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Clinical Models and Evaluation Measures in the Study of Experimental Anxiety

REVIEW

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Abstract

Objectives: the following review aims to present accumulated evidence in the literature around the main human models for induction of anxiety and the measures frequently used for its evaluation.

Method: It was made a bibliographic research having as source of research articles listed by Pubmed and Medline databases and research in specific books which have investigated the main human models for experimental anxiety induction and the measurements frequently used for its evaluation.

Discussion: Both the psychological and chemical models for anxiety induction present ethical limits and are constituted of fundamental links between basic research and therapeutic tests done with the patients. The psychological and/or physiological measures for evaluating experimentally produced anxiety reflect body changes that express the level of the elicited anxiety.

Conclusion: The use of clinical models and evaluation measures in the study of experimental anxiety makes possible, under the scientific research, understanding the neurobiological substrate of anxiety in its pathological manifestation, beyond evaluating drugs with anxyolitic potential.

Keywords
Anxiety; Scales; Evaluation; Measures; Psychopharmacology.

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Introduction

Anxiety is a universal experience characterized as a human emotional state like love, hate, anger, happiness, shame and blame [1]. It is an emotional reaction perceived as provisional by conscience and characterized by subjective feelings of tension, apprehension, nervousness and concern, which intensifies the autonomic nervous system's activity, results in changes like increasing the heart rate, breathing pattern, arterial blood pressure, besides shakings, sweating and uneasiness [2]. Such changes are always adaptive and aim at the highest degree of success of the individual, besides being connected to genetic heritage [1].

It caused when the person is exposed to a threatening environment/situation, resulting in characteristic neurophysiologic processes. Thus, anxiety implies an aversive condition, some degree of uncertainty or doubt and a way of impotence of the organism in a given situation. It is composed by emotional/behavioral and physiological factors [3].

In the emotional aspect, the individual may show fear, insecurity, misgiving, thoughts of catastrophes and increase in the alert or vigil period. From the physiological perspective, anxiety is a state of brain function in which there is activation of the hypothalamic-pituitary-adrenal axis (HPA) resulting in neurovegetative symptoms as insomnia, tachycardia, paleness, increase in the perspiration, muscle tension, shakings, dizziness, intestinal disorders, among others [3, 4, 5].

Anxiety is traditionally classified in two ways: trait and state anxiety. The former is related to the more stable individual differences in the anxiety predisposition, consisting of a personality tendency for developing different degrees of anxiety facing life stimuli. The latter is an emotional transitory condition characterized by consciously perceived unpleasant feelings of apprehension and tension and heightened autonomic nervous system activity [3, 6].

The discovery of drugs with therapeutic potential for anxiety in its pathological manifestation involves the development of scientific researches that use animal and human models of anxiety. The human models which induct anxiety, though less practical, more expensive and with strong ethical limits, are fundamental links between the basic research and the therapeutic tests done with patients. In these models, the anxiety is experimentally inducted in humans by external stimulation/situations that represent a sort of threaten or through drugs (chemical challenge) that may induct subjective feeling of anxiety. Those which subject the individual to emotional stimulation or specific situations are classified as "psychological models". Those which involve drugs, generally with clarified mechanism of action or in controlled conditions, for induction of anxiety are classified as "chemical models" [7, 8, 9].

In order to evaluate elicited anxiety in the human models for anxiety induction, it is commonly used psychological and/or physiological measures. The psychological measures implicate the use of psychometric scales and the physiological ones the measurement of parameters that reflect the organic changes produced or resulting from the elicited state of anxiety [9, 10].

There is a need for studies to compile the experimental models most commonly used in humans in line with the discussion of the ways to assess anxiety. Since these observations the following study aims to present the accumulated evidences in the literature around the main human models for anxiety induction and the measures frequently used for evaluation of the experimental anxiety state produced.

Method

In order to perform the following study, an integrative review of the literature was made, with articles listed by Pubmed and Medline databases, beyond a research in specific books and specific thesis which have investigated the main human models for ex-

perimental anxiety induction and the measures frequently used for its evaluation.

The key words used for the search were "anxiety", "human models" and "anxiety evaluation" using specific Booleans from these databases in order to obtain several combinations of search, maximizing both reach and quality of research. No exclusion criterion was used.

For the accomplishment of this study an integrative review of the literature was conducted, with the purpose of grouping and synthesizing scientific publications to organize results about specific theme, this method of research provides to readers relevant data of a certain subject, in different places and moments, updating and facilitating the methodological adaptations of new researches [11].

