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Psychopharmacological treatment in borderline personality disorder

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Borderline personality disorder is a disorder with important social and clinical repercussions, which has been treated mainly by psychotherapy. In recent years, the syndromic analysis of this disorder has allowed us to identify different symptoms capable of being improved with psychopharmacology treatment. Thus, its complex symptomatology could be included in four clinical dimensions: impulsive-aggressive, affective instability, cognitive-perceptive and anxiety-inhibition. Antidepressants, mood stabilizers, antipsychotics, anxiolytics, or more recently omega-3 fatty acids have shown efficacy in the treatment of symptomatic dimensions of this disease.

We have reviewed scientific articles (reviews, clinical trials or clinical guidelines) published over the last ten years and have proposed therapeutic algorithms for psychopharmacology management in these patients.

Key words:
Borderline personality disorder. Treatment. Affective instability. Impulsivity. Aggressivity. Anxiety. Cognitive-perceptive disfunction.

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Tratamiento biológico del trastorno límite de la personalidad

El trastorno límite de la personalidad es un trastorno con importantes repercusiones clínicas y sociales y del que hasta el momento se ha realizado un abordaje principalmente psicoterapéutico. En los últimos años el análisis sindrómico del trastorno ha posibilitado identificar diferentes síntomas susceptibles de ser tratados psicofarmacológicamente. Así, la compleja clínica del trastorno límite de la personalidad se podría englobar en cuatro dimensiones básicas: impulsivo-agresiva, inestabilidad afectiva, cognitiva-perceptiva y ansiedad-inhibición. Tanto los antidepresivos como los eutimizantes, los antipsicóticos, los ansiolíticos o, más recientemente, los ácidos grasos omega 3 han demostrado eficacia en el tratamiento de las dimensiones sintomáticas de este cuadro.

Se plantea realizar una revisión bibliográfica sobre los artículos científicos (revisiones, ensayos clínicos o guías clínicas, etc.) publicados en los últimos 10 años y proponer algoritmos terapéuticos de actuación en el manejo psicofarmacológico de estos pacientes.

Palabras clave:
Trastorno límite de la personalidad. Tratamiento. Inestabilidad afectiva. Impulsividad. Agresividad. Ansiedad. Distorsión cognitivo-perceptiva.

INTRODUCTION AND BASIC ASSUMPTION OF THE TREATMENT

It is known that between 10 % and 15 % of the population suffers a personality disorder, a percentage that increases to 50 %-60 % when we consider out-patient psychiatric populations. On the other hand, 15 % of hospital admissions are caused by problems secondary to this diagnosis[1]. Specifically, there is a 2 % prevalence of borderline personality disorder (BPD) in the general population and up to 20 % among the psychiatric population, this accounting for an important burden on the health care, social and fam-ily level[2]. Until a few years ago, this disorder was basically treated by psychotherapy. However, use of psychodrugs to treat the nuclear dimensions is currently the common practice.

However, there is no fundamental symptom in BPD to be treated but rather there are many possible syndromic combinations, among them alterations in the impulsive, affective, cognitive sphere, in the attachment systems, feeling of emptiness and identity disorders. Each one of these seems to depend on different biological dysfunctions, such as limbic and frontal alterations and alterations in serotoninergic transmission associated to impulse lack of control; mood deregulation associated to affective instability; prefrontal alterations associated to cognitive-paranoid distortions; alterations of arousal and motivational systems associated to identity symptoms; deregulation of attachment systems involved in dependent traits and finally, alterations of the

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systems linked to extroversion and emotion seeking. Thus, this is a complex picture that has a large variety of symptoms that are clinically translated into repeated suicide attempts, self-aggressions, instability in interpersonal relationships, recurrent oscillations of the mood state, intense anger, toxic abuse, emotional instability, identity alterations, feelings of emptiness, panic of being abandoned, dissociative and/or paranoid ideation pictures[2,3].

The use of psychodrugs in BPD (up to 40% of the patients currently take an average of three or more associated drugs) is based on the specific benefit of the drugs on the remission of the nuclear symptoms: impulsivity, aggressivity, cognitive distortions, anxiety and/or emotional instability. Neurophysiologically, they are aimed at acting on the dysfunction of those neurotransmitters that mediate in the behavior responses and on the temperamental traits of vulnerability, on the acute symptoms of decompensation and on the comorbid pathology[4]. Long-term treatment is necessary and although there is no drug with an approved indication for BPD, many are useful and make it possible to conduct psychotherapy work with more beneficial results. However, it must be explained that there is an elevated variability in the therapeutic response of these patients and that the potential for collaboration varies from one patient to another[4-6].

