

Psychopharmacology of violence

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Psychopharmacology of violence

An introduction - part I

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This article is based on a presentation sponsored by the Committee on Psychopharmacology and presented at the AAPL Annual Meeting in Boston, October 2001.

For the purposes of this article aggression is defined as behavior that leads to the damage or destruction of a target entity.¹ Practically speaking, we are talking about the frequent occurrence of aggression or anger as a symptom deemed worthy of assessment and treatment by a patient, psychiatrist or others. Practically speaking, as clinical forensic psychiatrists, we are asked to do consultations on patients who present with violence. We are asked to consult to the community, to our colleagues in hospital settings, and also at specialty anger clinics or in correctional settings.

We would regard aggression using a dimensional model. In this model aggression is a symptom that cuts across many diagnostic groups. To take a reductionist point of view, in the end, aggression is determined by brain mechanisms and neurotransmitter systems. The assessment of violence should begin with a routine history and mental state examination. Careful attention should be paid to childhood factors correlated with violence. The clinician should record episodes of previous violence including provocation, character, and the patient's state of mind at the time. Risk factors for future violence should be considered and the clinician may want to use one of a variety of decision trees available such as the McArthur Decision Tree. An assessment should be made of the clinician's duty to protect and warn.

The reality is that assessments should be as thorough as possible in the circumstances but it is not always possible to do a full assessment. If possible, the use of the Overt Aggression Scale or a diary should be instituted as a baseline for outcome measurement. The clinician should always be alert for an underlying psychiatric disorder that may dictate treatment or lay the foundation for an algorithmic analysis.

The neurochemistry of aggression is likely due to a complicated imbalance of a number of neurotransmitters.² The exact mechanism may vary from case to case and is currently not well understood. Serotonergic, noradrennergic, dopamanergic, and gabaergic circuits have all been identified as playing a role with vasopressin, nitrous oxide and androgens having a role. Evidence seems to point to serotonergic transmitters having a primary role, perhaps as a final common pathway.^{1,3} The management of aggression often involves primarily the treatment of the underlying disorder. However, a careful analysis of aggressive episodes may result in specific treatment directed towards the aggressive behavior. The treatments may be psychosocial in nature and particular attention should be paid to the detection and treatment of substance abuse. However, in certain circumstances, psychopharmacological management is indicated and can be used as an adjunct to psychosocial treatment. A number of pharmacological agents have been

used in the treatment of aggression.⁴ These include antidepressants, anxiolytics, mood stabilizers, anticonvulsants, and typical and atypical antipsychotics. We hope to develop an algorithm evolved from that of McElroy⁵ to guide the clinician in treatment. It is anticipated that we will publish a series of articles in this Newsletter in the future analyzing the evidence available for each group of agents and discussing the use of the algorithm.

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Psychopharmacology of violence

Part II – Mood Stabilizers

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This article is the second of a series of articles based on a presentation sponsored by the Committee on Psychopharmacology and presented at the AAPL Annual Meeting in Boston in October 2001.

In the first article, we gave a brief introduction to the psychopharmacology of violence. In the ensuing articles, we will present a brief summary of a review of the literature, and finally, use this as a basis for a rational algorithm to aid the clinician.

For the purposes of these reviews, we performed a computerized review of the literature using Medline and Psylit, searching the key words medication and aggression. The search strategy primarily included randomized control trials, clinical trials, open label trials and chart reviews from 1978 until the present. We have adapted the Canmat Workgroups levels of evidence to guide our conclusions.ⁱ (see boxed table)

Lithium

Lithium, a well-established agent for bipolar affective disorder, has been demonstrated to decrease aggressive behavior in both humans and animals. Early studies by Sheard first demonstrated the efficacy of lithium.ⁱⁱ A number of studies have suggested that lithium is also useful in mentally retarded, depressed, and drug dependent individuals, the acutely agitated patient and in children and adolescents. Lithium should be considered a Level I agent for the treatment of long-term aggression in a variety of disorders.

Valproic Acid

Established as an anticonvulsant, this agent was quickly recognized and later established as a prophylactic treatment for bipolar disorder. By extension, it has been used in the management of aggression in a variety of patient populations. These include borderline personality disorder, atypical bipolar illness, traumatic brain injury, dementia and chronic schizophrenia.ⁱⁱⁱ It may also be useful in children. In practice, valproic acid is quite acceptable to patients, has a favorable side-effect profile and is therefore a most useful addition to our armamentarium. It may be particularly useful if one is reluctant to use lithium in a patient with seizure disorder who has aggressive outbursts. Although a promising agent, the evidence should only be considered at Level III at this stage. It should also be noted that it is contraindicated in those with significant hepatic dysfunction and a lot of the patients we see may have hepatic damage from substance abuse and attendant illnesses, so the clinician should be aware of this factor.