Were used as research source the databases Pubmed, Medline, besides researches in books and thesis. In the databases were used the key words "anxiety", "human models" and "evaluation of the anxiety" been used the specific Booleanos in order to obtain several search arrangements, maximizing both reach and quality of research. No exclusion criterion was used.

The articles were read carefully to select the ones that investigated the main human models of induction of experimental anxiety and parameters frequently used to evaluate the elicited anxiety. Since it is an integrative review of a limited theme, it was not restricted to publication year.

Results and Discussion

Psychological Models of Anxiety Induction

The psychological models frequently used in the study of experimental anxiety are: Aversive Conditioning to Tones (ACT), Simulated Public Speaking (SPS), Stroop Color-Word Test (SCWT) and Fear-potentiated Startle (FPS) [7, 10].

Aversive Conditioning to Tones (ACT)

The ACT is a model that starts with the evidence that the initially harmless stimuli become able to provoke responses that anticipate anxiety after being paired with aversive stimuli and that emotional states, like anxiety, come with increase in the activity of the palm sweat glands, which are under the sympathetic nervous system 's neural cholinergic control. Such activity can be evaluated by the skin conductance responses – SCR) [12].

From those findings Vila and Beech developed a model for aversive conditioning in which they evaluated the SCRs resulting from blue luminous stimuli, before and after being paired with white noise of aversive intensity. Guimarães and co-workers made some adaptations and started to use it as a psychophysiological model of anxiety [10].

In the model proposed by Guimarães et al, the volunteer listens to a sequence of 10 neutral tones with differing intervals. In this phase there are SCRs with wide ranges. The 11^{th} tone is followed by the aversive white noise. Right after one minute, the sequence of neutral conditioned tones is applied. In this phase, the SCRs with wide range reappear and keep elevated until the end of the experiment [7, 13].

In another model used by Brignell and Curran, colored circles were presented on a computer screen paired with a white noise of 100db. The experiment was subdivided into four phases (habituation, acquisition, continuous reinforcement, partial reinforcement, acquisition, extinction) and aimed to compare the affects of diazepam and methylphenidate on conditioned fear [14]. Neumann, Waters and Westbury found that use of unpleasant sounds (sound of scraping a metal plate) is an alternative for research on aversive conditioning, since they have lower ethical limitations when compared to shocks and loud sounds, especially when the sample is composed of children adolescents [15].

Simulated Public Speaking (SPS)

The SPS starts from the premise that speaking in public provokes anxiety for great part of the people, especially among students. Originally proposed by McNair et all (1982) and modified by Guimarães et al. (1987), this model basically consists of submitting the individual to an anxiogenic task which is performing a four-minutes speech facing a video camera and, later, analyzing the performance of the volunteer [12].

Such model is frequently used in the pharmacology field for evaluating new drugs. The SPS inducts anxiety and the effect of the tested drugs over the generated anxiety is evaluated through physiological measures, like arterial pressure and heart rate, and psychometric measures using scales for evaluating subjective states such as Spielberger's State-Trait Anxiety Inventory (TSAI) and Visual Analogue Mood Scale (VAMS) developed by Norris [7, 10].

Applying this method made possible the detection of anxyolitic effects with several compounds, such as diazepam, lorazepam, clomipramine and cannabidiol, which is a compound extracted from marijuana [16, 17]. Researches have been developed using the SFP to identify anxiolytic potential in plant substance, among these substances, essential oils have been highlighted and present a clinical relevance of aromatherapy for anxiety [18].

Stroop Color-Word Test (SCWT)

The SCWT is frequently used to elicit discrete states of anxiety in volunteers. It was proposed by Stroop in 1935 and standardized by Nakano et al in 1878. The test is based on the production of a cognitive conflict that may induce anxiety. The model consists of using three black cards with elements arranged in a 10x10 matrix, with lines and columns. One card contains only one word, and it is named word card, the other contains only colors (color card), and the third, the color-word card, contains colors and words which are discordant, for instance, the word red printed in a green card. For the proceeding, the volunteer is required to read aloud the word card, to name the colors of the color card and, finally, to name the colors in the color-word card as fast as possible. The higher the psychological stress resulting from the test, the slower and less acute will be the performance. The anxyolitic drugs reduce the injury to the performance [7].