In the year 2001, the American Psychiatric Association (APA) presented a clinical practice guideline for the treatment of BPD, the following guidelines standing out among those proposed[7]:

- For the management of the affective deregulation symptoms (liability, inappropriate anger, bursts of temperament, depressive episodes), the APA proposes a selective serotonin reuptake inhibitor (SSRI) as first line treatment. If this is not effective, they recommend changing to a second SSRI. If partial efficacy has been achieved, then they recommend adding low doses of antipsychotics for the anger or clonazepam for the anxiety and/or changing to a monoamine oxidase inhibitor (MAOI). As the final option, the use of mood stabilizers (lithium, carbamazepine or valproate) is suggested.
- In the control of impulsive symptoms (impulse of aggressivity, self-mutilation, self-destructive behavior) the APA maintains the SSRI, as the first therapeutic option, leaving the use of low doses of antipsychotics as the second line treatment. It both strategies fail, it proposes adding mood stabilizers or MAOI. If efficacy has not been achieved after following these guidelines, treatment with typical antipsychotics is recommended.
- In order to approach cognitive distortions (preferentiality, suspiciousness, paranoid ideation, derealization, hallucinations), initiating treatment with low doses of antipsychotics is suggested. If the efficacy is partial, the APA recommends increasing the dose. If partial efficacy continues to exist and affective symptoms are present, the guideline recommends associating SSRI or MAOI. If there is partial efficacy without affective symptoms, it suggests associating atypical neuroleptics or clozapine at greater doses.

The recommendations made in the APA guide has been under debate since there is not enough scientific evidence regarding the other available guidelines and research studies are needed to support the recommendations indicated[8-10].

In the year 1991 Siever and Davis[11] proposed four temperamental dimensions based on pathological structures on which the biological treatment of BPD was mainly based:

- Impulsivity-aggressivity dimension.
- Emotional instability dimension.
- Cognitive-perceptive dimension.
- Anxiety-inhibition dimension.

Both affective deregulation and elevated impulsivity in these dimensions are considered nuclear dimensions of the underlying psychopathology of BPD[22]. The therapeutic approach of each one of them is based on the fact that each one depends on an biological dysfunction.

The impulsive dimension that is responsible for the self-injury behaviors (drug intoxications, physical injuries, self- and heteroaggressivity) and a predisposition to toxic abuse behaviors and bulimic behaviors, from a neurobiological point of view would basically depend on a serotoninergic neurotransmission dysfunction (low levels of serotonin are associated to greater impulsivity). Together with that, frontal hyperfunction seems to play a relevant role. Thus, the cortical areas involved in the inhibitory control do not perform adequately[12-14,20]. Recently, the involvement of GABAergic, noradrenergic, dopaminergic and glutamatergic agents in the modulation of aggressive behavior has been suggested[15](table 1).

The affective instability dimension is characterized by the existence of an emotional liability that occurs with mood changes, dysphoria, increase of irritability and anger which can also influence impulsive behaviors. This dimension has been related within the BPD to limbic system dysfunction, excess of acetylcholine (dysphoria) and excess of norepinephrine responsible for emotional hyperreactivity (award seeking that is translated into intolerability to frustration and manipulative behaviors) (table 2).

Suspicion, interpretative distortions, lack of downscaling, existence of micropsychosis (brief psychotic episodes) and paranoid ideation depend on the cognitive-perceptive dimension. This dimension is involved in the regulation of the basic elements of interpretation and its dysfunction would depend on prefrontal areas and cortical-subcortical connections as well as on the existence of a cortical dopaminergic deficit from a neurochemical point of view (table 3).

Table 1 Biological and symptom bases of the impulsive-aggressive dimension in BPD

Impulsive-aggressive dimension
- Incapacity for reflection prior to the act
  - Difficult to resist impulses
  - Precipitation in response to stimuli
- Impulsive-destructive response

Symptomatic manifestations
- Verbal or physical violence/lack of control
- Self-injuries, suicide
- Substance abuse/bingings

Located in
- Amygdala. Anger
- Ascending reticular substance. Impulse
- Cortical areas. Inhibitory control

Neurochemical
- Serotonin deficit produces impulsivity
- Dopamine excess produces impulsivity
- Frontal deficits are associated to impulsivity

Finally, the anxeity-inhibition dimension would depend on the regulation of the response to danger and would occur with anxiety, fear, behavioral inhibition or feeling of emptiness, among others. Amygdala and septum-hippocampus structures would be involved in its dysfunction with serotoninergic hypersensitivity, hypersecretion of CRH and neurochemical gabaergic deficit (table 4).

