

Medications for Aggressiveness in Prison: Focus on Oxcarbazepine

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The literature regarding the use of medication for impulsive aggression, both in a prison setting and outside of prison, is briefly reviewed. The rationale for using oxcarbazepine for impulsive aggression in prison is presented, focusing on the evidence (though limited) of efficacy, the lack of frequent significant side effects, and the cost/benefit ratio, compared with other options.

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People who are excessively aggressive and impulsive may be more likely than others to be in prison. Some of these inmates respond to the traditional behavioral approaches of correctional institutions, learning sufficient self-control to manage satisfactorily in a prison environment, and some have psychiatric diagnoses, such as bipolar disorder or schizophrenia, that typically respond to standard treatments.

Others, however, can be difficult to treat and may be aggressive even in prison. There is no one Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)¹ diagnosis that applies to most of these patients. Some may have residual attention deficit/hyperactivity disorder (ADHD),² and some may have psychiatric diagnoses such as borderline or antisocial personality disorders, intermittent explosive disorder, or impulse control disorder NOS,³ which do not have standard approved medication treatments. How best to treat such inmates is a matter of opinion, with little solid research available. There is no medication approved by the U.S. Food and Drug Administration for the treatment of impulsive aggression.

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The literature⁴ categorizes aggression in various ways, but the most common distinction is between impulsive aggression and predatory aggression. Predatory aggression is seen in hunting (among animals) and may be related to the aggressive acts perpetrated by organized crime groups. The treatments that have been studied for aggression have primarily involved patients with impulsive aggression. In certain settings (e.g., gang warfare), impulsive aggression may be ego syntonic to the perpetrator, and he may not see it as a problem requiring medication. However, with increasing age and mounting difficulties attributable to aggressive behavior (in a prison setting), many individuals for whom impulsive aggression may have been ego syntonic in the past may want to reduce their aggressiveness.

Review

The literature on medications for treatment of aggression is sparse. In the 1970s, there were several studies^{5–7} in which lithium was evaluated in aggressive prison inmates, with generally positive results. Barratt *et al.*,⁴ in a double-blind study involving inmates in Texas prisons, found phenytoin to help more than placebo in patients with impulsive aggression, and Kamath *et al.*,⁸ surveying divalproex use in the Connecticut prison system, found that it was used in nonbipolar inmates to treat impulsivity and mood lability and that it seemed to be most helpful in inmates with impulsive aggression. Partly because of the legal and ethics-based view that a prisoner, inherently (due to his incarceration) may not be able to give truly free informed consent, it has been extremely difficult in most states to conduct studies

among prison inmates. Therefore, our knowledge base is limited regarding which, if any, medication is most helpful for aggressive and impulsive prisoners. Also, in prisons, psychiatrists may have more restrictions than they do in other settings in regard to prescribing off-label medication.

Even outside of prison settings, there have been relatively few studies of medications to treat aggressiveness. The literature is anything but clear, as indicated by the disparate conclusions of several recent reviews. For example, Stanford *et al.*, in a review of the pharmacologic treatment of impulsive aggression with antiepileptic drugs, stated that “strong evidence for efficacy in impulsive aggression exists from randomized control trials for most of the common AEDs (antiepileptic drugs) (phenytoin, carbamazepine, oxcarbazepine, lamotrigine, valproate/divalproex sodium, topiramate)” (Ref. 9, p 383). Clinically, they recommend phenytoin as the AED of first choice, with carbamazepine or valproate/divalproex sodium as secondary options. On the other hand, Goedhard *et al.*, in a systematic review, concluded that only “weak evidence for antiaggressive affects [sic] of antipsychotics, antidepressants, anticonvulsants, and beta blocker drugs was found” (Ref. 10, p 1013). (There were not many studies between 2006 and 2009.) Volavka *et al.* similarly concluded that “anticonvulsants and lithium are widely used with the intent to control aggression but their efficacy lacks strong evidential support” (Ref. 11, p 123). They indicated that there is also evidence that atypical neuroleptics, SSRIs (selective serotonin reuptake inhibitors), antiandrogen agents, and β -adrenergic blockers may be effective. In the most thorough review at that time, Fava,⁷ in addition to summarizing data indicating that lithium may be effective for the treatment of aggression among nonepileptic prison inmates, suggested that anticonvulsants should be the treatment of choice for patients with rage outbursts and abnormal EEG findings, but the evidence that valproate and carbamazepine are effective for treating aggressiveness without a seizure disorder is equivocal. Fava also indicated that phenytoin has been found to be effective for the treatment of aggressiveness only in a prison population. Pabis and Stanislav concluded that lithium or propranolol should be considered as first-line “antiaggressive agents in patients without comorbid psychiatric disorders” (Ref. 12, p 278).

