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Antiepileptic drugs in the control of the impulses disorders

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The disorders classified as control of the impulses; explosive intermittent disorder, pathological gambling, kleptomania, pyromania, pathological gambling, hair pullers, compulsive purchases, skin picking and onychophagia are a heterogeneous set of clinical entities, most of them with little prevalence. Nevertheless, they cause important personal and social dysfunctions and present great comorbidity with other psychiatric disorders. Antipsychotics, antidepressive agents, serotoninergic agonists, naltrexone, beta blockers antiandrogen, lithium and anticonvulsants have been used in their pharmacological treatment. Currently, interest is growing on the use of the antiepileptics because their possible usefulness has been described in these disorders. However, the neurobiological effects are only partially known in some cases. We have reviewed the literature regarding the treatment of these disorders with mood stabilizers, (lithium, carbamazepine, valproate, phenitoin, oxcarbazepine, topiramate, lamotrigin, leviteracetam) and have described those studies on which the current knowledge and evidence are based. The results must be considered as provisional and must be updated in the future, since they are mostly based on case reports, case series or opened clinical trials, their being little knowledge based on double blind clinical trials.

Key words:
Impulse control disorders. Antiepileptic drug. Explosive intermittent disorder. Pathological gambling. Kleptomania. Pyromania. Hair pullers

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Trastornos del control de impulsos y tratamiento con antiepilépticos

Los trastornos clasificados como del control de los impulsos; trastorno explosivo intermitente, ludopatía, cleptomanía, piromanía, juego patológico, tricotilomanía, compras compulsivas, rasgado compulsivo y onicofagia, son un conjunto heterogéneo de entidades clínicas, la mayoría de ellas poco prevalentes. Sin embargo producen importantes disfunciones personales y sociales y presentan gran comorbilidad con otros trastornos psiquiátricos. En el tratamiento farmacológico se han utilizado fármacos antipsicóticos, antidepresivos, agonistas serotoninérgicos, naltrexona, betabloqueantes antiandrógenos, litio y antiepilépticos. En la actualidad existe creciente interés sobre el uso de los antiepilépticos, ya que se ha descrito la posible utilidad en estos trastornos, sin embargo en algunos casos sólo se conoce parcialmente las acciones neurobiológicas.

Se revisa la literatura referente al tratamiento de estos trastornos con eutimizantes (litio, carbamazepina, ácido valproico, fenitoína, oxcarbazepina, topiramato, lamotrigina, leviteracetam) describiéndose los estudios en los que se basa el conocimiento actual. Los resultados deben ser considerados provisionales y ser actualizados en el futuro, pues están basados mayoritariamente en casos clínicos, series de casos o ensayos abiertos, existiendo poco conocimiento fundamentado en ensayos clínicos doble ciego.

Palabras clave:
Trastornos del control de los impulsos. Antiepilépticos. Trastorno explosivo intermitente. Ludopatía. Cleptomanía. Piromanía. Tricotilomanía.

INTRODUCTION

Impulsivity is defined as a rapid, unplanned reaction to external and internal stimuli without regard to the negative consequences of this action on the individual or other persons.[1] Its clinical manifestation is varied. One of the most outstanding is aggressive and/or violent behavior although, as will be described, there are other forms of impulsivity without aggressivity.

Impulse-Control Disorders have been defined as harmful behaviors performed in response to irresistible impulses. In the *Diagnostic and Statistical Manual of Mental Disorders IV- Revised Text* (DSM-IV-TR),[2] an impulse-control disorder is defined as the failure to resist an impulse, drive, or temp-

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tation to perform an act that is harmful to the person or to others. It is established in that manual that the subject perceives a growing sensation of tension or interior activation in most of the impulse-control disorders before committing the act and then experiences pleasure, gratification or relief when performing it, and there may or may not be any later regret. In the International Classification of Diseases (ICD-10),[3] these disorders are also classified as repeated acts that have no *clear rational* motivation and, generally, harm the patient's own interests and those of other people. It also establishes that the behaviors are associated to impulses to act when they cannot be controlled. In the DSM-IV-TR, intermittent explosive disorder, kleptomania, pathological gambling, pyromania, trichotillomania (hair pulling), and not otherwise specified impulse-control disorders are included in this category, these being very similar in the ICD-10.