Carbamazepine

This is a medication that has been found to be particularly effective in the treatment of partial complex seizures arising in the temporal lobes. Although the debate about the relationship between epilepsy and aggression continues, most would agree that many aggressive individuals have suffered from limbic system dysfunction. Research and

clinical experience have demonstrated that carbamazepine may be useful in decreasing aggression in a number of patient groups. These include borderline personality disorder, atypical psychosis with episodic hostility, schizophrenic patients with temporal lobe abnormalities, and also dementia.^{iv}

Level I evidence exists for the use of carbamazepine although further trials would still be helpful in clarifying whether it should only be used in those with abnormal EEGs and whether it is less useful in those with normal EEGs.

Conclusions

The literature on the use of mood stabilizers and two anticonvulsants, which have also been used as mood stabilizers, in the treatment of chronic aggression has been briefly summarized. Varying evidence and clinical experience suggests that these agents are effective for patients who exhibit aggression in a wide range of syndromes. They are most helpful when the aggression is in the context of bipolar affective disorder.

It is concluded that the anticonvulsants are primarily indicated when there is evidence of organicity, especially if supported by EEG evidence. Future research on these agents and the newer anticonvulsants hold great promise in the management of long-term aggression.

In further articles in this series, we will review other agents commonly used in the management of aggression. In the final article, we will present an evidence-based algorithm for the management of long-term violence to help guide the clinician.

References

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CRITERIA FOR LEVELS OF EVIDENCE

<u>Level</u>	<u>Criteria</u>
1	Metaanalysis or replicated randomized controlled trial (RCT) that includes a placebo condition
2	At least 1 RCT with placebo or active comparison condition
3	Uncontrolled trial with 10 or more subjects
4	Anecdotal case reports

Modified from Segal et al (2000)

Psychopharmacology of violence Part III

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This article is the third in a series of articles based on a presentation sponsored by the Committee on Psychopharmacology and presented at the AAPL Annual Meeting in Boston in October 2001.

In the first two articles, we outlined an introduction to the psychopharmacology of long-term violence and the methods used in this review. We also reviewed the literature on the use of the mood stabilizers and anticonvulsants concluding that varying confirmatory levels of evidence exist for the use of these medications. This is especially true where the violence occurs in the context of bipolar mood disorder and organicity, particularly if supported by EEG evidence (in the case of anticonvulsants). In this article we will look at the use of the benzodiazepines, beta-blockers, and antipsychotics.

Benzodiazepines

The majority of patients whom we see on a daily basis in the jails and prison requesting treatment for aggressive behavior have been prescribed benzodiazepines by their general practitioners. However, none of the standard textbooks on psychiatry or pharmaceutical publications recommend the use of these agents in long-term aggression. It should also be noted that these same references note that benzodiazepine use should be avoided in patients with a history of alcohol or substance abuse, thereby excluding many of the patients to whom we consult. It is hypothesized that the reason for this paradox is analogous to Dr. Tom Gutheil's "Catch 22" or "psychiatric Calvinism" in the treatment of borderline patients.^v Dr. Gutheil notes that patients like what is bad for them but do not like what is good for them. This paradox can be explained based on experimental paradigms. Early studies by Lion^{vi} found that oxazepam was useful in decreasing hostility as measured by the Buss-Durkee Hostility Scale, a self-reporting scale. Later experiments by Bond & Lader^{vii} on healthy volunteers give us some insight into this phenomenon. In this experiment, which has been replicated a number of times by the same and different researchers, healthy volunteers demonstrate increased aggression as demonstrated by the volume of noise they intend to administer to an opponent in a laboratory. This and other studies show that subjectively benzodiazepine and alcohol groups rate themselves as less hostile, yet objectively are more hostile to others. Benzodiazepines may be useful in the treatment of acute agitation, especially in conjunction with neuroleptics and in some studies possibly chronic aggressive behavior^{viii}, and possibly as an adjunct to antipsychotics in those with chronic psychosis.

A number of papers demonstrate that other benzodiazepines may increase aggression for a proportion of patients treated solely for anxiety^{ix} and other authors have postulated that a certain amount of patients may exhibit a paradoxical dyscontrol syndrome when treated with benzodiazepines. Many authors agree that benzodiazepines should actually be avoided and may be contraindicated in those with chronic impulsive, explosive disorders.