The Volavka *et al.*¹¹ review illustrates a common problem in evaluating what has been called evidence-based medicine. Patented drugs, such as the atypical neuroleptics, have been more extensively studied (funded by drug companies) than have drugs without patent protection. Thus, the evidence base is inherently biased toward patented drugs. It is unlikely that drug companies will fund studies of generic medications for the treatment of aggressiveness (e.g., a study comparing lithium and oxcarbazepine). The National Institute of Mental Health (NIMH) or other nonprofit organizations might fund such studies, but to conduct large studies to compare many of these agents in different populations would probably be prohibitively expensive. Thus, one must rely on factors other than hard evidence on which to base the choice of medication for aggressiveness.

Choosing Among Medication Options

Several concerns require discussion when trying to synthesize the available studies. A study of a particular medication in a particular population was sometimes prompted by factors extraneous to the general question of which medication works best for which patients. For example, in the early 1970s, two groups^{5,6} studied lithium in prison populations. At that time, lithium was the only medication approved and widely used for bipolar disorder (none of the anticonvulsants had yet been found to be helpful for bipolar disorder), and so it was a reasonable medication to try for aggressiveness. That lithium was found to be helpful in reducing aggressiveness in a prison population does not necessarily suggest that it is more helpful than anticonvulsants or other medications, either in a prison population or in aggressive patients in general. Also, most of the studies evaluating the use of propranolol and other β -blockers for aggressiveness were conducted at one of several sites¹³ that happened to treat primarily patients with organic brain damage. While the rationale at the time, that aggressiveness was related to excessive adrenergic activity, was quite reasonable, it would be just as reasonable, currently, to try other medications in aggressive patients with organic brain syndromes. That propranolol has primarily been evaluated in aggressive patients with organic brain damage (similar to the situation in prisoners taking lithium) is therefore more serendipitous than based on a clear rationale that this medication would be particularly helpful in this population. Ideally, large studies would

systematically compare potentially useful medications in different populations. As it is, trying to formulate recommendations is like trying to complete a jigsaw puzzle with most of the pieces missing.

If patients have evidence of other psychopathology, then a drug that may treat their aggressiveness in addition to their other psychopathology should probably be the first choice. For example, a patient with psychotic features and aggressiveness, especially if the aggressiveness seems to be due to the psychotic symptoms, should be treated first with a neuroleptic. Similarly, since there is evidence that SSRIs can sometimes reduce aggressiveness, a patient who has depressive features and aggressiveness (which, again, may or may not be related to the depressive symptoms) should probably be treated with an SSRI initially. A patient with bipolar features and aggressiveness should be treated initially with a medication for bipolar symptoms that may reduce aggressiveness, such as lithium or one of the anticonvulsants used for bipolar disorder.

ADHD involves other considerations. Patients with ADHD may be aggressive and impulsive, but the use of stimulants in prison is problematic, given the diversion and sale of medications in prison and the tendency of prisoners to feign symptoms to get their medication of choice. It is unclear whether atomoxetine, which improves concentration in ADHD patients, alleviates aggressiveness. (A study is under way in Norway; ClinicalTrials.gov Identifier NCT00356070.) It is also unclear how best to diagnose aggressive patients who had ADHD as children, but who, as adults, have neither clinically significant attentional difficulties nor most of the other types of impulsivity described in the DSM-IV criteria for ADHD. Since impulsive aggression is generally a more significant problem in prison than is difficulty in concentrating, it is reasonable to focus treatment on the aggressiveness rather than on other features of ADHD. For these patients and for the sizeable number of patients who do not have Axis I disorders and whose aggressiveness is clinically significant in prison, the choice of which medication to use is unclear.

