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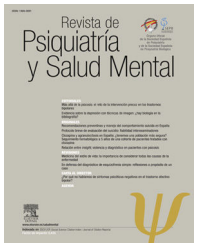

EDITORIAL

Disruptive treatments in psychiatry☆

Tratamientos disruptivos en psiquiatría

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The history of psychiatry is replete with times when therapeutic advances were made but also crucial moments where truly disruptive changes came about. Perhaps one of these moments, for its symbolism, was the release of mental patients from their shackles by Father Jofre. Another controversial event was the discovery of the anti-aggressive properties of psychosurgery by the neurosurgeon and alienist Edgar Moniz, which won him the Nobel Prize. Treatments regarded as revolutionary in their time, such as lobotomy, are now questioned but it is a forgotten fact that they were the only solutions for extremely severely ill patients who self harmed and for whom no effective treatments were then available. However, the problem of truly disruptive treatments, and particularly those from way back, when not many options existed, is that their usage was abusive, seeking to resolve all difficulties with the same tool. The use of lobotomy was definitely abusive and was even used in patients for whom the benefit/risk profile was not justified and the patient's opinion was listened to far less than it is now.

The first treatments which changed the history of psychiatry

In my opinion, anticonvulsant therapy (ACT) is the first disruptive treatment in mental health which has remained in effect since its infancy. Obviously the technique has improved and patient participation in decisions as well. ACT is one of those treatments which was also used abusively, generally with good intentions to improve severely ill patients who were resistant to other treatments, but in many cases they had diseases which nowadays we consider would not require ACT, such as serious obsessive disorders or personality disorders. However, the main barrier to current ACT usage is the social stigma attached to it. This stigma, as we will comment upon directly, is also one of the causes why advances in psychopharmacology rarely arouse the same public enthusiasm as those for cancer treatment and other non psychiatric diseases. At present psychotherapies receive a much better press than psychiatric medications.

Perhaps on top of the podium of disruptive treatments for mental illnesses is *chlorpromazine*. The appearance of antipsychotics enabled a large number of mentally ill patients to be de-institutionalised and for millions of people suffering from psychotic symptoms, manic symptoms, confessional syndromes and agitation to return to the real world. Although schizophrenia was not cured, both chlorpromazine and all of its subsequent offshoots have led to one of the most significant changes in the history of humanity. Among these drugs *haloperidol*, *risperidone* and the other so-called ''atypical'' or ''second and third generation'' drugs are outstanding. However, the one which deserves a special mention and is part of the select group of ''current disruptive treatments'' is *clozapine*. Clozapine acts in a different way to the other antipsychotics, particularly due to its efficacy in treatment-resistant schizophrenia.[1] Although it is not a particularly effective drug in negative and cognitive symptoms which, for many represent the greatest challenge in the treatment of schizophrenia, its effectiveness in patients who do not respond to other antipsychotics means that this drug is a valuable and underused tool.[2] We

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are still unaware as to which aspect of its mechanism of action makes it so exclusive. Within the group of first and second generation antipsychotics, special mention needs to be made of the dosage innovation of its depot and slow release formulations.[3] These drugs have a superior effect to their oral equivalents because therapeutic adherence is improved.[4,5]

What should we say about the supposed discovery of monoamine oxidase inhibitors (MAOIs), such as *iproniazid,* and the first trycyclic, *imipramine*? How many lives have been saved by antidepressants? Although it is true that both iproniazid and imipramine are used far less now than in the past, both drugs initiated a phase in which the treatment of severe depressions stopped being exclusive to the ACT area. For moderate depressions, the first antidepressants improved the quality of life of many patients, at the cost of upsetting adverse effects (like the anticholingerics) or in the case of the MAOIs, potentially dangerous interactions. It was not until the invention of selective antidepressants among which we would highlight *fluoxetine* - not the first but the one that revolutionized the market for the public and the press -access to antidepressant treatments for mild and moderate depressions became mainstream. This was due to its higher benefit/risk compared with trycyclics and MAOIs, resulting, for example, in psychopharmacology reaching the same level of popularity as psychoanalysis.

A long time before the discovery of fluoxetine, and even before that of chlorpromazine (we do not intend to establish a chronological order because some drugs were discovered many years ago but their application in mental illnesses was delayed more than others), the famous Cade publication on the properties of *lithium* salts was produced. Without a doubt lithium is one of the disruptive treatments in the history of psychopharmacology which has best resisted the passage of time.[6] Although the use of anticonvulsants marginalised lithium (especially in United States) for several decades and although this was a drug with a tight therapeutic margin which required monitoring, lithium remains fully in vigour[7,8] and in some patients has no replacement. Drugs like valproate, carbamazepine and lamotrigine are still highly important but perhaps are not at the level of being classed as disruptive.

Benzodiazepines are still popular drugs (no doubt among their consumers more than their prescribers). They are very safe drugs (which is why they have displaced barbiturates), but with a highly addictive potential. They are the drugs of choice in acute anxiety crises and in insomnia. The most paradigmatic benzodiazepine is most probably *diazepam*.

