hours compared to placebo and produced similar sedation to antipsychotic medication. When comparing benzodiazepines plus antipsychotic medication to antipsychotic medication alone, there was no difference in the need for additional medication to achieve sedation between the two treatments but there was a higher rate of extrapyramidal symptoms in the group that received antipsychotic medication alone⁶⁶. The finding that patients treated with antipsychotic medication alone had higher rates of extrapyramidal side effects is consistent with the study of Huf et al., who showed that in a group of 316 patients that received intramuscular medication for sedation for aggression subjects who received haloperidol alone had more extrapyramidal symptoms than subjects who received haloperidol plus promethazine⁶⁷.

Antipsychotic medications vary in their extrapyramidal side effects based on potency of dopamine receptor antagonism and affinity for other receptors, such as the muscarinic cholinergic receptor, with lower potency antipsychotic medications generally having less extrapyramidal side effects than higher potency antipsychotic medications. There is a growing body of evidence that newer generation antipsychotic medications other than clozapine do not have a specific reduction in extra pyramidal side effects side effects above and beyond the potency and inherent anticholinergic effects⁶⁸. However, few controlled trials have compared older generation and newer generation antipsychotic medications for acute aggression.

Pharmacotherapy of Chronic Aggression

As mentioned above, the goal of pharmacotherapy of chronic aggressive behavior is elimination or reduction of aggression without producing general sedation or other intolerable side effects. Although there are a large number of case reports and open label trials of various medications for aggression⁶⁹, there are relatively few double blind placebo controlled trials of medication for chronic aggressive behavior. Since there is a substantial placebo effect in the treatment of aggression (similar to virtually every other psychiatric and non-psychiatric medical disorder), it is difficult to assess the efficacy of pharmacotherapy from open label trials and case reports should be evaluated with some skepticism. Listed below are the most commonly used classes of medications for chronic treatment of aggression along with the evidence supporting their use for this indication and potential drawbacks.

Antipsychotic Medication

As described above, antipsychotic medication is used routinely alone or in combination with benzodiazepines or promethazine for the treatment of acute aggression. However, for the treatment of chronic aggressive behavior, where sedation is not an acceptable side effect, there is little evidence to support the use of first generation antipsychotic medication. However, there is some data to support a specific anti-aggressive effect for at least some of the second generation antipsychotic medications.

In children with mental retardation, and autism, and adults with dementia there is data to support a specific anti-aggressive effect which appears to be separate from the sedative effect of risperidone at least at lower doses²⁹. In a meta-analysis by Ballard and Howard (2006), the conclusions were that risperidone at 1 and 2 mg daily produced a significant improvement in aggression in patients with dementia⁷⁰. Further, in patients with schizophrenia, there is evidence that risperidone may reduce aggression to a greater degree than first generation antipsychotic medication⁷¹. The main drawbacks with risperidone are related to side effects of extrapyramidal symptoms, orthostasis, and sedation. As mentioned above, there is a growing body of evidence that newer generation antipsychotic medications do not have lower extrapyramidal side effects than older generation antipsychotic medications⁶⁸. In addition, the FDA has added a “black box” warning to risperidone and other antipsychotic medications regarding the increased mortality in elderly dementia patients treated with antipsychotic medication, largely related to cardiovascular or infectious causes²⁹. Other second generation antipsychotic medications have also been studied for chronic aggression in patients with dementia. In the meta-analysis by Ballard and Howard (2006), in addition to risperidone, olanzapine produced a significant improvement in aggression in patients with dementia at a dose of 5–10 mg per day⁷⁰. Less data is available for other second generation antipsychotic medications. One study of quetiapine found a significant worsening of agitation, possibly related to quetiapine’s effects on muscarinic receptors or BDNF⁷² but one study of aripiprazole did indicate improvement in agitation⁷³. Similar to findings in dementia patients, there is some evidence from small scale and open label studies that other second generation antipsychotic medications reduce aggression in patients with conduct disorder, but these conclusions need to be replicated in larger controlled studies⁷⁴.