Table 2 Biological and symptom bases of the affective instability dimension in BPD

Affective instability
- Regulates baseline mood
- Regulates mood reactivity
- Regulates behaviors in face of emotional frustration

Symptomatic manifestations
- Baseline dysphoria
- Brief reactive dysthymias
- Intolerance to frustration/demand

Located in
- Limbic system
- Medial raphe
- Locus ceruleus

Neurochemical
- Serotonin deficit produces hypersensitivity
- Acetylcholine excess produces hypersensitivity
- Norepinephrine excess produces hyperreactivity

Table 3 Biological and symptom bases of the cognitive-perceptive dimensions in BPD

Cognitive-perceptive dimension
- It regulates the basic elements of the interpretation of the stimuli. Affective content, proportionality

Symptomatic manifestations
- Suspiciousness, interpretative distortions
- Lack of downscaling
- Paranoid ideation. Reference ideas
- Micropsychosis

Located in
- Prefrontal areas
- Cortical-subcortical connections

Neurochemical
- Cortical dopamine deficit

BIOLOGICAL TREATMENT OF BPD

Impulsivity/aggressivity dimension

Up to now, many drugs have been used as anti-impulsive agents, although none has this indication in the data sheet. The following are included among the different strategies used in this dimension:

– Serotoninergic potentiation (lithium, selective serotonin reuptake inhibitors, serotonin and selective serotonin and norepinephrine reuptake inhibitors, monoamino oxidase inhibitors).

Tabla 4 Biological and symptom bases of the anxiety-inhibition dimension in BPD

Anxiety-inhibition dimension
- It regulates the response to danger

Symptomatic manifestations
- Anxiety, dysphoria
- Fear, inhibition, concern
- Feelings of emptiness

Located in
- Amygdala
- Septum-hippocampus

Neurochemical
- Serotonin (hypersensitivity)
- CRH (hypersecretion)
- GABA (deficit)

- Noradrenergic antagonism (propanolol, clonidine, desipramine).
- Dopaminergic antagonism, mainly on the level of D2, D3, D4 receptors (antipsychotics).
- GABA potentiation.
- Glutamatergic inhibition (as in the case of antiseizure drugs).
- Opioid antagonism (naltrexone).
- Acetylcholine antagonism.

Antidepressants

Selective serotonin reuptake inhibitors (SSRI) have been widely studied and have demonstrated their efficacy in the management of impulsivity in patients with BPD. These drugs have few side effects and a very safe profile in the case of overdosage. Thus, they are considered to be one of the treatments of choice for the treatment of impulsivity. In many cases, their efficacy appears from the first week and is independent of the therapeutic benefit on depression. The fact that one SSRI is not effective does not predict that another one will be ineffective and the treatment duration depends on the comorbidity, exposure to stressing life events, treatment of the vulnerability traits and acquiring of skills in psychotherapy. In general, all the SSRI improve impulse control, improve information processing and reduce the dysphoria that often causes impulsive behaviors.

Fluoxetine has shown its efficacy in impulsive lack of control, decreasing impulsivity and self-injury behaviors and the sensation of rejection[16-18]. It has also been related with greater treatment adherence. On the other hand, improvement compared to placebo has been observed in verbal aggression and aggresivity against objects[19]. The findings suggest a rapid improvement of impulsive behavior from the first week of treatment and decrease of impulsive-aggressive behavior independently of the depressive status of the patient with mean doses of 80 mg/day[20-22].

Sertraline seems to decrease the irritability and impulsivity in these patients and some authors indicate an improvement in self-injury behavior after one year of treatment[19,23]. Furthermore, it also achieves an improvement in treatment adherence and is effective independently of the state of anxiety or depression with mean doses of >200 mg/day[24].

Another SSRI, paroxetine, has been associated to a greater decrease in self-mutilations, self-directed anger and has shown a significant decrease in all the SCL-90 subscales with mean doses of 315 mg/day[19,25].

Other SSRI have also shown to be effective both in double blind as well as open-label studies (fluvoxamine, citalopram).

However, SSRI seem to have some tolerability in their drug efficacy since it has been observed from a clinical point of view that some patients relapse after some months in their impulsive behaviors. Considering this feature, the dual inhibitors could show interesting results. In this sense, venlafaxine has been shown to be effective in controlling impulsive behavior either as an initial intervention or as an alternative if fluoxetine or sertaline has previously failed[26].

