

# Pharmacological treatment of impulsivity and aggressive behavior

## Tratamento farmacológico da impulsividade e do comportamento agressivo

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### Abstract

*Impulsivity and aggressive behavior occur frequently in a variety of psychiatric disorders and neurological diseases. Two lines of treatment could be employed, the treatment of the disorder or disease in which these symptoms occur or the treatment of the impulsivity and aggressive behavior itself. This second approach considers that there are neurobiological similarities underlying these behaviors regardless of the "primary" diagnoses with which they are associated. Imbalance between limbic bottom-up drives, exerted by structures like the amygdala, and prefrontal top-down control mechanisms could be the ultimate reason for an aggressive-impulsive behavior. The role of serotonin, noradrenalin and dopamine were comprehensively investigated with regards to impulsive and aggressive behavior and these neurochemical data were further integrated with the neuroanatomical model, providing the bases to the rational pharmacological approach of these behaviors.*

**Descriptors:** Aggression; Borderline personality disorder; Impulsive behavior; Neurological manifestations; Symptoms, mental

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### Resumo

*A impulsividade aumentada e o comportamento agressivo ocorrem frequentemente em uma série de transtornos psiquiátricos e de doenças neurológicas. Duas abordagens de tratamento podem ser empregadas: o tratamento do transtorno ou da doença em que esses sintomas ocorrem ou o tratamento da impulsividade e do comportamento agressivo. Este segundo enfoque considera que há similaridades neurobiológicas subjacentes independentemente dos diagnósticos "primários" a que elas estejam associadas. O desequilíbrio entre os impulsos límbicos ascendentes, exercidos por estruturas como a amígdala, e os mecanismos de controle pré-frontais descendentes poderiam ser a razão última de um comportamento agressivo-impulsivo. Os papéis da serotonina, da noradrenalina e da dopamina foram amplamente investigados com relação ao comportamento impulsivo e agressivo e esses dados neuroquímicos foram ainda integrados ao modelo neuroanatômico, fornecendo as bases para a intervenção farmacológica sobre esses comportamentos.*

**Descritores:** Agressão; Transtorno da personalidade borderline; Comportamento impulsivo; Manifestações neurológicas; Sintomas psíquicos

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## Introduction

Impulsivity and aggressive behavior are not classical psychiatric diagnoses like schizophrenia, depression, bipolar or borderline personality disorder. They are symptoms that could occur in almost all psychiatric disorders and in some neurological or systemic diseases. Therefore, it may be the case that the treatment of impulsivity and aggressive behavior demands an alternative approach to the treatment of the “primary” disorder. For example, perhaps antidepressants could be used for the treatment of a patient with major depression and aggressive behavior, which could resolve the depressive state and therefore treat also the aggressive behavior linked to the depression. Alternatively, a complementary approach might be required.

The problem with this interpretation is that what is considered the “primary” disorder is an arbitrary statement based on a clinical point of view. From a neurobiological standpoint, impulsivity, aggression or violent behavior are diagnoses like any other psychiatric or neurological conditions. In other words, they can be viewed as diagnoses per se, since they could share some phenomenological and biological similarities in spite of the “primary” diagnoses with which they are associated.

In this article, psychopharmacological approaches to the treatment of impulsive, aggressive and violent behavior will be discussed. However, I will only approach the aggressive and violent behavior that is impulsive or reactive and not instrumental, as this has some differences in neurobiology and treatment.<sup>1,2</sup>

## Definition of aggressive behavior

There are many ways to classify aggressive behavior, for example by the targets (directed to objects, persons or self), mode (physical or verbal) or intensity. Two classifications have important correlates with neurobiological issues. The cause of aggression (intermittent impulsive aggression, associated psychiatric axis I or II disorder, secondary to neurological or medical diseases or by the use of drugs) and the concept of impulsive versus premeditated aggression. Premeditated aggression is a planned behavior not usually associated with frustration or provoked by immediate threat. In contrast, impulsive aggression is not planned but is associated with the perception of immediate threat or frustration, negative emotions like fear or anger, and characterized by high levels of autonomic arousal.<sup>3</sup> Impulsive or reactive aggression may be considered a normal and desirable reaction to environmental threats or pathological when its intensity is disproportionate or when it is misdirected, generating negative consequences.

