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ANXIETY - THERAPEUTIC OPTIONS FROM PAST TO PRESENT

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ABSTRACT

Anxiety is a diffuse fear of an object, rather potential than present, it is detached from concrete and projected in the future. It associates psychomotor restlessness and has neurovegetative response. Anxious symptoms create a discomfort that patients experience with great difficulty. Whether we are talking about generalized anxiety, or we are talking about anxious paroxysms, patients call for help, sometimes in Emergency Room (ER) because of irrational fear of death, or fear of madness. The anxiety disorder is common in all medical healthcare offices, but especially in psychiatry. The therapeutic attitude is based on the same principles everywhere, but there are situations in which the treatment differs and psychotic anxiety, the particular form requiring admission into specialized service, is under discussion here. If in the past, the first intention was benzodiazepine (BZD) anxiolytics at the moment, they are increasingly finding their place in the therapeutic scheme. The beneficial effect installs quickly, but when balancing the balance versus risk, balances often tend to overcome the anxiolytic classics. Nowadays, more frequently, protocols recommend administering SSRI antidepressants to treat anxiety. In the case of emergency in which anxiety occupies a main place, such as psychotic anxiety, it is necessary to prescribe antipsychotics, especially atypical antipsychotics. For these reasons, we aim to share our experience for patient benefit.

Keywords: anxiety, anxiety paroxysms, benzodiazepine anxiolytics, SSRI antidepressants.

INTRODUCTION

Anxiety disorders are commonly medical conditions, in general medical practice and more frequently in psychiatry practice. They include a wide range of symptoms requiring treatment due to their disabling potential. Anxiety is perceived as "fear without object" (Predescu & Brasla, 1976, pp. 386-391; Piaget, 1964, p. 47). Normally anxiety occurs as a transient response to new experiences, spent or anticipated changes if, or under stress. In these situations, it is a factor of progress, making it possible to successfully overcome the moment. Anxiety with clinical significance is an inadequate response to a given stimulus or just anticipated whether it is real or imaginary (Sandu, 2021a; 2021b). From the clinical point of view, there is no external stimulus objectively triggered in causing anxious symptoms. However, the experiences are persistently intense, which determine anxious behavior avoidance or social withdrawal. The prevalence of anxiety disorders worldwide is increased without having the right data due to sub diagnostics and the lack of correct mapping. According to the Epidemiological Catchment Area (ECA) study conducted by the National Mental Health Institute of the U.S. (National Institute of Mental Health) lifetime prevalence of anxiety

disorders is 14.6% and one year is 12.6% (Udristoiu & Marinescu, 2012, p. 160). Also, in the U.S. the magnitude of the phenomenon has been measured between 1990 and 1992 and the National Comorbidity Survey (NCS) has determined that the prevalence of anxious conditions was 25%, with a gender distribution of 19% for men and 33% for women (Udristoiu & Marinescu 2012).

Clinically, two major elements of anxiety disorders are described: psychiatric manifestations and somatic manifestations.

Psychiatric manifestations include anxious symptoms in which anxiety, fear without cause and worry are the essential elements in establishing the diagnosis (Paduraru et al., 2019). Concern is perceived as a high negative potential. Sometimes the intensity of symptoms is elevated, which will cause paroxysms that can be felt as an imminent death sensation, or the fear of madness. Along with the anxiety component there is also described the cognitive component, which is responsible for lowering the attention concentration capacity, but with selective voluntary hyperpyrexia, short-term memory difficulties. From the somatic point of view, anxiety disorders may occur dizziness, sweating, diarrhea, palpitations, tachycardia, psychomotor restlessness, hypertension (HTA) paroxysms, especially paresthesia of the limbs, tremor and nodule in the throat. Physical symptoms occur repeatedly, and they are not subject to voluntary control, they are not simulated and cannot be deliberately determined. Concerned about the functioning of his or her body, the anxious patient checks his pulse, checks the appearance in the mirror, and facies express fear, terror, terror. It can often associate the feeling of suffocation, the impression that the heart can stop from one moment to the next, pain in various areas of the body, often abdominal and sweating. Trying to systematize the generalized anxiety in main and secondary symptoms, the first category includes the inability to relax, restlessness, fatigue, disproportionate responses, muscle tension, sleep disruptions, difficulty concentrating, irritability, and in second nausea or abdominal pain, sweating, dry mouth, tachycardia and their perception as palpitations, tremor (Nutt & Balenger, 2005, p. 10).