The use of tricyclic antidepressants (TAD) is controversial due to their adverse effects and the risk of lethality in case of overdosage. The most relevant data on the use of TAD are related with amitriptyline that seems to decrease the depressive symptoms and indirect hostility and consequently would play a role in improvement of self-control[27].

At present, MAOI[28] are not used very much, but their efficacy in atypical depressive symptoms and in the management of anger, hostility and impulsivity must be kept in mind, demonstrating their benefit in the studies done in this regards. Tranylcypromine, administered at mean doses of 40 mg/day and phenelzine have been able to control symptoms of impulsivity and self-aggressions in longitudinal studies[28-31].

In summary, SSRI are the drug of choice in the control of impulsive behaviors. Their efficacy appears before the improvement in the affective picture, this being already seen from the first week and its efficacy is independent of the concomitant depressive or anxious condition of the patient. The duration depends on the exposure to life stressing events, to the treatment of the trait and/or to the acquiring of skills in psychotherapy. On the other hand, it must be remembered that the lack of efficacy of an SSRI does not predict lack of efficacy of another one. Finally, the available data suggest that dual inhibitors may be effective, while the use of TAD is questionable and the MAOIs would present greater utility if there is comorbidity with histeroid dysphoria or atypical depression.

Mood stabilizers

Lithium and anti-seizure drugs (topiramate, gabapentin, valproate, carbamazepine, oxcarbamazepine, lamotrigine) have been demonstrated to improve impulsivity and self-destructive behavior symptoms and have proven utility when the cyclothymic traits are significant. There are many references in the literature on the use of these drugs in BPD.

Different authors have suggested that lithium achieves a reduction of the violence episodes and improvement of impulsive aggressivity, achieving a more reflexive behavior[31,32]. However, its pharmacological profile prevents it from being considered a drug of first choice, given the important risk in case of drug intoxications or suicide attempts that are so common in this type of patient. Another limitation is that cases of exacerbation of aggressivity

in patients who have behavioral lack of control associated to epilepsy have been reported[33].

Carbamazepine has been associated to a significant decrease in the number of suicide attempts and of serious episodes of lack of control, with improvement of the anxiety, anger and euphoria. It achieves a significant decrease of the impulsivity and a more reflective behavior in patients with BPD[29]. As in the case of lithium, this drug is considered to be a risk in case of intoxications due to its profile of side effects. The mean doses indicated in the studies reviewed are 600-1,200 mg/day[29].

Another one of the anti-seizure drugs studied most is Valproic Acid. This has also been demonstrated to be useful in this group of patients and is associated to improvement of agitation and aggression pictures as well as to an improvement in irritability, anxiety, anger, impulsivity and in hypersensitivity to rejection. It achieves a global improvement[22,34,35]. In another study, the use of valproic acid is associated with improvement of impulsive aggressivity and irritability in patients who had not responded previously to fluoxetine[36]. However, statistically significant improvements were not seen in the depressive component[37]. In general, it can be stated that valproic acid is a well-tolerated and effective drug in the treatment of global severity and nuclear symptoms of the borderline disorder. The mean doses used are 1,500 mg/day[38].

In turn, lamotrigine has been shown to be effective in decreasing impulsive, aggressive behaviors and in the management of anger[39,41,41]. It is suggested that its mechanism action would depend on its antiglutamatergic and neuroprotector effects[42]. The doses used are close to 100-200 mg/day.

Gabapentin has been the least studied, although it seems to improve irritability and there is an improvement of reflexive behavior.

Considering the efficacy of carbamazepine, oxcarbamazepine may be a promising drug with the advantages of its beneficial profile of side effects in regards to the former. In fact, in a recently performed study it was demonstrated that it improved impulsive behavior and affective instability of borderline disease[43]. The mean doses recommended would be about 900-2,400 mg/day.

Finally, one anti-seizure drug that has been studied recently is topiramate. This has demonstrated its efficacy in all the spectrum of impulsive behaviors with excellent tolerability. In the BPD, different studies have demonstrated its efficacy in the control of self-injury behaviors and in the reduction of anger, with mean doses of 250 mg/ day[44,45]. In another double blind, placebo controlled study, treatment with topiramate made it possible to achieve a significant decrease in aggresivity (hostility-state vs. trait)[46,47].