## Neurobiology of impulsivity and aggressive behavior

Impulsive aggression can be viewed as a lower threshold for activation of aggressive responses to external stimuli without adequate reflection or regard for the aversive consequences of the behavior.<sup>3</sup> It can be conceptualized as an imbalance between the top-down control, provided by the orbital frontal cortex and the anterior cingulate cortex, involved in the adaptation of the behavior to social and future expectations and in predicting expectancies of reward and punishment,<sup>4</sup> and the bottom-up drives generated in limbic structures such as the amygdala and insula.<sup>3</sup>

Impulsive aggression could be due to several different impairments in the circuit involved in response to environmental stimulus. The treatment will depend on the location of the problem within the circuit. Initially, the environmental stimulus is processed by the auditory, visual and other sensory processing centers (alcohol, drugs or metabolic disturbances could distort the sensory perception

leading the stimulus to be perceived as threatening), then this information is modulated in early information processing centers in visual and auditory integration areas and in association regions like prefrontal, temporal and parietal cortices (information is modulated by cultural and social factors, could be distorted by processing deficits leading to paranoid ideation, and influenced by negative schema secondary to developmental stress or trauma or enduring negative experiences), and finally this stimulus is processed according to past emotional conditioning in the amygdala and related limbic areas that produce the bottom-up drives that will be modulated by top-down control mainly generated by the orbital frontal cortex and the anterior cingulate cortex, as previously mentioned.<sup>3</sup>

Imbalance between limbic bottom-up drives and prefrontal top-down control mechanisms could be the ultimate reason for an aggressive-impulsive behavior, but other mechanisms in psychiatric conditions such as mood disorders, post traumatic stress disorder or borderline personality disorder may also be involved.<sup>5</sup> The top-down structures are comprised mainly by the orbital frontal cortex and the anterior cingulate cortex. The first historical evidence of the involvement of these structures in the control of limbic drives was the famous case of Phineas Gage, who in the nineteenth century was injured and lost his anterior and mesial orbital frontal cortex and anterior cingulate cortex. He became irritable, angry and showed poor social judgment after this injury.<sup>6</sup> Structural and functional imaging studies showed the involvement of these regions in the modulation of impulsive and aggressive behavior in a variety of psychiatric diagnoses.<sup>3,4</sup> Moreover, healthy volunteers presented blood flow reduction in the orbital frontal cortex when in an unrestrained aggressive scenario.<sup>7</sup>

The bottom-up drives are exerted by limbic structures like the amygdala. Enhanced responses of the amygdala have been observed in patients with borderline personality disorder in response to a variety of negative situations.<sup>3,8</sup>

A number of different neurotransmitters, like serotonin, dopamine, noradrenalin, among others, are involved in the balance between the bottom-up drives and top-down control of aversive or provocative stimuli.<sup>3,9</sup> The identification of the role of these neurotransmitters is critical for the development of pharmacological strategies for the control of impulsive aggressive behavior.

An impressive number of studies, using different techniques in clinical or pre-clinical research, have linked serotonin hypo-function with impulsive or aggressive behavior.<sup>9</sup> The first historical evidence of the contribution of serotonin in the inhibition of such behavior was produced by a Scandinavian group three decades ago.<sup>10</sup> They reported that depressive patients with reduced cerebrospinal fluid concentrations of the major serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) were significantly more likely to have had previous suicide attempts than depressive patients with normal concentrations of this metabolite. This finding was specifically linked to those patients that had employed more violent strategies to attempt suicide. Another important study was made two decades ago<sup>11</sup> and utilized a pharmacological challenge strategy to access central serotonin activity in affective or personality disorder patients with impulsive aggressive behavior. They administered fenfluramine, that is a serotonin releasing and uptake-inhibiting drug, and measured the release of prolactin provoked by this challenging test. They found an inverse correlation between prolactin levels after fenfluramine and the history of suicide attempts in affective or personality disorder patients. They also found an inverse correlation between prolactin levels after fenfluramine and impulsive aggressive behaviors only in personality disorder patients.