Some of the drugs used earliest for aggression, such as lithium and propranolol, are used less often now because of their potential side effects and the difficulties involved in administering them. Some of the anticonvulsants are easier to administer and have fewer side effects.

Prisons are among the most litigious of environments.¹⁴ By law, inmates have access to legal help and information, and they have the time and motivation to sue. This possibility supports recommending medications less likely to cause side effects. Thus, propranolol would not be a first-choice drug, given its cardiovascular effects and the complexity of administering it, by gradually increasing to high doses, as described by Yudofsky *et al.*¹³ SSRI antidepressants would pose risks if impulsive aggression, as some believe,¹⁵ is related to bipolar disorder (with the risk of inducing mania or rapid cycling). Antipsychotics, including atypicals, have several well-known significant side effects, and lithium has significant side effects and is somewhat difficult to administer. Some anticonvulsants (e.g., lamotrigine) also have potentially serious side effects. Thus, of the various options for which there is some evidence of efficacy, the anticonvulsants with relatively few side effects may be the most reasonable first-choice options.

To summarize, it is unclear which medication for impulsive aggression is most efficacious. This question is even more problematic in a prison setting, with even less basis for recommendations. Given the nonprison literature and the sparse prison literature, it seems that lithium or anticonvulsants may be the most generally useful medications for impulsive aggression in inmates who have no other diagnosis with a standard treatment. In considering side effects, the anticonvulsant with the fewest may be the most reasonable first choice.

The Rationale for Oxcarbazepine

In psychiatry, theories often follow evidence of efficacy, rather than predicting it. However, there are reasons to think that medications that alleviate complex partial (or temporal lobe) epilepsy are more likely than other anticonvulsants to reduce aggressiveness, since complex partial seizures involve the limbic system, which also modulates aggressiveness. Siegel *et al.* recently reviewed the neurobiological basis for aggressiveness in animals and humans and stated, "Anti-epileptic drugs are frequently directed against seizures whose primary foci are situated within limbic system structures comprising principal components of the temporal lobe that also powerfully modulate aggressive behavior" (Ref. 16, p 15).

In the 1980s, carbamazepine became the anticonvulsant of choice for epilepsy associated with irrita-

bility and for temporal lobe epilepsy (see references in Mattes¹⁷). Because of the relationship between aggression and the temporal lobe and related limbic structures, carbamazepine also began to be studied for impulsive aggression in nonepileptics, but the few placebo-controlled trials evaluating carbamazepine for aggressiveness have been small and in diverse patient groups. (For example, DeVogelaer¹⁸ studied 20 diagnostically diverse agitated and aggressive patients already on neuroleptics.) Young and Hillbrand,¹⁹ in a review, concluded that carbamazepine reduces aggressiveness. Not all anticonvulsants reduce aggressiveness; for example, divalproex sodium may be effective,^{9,20} but levetiracetam does not appear to be helpful.²¹ A double-blind, placebo-controlled study of 48 outpatients with impulsive aggression²² showed significant benefit from oxcarbazepine.

Oxcarbazepine is a more recently marketed anticonvulsant that is structurally similar to carbamazepine. Like carbamazepine, it appears to be particularly helpful for temporal lobe (or complex partial) seizures, and it may also have mood-stabilizing effects.²³ Although carbamazepine has been studied more than oxcarbazepine for aggressiveness, the epilepsy literature generally suggests that the two are more or less equivalent in effectiveness when used for complex partial seizures (though there are differences between the two²⁴). Legros *et al.*²⁵ reported that among Belgian neurologists, carbamazepine and oxcarbazepine were the first choice for focal epilepsy with partial seizures. Tecoma,²⁶ in a review of oxcarbazepine, concluded that its efficacy for seizures compares favorably with carbamazepine in clinical trials and that oxcarbazepine has fewer side effects, including less potential for hepatotoxicity. Similarly, Schmidt and Elger observed that oxcarbazepine is often better tolerated than carbamazepine and stated that “oxcarbazepine should be preferred over carbamazepine and older AEDs because of its proven efficacy and excellent side effect profile in children, adolescents and adults with partial seizures” (Ref. 24, p 627). Reinikainen *et al.*²⁷ also found the antiepileptic efficacy of oxcarbazepine to be comparable with that of carbamazepine, but with fewer side effects. Horga de la Parte and Horga²⁸ determined that oxcarbazepine has much reduced risk of blood dyscrasias and a lower risk of cardiotoxicity and neurotoxicity, compared with carbamazepine, in part because of the absence of a 10-11-epoxy metabolite from oxcarbazepine. They indicated that oxcarbazepine is the treat-