CONCEPTUALIZATION OF THE DISORDERS

Intermittent explosive disorder refers to the appearance of severe isolated episodes of aggressivity out of proportional to the precipitating event. The subject who suffers it generally reactions with unusual violence, this occurring in mentally healthy persons. The episode is often preceded by a stressor event that is outside of the individual's control (e.g. death of a loved one, disease). It may represent the purest form of impulsivity, of not being contaminated by other disorders that favor it.[4] Non-specific abnormalities of the electroencephalogram that seem to indicate some congenital or post-traumatic neurological fragility and that cannot be grouped as real lesion have been observed in up to 30% of the cases[5]. It is more frequent in men, who initiate the episodes at the end of adolescence and rarely after 30 years of age. In some women, the disorder becomes more intense in the premenstrual phase.[5,6]

Kleptomania is characterized by the tendency to commit robberies that are not justified either by need or by desires to harm the victim. In the ICD-10, it is defined as the repeated failure to resist the impulse to steal objects that are not acquired for personal use or for monetary gains. It has been related with the affective spectrum disorder.[7] Its prevalence is little known but it is estimated that one out of every 1000 persons suffer it, affecting at least 5% the shop thiefs[2]. It is more common in women than in men. It generally begins in adolescence or onset of the adult age and often follows a chronic or episodic course.[7] It has high comorbidity with the major depressive disorder (75%), obsessive-compulsive disorder (OCD) (75%), post-traumatic stress disorder (75%)[8], bulimia nervosa (50%) and generalized anxiety disorder (25%).

Pyromania is a little known disorder.[9] It is characterized by the repeated setting of fires with no apparent reason, such as financial gain, vengeance or political extremism, interest in observing fires and feelings related with increased tension before committing the act and intense excitement immediately after doing it. Its prevalence is unknown. There are some unsystematized old studies in which the clinical characteristics are described. It is likely that it is more frequent in men and it generally initiates in adolescence or the onset of the adult age.[8]

Pathological gambling or ludopathy is recognized by preoccupation with playing, by considering the money spent or time spent as excessive, continuous or intermittent thinking about the game itself with development of tolerance and intense desire to play, loss of control on the bets in spite of the harm caused and the appearance of a disorder, whether financial, social or psychological. It occurs more often in men and it is estimated that between 1% and 3% of the adult population suffers from this disorder during their lifetime. There are populations in which these values increase alarmingly, such as among the mental patients.[10]

Trichotillomania is defined as the act of pulling out one's hair, with continuous hair loss. Most of the patients pull out hairs from different body areas, the most common being, in decreasing order, the scalp, eyebrows and eyelashes, pubic area, face and limbs. A total of 90% of the adult patients are women.[11]

Within the not-otherwise specified impulse-control disorder, those that do not fulfill the diagnostic criteria for any specific disorder are included. Compulsive shopping, onychophagia (nail biting) and psychogenic excoriation could be included in this section, although these diagnoses are not specifically included in either the ICD-10 or the DSM-IV-TR. However, it has been described that they cause important morbidity, personal and social dysfunction and financial problems.

Compulsive shopping is understood to be intrusive and persistent irresistible and uncontrollable impulse to senseless buying as well as increased tension and anxiety together with impulse and relief of tension or pleasure sensations in the act of buying. It is a little known disorder and also a polemic one since the limit of normality in certain societies in which consumerism reigns is difficult to define.[10]

Compulsive skin picking consists in the behavior of scratching, scraping, picking at or squeezing the skin in response to itching or another dermal sensation or in order to dig at a dermal lesion. It causes significant stress for the patients. Most have sociolaboral dysfunction and medical complications, some so severe that they require surgery. It represents 2% of the patients who come to the dermatology medical office. It may begin in adolescence or adult age and its mean duration is 5 to 18 years, it having a better prognosis in patients in whom the course is less than one year.[12]

Onychophagia consists in the repeated and severe biting of the nails. The cuticles and skin around the nails are also generally bitten and bitten off. It is similar to an impulse-control disorder because there are automatic, irresistible behaviors and it is associated with an increase in tension before this behavior and subsequent relief after it. There are no studies on the epidemiology of this disorder.