Serotonin regulates prefrontal cortical regions like the orbital frontal cortex and anterior cingulate cortex by acting on 5-HT<sub>2</sub> receptors.<sup>3</sup> In a number of different research paradigms it was found that there is a different and complementary role of the two 5-HT<sub>2</sub> receptors, 5-HT<sub>2A</sub> receptors being involved in increased impulsivity and aggression and 5-HT<sub>2C</sub> receptors in decreased impulsivity and aggression.<sup>3</sup>

The catecholamines, dopamine and noradrenalin, are also involved in the modulation of impulsive aggressive responses, controlling the activity of prefrontal lobe cortical regions.<sup>3</sup> Irritability correlates with the growth hormone response to the alpha<sub>2</sub> adrenergic receptor agonist clonidine.<sup>12</sup> The effect of dopamine is less clear and seems controversial; for example, methylphenidate, which increases dopamine activity, can diminish impulsive behavior in patients with attention deficit and hyperactive disorder (ADHD)<sup>13</sup> while antipsychotic drugs, which are dopamine blockers, can also diminish such behavior.<sup>9</sup>

Glutamate and GABA modulate limbic regions that generate bottom-up drives related to impulsive aggressive behavior.<sup>3</sup> Beta-adrenergic and AMPA receptors seem to be involved in the modulation of emotional aspects of the memory in the amygdala.<sup>14,15</sup> A deficiency in such mechanisms may increase the response to adverse stimuli.

### Pharmacological treatment of impulsive and aggressive behavior

Two main approaches could be employed in the treatment of impulsive and aggressive behavior. The first is to treat the "primary" disorder of which this behavior is considered a part. For example, if impulsive and aggressive behavior occurs in a bipolar patient with mania, the correct approach is the treatment of the mood disorder. Even from this point of view there are situations where the neurobiological background can help in making the better choice. For example, if impulsive and aggressive behavior occurs in a patient with dystimia, the use of serotonergic or noradrenergic antidepressants can have opposite effects on such behavior.

The second approach is to treat impulsive aggressive behavior as a psychiatric disorder in itself. It is based on the fact that such behavior has some neurobiological mechanisms that occur independently of the associated psychiatric disorder. For example, serotonergic dysfunction can be observed in impulsive aggression in patients with depression or borderline personality disorder<sup>3</sup> and the brain circuit involved is the same across the different psychiatric disorders.<sup>16</sup> As they share the same neurobiological aspects, the different manifestations of impulsive aggressive behavior, occurring in a variety of psychiatric disorders, can be dealt with by applying the same pharmacological approach acting on key targets, such as serotonin or prefrontal cortex. The drugs that have been proven effective in the treatment of impulsive aggressive behavior are the mood stabilizers lithium, carbamazepine, oxcarbazepine, valproate and topiramate, the anti-psychotics clozapine, olanzapine, quetiapine among others, the beta-adrenergic blockers, the 5-HT<sub>1A</sub> receptor partial agonist buspirone, the essential fatty acid omega-3 and anti-androgens. In a systematic review of the evidence for pharmacological management of outwardly directed aggressive behavior (excluding emergency situations) in adult psychiatry, the authors included thirty-five randomized controlled trials conducted with patients suffering from schizophrenia, cluster B personality disorders, post traumatic stress disorder, autistic disorder, intermittent explosive disorder, attention-deficit/hyperactivity disorder, anorexia nervosa, and depressive disorder and found weak evidence for anti-aggressive effect of anti-psychotics, antidepressants, anticonvulsants, and beta-adrenergic blockers.<sup>17</sup>