MANAGEMENT OF ANXIOUS DISORDERS

The anxiety symptoms are so invaliding to disrupt the life and activity of any person. Suffering causes avoidance of any situation or place that may be related to triggering any anxiety disorder. Sometimes patients with anxious complain consider somatic symptoms to be caused by a serious risk of vital illness such as myocardial infarction. The therapeutic intervention is required; it has been a therapeutic priority long before. The way to initiate a therapy differs over time. In the 1980s, anxiolytics were recommended in "moderate doses" for 2-4 weeks (Predescu, 1998, p. 829; Predescu 1976, p. 179). The recommendation was for benzodiazepine anxiolytics: diazepam, medazepam, hydroxyzine but also chlordiazepoxide, opipramol, amobarbital sodium in combination with various other substances. Introduced into medical practice for over 50 years their use has gained a great deal. This is due to the rapid response and improvement of symptomatology and good tolerability. Initially called tranquilizers, later known as anxiolytic, ataractic, were recommended for the treatment of neurotic states, and they were accredited with the installation of psychic, somatic and vegetative serenity.

Tranquilizers / anxiolytics are a pharmacological class that includes groups of drugs whose principal psychopharmacological action determines diminishing anxiety, reducing mental state, controlling excitement states - psychomotor agitation, also improving behavioral disorders, balancing emotional reactions, but also other effects: miorelaxant, anticonvulsant and antihistamine, secondary benefits of blockade of beta-adrenergic receptors (Marinescu, 2011, pp. 103-112).

In previous classifications, anxiolytic medication was framed in minor tranquilizers that were differentiated by major tranquilizers that included classical neuroleptics (Delay & Deniker 1961, p. 374; Gittelman & Klein 1984; Tyrer, 1977). Nowadays there are several types of substances that have the main anxiolysis effect, and the most used are benzodiazepines (BZDs). Besides these, they include the following subclasses: Azospirodecandions (Buspirona), Carbamates (Meprobamate), Beta-blockers (Propranolol), GABA transporter inhibitors (Tiagabine), other tranquillizing or anxiolytic agents, Sedative antihistamines Benzodactamine (Tacitine), barbiturates that also have hypnotic, anxiolytic and anticonvulsant effect, other psychotropic drugs: sedative neuroleptics, antidepressants, anxiolytics (Marinescu, 2011). Benzodiazepines have been widely prescribed since the 1960s to 1980s for anxiety disorders by psychiatrists, family physicians, internists, because the level of knowledge shows that the efficacy is good, the tolerability is good, with a high degree of safety, compared to other anxiolytics such as barbiturates and meprobamate (Schatzberg & Nemeroff, 2004, pp. 371-383). Retail sales of benzodiazepines reached a maximum of 87 million / year in 1973-1975, and the US has the largest sales volume in the world. If diazepam initially occupied the primary site, over the course of time, sales of short-chain elimination half-drugs (alprazolam) increased compared to long-acting drugs (diazepam) (Marinescu, 2011). In the 1990s, there was a shift in the share of sales in the sense of their growth in favor of SSRIs (selective serotonin reuptake inhibitors), which became the main therapeutic alternative to anxiety disorders. In the USA. between 1979 and 1990 the consumption of benzodiazepines fell from 11.1% to 8.3%. Initially, the mode of action of benzodiazepines was not known, and it began to be elucidated after 1977 when the benzodiazepine receptors, the Central Nervous System (CNS) GABA receptors, were discovered. Currently, there are three

types of GABA receptors: GABA-A, GABA B and GABA C. In addition to these receptors involved in anxiety, alpha-2-delta (α2δ) ligands have also been shown to play an important role in blocking glutamate release. As substances involved in subunit (α2δ) binding are pregabalin and gabapentin (Stahl, 2018a, pp. 397-400).