NEUROBIOLOGICAL BASES OF THE IMPULSE-CONTROL DISORDERS

The most extensively found neurobiological disorder in the literature in the impulse-control disorders is the serotoninergic deficit,[13,14] although there are no biological studies on kleptomania or on pyromania. It has been described in recent studies that there are also alterations in other neurotransmission systems[4], such as noradrenergic hyperactivity, dopaminergic dysfunction and cholinergic dysfunction, an increase of testosterone and endorphins, hypofunction of the hypothalamic-pituitary-adrenal axis, GABAergic hypofunction and glutamatergic hyperfunction.[14] All of this is consistent with the clinical experience, in which drugs such as antiepileptics, without serotonergic action, can also modulate impulsive, aggressive, and other behaviors. Thus, the participation of other neurobiological mechanisms is clear. Furthermore, in some conditions related with the impulse-control disorder, there are genetic and neuroanatomical alterations that could be related with congenital or posttraumatic neurological fragility.[5]

DRUG TREATMENT

Different drugs have been used in the treatment of impulse-control disorders: conventional neuroleptics, new antipsychotics, selective serotonin reuptake inhibitors (SSRI), serotinergic agonists, beta blockers, naltrexon, central stimulants, anti-androgenics, lithium and anti-epileptics. Currently, there is a growing interest about the new antiseizure drugs since there are some controlled studies that suggest that they have therapeutic effectiveness.[14]

The term mood stabilizer is used to refer to a heterogeneous combination of anti-epileptic or antiseizure drugs and lithium, that have different neurochemical effects (table 1). These can be divided clinically into three groups.[4]

1) Lithium carbonate, basically used for the treatment of manic episodes and bipolar disorder type I prophylaxis

2) Carbamazepine and valproic acid. Both were initially used in the treatment of epilepsy, their indication later being approved for treatment of manic episodes and bipolar disorder type 1 prophylaxis.

3) The new generation of anti-seizures: gabapentin, topiramate, lamotrigine, oxcarbazepine, vigabatrin and levetiracetam. They are the group which, together with valproate, have generated the highest expectations in relationship with the treatment of impulsivity or impulse dyscontrol.

Table 1 Neurochemical effect of the mood-stabilizing drugs

Lithium	It modulates calcium and protein kinase C mediated processes by the second phosphatidylinositol messenger system
Valproic acid	Modulation of the GABA system
	It eliminates depolarizations by NMDA
	It regulates glial glutamate transporters
	It reduces AMPA receptors
Carbamazepine	Blockage of Sodium channels
	It inhibits glutamatergic neurotransmission
	It inhibits the rise in *intracellular free* calcium *induced* by *NMDA* and *glycine*
Lamotrigine	Inhibition of pre-synaptic calcium and sodium channels
	Stabilization of the membrane
Topiramate	It strengthens the GABA action
	It inhibits Sodium and Calcium currents
	It inhibits the glutamatergic activity
Oxcarbazepine	It blocks Sodium and Calcium type N, P and R channels
	It inhibits glutamatergic activity
	It increases potassium channel permeability
Gabapentin	It increases intraneuronal GABA
	It inhibits Glutamate release
Vigabatrin	Modulation of the GABA system: irreversible inhibition of the GABA transaminase
	It decreases glutamatergic transmission
Levetiracetam	Little known
	Blockage of potassium currents

The first hypothesis on the action mechanism of mood stabilizing agents were based on a possible modification of ion transfer (sodium, basically) on the capacity of altering the electrophysiological properties of the neuronal membranes. After, the influence on the transportation of choline and amino acids or on the capacity to alter monoaminergic, cholinergic or GABAergic transmission, fundamentally in the modulation of the glutamatergic and GABAergic system, stood out. However, in recent years, most of the lines of research have been aimed at understanding the molecular mechanisms related with the signal transduction in post-synaptic neurons, where multiple neurotransmission systems converge, such as the metabolism of the phosphoinositides and the adenylatocyclase pathway. In this way, there has been more extensive study on the influence of the mood stabilizing drugs on the dif-

ferent protein G fractions, which promote the nuclear activation of the genic transcription factors and the synthesis of neuron growth factors.[15]