## Mood stabilizers

### 1. Lithium

Very early on, lithium was proposed for the treatment of impulsive and aggressive behavior. John Cade, in his famous 1949 paper, was the first to suggest that lithium might have anti-aggressive effects.<sup>18</sup> Several studies, the majority of them open trials, pointed to an anti-impulsive and anti-aggressive effect of lithium on different diagnoses such as personality disorders, schizophrenia, unipolar depression and mental handicaps.<sup>18</sup> A single-blind study comparing lithium to a placebo in a maximum-security prison showed the efficacy of this medication in reducing self-rated aggressive affect as well as decreasing the incidence of disciplinary sanctions.<sup>19</sup> The same author made a double-blind placebo-controlled trial with sixty-six inmates from a medium-security prison during 3 months, and found that the use of lithium was associated with a significant reduction in infractions.<sup>20</sup> Considering child abuse as an aggressive behavior, we conducted an open trial with eight mothers with dystimia and personality disorder who physically abused their children.<sup>21</sup> Lithium was effective in reducing their abusive behavior, which was impulsive-aggressive, against their children, and was also effective in reducing the overall aggressiveness of these mothers. Lithium is also effective in preventing suicide, as demonstrated by a retrospective cohort study with a population based sample of 20638 health plan members diagnosed with bipolar disorder.<sup>22</sup> Risk of death by suicide was 2.7 times higher during treatment with divalproex than during treatment with lithium, and also the chance of suicide attempts were higher during treatment utilizing divalproex in comparison with the treatment employing lithium. The mechanism underlying the anti-impulsive and anti-aggressive effect of lithium is not clear, but could involve an increase in serotonergic function as well as a decrease in catecholaminergic function.<sup>18</sup>

### 2. Anticonvulsants

#### 1) Carbamazepine and oxcarbazepine

There is substantial evidence in the literature pointing to the efficacy of carbamazepine in the treatment of impulsive aggression in a variety of neurological and psychiatric situations, such as seizure disorder, traumatic brain injury, middle cerebral arterial stroke, Alzheimer's disease, attention deficit/hyperactivity disorder, personality disorder, schizophrenia among others. However, the majority of published studies involve open trials. Carbamazepine (average dose 820mg/day) leads to a highly significant reduction in the severity of behavioral dyscontrol in patients with borderline personality disorder in a double-blind placebo-controlled crossover study.<sup>23</sup> Carbamazepine (mean serum level of 5.3µg/ml) was effective in the treatment of agitation and aggression in a group of patients with Alzheimer's disease, vascular and mixed dementia as demonstrated by a double-blind placebo controlled study.<sup>24</sup> This medication also proved to be effective in reducing the impulsive aggressive behavior of men in another double-blind placebo controlled parallel group study, where carbamazepine, valproate, phenytoin and placebo were compared.<sup>25</sup>

Oxcarbazepine was effective in reducing impulsive aggression in a double-blind, placebo controlled study in patients showing significant impulsive aggression without other psychiatric symptoms.<sup>26</sup> The dosages used vary from 1200 to 2400mg/day.

#### 2) Valproate

The use of valproate (valproic acid and divalproex) followed in the path of carbamazepine in psychiatry. It was first used in the treatment of mania and prophylaxis of bipolar disorder. It was later employed in the treatment of impulsive aggressive

