Part II: The Psychopharmacology of Long-Term Aggression—Toward an Evidence-Based Algorithm

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Abstract: The following is the second of three articles on the psychopharmacology of chronic aggression. A review of the literature demonstrates that evidence exists for the use of these agents in various syndromes presenting with aggressive behaviour. In this article, using similar methodology, we review the use of antidepressants and anxiolytics, including serotonin reuptake inhibitors (SRIs), trazodone, buspirone and the benzodiazepines.

In the third article, we hope to summarize the content of all three articles and present an algorithm that is a rationalized, evidence-based treatment guide, which we hope will help the practising clinician.

Résumé : La psychopharmacologie du comportement agressif de longue durée vers un algorithme fondé sur des données probantes
Il s’agit du deuxième d’une série de trois articles sur la psychopharmacologie du comportement agressif chronique. Une analyse de la documentation révèle des preuves de l’utilisation de ces agents dans divers syndromes qui accompagnent le comportement agressif. Dans cet article, à l’aide d’une méthodologie semblable, nous examinons l’utilisation des antidépresseurs et des anxiolytiques, y compris les inhibiteurs spécifiques du recaptage de la sérotonine (ISRS), la trazodone, la buspirone et les benzodiazépines.

Dans le troisième article, nous espérons résumer le contenu des trois articles et présenter un algorithme qui soit un guide de traitement raisonné et fondé sur des données probantes et qui, nous l’espérons, sera utile au clinicien actif.

Key Words: aggression, selective serotonin reuptake inhibitors (SSRIs), trazodone, buspirone, benzodiazepines

Method

The first article (1) introduces the subject and reviews the use of lithium and of anticonvulsants. We conducted a computerized search through Medline (PubMed) and PsychINFO (PsychLit), using the following key words: “drug name” and “aggression or violence.” References that revealed clinical trials, randomized controlled trials and reviews were selected. In certain cases noted in the text, letters to the editor were included. We have attempted to critically review these studies and to arrive at an algorithm based on the evidence, as well as on our practical experience. We will present the algorithm to you as part of our conclusions in the third article.

Selective Serotonin Reuptake Inhibitors

Two reviews of the neurobiology of aggression suggest that evidence continues to accumulate indicating that the neurotransmitter serotonin holds the key to a neurobiological model (2,3). To test the hypothesis that indices of central serotonin function inversely covary with indices of impulsive aggressive behaviour, Coccaro, Astill, Hebert and Schur administered fluoxetine to three patients with personality disorders (4). They noted that, by the first week, aggression had decreased in all three patients, and this was most marked by the fourth week. Two patients had significant adverse life events in the last two weeks and showed an increase in aggression. Fava and others tested fluoxetine in a single 20-mg daily dosage on a subset of depression patients who exhibited anger attacks (5). In 71 per cent of the 85 completers, anger attacks disappeared. They noted that, given the symptomatology, many of these patients might have had borderline personality disorder (BPD). Using an endocrine challenge, they tested a subset of these patients with anger attacks to attempt to differentiate them from 13 patients without anger attacks. The authors found that, indeed, a significant blunting of prolactin response existed in the patients with anger attacks, suggesting attenuated serotonergic activity responsive to fluoxetine.

These articles result from a presentation given at the winter meeting of the Canadian Academy of Psychiatry and the Law; March 2002.

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In a study of 13 patients with BPD, which was designed to measure response to fluoxetine, Salzman and others noted significant improvement in several indices, including global mood, global functioning and depression (6). Using objective and subjective measures, however, they found that the most striking finding was a decrease in anger, independent of any change in depression. This was a placebo-controlled, double-blind trial.

Davanzo and colleagues studied the effectiveness of paroxetine on aggressive and self-injurious behaviour among adults with mental retardation (MR) (7). Results of this open trial indicate that paroxetine was effective in reducing aggression severity and severity of self-injury assessed at month one of the trial but did not remain statistically significant thereafter.