One second generation antipsychotic that does have some additional evidence that it reduces aggression independent of sedative effects is clozapine⁷⁵. The majority of the evidence supporting a specific anti-aggressive effect of clozapine comes from studies of patients with psychosis⁷⁶. In addition to the drawbacks of other second generation antipsychotic medications, clozapine also has a risk of a potentially lethal reduction in white blood cell count which limits its use to patients who are refractory to other medications.

Lithium

One of the earliest placebo controlled trials of a medication for chronic aggressive behavior was carried out by Sheard et al.,⁷⁷ in which 66 male prisoners (age 16 to 24), without a prior history of prior treatment for a psychiatric disorder were treated with lithium or placebo in a double blind fashion for up to three months. Results of the study showed that the subjects treated with lithium had a significant reduction in aggressive behavior compared to the placebo treated subjects.

Since the study by Sheard et al., a number of other studies have examined lithium as a treatment for chronic aggression showing similar results in a variety of patient groups including patients with mental retardation and children with conduct disorder^{78, 79}. As with anticonvulsants, (described in detail below) there is some evidence that lithium is most effective in patients with affective or impulsive aggression, as opposed to premeditated aggression⁸⁰. The main drawbacks with lithium as a treatment for chronic aggression are the side effects and need for blood level monitoring. Lithium has a narrow therapeutic window, with a potential for substantial toxicity if blood levels exceed recommended levels of 0.6 to 1.2 mEq/l. Even if blood levels are maintained in this range, lithium has side effects that include tremor, sedation, nausea, and polyuria; there is some evidence that patients with head trauma may be at greater risk for neurotoxicity, especially if these patients are also taking antipsychotic medication⁸¹.

Anticonvulsants

Anticonvulsant are probably the most widely studied class of medications for treatment of chronic aggression. One of the first double blind placebo controlled trials of anticonvulsants for aggression was carried out by Barratt and colleagues, who compared phenytoin to placebo in inmates with violent behavior⁸². In that study subjects were treated with 300 mg of phenytoin daily in divided doses. Results of the study were that inmates who had impulsive aggression showed a significant reduction in aggressive behavior compared to placebo, but no change in premeditated aggression. It should be noted that subjects with a known history of seizures were excluded from the study, suggesting that effects of anticonvulsants on aggression are independent of effects on seizures. A second study supported the findings of Barratt et al of reduced impulsive aggression in patients treated with phenytoin⁸³, and a third study showed that effects of phenytoin on impulsive aggression were similar to effects of valproate⁸⁴. Phenytoin was well tolerated at the dose used in these studies, which produced blood levels that were on average lower than those used to treat epilepsy.

Valproate/divalproex has also been studied for aggression in several clinical trials. Donovan⁸⁵ reported a greater number of children and adolescents with disruptive behavior disorders responding to divalproex compared to placebo for explosive temper and mood lability in a small scale study. Similar results were found in a small scale study comparing valproate to phenytoin and carbamazepine⁸⁴. However, another small scale study in patients with pervasive developmental disorders did not find a significant difference between valproate and placebo treated subjects⁸⁶. A multicenter placebo controlled trial of divalproex for impulsive aggression also did not find a significant reduction in aggression in patients overall but there was a significantly greater response in the subset of patients with cluster B personality disorders⁸⁷. Based on studies to date, a recent Cochrane database meta-analysis concluded that although there is some evidence supporting valproate/divalproex for aggression, further research is warranted⁸⁸.

Studies of other anticonvulsants also have reported mixed results in the treatment of aggression. A study by Cueva in patients with conduct disorder did not find a difference in

response between carbamazepine and placebo ⁸⁹, but a small-scale study comparing carbamazepine to valproate and phenytoin found that carbamazepine did reduce impulsive aggression although the onset of action of carbamazepine was slower than the other two drugs ⁸⁴. Similarly, a small scale trial in patients with borderline personality disorder showed decreased behavioral dyscontrol in patients treated with carbamazepine compared to patients treated with placebo ⁹⁰.