ment of choice for partial seizures and is recommended by several international guidelines.

To the extent that anticonvulsants reduce impulsive aggression, it is unclear whether any reduction in aggression is related to mood stabilization or to anticonvulsant activity, or whether different subgroups of patients will be identified who differentially respond to different medications. Of note, Siegel *et al.*¹⁶ discussed several neurotransmitters that seem to play a role in aggressive behavior, including serotonin and GABA. Oxcarbazepine and carbamazepine may act through GABA receptors.²⁹

The Need for Clinical Correlation

Despite the rationale for evaluating oxcarbazepine in impulsively aggressive prisoners, there is little documentation of efficacy. As mentioned earlier, controlled research protocols are difficult to implement in prisons, and even case reports of inmates are difficult to publish for ethics-related and bureaucratic reasons. Generic oxcarbazepine is not on the formulary at the New Jersey Department of Corrections. (It was initially excluded because of cost considerations; now, it may be mainly because of inertia; there is no rationale, to my knowledge, for having carbamazepine on the formulary but not oxcarbazepine.) Therefore, my personal experience in using oxcarbazepine to treat aggressive inmates is limited, despite my having worked one day per week at a New Jersey State Prison for the past three years. Anecdotally, there have been several inmates whose aggressiveness has apparently decreased as a result of treatment with oxcarbazepine. Clearly there is a need for oxcarbazepine to be tried in a large number of aggressive inmates, both clinically and in controlled research studies.

Discussion

Given the available evidence, one cannot convincingly conclude that carbamazepine or oxcarbazepine is more efficacious than phenytoin or other options for treating impulsive aggression. The advantages of carbamazepine and oxcarbazepine are primarily theoretical (especially compared with phenytoin) and include their supposed greater effect on temporal lobe and limbic activity. One can make a case, however, for concluding that oxcarbazepine is one of the easiest medications to use for aggressiveness, with less associated risks than most other options (e.g., lithium, beta blockers, atypical neuroleptics, and carbamazepine). Other anticonvulsants (e.g., gabapentin)

may have even fewer side effects, but have less evidence of efficacy. If one weighs all factors (i.e., side effects, ease of administration, and efficacy), assuming that the evidence of efficacy for carbamazepine is also relevant to oxcarbazepine, and theoretical considerations, the case for considering oxcarbazepine as a first option for treating aggressiveness and excitability in prison is strong, but not compelling.

Oxcarbazepine requires only twice-daily doses, compared with three times daily for standard carbamazepine. It is available in 150-, 300-, and 600-mg sizes and can be gradually increased to 1200 mg twice daily. No regular laboratory tests are required, although it can lower serum sodium, and checking sodium at the effective dose (or at 1200 mg/day) is prudent. It, like carbamazepine, can induce its own metabolism, and so a dosage increase may be needed after initial stabilization. Drug interactions can occur (e.g., with birth control pills and other drugs metabolized by liver enzymes 2C19 or 3A4/5). By inducing enzymes, oxcarbazepine can reduce the blood levels and effectiveness of birth control pills. Oxcarbazepine is off patent, with the generic produced by three companies in the United States, and is therefore not particularly expensive.

It seems that oxcarbazepine should be more widely considered for impulsively aggressive prison inmates (and for impulsively aggressive patients not in prison). In states that allow it, placebo-controlled studies would be helpful and important in evaluating efficacy. Such studies should consider using the modified criteria for intermittent explosive disorder, developed by Coccaro *et al.*³¹ and the revised Overt Aggression Scale-Modified (Mattes).³²

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