Intermittent explosive disorder

Different drugs have used with good results in the approach to this disorder, for example, carbamazepine in an open-label clinical trial with 52 patients,[17] phenitoin in a double blind clinical trial with 16 patients[18] and lithium in a placebo-controlled clinical trial with 66 patients.[19] The valproic acid drug has been studied the most, although its results are contradictory. A series of 27 cases was used. Of these, 93% had comorbidity with affective disorders and 43% with Substance abuse disorders, with good results.[6] There is a 10-week long open-label clinical trial including 10 patients in which the effect of valproate is evaluated in aggressive impulses, of patients with personality disorders who do not respond to SSRI. In them, the use of the drug (200-400 mg/day dose) decreases irritability and impulsive-aggressive behaviors.[20] However, there is only one randomized, placebo controlled double blind clinical trial published with valproate, that included 96 patients with cluster B personality disorder, 116 with intermittent explosive disorder and 34 with post-traumatic stress disorder. The patients were treated for 12 weeks with valproate semisodium vs. placebo. Valproate was superior regarding the decrease of violence and irritability of the personality disorders and against the global severity of the disease, but not in the two other disorders.[21] A clinical trial has been conducted with oxcarbazepine vs placebo with 48 patients, at a dose of 1,200 mg/day up to 2,400 mg/day vs. placebo for 10 weeks. Its utility in the decrease of aggressive behaviors has been demonstrated.[22] The same group used levetiracetam, at a dosage of up to 3,000 mg/day, in a 10-week long clinical trial with 40 patients vs. placebo, without detecting any improvement.[23] Other drugs, such as topiramate, have been used in heteroaggressivity episodes in patients with personality disorders with good short and long term results.[24]

Kleptomania

There are works in which lithium and valproic acid have been used with good results. Lithium in combination with fluoxetine has been effective in several studies.[7] One case has been published that has shown good response to valproic acid in combination with 20 mg of fluoxetine in a patient with mixed mania and kleptomania.[25] The same group published a series of 20 cases, in which treatment with carbamazepine in combination with clomipramine did not improve the symptoms of kleptomanía.[26] There are a series of 3 cases with good response to topiramate at doses of up to 150 mg, alone or together with fluoxetine.[27] One case has been published in which a patient suffering from kleptomania that developed simultaneously with the appearance of temporal lobe epilepsy improved with topiramate.[28]

Pyromania

It has been suggested that persons with impulsive fire setting behaviors have abnormalities in serotinergic transmission.[29] However, there may be other neurobiological alterations, since there are reports on clinical cases with response to anti-androgenic medication.[30] Valproic acid together with olanzapine has been used in a patient with pyromania behaviors, with improvements,[31] as well as in a child with epilepsy, in whom the baseline disease also improved.[32] There are two reports about treatment with carbamazepine of epileptic children with pyromania behaviors, in whom not only the epilepsy resolved but also the pyromania behaviors.[32] Therefore, it seems plausible that the biological treatments reduce this dangerous behavior.[31] Due to the characteristics of pyromania, there are no systematic studies on therapeutic response. Those conducted are on the psychotherapeutic interventions and the few cases published are comorbid or those receiving polymedication.

Pathological gambling

Antiepileptic drugs alone or combined with other drugs have been used in the drug treatment of these patients, with unequal results.

Carbamazepine was studied as a possible treatment for pathological gambling. In 1994, a double blind clinical trial using up to 600 mg/day was published. Good response to the treatment was described, suggesting its possible efficacy.[33] Lithium or valproic acid was used in the first controlled clinical trial on treatment with mood stabilizers. It included 42 patients and both groups improved, so that the utility of both drugs was suggested.[34] Topiramate was compared with fluvoxamine in a randomized clinical trial with 31 patients. It was observed that the patients of both treatment had total or partial decrease in pathological gambling behaviors.[35] The same team made a 12-month follow-up naturalistic study with 43 patients in whom several pharmacological strategies, among them topiramate, were tested. The clinical trial was conducted in patients who responded to four drugs (fluvoxamine, topiramate, bupropion or naltrexone) and the efficacy of the medication was evaluated over 6 months as well as the existence of long-lasting effects of the symptoms for 9 months more. During the first 3 months, the patients continued to receive the treatment and then did not receive it in the next 6 months. It was hypothesized that if the patient responded to the medication during the drug treatment phases, the effect would be maintained without the drug. There were no significant differences and during the first 6 months

without the drug, 33% of the patients who received topiramate responded.[36]