behavior, but in this condition the evidence is less persuasive. However, some well conducted research suggests some efficacy of these compounds in the treatment of impulsive aggression. In a double-blind parallel group multi-centered study comparing olanzapine+placebo, olanzapine+divalproex, risperidone+placebo and risperidone+divalproex in schizophrenic patients, treatment with the combination of antipsychotic drugs plus divalproex was more effective in diminishing hostility than the treatment with either olanzapine or risperidone alone, only in the first week of the trial.<sup>27</sup> The effect of the combination of drugs (divalproex+antipsychotic drug) on hostility was independent of the effect of the same treatment on other psychotic symptoms. In another retrospective, case-control study, with schizophrenia, schizoaffective and bipolar disorder patients hospitalized in a maximum security hospital, the effect of valproate and topiramate on aggressive behavior was evaluated.<sup>28</sup> Both medications were able to reduce aggressive behavior alone or in combination, but valproate was more effective in reducing the intensity of episodes of agitation. In a double-blind placebo controlled multi-center study, the effect of divalproex (500 to 2250mg/day) on aggressive behavior was measured in outpatients with cluster B personality disorders, intermittent explosive disorder or post traumatic stress disorder.<sup>29</sup> The medication was ineffective in diminishing aggressive behavior when all diagnoses were analyzed together, but effective in reducing such behavior only in patients with cluster B personality disorders. The same investigators, in another study, showed that divalproex was effective in reducing impulsive aggression of patients with borderline personality disorder in a double-blind placebo controlled study.<sup>30</sup> Patients with higher baseline scores for impulsiveness and aggression responded better. Subsequently, the same author carried out an open trial with extended release divalproex in patients with borderline personality disorder and found the same results, the medication was effective in reducing aggressive behavior, independently of the drug's effect on other symptoms of the personality disorder.<sup>31</sup>

### 3) Topiramate

Topiramate has been shown to be efficient in the treatment of impulsive aggressive behavior of borderline personality disorder patients. Initially, two double-blind placebo-controlled studies demonstrated the efficacy of topiramate (250mg/day) in the control of anger in these patients, one using a female and the other a male sample.<sup>32,33</sup> The 18-month follow-up of the latter study confirmed the previous results.<sup>34</sup> We had previously proposed that the effect of this drug in controlling the impulsive aggressive symptoms of borderline personality patients was at least partially based on the effect that the drug has on the extinction of traumatic memories that trigger the overreaction to the environmental cues related to the idea of abandonment and rejection.<sup>35,36</sup>

### 3. Omega-3 fatty acids

Omega-3 fatty acids, mainly eicosapentaenoic (EPA) and docosahexaenoic (DHA) have been investigated in relation to several psychiatric disorders, like schizophrenia, bipolar, attention deficit disorder and impulsive behavior, with positive results. Some studies addressed the effect of omega-3 on impulsive and aggressive behavior. A double-blind, placebo-controlled study found that supplementation mainly with EPA and DHA diminish anger in substance abusers.<sup>37</sup> Another double-blind placebo-controlled study showed that administration of EPA reduces aggression in patients with borderline personality disorder.<sup>38</sup> Many potential action mechanisms could be evoked to explain the role of omega-3 fatty acids in treating psychiatric disorders and their effect on impulsive

and aggressive behavior. For example, omega-3 seems to diminish PKC-dependent transduction<sup>39</sup> and plasma concentrations of omega-3 are correlated to 5-HIAA cerebrospinal fluid levels.<sup>40</sup>

### 4. Beta-blockers

Although not frequently used with this purpose in clinical setting, there is a significant amount of research demonstrating the efficacy of beta-blockers in the treatment of impulsive aggressive behavior in many different psychiatric and neurological conditions. For example, two double-blind placebo controlled crossover studies showed the efficacy of propranolol and pindolol in reducing assault behavior in a sample of patients with organic brain disease.<sup>41,42</sup> An add-on open trial using propranolol in a sample of 20 chronically hospitalized aggressive patients with a variety of diagnoses (schizophrenia, schizoaffective disorder, drug abuse, seizure disorder, organic personality disorder and borderline personality disorder) followed by a double-blind study where the respondents were included either in a group in which the medication was maintained or in another group in which the medication was discontinued, demonstrated the effectiveness of this drug in reducing aggressive behavior.<sup>43</sup> As usual with the use of propranolol in the control of aggressive behavior, the doses of the beta-blocker are higher than those normally used in cardiology. In this study particularly, the doses were very high, propranolol was introduced at a dosage of 20mg qid and augmented 20mg qid every four days until the dose of 400mg a day was reached and then increased in 20mg qid every day until the dose of 1440mg a day or 20mg/kg was reached (whichever was higher).<sup>43</sup> In spite of this dosage, few side effects were reported, for example, only one patient developed asthma and seven complained of dizziness. Interestingly, nadolol, which is a water soluble compound that does not easily cross the blood brain barrier, was also able to diminish the aggressive behavior in chronically psychiatric patients in a double-blind placebo controlled study.<sup>44</sup> This suggests a double mechanism of action of beta-blockers in the control of impulsive aggressive behavior, one in the central nervous system and another in the peripheral.