Fear-potentiated Startle (FPS)

The FPS is based on the evidence obtained with lab animals in which it was observed the increase of the range of jump responses to acoustic stimuli in the presence of neutral stimulus that has been previously paired with primarily aversive stimulus (electric foot shock) [7].

In humans, Grilon and co-workers structured a model that applies the threaten of electric shock to model the startle, measured by the eye blink reflex, provoked by intense sound stimulus [6, 7]. In the proceeding, the volunteer is placed in front of two lamps, one is red and the other is green, and a digital timer. The red light signs that the shocks may occur (threaten condition) and the green light signs the absence of shocks (safe condition). The reflexes are registered in three experimental phases [7].

Chemical Models for Inducing Anxiety

The chemical models involve several substances used for provoking anxiety in humans. In such models the substances commonly used for provoking anxiety in humans are: caffeine, pentylenotetrazol (PTZ), flumazenil, lactate, Carbon Dioxide (CO_2) and adrenergic agonists (noradrenaline, adrenaline and isoprenaline). Serotonergic drugs such as the agonist meta-Chlorophenylpiperazine (mCPP) and neuropeptides, as Cholecystokinin (CCK) and the corticotrophin-releasing hormone (CRH), are also used to induct anxiety both in healthy volunteers and patients with anxiety disorders [7, 12, 19, 20].

Caffeine was one of the first substances used for inducing anxiety in humans. It is still questionable, nowadays, its use in healthy volunteers for anxiety production. Its mechanism of action is possibly related to the antagonism of adenosine receptors. In the past, the PTZ and benzodiazepine inverse agonists were a lot used to elicit anxiety. However, they are not used anymore because they provoke strong anxiety and convulsion [12]. It can increase alertness and well-being, help concentration, improve mood and limit depression [21].

The flumazenil anxiogenic activity is provoked by its antagonist action over benzodiazepine receptors. The administration of flumazenil in patients with panic disorders being treated with benzodiazepine for a long time has produced panic attack [1].

The lactate and the carbon dioxide are very used for eliciting panic anxiety. The inhalation of high concentrations of CO_2 provokes the feeling of suffocation and changes in the cerebral blood flow produced by hypercapnia, causing, then, sympathetic activation and panic symptoms [22].

The result of the anxiety produced by the use of adrenergic and serotoninergic drugs is changeable and, sometimes, even contradictory. The adrenergic drugs provoke anxiety due to increase in sympathetic activity though such anxiety is considered superficial in some studies. The serotoninergic agonists induct anxiety, according to a study [23], but according to another [24] such effect was not observed.

Among the neuropeptides the CRH and the CCK-4 are the most used in human anxiety induction, especially panic. The CRH inducts peripheral symptoms of anxiety and the CCK-4 produces panic symptoms in healthy volunteers and in patients [12].

Measures for Evaluating Experimental Anxiety

The use of human models for experimental anxiety induction requires, for the evaluation of the produced state, the use of psychological and physiological measures [9].

Psychological Measures for Anxiety Evaluation

In order to evaluate subjective experiences related to anxiety, the use of psychometric scales is considered a psychological measure [8].

The scales of evaluation are classified in two big groups: the rating scales which are filled in by the observer and the self-evaluation scales, which are filled in by the volunteer himself. The choice of a scale of anxiety must consider the aspects highlighted in it, for there are scales that measure normal anxiety and others as pathologic or that approach specific aspects of the emotions, such as mood, behavior, physical symptoms, and more. The scales must be used in a standardized and reproducible way, since there is low correlation between physiological, behavioral and subjective parameters related to the anxious behavior [7].

The more frequently used scales for anxiety evaluation include: a) rating scales: Hamilton Anxiety Scale (Ham-A; Hamilton, 1959), Beck Anxiety Scale (Beck et al., 1988), Clinical Anxiety Scale (CAS; Snaith et al., 1982), Brief Anxiety Scale and Brief Psychiatric Rating Scale (BPRS; Overall et al., 1962); b) self-evaluation: Spielberger's State-Trait Anxiety Inventory (TSAI; Spielberger et al., 1970), Zung Anxiety Scale (Zung, 1971), Taylor Manifest Anxiety Scale (Taylor, 1953), symptom checklist (SCL-90; Derogatis et al., 1973), Poms (*Profile of Mood States,* POMS; Lorr e McNAir, 1984) and hospital anxiety and depression scale (Hads; Zigmond; Snaith, 1983) [25, 26].