Hellings and associates conducted an open trial that assessed the efficacy of sertraline in controlling aggression and self-injury among nine adult outpatients with mental retardation and autistic disorders (8). The authors cite an overall improvement in Clinical Global Impression (CGI) scores in eight cases and worsening of agitation and self-picking in a single patient. The authors suggest that the improvement in CGI ratings of illness severity in eight of nine subjects contributes to existing data pointing to the effectiveness of serotonergic agents in treating aggression and self-injurious behaviour in patients with MR and autistic disorder.

Results from an open trial of 42 adults with pervasive developmental disorder (PDD), including autistic disorder, Asperger’s syndrome and PDD not otherwise specified (NOS) indicate that sertraline was positively associated with an improvement in behaviour ratings. McDougle and associates report that 57 per cent of individuals included in the 12-week trial showed significant improvement in repetitive and aggressive symptomatology (9). Reportedly, according to CGI scale results, 68 per cent of individuals with autism and 64 per cent of those with PDD NOS were classified as treatment responders, while no individual with a diagnosis of Asperger’s syndrome was classified as a treatment responder. In an earlier double-blind, placebo-controlled trial, McDougle and colleagues reported on the antiaggressive properties of fluvoxamine in treating adults with autistic disorder (10). Results indicate that, of the 15 subjects treated with fluvoxamine, eight were identified as responders. Conversely, none of the 15 subjects in the placebo group were classified as responders. Results found fluvoxamine superior to placebo in reducing aggression and maladaptive behaviour. With respect to treating aggression and irritability after closed head injury, Kant and colleagues found that sertraline was positively associated with a reduction in aggressive symptomatology and irritability (11).

In a study on aggressive behaviour in psychiatrically hospitalized adolescents, Constantino, Liberman and Kincaid found no significant differences during treatment with serotonin reuptake inhibitors (SRIs) (12). Troisi and colleagues report that fluoxetine was associated with significant changes in Overt Aggression Scale Modified (OAS-M) ratings of total aggression, verbal aggression and self-aggression among a sample of inpatient adults with MR and epilepsy (13). Overall, 9 of the 19 patients included in the fluoxetine trial showed an increase in aggressive behaviour during fluoxetine administration. Withdrawal from fluoxetine treatment led to a decrease in aggressive behaviour to below pretreatment levels. The authors speculate that this effect may be the result of a drug interaction or a fluoxetine overmedication, or it may point to the serotonergic effect of fluoxetine in modulating aggressive behaviour among adult inpatients with MR and epilepsy.

Prompted by isolated reports that a small proportion of people may display paradoxical aggression when treated with SRIs (14), Heiligenstein, Beasley and Potvin did a comprehensive metaanalysis that attempted to discover a possible association between fluoxetine and aggression (15). They found that the data suggested fluoxetine had a strong antiaggressive effect. Subsequent studies—such as Coccaro and Kavoussi (16), Kavoussi and Coccaro (17) and Vartianen and others (18)—confirmed the efficacy of the SRIs in aggression treatment. These studies suggest that these agents are well tolerated, with the main side effects generally being nausea, diarrhea and insomnia, which generally wear off after the first two or three days of administration. They also have the added benefit of antidepressant and antianxiety properties, which may or may not be independent of their antiaggressive effect. As Eichelman postulates, both animal studies and laboratory research on human subjects point to the inverse relation between central serotonin activity and aggression, thus leading us to conclude that the SRIs may be both the rational and the empirical pharmacologic agents for treatment of aggressive behaviour (19).