The high dosages required to achieve an anti-aggressive effect may cause concern and inhibit the use of these drugs in these conditions. However, peripheral effects of beta-blockers, such as lowered blood pressure and bradycardia, are frequently saturated with 280mg/day. Consequently, further increase in the dosage is not usually associated with cardiovascular side effects.<sup>45</sup> Nevertheless, special attention should be given to the development of asthma.

### 5. Antidepressants

Although some antidepressant drugs, like the selective serotonin re-uptake inhibitors (SSRIs), could increase serotonergic activity in the central nervous system, and serotonin is highly involved in the control of impulsive aggressive behavior,<sup>10</sup> these drugs are not often suggested for the treatment of aggression. However, when an antidepressant medication is necessary, as in the case of the treatment of depression, and an anti-aggressive intervention is also useful, an SSRI is clearly a more suitable choice than an antidepressant that enhances noradrenergic or dopaminergic activity, which could have the opposite effect, leading to increased impulsivity and aggressive behavior. For example, in a double-blind placebo controlled study with normal volunteers, paroxetine was able to reduce hostility.<sup>46</sup>

Another interesting study assessed the effect of fluoxetine on impulsiveness and aggression in borderline personality disorder patients genotyped for long and short allele of the serotonin

transporter polymorphism.<sup>47</sup> The short allele is associated with a worse response to SSRIs in depression. The same result was obtained in relation to impulsiveness and aggression in these borderline patients, that is, long-allele carriers responded better than short-allele carriers, suggesting that the effect of the drug in reducing these behaviors occurs through serotonin enhancement.

## 6. Atypical antipsychotics

Antipsychotic medications have been used to control impulsivity and aggressiveness in a variety of clinical entities such as schizophrenia, schizoaffective disorder, and bipolar disorder, where they have a double function, the treatment of the disorder and the behavior dyscontrol. Furthermore, it can also be used in other clinical situations to treat impulsivity, like dementia, autistic disorder or borderline personality disorder. These medications can also have a sedative effect that could reduce impulsive aggressive behavior. However this effect is not suitable in chronic treatment because of the cognitive and motor consequences, which hinder daily activities. Only the anti-impulsive and anti-aggressive effects of the anti-psychotic drugs that are independent of the sedative effect will be discussed here.

### 1) Clozapine

The theory that clozapine is a highly effective drug with which to treat aggressive behavior is supported by clinical research. In a double-blind clinical trial, clozapine was compared to olanzapine, risperidone, and haloperidol in the treatment of hostility and aggressiveness in a group of inpatients with chronic schizophrenia and schizoaffective disorder.<sup>48,49</sup> Clozapine was more effective than haloperidol and risperidone in reducing hostility, while no difference was found between risperidone, olanzapine and haloperidol.<sup>48</sup> The effect of clozapine on hostility was independent of its effect in the treatment of psychoses. In a re-analysis of the data provided by the same sample, clozapine proved better than haloperidol at reducing the number and severity of aggressive incidents, while also demonstrating superior anti-aggressive properties in treatment-resistant patients than other medications.<sup>49</sup> The same team made another double-blind parallel trial comparing clozapine, olanzapine and haloperidol in the treatment of physical assaults and other aggressive behaviors in violent patients with schizophrenia and schizoaffective disorder.<sup>50</sup> They found that clozapine (dosage ranged from 200 until 800mg/day) was superior to both olanzapine and haloperidol in controlling overall aggression, physical aggression and verbal aggression, and superior only in relation to haloperidol in controlling aggression against property.