In conclusion, benzodiazepines should not be considered as a first or second line treatment in the management of long-term aggression. They should be used with particular caution and may even be contraindicated in those with a previous history of dyscontrol, those with a previous history of substance abuse, those in prison settings^x and in the elderly.^{xi}

Beta-Blockers

A number of excellent trials across a spectrum of diagnoses have proven that beta-blockers are effective in the treatment of long-term aggression. An early double-blind placebo-controlled trial by Greendyke and colleagues demonstrated their use in brain damaged, aggressive patients.^{xii}

Further trials have proven their use in mixed psychotic disorders, acutely aggressive schizophrenics, paranoid schizophrenics, the developmentally delayed and young adults. The evidence reaches the Level I threshold. They may also be useful in patients with rage outbursts in the context of ADHD and intermittent explosive disorder.

The practical use of these medications can be somewhat limited by the fact that they are contraindicated in the presence of certain cardiovascular disorders, asthma or diabetes. The experimental trials have used very high doses of these agents over a long period of time. Our experience suggests that much lower doses can be used and this avoids some of the cardiovascular side effects. Oft neglected, these agents should be strongly considered as proven agents for the treatment of long-term aggression.

Antipsychotics

Psychiatrists are called upon on a daily basis to treat aggression in the context of schizophrenia, paranoid disorders, manic disorders, and organic states. The use of antipsychotic medications is well established for the treatment of these disorders. In acute states, antipsychotics can be augmented by benzodiazepines.

The atypical antipsychotics may have specific anti-aggressive effects related to their affinity for 5HT⁶ and 5HT⁷ receptors. At least twelve trials have demonstrated the efficacy of clozapine in aggressive patients. It has also been demonstrated to have anti-aggressive effects in patients with borderline personality disorders and severely learning disabled inpatients. Similarly, risperidone may have a specific anti-aggressive effect as demonstrated by an elegant trial by Csobor and colleagues.^{xiii} Risperidone has also been demonstrated to be effective in adults with autistic disorder, elderly patients with dementia, and children and adolescents with aggression in the context of various disorders. We await further trial of these agents in aggression in the context of non-psychotic disorders, although clinical evidence seems to suggest that they may have a role to play.

Conclusions

Benzodiazepines, although frequently prescribed, are not considered effective in the treatment of long-term aggression. Beta-blockers are proven to be effective in the treatment of aggression over a range of disorders. The atypical antipsychotics may have specific anti-aggressive effects. In further articles, we will review the literature on the antidepressants and finally present an algorithm to guide the clinician.

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Psychopharmacology of violence Part IV

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This article is the fourth in a series of five articles based on a presentation sponsored by the Committee on Psychopharmacology and presented at the AAPL Annual Meeting in Boston in October 2001.

In the first three articles, we have given an introduction to the psychobiology and assessment of aggression. We have also presented our methods for reviewing the published literature on aggression. Article II reviews the literature on the mood stabilizing agents including the anticonvulsants. Article III reviews the use of benzodiazepines, beta-blockers and antipsychotics. In this article we will review the literature on the use of SRI's, trazadone, and buspirone. We have used similar methodology as described in paper two.

As noted in our first article, a substantial literature emerges suggesting that low central serotonin function may be strongly associated with impulsive, aggressive behavior. Based on this hypothesis, Coccaro¹ administered fluoxetine to three patients with personality disorders. Based on the limited success of this experiment, a number of other researchers used the SRI's on depressed patients with anger attacks² and borderline personality disorders.³ Other studies have looked at the effectiveness of SRI's on aggressive and self-injurious behavior amongst adults with mentally retardation, autistic disorders, PDD and Asperger's Disorder.

There have been reports of some paradoxical increase in aggression in some people,⁴ although this would be only a very small proportion. Overall, the evidence suggests that these agents are well tolerated with few and temporary side effects. They also have the added benefit of having anti-anxiety and antidepressant properties - probably independent of their anti-aggressive effect. They should be considered both rational and empirical pharmacological agents for treatment of aggressive behavior.⁵

Buspirone

Buspirone is an anxiolytic agent having 5HT 1a receptor serotonergic effects. Level 3 evidence exists, including open trials and anecdotal experiences, of the use of this agent in the treatment of long-term aggression. It has been used in both adults and children with diagnoses of developmental delay, closed head injury, autism, dementia, and Huntington's.