Methylphenidate is, without a doubt, one of the psychopharmacological treatments with the greatest effect. It has changed the lives of many children and should therefore also be included in the list of disruptive treatments.

With regard to addictions, *naltrexone and methadone* are by far the most important.

Psychotherapies

From an historic and cultural viewpoint, probably *psychoanalysis* is the psychotherapy with the greatest impact ever. Notwithstanding, its validity is highly questioned and these days cognitive-behavioural techniques and psychoeducation are being used much more. *Cognitive-behavioural therapy* is the treatment of choice for most anxiety disorders, obsessive disorders, eating disorders and behavioural addictions, and it is highly recommended for depression and other diseases when combined with psychopharmacology. It is an essential element for most treatments for children and teenagers. *Psychoeducation*[9] and early psychological interventions[10,11] whilst following a medical model aim to empower patients and family members for better handling of moderate and severe mental disorders. Its use has been imposed as an essential complement to pharmacological treatments. *Motivational therapy* is essential for addictions. There is also evidence for dialectic behavioural therapy in some personality disorders.[12] Other interventions, such as activation therapy or mindfulness do not yet offer any conclusive data for most indications.[13] Many of these techniques are undertaken in group environments.

Potentially disruptive treatments

We say ''potentially'' because their real clinical impact is yet to be proven. Among them are the *brain stimulation techniques* (magnetic, transcraneal, deep brain) and the new glutamatergic and GABAergic action drugs. Also online and mobile device psychotherapies.[14] There is some evidence to suggest that stimulation techniques are effective on depression, but many questions remain regarding stimulation parameters (area, intensity, frequency). At present there is no solid evidence for other indications.Esketamine is an isomer of ketamine administered intranasally and has an enormous potential as a very fast acting antidepressant with antisuicide action.[15,16] Its genuine opportunities to revolutionise the treatment of affective disorders and suicide will shortly be observed, when its use is generalized after approval by the regulatory authorities. Other antagonists and glutamatergic receptor modulators are under investigation, together with drugs with hallucinogenic potential such as psilocybin (a substance present in some fungi with action similar to that of lysergic acid or LSD) or methylendioxymethamphetamine, which could suppress undesirable memories in patients with post traumatic stress syndrome.[17] The GABAergic route however already also has a drug which has been approved in the United States: *brexanolone* or alopregnanolone, a neurosteroid with an agonist action of the GABA-A receptor (actually a positive alosteric modulator) with proven efficacy in infusion of 60 h in postnatal depression.[18] *Zuranolone* uses a similar mechanism of action but may be administered orally and already has positive data not just for postnatal depression but also for major depression in general.[19] It is a drug with an excellent tolerability, ultra-fast action and episodic dosage (no maintenance treatment is required) like brexanolone, and with the advantage of oral formulation. Preliminary results would need to confirmed to verify its impact on clinical practice.

Shortcomings

There are many. We need disruptive treatments for anorexia, disorders of the autistic spectrum, dementias, bipolar pathologies, etc., and we need to improve what we already have with regards to efficacy and tolerability in all

mental disorders. We have reasons to be optimistic since there is an increasingly wider social awareness regarding the need to effectively treat mental disorders (although we are still dragging far behind the interest aroused in other areas of medicine) and unfortunately it is true that the rate and prevalence of mental disorders is on the rise.[20]

Ranking

What is the most important disruptive treatment in the history of psychiatry? The answer is highly individual. There are arguments for all opinions (some defend less conventional options which we have not explicitly mentioned, such as naloxone, olanzapine, alprazolam or amphetamine) and *rankings* are always rather arbitrary but also fun. It is probable that, among psychotherapies, the treatment with the highest historical and cultural impact is psychoanalysis but the one capable of improving the most illnesses for which there are few pharmacological treatments is cognitive-behavioural therapy and the best co adjuvant treatment could be psychoeducation, either individual or in a group. From a historical viewpoint, the podium would possibly be a tie between clorpromazine (the first antipsychotic), ACT and lithium, contending with imipramine (or, more symbolic than this, iproniacide). From the viewpoint of clinical disruption, regardless of the history, candidates would be clozapine, fluoxetine (and the other ISRS) and the new one, lithium, and not least methylphenidate. Due to their social impact, the benzodiazepines should be on the list. In a survey undertaken among senior researchers in the Centre for Biomedical investigation in the Mental Health Network[21] (a relatively small but select group of experts in mental illness treatment), the most voted were, in this order, fluoxetine (representing the selective serotonin reuptake inhibitors), chlorpromazine and diazepam (representing the benzodiazepines).

One question we should ask as clinicians is to what extent we are taking advantage of the potential of disruptive drugs which still form part of our pharmacopoeia. Do we use clozapine enough? And Lithium? These 2 drugs (possibly my 2 favourites, if I may say so) are underused by aspects relating to the (relative) complexity of their prescription. The same occurs with ACT. Its appropriate use may be considered an indicator of quality in clinical practice,[22] pending advances in precision psychiatry which leads to better fine-tuning of all available treatments.[23] I hope that the readers of this article are encouraged to do their own ranking and to examine their clinical practice in search of opportunities to offer their patients the really disruptive treatments we have and will possibly have in the future.

Conflict of interests

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