In conclusion, the anti-seizure drugs have shown a clear improvement in the impulsivity symptoms, self-destructive behaviors and reflexive capacity of these patients. In general, all the mood stabilizers have been effective, although some, such as topiramate or oxcarbamazepine, due to their adequate tolerability profile and wide spectrum impulsive action, seem to be among the most promising. It should be stressed that lack of efficacy with a mood stabilizer does not predict lack of efficacy with another one. Finally, lithium would be considered a second line drug due to its lethal risk in the case of overdoses.

Antipsychotic

Antipsychotic drugs are a group of drugs that are widely used in BPD even though they do not have a clearly defined indication. In general, lower doses are used then those used for psychotic disorders since it is considered that low doses are effective and that their use will also avoid the side effects which these patients are very sensitive to.

In BPD, treatment with typical antipsychotic drugs makes it possible to reduce impulsivity and self-injury behaviors. However, an elevated incidence of adverse effects is reported[30,31,48-50]. Currently, their indication is limited to the treatment of serious episodes[28].

The introduction of atypical antipsychotic drugs which have a better profile of side effects has led to the preferential use of these drugs over the typical ones. As with the typical anti-psychotic drugs, they would reduce self-injury and impulsive behaviors with lower doses than those used in psychoses. Intramuscular administration forms for use in emergencies for the treatment of the episodes and depot forms that improve therapeutic adherence and achieve global stabilization stand out.

Studies with clozapine, at mean doses ranging from 250-450 mg/day, have found a significant improvement of aggressivity and global psychosocial functioning[51,52].

Olanzapine has been the drug studied most among atypical antipsychotics. Five double blind, placebo-controlled studies and several open label studies that have demonstrated its efficacy in the reduction of impulsive behaviors, aggressivity, self-aggressions, hostility and personal hypersensitivity with a good tolerability profile have been conducted[21,22,53-55]. Specifically, in one of the studies olanzapine obtained better results than fluoxetine in the control of impulsivity in BPD[21]. The mean doses used ranged 5-10 mg/day[55].

Another one of the atypical antipsychotics that have been effective in the control of impulsivity of BPD is risperidone. The data suggest that it achieves a significant reduction of aggressivity and self-aggressions using a dose of 1.3 mg/day[56,57]. In our experience, the depot form of this antipsychotic drug is especially beneficial. It achieves global stabilization, better therapeutic adherence, and a decreasing in impulsive behaviors.

Finally, the Pérez-Sola group has reported positive results in an open label study with i.m. ziprasidone for the control of acute impulsivity in emergency situations (100 mg intramuscular dose). In addition, its excellent tolerability when administered orally makes this administration pathway a good option for the management of impulsivity[58]. Finally, although quetiapine and aripiprazole have been studied less, they have also been shown to control impulsivity and self injury behaviors in patients with BPD (at doses of 300-700 mg for the former and 10-15 mg for the latter)[59,60].

In conclusion, it could be stated that the studies performed up to now suggest that atypical antipsychotic drugs are the medicine of choice within this group, olanzapine being the drug studied most and that the i.m. form, mainly ziprasidone, and the deport form of risperidone are very beneficial to achieve stabilization and better adherence.

Omega-3 fatty acids

Treatment with omega-3 fatty acids is an innovative therapy that seems to be beneficial in BPD. It is based on the fact that the administration of eicosapentaenoic acid (EPA), a structural component of the neuronal membranes, and of docosahexaenoic acid (DHA), that participates in neuronal activity, would improve brain functioning. Thus, recent studies support that 1 g/day of EPA would decrease the aggressivity and severity of the depressive symptoms[61-63]. Omega-3 fatty acid enriched diets have been administered in many units specialized in BPD with good results.

Figure 1 shows a proposal in algorithm form for the treatment of impulsive dimension, taking the data supplied by the literature into account. Traditionally, SSRI were the first option for the control of impulsive behaviors. However, the results of different studies questioned this and made it possible to place atypical antipsychotics and mood stabilizers at practically the same level of choice.