Clozapine is also effective in the treatment of impulsive aggressive behavior of patients with diagnoses other than schizophrenia or schizoaffective disorder. For example, in a small open trial where five carefully described patients with heterogeneous diagnoses and a persistent violent behavior, clozapine (50 to 275mg/day) was effective in reducing the number of violent episodes as well as the need for seclusion and restraint, irrespective of the "primary" diagnoses.<sup>51</sup> In a retrospective study with seven patients with borderline personality disorder and persistent psychosis, a treatment with clozapine was effective in reducing incidents of self-mutilation, seclusion and injuries to staff and peers.<sup>52</sup>

### 2) Olanzapine

Although lacking the same status that clozapine has among clinicians in the control of aggressive and violent behavior, a notion supported by research,<sup>50</sup> there is also evidence for the use of olanzapine in the treatment of impulsive aggressive behavior. In an observational three year follow-up study with schizophrenic

patients in the community that were treated with olanzapine or risperidone, patients treated with olanzapine for one year or more showed significantly lowered aggression, in contrast, no significant antiaggressive effect was observed in patients receiving risperidone for one year or more.<sup>53</sup> In an open trial study in which olanzapine was given to patients suffering from borderline personality disorder and dysthymia it was able to strongly reduce symptoms of anger and interpersonal sensitivity, which is related to the impulsive reactions presented by these patients.<sup>54</sup> In a double-blind placebo controlled study with patients suffering from borderline personality disorder, olanzapine was effective in diminishing the symptoms of anger and hostility and interpersonal sensitivity.<sup>55</sup> In another double-blind placebo controlled study with borderline personality disorder patients, where all patients were treated with dialectical behavioral therapy and were randomly assigned to receive olanzapine or placebo, the group treated with olanzapine (mean dose of 8.83mg/day) showed a significant improvement over placebo in impulsive and aggressive behavior.<sup>56</sup> In an open-label, retrospective naturalistic trial, olanzapine was added to multiple psychotropic medications given to intellectually disabled patients presenting self-injurious, aggressive and disruptive behavior.<sup>57</sup> Olanzapine was effective in diminishing the target behavior, reducing aggression and self-injury, destructive and disruptive behaviors in comparison with the previous treatment. In a multicenter double-blind, placebo controlled study olanzapine in low dosages (5 to 10mg/day) was effective in treating agitation and aggression in patients with Alzheimer's disease.<sup>58</sup>

### 3) Quetiapine

Recently, some research has suggested the efficacy of quetiapine in treating impulsive aggressive behavior in a variety of psychiatric disorders and neurological diseases such as borderline personality disorder, conduct disorder in children, dementia and traumatic brain injury, among others. In a double blind placebo-controlled study with adolescents presenting conduct disorder, quetiapine was effective in reducing aggressive behavior in all behavioral or symptom measures employed.<sup>59</sup> In an open-label trial with borderline personality disorder patients treated for 12 weeks, quetiapine (dose ranging from 100 to 800mg/day) was able to reduce impulsivity, hostility and anger, and also to improve performance in the Stroop Color Word Task and in the IOWA Gambling Test, data that support the anti-impulsive effect of the drug in these patients.<sup>60</sup>

## 7. Methylphenidate

It was mentioned above that serotonin is the central nervous system amine most studied in the context of impulsive and aggressive behavior, as demonstrated by several studies using different research paradigms in clinical and pre-clinical research.<sup>9</sup> It was also cited that noradrenalin can regulate impulsive aggressive behavior, essentially having an opposite effect when compared to serotonin, augmenting this behavior.<sup>9</sup> Finally, dopamine has a double action as demonstrated by the anti-impulsive effect of medications that antagonize this neurotransmitter such as antipsychotic drugs,<sup>9</sup> while the same effect is achieved with drugs that enhance dopaminergic activity such as methylphenidate.<sup>13</sup> This example shows the importance of understanding not only the effect of a neurotransmitter in impulsive aggressive behavior, as if the brain worked like an endocrine gland, but also the necessity to keep in mind the fact that neurotransmitters act in brain circuits, and the same neurotransmitter could have opposite effects, depending on the brain dysfunction.