Buspirone

Buspirone has serotonergic effects, acting at the 5HT1a receptor. It has been established in treating generalized anxiety disorders and as an augmenter in patients with major depression. In a retrospective chart review on 20 patients, buspirone showed significant antiaggressive effects on organically induced aggression (20). In a study of 48 parolees, Cherek and others demonstrated that the
reports are single-case reports and open trials with minising evidence of buspirone’s efficacy, the above-noted those with Huntington’s disease (30) are among the numerous individuals with autism (27,28), those with dementia (29) and buspirone’s efficacy with developmentally delayed individuals (23–25), those with closed head injury (26), individuals with autism (27,28), those with dementia (29) and those with Huntington’s disease (30) are among the numerous studies. While these findings contribute to existing evidence of buspirone’s efficacy, the above-noted reports are single-case reports and open trials with minimal study subjects.

Trazodone
Trazodone is a triazolopyridine derivative which, at its introduction, had a unique chemical structure—one of the first antidepressants to depart from the tricyclic structure. Its mode of action would appear to be as a potent antagonist at the 5HT2A and 5HT2C receptor sites. It is also a weak SRI. In addition, it possesses alpha-adrenergic antagonist activity, which is responsible for the unwanted effects of orthostatic hypotension, dry mouth and priapism.

Several studies suggest that trazodone is effective in the treatment of elderly patients with organic disorders (31–33). However, small sample sizes of four to ten patients limit the generalizability of these findings. Other studies have reported on the utility of using trazodone with L-tryptophan in aggressive individuals with MR (34–36) and in hospitalized children with severe behavioral disturbances who were previously nonresponsive to other agents (37). In a single case study of a 12-year-old boy with bilateral frontal lobe atrophy, trazodone administration was associated with improved impulsivity, hyperactivity and aggressiveness (38).

Like any medication, although the side effects are minimal, its use requires serious consideration. The possibility of priapism, which may need surgical intervention, is rare but significant. Grand mal seizures have also been reported in those with a preexisting seizure disorder. It should also be used with caution in those who have preexisting cardiac conditions. The clinical research, however, tends to support the everyday experience that trazodone is a useful agent in the long-term treatment of aggressive behavior. It is nonaddictive, has few troublesome side effects and is effective across the broad spectrum of the life cycle. What makes it particularly useful is that it possesses anxiolytic, antidepressive and hypnotic effects, as well as the noted antiaggressive effects. All these effects can be useful in the populations that we see in general forensic practice, who have various comorbid disorders.

Benzodiazepines
It is our anecdotal experience that the class of drugs that general practitioners and psychiatrists alike still most commonly use for treatment of long-term aggression are the benzodiazepines. Notably, in the standard North American textbook on psychiatry (39), aggression is not mentioned as an indication for this class of medications. Similarly, in the Compendium of Pharmaceuticals and Specialties (CPS), treatment of long-term aggression is not mentioned as an indication for benzodiazepines (40). The CPS also notes that benzodiazepine use should be avoided in patients with a history of alcohol or substance abuse, which encompasses many, if not all, the patients that we see who are repeatedly prescribed these medications over the long term. We would hypothesize that the reason for this paradox lies in what Dr. Tom Guthheil has variously called the “Catch 22” of the treatment of borderline patients, or “psychiatric Calvinism,” whereby patients like what is bad for them but do not like what is good for them (personal communication). Although Dr. Guthheil was referring to the treatment of BPDs, we would analogize this to the long-term treatment of aggression. We will also present some evidence that is based on experimental paradigms, which will help to explain this paradox.
Benzodiazepines are a group of medications that act on specific gamma-aminobutyric acid receptors, known as BZ-GABA receptors, that have been isolated in the brain. The probable mode of action is the enhanced opening of chloride channels, thereby decreasing cellular excitability, which enhances the inhibitory effect of GABA. The onset and duration of action are proportional to the lipid solubility of a particular compound. Although animal studies suggest a taming effect, this depends on the species and type of aggression; thus, the literature must be considered equivocal (41). While it has been postulated that benzodiazepines may be useful for short-term management of agitation and aggression—either combined with neuroleptics (42) or as an adjunct to the more delayed effects of lithium (43,44)—little evidence exists for their clinical utility in treating long-term aggression.