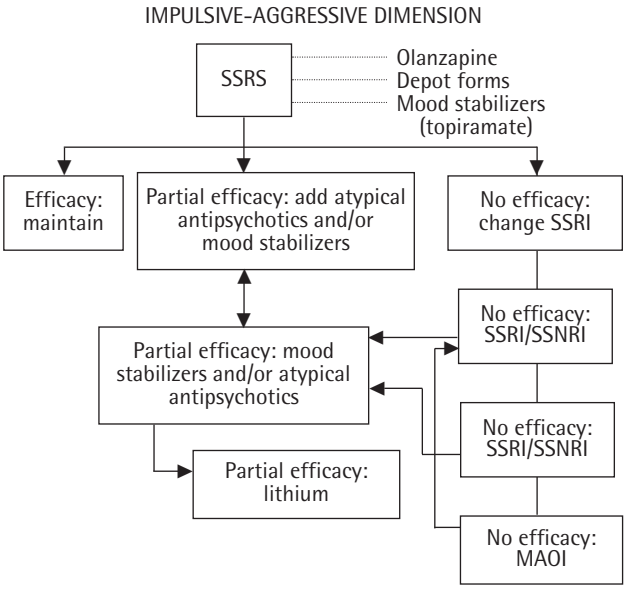

Figure 1 *Algorithm proposal for the treatment of the Impulsive dimension of BPD. (Traditionally, the SSRIs are considered to be the treatment of choice. However, with the data available, different atypical antipsychotics or mood stabilizers could also be the treatment of choice.)*

Afecctive instability dimension

Affective lability and the depressive symptoms in these patients are heterogeneous and are derived from the lack of empathy, boredom and mood instability that is sometimes secondary to life crises. At times, if these symptoms are not treated, they may crystallize into a depression episode. Antidepressants, mood stabilizers and some antipsychotics have been used for the treatment of this dimension. Figure 2 shows an algorithm proposal for the approach to this dimension.

Antidepressants

SSRI have demonstrated a clear improvement in the mood status, improving the perception of the self-image and development of interpersonal roles. The efficacy of the SSRI has been studied in multiple and different works with positive results that support their indication in this dimension.

Specifically, Norden et al. demonstrated that fluoxetine improved hypersensitivity to rejection, anger, depressive mood, emotional lability, irritability, obsessive-compulsive symptoms and anxiety and the Cornelius group suggested

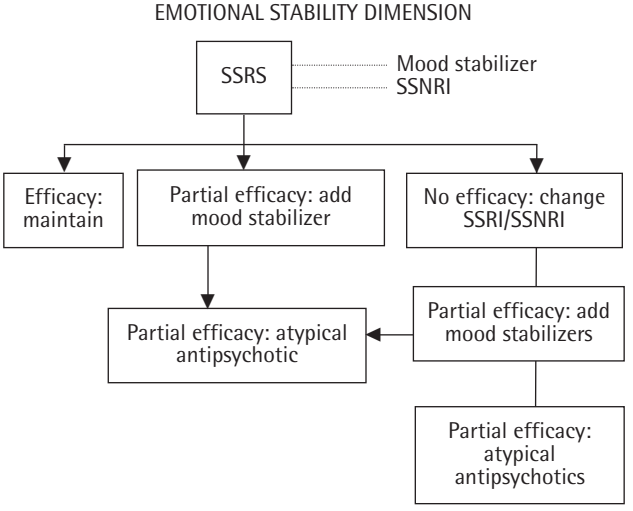

Figure 2 *Algorithm proposal for the treatment of emotional instability dimension in BPD.*

that fluoxetine achieves a significant decrease in symptoms of depression, hostility, paranoia, somatization and obsessive-compulsive symptoms in addition to a significant improvement of global functioning (at doses of 20-40 mg/day[17,64].

In turn, sertraline appears to decrease irritability and affective symptoms in BPD[19]. On the other hand, both paroxetine and fluvoxamine have been effective in borderline patients with depressive symptoms associated to states of anxiety and with affective instability[65]. Finally, within the SSRI group, Citalopram has been shown to be useful in patients with depressive pictures with inhibition symptoms[66].

Up to now, there are few studies that support the efficacy of dual antidepressants in the treatment of affective instability in BPD. However, the noradrenergic and serotoninergic regulation achieved by these drugs seems to be able to provide excellent results in the management of dysphoria, apathy and the brief depressive symptoms typical of these patients.

With the TAD, paradoxical responses have been reported and, in some cases, effective deterioration (amitriptyline, imipramine)[27,29]. This, together with their potential life-threatening risk in the case of overdosage make it necessary to consider these drugs as a third line treatment of BPD. In regards to MAOI, their use is also limited even though they have shown good evidence of efficacy in mood stabilization, improvement in hedonic capacity and reduction of anxiety (phenelzine, tranylcypromine)[29,30]. Among their indications, atypical depression or worsening of the typical depression as well as hypersensitivity to rejection are included when other antidepressants have failed[67].