Despite the limited evidence, it is a useful agent in the treatment of long-term aggression. Since it also has anxiolytic and some antidepressant effects, it is helpful in addressing comorbidity. It does not cause dependence and is generally not considered a drug of abuse and can, therefore, be used in those patients with substance abuse.

Trazodone

Trazadone was one of the first antidepressants to depart from the tricyclic structure. It appears to be a potent antagonist of the 5HT 2a and 5HT 2c receptor sites as well as a weak SRI. Small open trials suggest that it may be effective in the treatment of aggression in elderly patients with organic disorders and hospitalized children with

severe behavioral disturbances. However, the evidence is only at a Level 3 to 4 stage at this time. The clinical research tends to support everyday experience that trazodone is a useful agent in the long-term treatment of aggressive behavior. It does not cause dependence and the side-effects, such as dry mouth and orthostatic hypotension, are generally well-tolerated. What makes it particularly useful is that it is a powerful hypnotic as well as having anxiolytic and antidepressive effects (sleep disorders being common in these populations who often have a variety of comorbid disorders). Our own anecdotal evidence is supported by many clinicians who find it most helpful but it should be noted that its use is not, as yet, well supported by good research evidence.

Conclusions

In conclusion, the SRIs are both effective and rational agents in the treatment of aggression supported by Level 1 evidence. Buspirone is only supported by Level 3 evidence but is a useful addition to our armamentarium. Trazodone is heavily favored clinically by these authors but is only supported by Level 4 published evidence in the treatment of aggression.

In the final paper in this series, we will present an evidence-based algorithm as a guide to clinicians in the treatment of aggressive disorders.

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Psychopharmacology of violence Conclusions and use of an algorithm

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This article is the fifth in a series of five articles first presented at the AAPL Annual Meeting in Boston in October 2001.

In the first articles we presented an introduction to the assessment and neurobiology of those presenting with chronic aggression or violence. In subsequent articles, we have summarized a review of the literature of the major pharmacological agents that have been evaluated for the treatment of chronic aggression. We have not addressed the treatment of acute aggression noting that it has been covered extensively elsewhere, nor have we specifically focused on the treatment of aggression in children and adolescents, although we have touched upon this at times.

In this final article, we would like to introduce an algorithm to our readers that we hope will be useful in aiding the clinician. It is our aim that the algorithm is as far as possible evidence-based, rational and also user friendly. We note that the assessment of the aggressive patient should be as thorough as possible with the aim of reaching a diagnosis, directing the clinician to the available treatments for the underlying disorder. If possible, pharmacological treatment should be considered adjunctive to psychosocial interventions particularly using a cognitive-behavioral approach. We also advise that the clinician addresses substance abuse issues. As a general principle, we advocate continuing education of the patient including giving them information regarding the rationale for treatment. It is essential to attempt to build up adequate doses of medication for adequate time.

The algorithm is an evolution of the instrument originally designed by McElroy.¹ As can be noted from the algorithm, the first task is to search for the presence of partial complex seizures or an abnormal EEG. If there is a positive finding, then the use of carbamazepine or valproate should be considered a first line treatment.

If the assessment suggests a dementia, then the first line of management could also be a mood stabilizer with second line treatments such as beta-blockers, trazodone, buspirone or typical antipsychotics tried sequentially. If there is a psychotic disorder, the use of antipsychotics perhaps specifically the atypical antipsychotics should be considered with second line treatment of adjunctive mood stabilizers, beta-blockers or buspirone.

If there is thought to be an affective disorder present, then a crucial distinction should be made between a purely depressive disorder and a bipolar disorder. If there is a purely depressive disorder, then SRIs, possibly with adjunctive use of buspirone, and perhaps beta-blockers, should be considered. In the bipolar or manic group, mood stabilizers represent the first line of treatment but the adjunctive use of atypical antipsychotics is an effective management strategy.

In the absence of a major mental disorder, we are left with a mixed group including personality disorders, intermittent explosive disorders, and adult ADHD. In this group, psychosocial interventions are most important but adjunctive

psychopharmacological treatment would rationally start with the use of SRIs and the second line treatments as noted above.