Though research is less extensive, newer anticonvulsants have been reported to reduce aggression in acute laboratory models and in controlled trials. Using a laboratory model of human impulsive aggression, aggressive behavior was diminished following acute doses of Gabapentin ⁹¹, Tiagabine ⁹², and Topiramate ⁹³. In one clinical trial, Topiramate reduced aggression as measured by the State Trait Anger Expression Inventory in patients with borderline personality disorder ⁹⁴. Likewise, oxcarbazepine has been reported to be more efficacious in reducing impulsive aggression in an outpatient trial ⁹⁵. A few controlled studies have also reported negative results. A trial reported that levetiracetam showed no difference from placebo in reducing impulsive aggression ⁹⁶.

Selective Serotonin Reuptake Inhibitors

Although selective serotonin reuptake inhibitors (SSRIs) are widely used clinically for the treatment of aggression, there are relatively few controlled trials published on the efficacy of SSRIs for aggression. Fluoxetine is the most widely studied of the SSRIs for aggression. Two studies reported reduced decreased anger ⁹⁷ and verbal aggression ⁹⁸ in patients with personality disorders. Another study using fluvoxamine showed a reduction in mood shifts in borderline personality disorder patients treated compared to placebo but no significant difference in aggression scores ⁹⁹. A more recent study reported that citalopram produced a significant reduction in anger and hostile affect in patients with high hostility scores but who were otherwise healthy ¹⁰⁰. The same study reported a reduction in aggression but this only occurred in the female subjects.

There is also some data on effects of SSRIs on aggression in patients with dementia. A study comparing citalopram to risperidone showed that both treatments reduced agitation symptoms and psychotic symptoms but citalopram was associated with fewer side effects ¹⁰¹. Another study of citalopram, perphenazine, and placebo in dementia patients showed that only citalopram was associated with improvement in agitated aggression ¹⁰².

Beta Blockers

Although there are relatively few controlled trials with beta adrenergic agonists, where these drugs have been most extensively studied is in patients with a history of traumatic brain injury. A recent Cochrane meta-analysis of the randomized clinical trials for aggression and agitation following brain injury concluded that the best evidence of effectiveness in the management of aggression and agitation in patients with brain injury was for beta blockers ¹⁰³. However, several caveats were noted in this evidence including the fact that the studies of beta blockers for aggression in brain injury patients were relatively small-scale, used large doses of beta blockers and did not assess global outcomes or long term follow-up. The two beta blockers that have been studied in controlled trials are propranolol ¹⁰⁴ and pindolol ¹⁰⁵, with neither drug being clearly superior based on the studies to date.

Summary and Conclusions

Aggression is a serious medical problem in a number of neurologic and psychiatric patient groups. It can be a sign of an underlying non-psychiatric medical disorder, or a symptom of a psychiatric or substance use problem. When faced with a patient that has aggressive

behavior the most important actions include ensuring safety of the patient and staff, followed closely by an evaluation of the etiology of the aggression. In acute aggression, physical restraints may be needed for a short period until the physical examination and clinical assessment have been made.

Pharmacotherapy for acute aggression involves sedating medications, which have risks in themselves and can make diagnosis difficult. Pharmacotherapy for chronic aggression has as a goal to reduce aggression without producing significant sedation and other side effects. Although there are several controlled trials showing efficacy of several different classes of medications for treatment of chronic aggressive behavior, these studies are relatively small in sample size and none of these medications are approved by the FDA for this indication. Further, all medications have side effects and a recent consensus statement supported the use of pharmacotherapy for aggression and agitation only after non-pharmacologic interventions had failed in patients with dementia due to risk of side effects¹⁰⁶. Thus, non-pharmacologic interventions such as reducing pain, improving sleep, and enhancing unit structure should be applied before pharmacotherapy.

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