In summary, the SSRI would be the treatment of choice for affective instability of BPD according to the literature since they have demonstrated efficacy and low life threatening risk in the case of overdosage. These drugs achieve an improvement in the depressive mood status, irritability, perception of self-image and interpersonal relationships. In general, the doses used are greater than those used in the depressive pictures. Of the SSRI, fluoxetine has been studied the most. There is little data on dual antidepressants. However, those cases in which dysphoria, apathy and life boredom predominate could benefit from these drugs because of the noradrenergic and serotoninergic regulation. Finally, the TAD and MAOI would be a third line treatment after failure with other antidepressants.

Mood stabilizers

As in other affective disorders, mood stabilizers have been used in affective deregulation of BPD.

Lithium has been used in affective deregulation and emotional instability because of its actions on the serotoninergic system. Based on this, its use in unstable personalities on the emotional level has been proposed. However, as has been commented previously, its toxicity profile in the case of overdose does not make it recommendable to be used as a first choice treatment.

Among the anti-seizure drugs, valproic acid has been demonstrated to act in the improvement of irritability, anxiety, anger, hypersensitivity, rejection and scores on general psychopathology scales in BPD, and that it achieves global stability of the patient[22,35]. The drug seems to be safe and effective in the treatment of women with BPD who have diagnostic morbidity with bipolar I disorder. It mainly acts on decreasing irritability and anger, impulsive aggressivity and improving tempestuous relationships with no clear relationship with the improvement of the depressive symptoms[8]. In this sense, Hollander also found no significant differences in the reduction of the depression symptoms in a group of patients with BPD[69]. Thus, it seems to be a drug that would act on a global level, establishing improvement without clear remission of the depressive symptoms, if these exist.

The remaining anti-seizure drugs, topiramate, oxcarbamazepine, or lamotrigine, have demonstrated efficacy in the treatment of affective instability of the borderline disorder. Specifically, lamotrigine improves emotional stability, decreasing depressive symptoms and stabilizing impulsive self-injury episodes[39,40,70]. On the other hand, the weight loss associated to treatment with topiramate may be useful in cases of atypical symptoms, such as binge eating or in those cases of emotional instability of BPD that have comorbidity with bulimia nervosa[29,35,69,22,45].

In general, mood stabilizers improve mood changes, irritability, anxiety and anger and strengthen the antidepressive effect of the antidepressants at the usual doses.

Antipsychotics

Different antipsychotics, especially the atypical ones, may be useful at low doses, in the management of affective symptoms in BPD. Some years ago, trifluoperazine was recommended for patients who fulfilled criteria for histeroid dysphoria. It achieved improvement of the affective symptoms such as symptoms of depression, anxiety, sensitivity to rejection and suicide attempt index[29].

Among the atypical antipsychotics, it has been demonstrated that clozapine improves depressive symptoms and emotional liability[49]. As in the control of impulsivity, olanzapine has been the drug studied most and the data suggest its efficacy in the rejection of interpersonal sensitivity, depression, anger-hostility and phobic anxiety[21,22,53-56,60]. Preliminary data suggest the efficacy of risperidone, quetiapine and ziprasidone in affective improvement in BPD[57-59].

Omega-3 fatty acids

As in impulsivity, treatment with omega-3 fatty acids seems to be beneficial. One gram/day of eicosapentaenoic acid (EPA) has been demonstrated to decrease the severity of depressive symptoms[61-63].

Cognitive-perceptive dimension

Use of atypical antipsychotics is the treatment of choice for suspiciousness, interpretive distortions, paranoid ideation and brief episodes of psychosis.

Antipsychotics

Efficacy of the antipsychotics in cognitive-perceptive disorders in BPD is based on the possible associated dopaminergic dysfunction. In fact, psychotic episodes have been described in these patients using dopaminergic agonists[71]. The use of low doses of antipsychotics makes it possible to reduce and control micropsychotic episodes, paranoid and referential ideation, psychotic regressions and mild conceptual disorganization[49].

Several studies have been done with typical antipsychotics (thioridazine, flupentixol, loxapine, thiothixene, chlorpromazine haloperidol)[48,49], with beneficial results. However, the greater tolerability and better treatment adherence achieved with the atypical drugs makes them the most indicated treatment.