Although dopamine could increase impulsive aggressive behavior, for example in patients with mania or hypomania, it diminished

this behavior in patients with ADHD.<sup>61</sup> A review of the literature including sixteen double-blind placebo controlled studies with pediatric samples reveals that methylphenidate has a medium to large effect in controlling aggression in ADHD.<sup>13</sup> In a double-blind placebo controlled study of children with ADHD, where 64.9% of the sample showed oppositional-defiant or conduct disorder, long-acting methylphenidate was effective in controlling impulsive aggressive behavior while the medication was active, in the school but not in the afternoon.<sup>61</sup> The medication was particularly effective in controlling milder symptoms, and lower effect size was observed for more severe aggressive symptoms. Methylphenidate's effect on impulsive aggressive symptoms could be linked to its effects increasing the efficacy of top-down structures that control the bottom-up drives, although it can also activate behavior.

### 8. Buspirone

Buspirone, a 5-HT<sub>1A</sub> receptor partial agonist, whose action increases the release of serotonin, has anti-impulsive and anti-aggressive effects in a variety of psychiatric and neurological diagnoses as demonstrated by a series of published single-case and open trials. For example, in an open-trial study, buspirone (dosage varying between 20 and 50mg/day) was administered to eight patients with mental retardation showing aggressive outbursts, self-injurious behavior and impulsivity. This medication was able to reduce these undesirable behaviors and improve sociability.<sup>62</sup>

### 9. Clonidine

Clonidine, an alpha<sub>2</sub>-adrenergic agonist, which preferentially affects pre-synaptic receptors (thus diminishing the release of noradrenalin), was used in psychiatry to treat opioid withdrawal (reducing the hyper-adrenergic activity),<sup>63</sup> mania<sup>64</sup> and aggressive behavior, mainly in children with ADHD, oppositional-defiant or conduct disorder.<sup>65</sup> For example, in an open trial, clonidine was effective in controlling aggressive behavior in a group of seventeen children with aggressive behavior characterized by cruel behavior

to others and destruction of property.<sup>66</sup> A blinded parallel group study with children suffering from ADHD with co-morbid aggressive oppositional defiant disorder or conduct disorder, where clonidine alone, clonidine+methylphenidate or methylphenidate alone were compared, showed that clonidine was effective alone or in combination with methylphenidate in controlling impulsivity, oppositional and conduct disorder symptoms.<sup>65</sup>

### Conclusion

Psychopharmacology, since its origin, has favored the psychiatric attitude to treatment – “one diagnosis, one pill”. And it is partially true in the classical psychiatric diagnoses such as schizophrenia, depression and bipolar disorder where anti-psychotic, antidepressants or mood stabilizer drugs may be prescribed. The treatment of impulsive aggressive behavior offers a different perspective where the classical approach is unsuitable. Impulsive aggressive behavior could occur within almost all psychiatric diagnoses and although it is found in a wide range of clinical situations, as different as brain injury, ADHD, schizophrenia, depression or borderline personality disorder, it shares the same neurochemical and neuroanatomical substrate. It represents a window to the brain that offers the opportunity to understand the underlying neurobiological process and so modify the treatment of the associated psychiatric or neurological diagnoses.

The study of the neurobiology of impulsive aggressive behavior, which together with the awareness of the evidence favoring or not a specific drug, represents the bases of the rational pharmacology of this prevalent clinical condition. It also provides psychiatry with a model where research, previously conducted independently, into the neurochemical and neuroanatomical substrates, is now perfectly integrated. It also offers psychiatry a golden opportunity to study and understand why co-morbidity occurs and is so frequent. Finally, these diagnoses challenge psychopharmacology to change the classical approach of “one diagnosis, one pill” in every clinical situation.

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\* Modest

\*\* Significant

\*\*\* Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

Note: PUCRS = Pontificia Universidade Católica do Rio Grande do Sul.

For more information, see Instructions for authors.

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