Pharmacologically it is determined by its action by improving the GABA-ergic transmission by blocking the GABA-A receptors / Cl ion channels. Receptor blocking causes the ion channels of Cl to open and penetrate the cell. BZD activates all three GABA-A receptor binding sites and in this way determines the anxiolysis effect. The use of benzodiazepine anxiolytics in the management of anxiety disorders is due to their mode of action, starting from their structural characteristics and in vivo behavior. The pharmacokinetic characteristics guide the clinician in their use. There are differences in intestinal absorption, distribution and elimination. The absorption rate is high in the digestive tract, those that are rapidly absorbed enter faster in action than those with slower absorption. Diazepam is one of them. Absorption after intramuscular injection is due to other factors. An example of lorazepam has good absorption rates in both administrations whereas clordiazepoxide has much better oral absorption than in the injectable form liposubility is another factor to be considered. Thus, at a physiological pH BZD passes the blood-brain barrier through diffusion determines the rapidity of the effect, but also its intensity. Diazepam is rapidly absorbed, being more liposoluble, reaching its maximum blood concentration after approximately one hour, but lorazepam has the intermediate absorption rate (Greenblatt et al.1983).

Depending on all the data outlined above, there are advantages and disadvantages in the use of the benzodiazepine anxiolytics used. Substances with short half-life have the following advantages: along with anxiety reduction, rapid action, especially in anxious paroxysms, low sedation, lack of accumulation in the body, and the possibility of administration to the elderly, but with caution. Disadvantages include multiple dose administration, faster deployment of addiction syndrome, rebound insomnia, and anterograde amnesia, which may precipitate the onset of cognitive impairment (Schatzberg &Nemeroff 2004).

The other type of benzodiazepines with longer half-life has, besides the anxiolytic effect, the benefit of less frequent administration, less frequent dosing, much lower fluctuations in plasma concentrations, less frequent depression, and less severe abstinence symptoms. Disadvantages are also present in these substances: the risk of drug accumulation, the greater possibility of psychomotor disorders during the day and the occurrence of diurnal sedation with its whole follow-up corollary.

Administration of benzodiazepine anxiolytics between benefit and risks. Anxiolysis in anxiety disorders is the main effect, which has led to their excessive use especially in the second part of the last century. The research that has been carried out and the data behind them reveal several side effects that make us wonder: is it worthwhile taking the risk of side effects? Every time we initiate a therapy, we have to balance it to what it is: to the potential therapeutic efficacy, or to the risks of adverse effects? We have tried to identify the most common adverse effects, but also to draw attention to the ones that may occur in various categories of affections or patients. The most common risk is the abuse of substances, the possibility of installing dependence on the entirety of symptoms. Then excessive sedation often occurs with daytime somnolence, which is why drivers and those who carry out activities requiring motor coordination should be warned. There is a possibility of detection state of residual daytime sedation even if benzodiazepine anxiolytics were given the night before. In the case of the elderly, there is the possibility of installing delirium, especially in case of administration of substances with long half-life, the possibility of triggering the cognitive disorder with amnesia fixation, confusing state (Radulescu et al., 2020). Aging and vertigo may also occur in the elderly, which may cause accidental fractures and fracture of the hip. As described effects: muscle hypotonia, fatigue, nystagmus, dysarthria, headache, somatic disorders such as respiratory, sleep apnea, administration of these substances is contraindicated in decompensated liver disease; administration is prudent and at low doses due to the risk of inducing hepatocellular carcinoma. The teratogenic risk, the newborn's reaction to breastfeeding after benzodiazepines, is also quoted (Schenker et al., 2022). Neurological disorders due to stroke after vascular accidents usually have minimal recommendation for treatment with anxiolytic agents due to the possibility of triggering paradoxical effects with agitation and extreme aging. In the case of affective disorders, the administration of these benzodiazepines may lead to manic reversal in the case of depression, or even more importantly, the risk of suicide may be triggered by triggering the suicidal ideation (Sadock & Sadock, 2002, pp. 63-74; Stahl, 2018b, pp. 5-11). Another important thing is the risk of associating alcohol consumption with anxiolytic medication due to the risk of substance abuse, but also by respiratory distress, disinhibition, then marked sleepiness.