Along this line, different investigators support the use of atypical antipsychotics in cognitive distortions of patients with BPD. Improvement of the symptoms of the cognitive-perceptive sphere is achieved with clozapine in this type of patient although this drug is reserved as a second choice due to the risk of agranulocytosis and other side effects[50]. Both risperidone (2-4 mg/day) and olanzapine (5-10 mg/day), ziprasidone (80-100 mg/day) or quetiapine (600 - 800 mg/day) have shown their efficacy in the treatment of cognitive-perceptive distortions in borderline disorder with reduced risk of extrapyramidal effects[21,54,56,58,59]. All of them improve paranoid ideation, conceptual disorganization, hostility and anger and psychotic regressions. The mean doses needed for this clinical stabilization are not very elevated and the efficacy appears within days or weeks. Finally, a duration greater than 3 months is recommended in order to achieve the desired therapeutic effect. In case of comorbidity with the axis I or frank psychotic symptoms, it would be necessary to increase the dose[21,50,54,59,60,72,73].

Inhibition-anxiety dimension

The symptoms derived from the anxiety-inhibition dimension may cause the least concern to the clinicians, although they have special relevance in the global functioning of the patient. Special mention has not been made of them in the different studies, among other reasons, because the previously indicted drugs may be useful for other dimensions. Treatment with antidepressants, mood stabilizers or benzodiazepines achieves a significant reduction in anxiety levels.

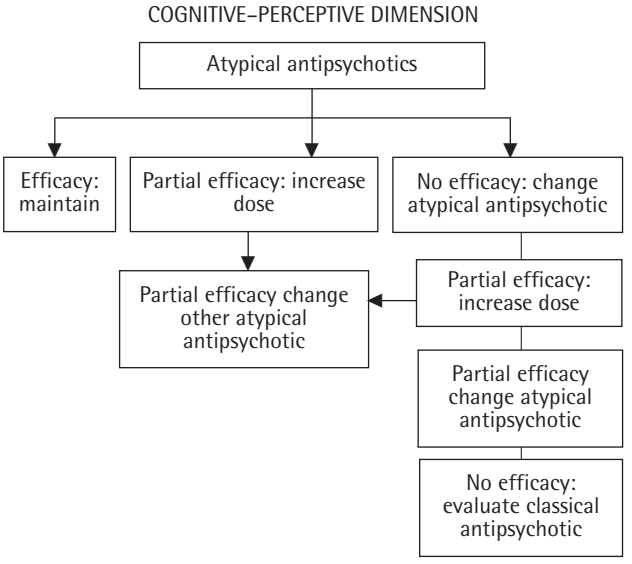

Figure 3 *Algorithm proposal for the treatment of the cognitive-perceptive dimension in BPD.*

Antidepressants

In regards to the SSRI, they improve the state of anxiety, agitation and dysphoria as well as inhibition, fears and concerns through 5HT regulation[7,22,64,68]. Based on the symptoms, either a sedative or activator profile would be chosen. The doses used for the treatment of anxiety in BPD would be the common ones in the treatment of other anxious-depressive pictures. The SSNRI, as in the rest of the dimensions, have been studied very little, although venlafaxine has demonstrated its efficacy in the reduction of anxiety in some[26].

Antipsychotics

It should simply be stated that the atypical antipsychotics could be used due to their «non-specific tranquilizing» effect and at low doses.

Mood stabilizers

Mood stabilizers, as is already known, participate in GABA regulation. Thus, they could improve this dimension when

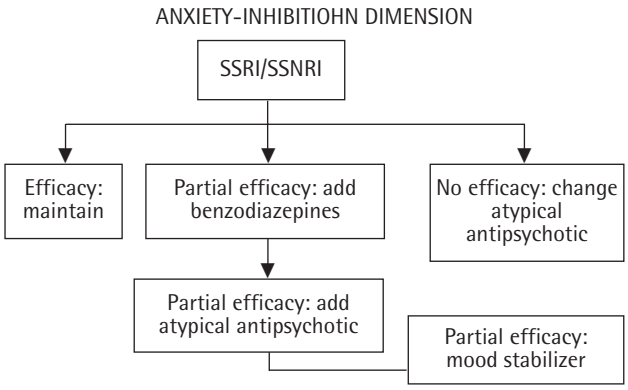

Figure 4 *Algorithm proposal for the treatment of anxiety dimension.*

prescribed in order to manage symptoms of any other one of the dimensions in which its use is considered as effective.

Benzodiazepines

Benzodiazepines, which act by reducing anxiety and dysphoria, would be useful in situations of crisis and in cases of elevated anxiety, it being recommended to use middle-long life benzodiazepines such as clonazepam at the usual doses[74,75]. However, it should be kept in mind that patients with BPD have a greater risk of abuse and in some cases, their use has been associated to a paradoxical effect of behavioral disinhibition (above all with alprazolam)[75].

Figure 4 shows the treatment proposal for this dimension.

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