Lion treated 65 patients for a period of four weeks in a double-blind controlled trial of clorazapaxide, oxazepam and placebo (45). He found that oxazepam was more effective than was clorazapaxide in reducing anxiety, as well as in one subscale of tests used to measure hostility. It should be noted that, this was a self-rating scale (the BUSS-Durkee Hostility Scale [BDH]).

Bond and Lader produced an interesting experimental paradigm, using 45 normal, healthy volunteers (41). They administered two dosages of lorazepam and two dosages of oxazepam to the subjects. The experiment demonstrated significant increases in aggression, as demonstrated by the volume of noise the subjects intended to administer to their opponent. The high-dosage lorazepam group selected the highest noise levels. This study was replicated using alprazolam with 48 healthy volunteers (46). This study included a drug-plus-alcohol group, a placebo-plus-alcohol group and a placebo group. This study showed that, subjectively, the alprazolam and alcohol groups produced self-rating scales that suggested decreased anxiety and decreased hostility. More recently, Bond and colleagues completed an eight-week, randomized controlled trial assessing the efficacy of alprazolam in regulating aggression among patients with panic disorder and agoraphobia (47). This study comprised an alprazolam-plus-placebo group and an alprazolam-only group. Results indicate that the alprazolam and placebo group reported decreased anxiety. The alprazolam-only group reported less hostility. On the behavioural task, the alprazolam-only group was more aggressive when provoked.

Benzodiazepines may be useful as an adjunct to neuroleptics. In their double-blind study that assessed the effectiveness of flunitrazepam in controlling aggressive behaviour among inpatients with active psychosis, Dorevitch and colleagues found that flunitrazepam effectively controlled aggressive behaviour, when compared with haloperidol (48). The authors suggest that the benzodiazepine flunitrazepam is a safe, effective and fast adjunct to neuroleptic treatment in controlling aggressive behaviour. In a double-blind comparison study of haloperidol and lorazepam, Bieniek and colleagues (49) report on the superior efficacy of combined treatment using these two drugs in regulating agitation (49). Reportedly, although groups in the study did not differ, authors indicate that a significantly greater proportion of subjects receiving combined treatment improved on OAS scores within 60 minutes into treatment.

Weisman, Berman and Taylor (50), in an experimental study, and Mathew, Dursun and Reveley (51), in a chart review, demonstrated that benzodiazepine use might increase aggression, even in patients treated solely for anxiety. In a thorough review, Dietch and Jennings postulated that less than one per cent of patients treated with benzodiazepines exhibit a dyscontrol syndrome (52). They noted that clonazepam may perhaps be the worst of these agents, producing aggression. This may be owing to its high potency and quick onset of action. Paradoxically, however, this agent is reported to have some serotonin-enhancing effects.

In conclusion, benzodiazepines should not be considered as a first- or second-line treatment in managing long-term aggression. They should be used with particular caution in those with a previous history of dyscontrol and of substance abuse. Similarly, they should be used with caution with those in prison settings (53) and with the elderly (54). Benzodiazepines appear to have a role in managing acute agitation and aggression, either as an adjunct to neuroleptics or as an adjunct to lithium.

Conclusions
This article is the second in a series of three on the psychopharmacology of long-term aggression. In this article, we first review the use of the SRIs and conclude that they are effective and are rational agents in treating aggression in various clinical syndromes. There have been isolated reports that a very small proportion of people may display paradoxical aggression. Likewise, some reports state that they were of no benefit in adolescents. Level 3 evidence supports the use of buspirone, and evidence supports a neurobiological model for its antiaggressive effect. The evidence at this stage is only at Level 3. Although clinical experience confirms the efficacy of trazadone, the published evidence is only Level 4. Even so, our experience and anecdotal evidence supports its use as an
antiaggressive agent. A third paper in this series will review the use of beta blockers and antipsychotics. We will also attempt to present an evidence-based algorithm to guide clinicians toward a rational basis for prescribing in this area.

References