If the first intention treatment recommendation in the 1970s was anxiolytics, especially benzodiazepines, towards the end of the 20th century they are being used in combination with tricyclic antidepressants, namely imipramine or clomipramine (Delay & Deniker, 1961; Gittelman & Klein, 1984).

At present, the management of anxiety from a psychopharmacological point of view requires a more complex approach, due to scientific arguments resulting from clinical trials, the argumentation of the neurotransmitters involved, clinical efficacy, but also latency until the therapeutic response is established.

Anxiety disorders, whether we are talking about generalized anxiety disorder, panic disorder, posttraumatic stress disorder, other reactions to severe stress, have first-line recommendations for SSRIs or SNRIs before benzodiazepines to which buspirone and α2δ ligands can be associated (Stahl, 2018b, pp. 93-98; World Health Organization, 1992). Here are quoted opinions on the use of benzodiazepine anxiolytics due of the risk of addiction, given that generalized anxiety disorder, for example, is a chronic disease and requires long treatment. Regarding the therapeutic attitude for chronic, recurrent anxiety, antidepressants are the first choice, the other psychotropic drugs are used only as adjuvant medication to augment the effect of antidepressants. The most recommended are SSRIs and SNRIs for the most common type of anxiety disorders (Sadock et al., 2009). Similarly, the therapeutic attitude of other authors, (Boyer, 1995**)** recommends first-line SSRI medication, which are more effective than alprazolam and imipramine in the treatment of anxiety. Doses will be customized by each patient and the type of anxiety disorder.

As a conclusion of all the above, it results that in recent years solid arguments have emerged in dethroning benzodiazepines from the first therapeutic line and passing them to the second place as associated medication. In this context, the SSRI antidepressant medication becomes the first choice. Although they act slower on anxiety symptoms, they are better tolerated in the longer term, with long-term efficacy, and for each type of anxiety disorder, the FDA recommends a certain substance (Stahl, 2018, pp. 139-144). The FDA guidelines for treatment of anxiety disorders are generalized anxiety - escitalopram, panic disorder - fluoxetine, social anxiety disorder - fluvoxamine, GAD, PTSD - paroxetine. SNRIs are also a therapeutic alternative, so venlafaxine has FDA recommendation for generalized anxiety disorder, panic disorder, and social anxiety. With regard to Duloxetine, it has an indication from the FDA for generalized anxiety disorder (Stahl, 2018b, pp. 301-306).

As with benzodiazepines, SSRI and SNRI antidepressants are advantages and disadvantages when used. Advantages include the following: lasting efficacy in all anxiety disorders, overdose safety, low weight gain, no risk of addiction. Concerning the drawbacks, it should be mentioned that the slow, delayed onset of the therapeutic effect may initially cause anxiety, gastritic side effects may occur at initiation of treatment, and sexual dysfunction throughout treatment (Udristoiu & Marinescu 2012).

CONCLUSIONS

In conclusion, we can state that a correct assessment should be made with the discovery of the possible therapeutic emergencies in which the main element is anxious paroxysms. The therapeutic attitude in the case of anxiety disorders depends on each individual patient, and the initiation of the treatment must take into account the intensity of the symptoms, the mode of action of each psychotropic used, the correct assessment of the benefit versus risk balance.

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