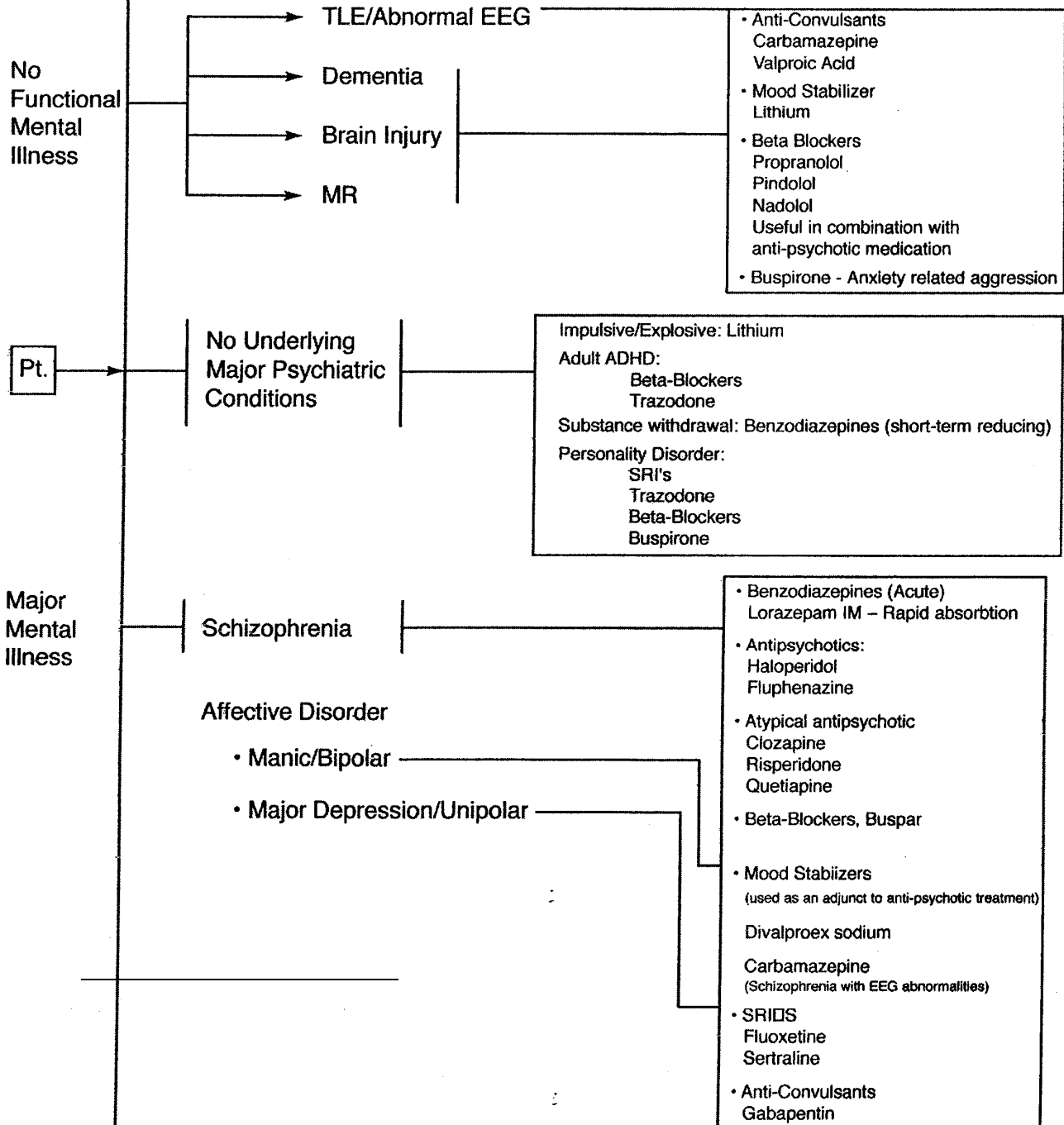
Inevitably, since aggression is a multi-factorial phenomenon, even in the presence of an underlying mental disorder, an algorithm such as this is less than perfect. It is also harder to come to an evidence-based algorithm such as could be used in depression, for example, due to the complexity of aggression. There is, therefore, considerable overlap between categories. It is also worthy of note that it is our experience that benzodiazepine addicts want benzodiazepines and do not like anything else as noted in our previous articles. People with benzodiazepine addiction and substance abuse have to get over withdrawal in order to benefit from the above-noted treatments. It is, therefore, important to support your patient through this and stick to your evidence-based principles in applying the algorithm.

see Figure 1 (adapted from McElroy 1999) next page

Reference

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Rx of Violence algorithm



Adapted from S. McElroy (1999). Recognition and treatment of DSM-IV intermittent explosive disorder. J Clin Psychiatry 1999; 60: S12