Guimarães et al (2004) have made a study that identified the most used scales in studies published in eighteen important psychiatric magazines in between 1990 and 1994. The Hamilton Anxiety Scale and the Spielberger's State-Trait Anxiety Inventory for clinical evaluation and self-evaluation, respectively, and the Norris Visual Analogue Mood Scale (VAMS), used in the form of analogue scale, were the ones which excelled in frequency of use [7].

Hamilton Anxiety Scale (Hamilton, 1959) makes possible the evaluation of anxiety seriousness in patients already diagnosed with anxiety disorders.

The items of this scale cover symptoms considered based on the reports provided by the patients, regarding a period of three days, at least [7].

Spielberger's State-Trait Anxiety Inventory – STAI (Spielberg et al, 1970) is constituted by two subscales each one with twenty items and that measure two forms of anxiety: trait anxiety, which is a relatively stable characteristic of the propensity to anxiety; and state anxiety, which is a transitory emotional state [8]. Thus, the state anxiety scores may vary in intensity according to the perceived danger. The trait anxiety scores, in turn, are less vulnerable to changes resulting from given situations and they stay relatively constant in time. The STAI may be applied both in normal and in anxious individuals [5, 26].

In both STAI subscales, each item can be scored until the value four. The total scoring can vary from twenty (when it is assigned value 1 to all the responses) to eighty (all the responses with value four). The attainment of a scoring that ranges from twenty and forty indicates low degree of anxiety, more than forty and less than sixty reflects an average degree of anxiety and above sixty until eighty indicates high degree of anxiety [26, 27].

The Visual Analogue Mood Scale- VAMS was originally proposed Norris (1971). In Brazil, Zuardi and Karniol, in 1981, translated it into Portuguese. It is constituted by sixteen pairs of adjectives, with opposite meanings, separated from each other by a line 100 mm thick on which the volunteer must write how he or she feels about each condition [7, 9, 17, 26].

Such format of scale is considered more easily understood and filled in, having a great power of differentiation between each specified item. The items are grouped as four factors: reassurance, physical sedation, mental sedation and satisfaction. The VAMS allows anxiety evaluation both in diagnosed anxious people and in individuals in several situations, like students reactions to tests, pain, dental and surgical procedures [7, 9, 17, 26].

Physiological Measures for Anxiety Evaluation

Several physiological measures are often used for measuring clinical models of anxiety. They are: Arterial Blood Pressure (AP), Heart Rate (HR), Skin Conductance (SC), Extremity Temperature (ET), Frontal Muscle Electromyography (FME), serum dosage of cortisol, among others that are collected by specific equipment. These measures reflect physiological changes provoked by the induction of the anxiety state. When used together they allow the investigation whether there is hemodynamic and thermal changes and alteration in the perspiration of extremities that generally happens in anxiety state [26].

The measure of AP and HR are taken considering that anxiety provokes somatic manifestations related to autonomic hyperactivity and hyperventilation [25]. The measure of extremity temperature is taken, since its alteration is one of the most frequent symptoms in anxious moments. The use of Frontal Muscle Electromyography is possible due to the important role this muscle plays in the facial expression and for it is a relevant tension and attention display. The Skin Conductance reflects palm sweating, which is a symptom frequently identified in anxiety states [25].

The physiological measures are collected through proper equipment such as the physiographer F1000 Instrumentation System, from Focused Technology. Using such equipment, surface electrodes are fixed in specific parts of the volunteer's body. The measures are collected through the equipment which registers the data, so that the researcher can analyze it later.

A study done by Almeida has used this kind of equipment. In the experiment, the HR were registered through two active electrodes Ag/AgCl fixed in the dominant fist and one ground electrode in the other fist. The ET was taken through fixation of the thermal sensor in the non-dominant hand's forefinger. The Skin Conductance was detected through two electrodes fixed in the non-dominant

palm and the FME was measured through fixation of two electrodes in the surface of the frontal muscle presentation area (or higher activation). The unit of measurement used to take HR it's beats per minute (bpm), for the ET it's Fahrenheit (°F), in SC it's micromoh (μMHO) and in FME the adopted unit is microvolt (μV) [24].

Conclusions

The models for anxiety induction analyzed show how it is possible to generate an emotional state such as anxiety in a controlled and systematized way. The evaluation of produced anxiety is possible due to rigorously selected/accompanied parameters that express the individual's level of suffering/commitment when facing the generated emotion. The use of such models and measures makes possible, under the scientific research, understanding the neurobiological substrate of anxiety in its pathological manifestation and evaluating drugs with anxyolitic potential.

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