It has been suggested that pathological gambling and Bipolar Disorder have a close relationship as they share symptoms and that a large number of patients with Bipolar Disorder have pathological gambling. There is a recently published clinical case of pathological gambling in Bipolar Disorder that responded to the simultaneous administration of Lithium and Topiramate. Thus, their complementarities and efficacy have been suggested. That is by the use of Topiramate has been proposed as coadjuvant treatment in the base of type II Bipolar Disorder and comorbid pathological gambling that do not respond to treatment with Lithium.[37]

Trichotillomania

Different drugs have been used in its treatment in small samples of patients. Lithium was effective in 8 patients out of a series of 10 with tricotillomania.[38] It is thought that this occurred because of its effects on the control of impulsivity, aggressivity and affective inestability.[11,38] Topiramate administered at a dose between 50-250 mg was used in a group of 14 patients with tricotillomania. A reduction in the clinical severity was observed and 6 out of the 9 patients who completed the study improved although the modification on the CGI (Clinical Global Impression) was not statistically significant. Thus, the probable efficacy of topiramate in the treatment of tricotillomanía has been described, although the results are not definitive.[39]

Not otherwise specified impulse control disorder

Compulsive buying

Hardly any studies or reports of the cases have been found. One series of 20 cases in which the utility of lithium and valproic acid is known. Of these, 95% had a history during their lifetime of affective disorders, 80% of anxiety disorders and 40% of impulse control disorders as well as 35% of eating disorders. In regards to them, 69% of those who received thymoleptic treatments showed a reduction or remission of the compulsive buying symptoms.[40] In addition, there is a recently published case of good response to topiramate at a dose of 150 mg/day.[41]

Compulsive scratching

The treatment used most has been the SSRIs. Works on the use of anti-epileptic drugs in this disorder are very scarce. A case series with three patients was published. It evaluated the efficacy of topiramate in Prader-Willi Syndrome in relationship to self-aggressive behaviors, it being described that it decreases self-injurious behaviors.[42] In an open-label study with 24 patients using lamotrigine in single drug therapy during 12 weeks at a dose between 25-300 mg/day, efficacy was described in two thirds of the patients, this being evaluated by the decrease in the number of minutes spent per day scratching. A mild tendency to a decrease in severity and the disease duration has been described in the subjects responding to lamotrigine.[43]

Onychophagia

The drug treatments used most are antidepressants. A series of 3 cases in which topiramate was used in patients with Prader-Willi syndrome with onychophagia, among other self-injurious behaviors, is known. A decrease of self-injurious behaviors has been documented with the drug.[42] There are 2 cases found in the literature with good response to oxcarbazepine in patients with eating behavior disorders, other psychiatric disorders and self-injurious behaviors. In the first one, it was found that when a dosage of 1,200 mg of oxcarbazepine per day was used, the self-injurious behaviors disappeared in a patient resistant to treatment with fluoxetine 80 mg and risperidone at 2 mg per day. In the second case, 1,500 mg of oxcarbazepine was added to 120 mg of fluoxetine and 200 mg of quetiapine per day to treat self-mutilation behaviors in a patient resistant to antidepressants, anti-epileptics, antipsychotics and electroconvulsive therapy (ECT), which then eliminated the symptoms[44].

CLINICAL MANAGEMENT

Impulse control disorders belong to the group of diseases low prevalence and atypical diseases. Thus, in order to provide adequate treatment, a correct evaluation of the clinical characterization is fundamental. As comorbidity with other psychiatric disorders is very common, validated instruments and diagnostic interviews should be used as far as possible to study the presence of the symptoms and of the associated disorders.

It is known that antiseizure and anti-epileptic drugs can be used to modulate impulsivity,[14] in psychotic patients,[45] in patients with personality disorders, anxiety disorders, mental retardation[46] or in patients with several substance dependencies.[47] In addition, positive effects have been described in alcohol and cocaine dependent users.[48,49] Currently, as has been described, the knowledge existing on its efficacy in the treatment of impulse control is mostly based on reports of patients, cases series or open label clinical trials. They have often been used as treatments of third and fourth choice, when no response to other psychodrugs could be obtained. It is clear that more studies are needed to be able to reach definitive conclusions and, given the lack of verified literature, the recommendations of work groups of experts groups must be fol-

Table 2 Drugs used in each disease and test on which they are based

	Explosive intermittent disorder	Kleptomania	Pyromania	Pathological gambling	Tricotillomania	Compulsives buying	Compulsive skin picking	Onychophagia
Lithium	1 (RCT)	1 (S)		1 (RCT,C)	1 (S)	1 (S)		
Valproic acid	3 (EC, E, C)	1 (S,C)	1 (C)	1 (RCT)		1 (S)		
Carbamazepine	1 (CT)	2 (S)	1 (C)	1 (RCT)				
Oxcarbazepine	1 (RCT)							1 (S)
Topiramate		1 (S,C)		1 (RCT,CT,C)	1 (CT)	1 (C)	1 (S)	1 (S)
Lamotrigine							1 (CT)	
Pheytoin	1 (RCT)							
Levetiracetam	2 (RCT)							

1: used with good response, 2; used without good response; 3: contradictory results.
C: clinical case; S: case series; CT: clinical trial; RCT: randomized clinical trial.

lowed.[50] The ideal treatment would be an anti-impulsive drug administered as single drug treatment. However, polytherapy is the most common. These drugs are generally combined with SSRI or with other drugs that have demonstrated their utility, such as naltrexone. It is sometimes necessary to associate them with sedatives, such as some of the antipsychotics or benzodizepines. The choice of the drug should be made based on the experiences described for each disorder (table 2), and on other factors (table 3). In patients with the risk of suicide, the safest medications must be used. Since experience is limited, the side effects should be adequately evaluated. Although there is more experience and more studies with lithium or the classical anti-epileptics,[18] especially with carbamazepine and valproic acid, it is known that they are tolerated worse and that drug interactions are less frequent and significant with the newer ones. The best dosage for these diseases has not been accurately described. The doses used vary greatly (table 4) and the studies have not been published for all of them. This indicates that they should be considered as provisional since they are based on small samples. It is likely that they will be modified, since there is the tendency to use the highest dose in the most recent works. In addition, it is possible that each disorder would need a different dose.

Table 3 Factors to evaluate when making the prescription

Previous clinical experiences
Clinical trials
Concomitant treatments
Difficulty or ease of making strict blood controls
Presence of medical contradictions
Background of tolerability of the patient to drugs
Risk of abuse
Risk of impulsive consumption of drugs
Lethality of drugs in overdosage

CONCLUSIONS

There are problems in the treatment of the so-called impulse control disorders due to the difficulties for clarifying the etiopathogeny of the impulsive behaviors and the very frequent existence of comorbidity. It is likely that they make up a combination of clinically related conditions, but with different neurobiological base. The advance in the research in neurosciences is making it possible to know the different mechanisms involved in these disorders. There is sufficient evidence to state that the serotonergic function is related, which is why drugs with action on this system have been used. However, treatment with these drugs is usually insufficient. Other neurotransmission systems have also been involved, so that the antiepileptics may also be useful in the treatment and should be tested.

Clinical studies having greater methodological strictness and that use more homogeneous samples that make it possible to clarify the indications and necessary doses need to be performed. In addition, it must be taken into account that the drug treatment for these disorders should be complemented with psychotherapy techniques, that have also been demonstrated to be effective in the management of these patients.

Table 4 Dose commonly used for impulse-control disorders

Drug	Dose used
Carbamazepine	600 mg
Oxcarbazepine	900 - 2,400 mg
Topiramate	50-250 mg
Valproic acid	200-2,000 mg
Lamotrigine	25-300 mg
Levetiracetam	Up to 3,000 mg

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