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A COMPARATIVE STUDY ON CES DEVICE AND DRUGS FOR THE TREATMENT OF MENTAL DISORDERS

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Abstract:

Brain is being the delicate organ, which are responsible for whole functioning of the body. But due to various mental health disorders such as depression, anxiety, stress, insomnia etc., it might be difficult for the brain to function properly. Various factors lead to such health issues, which need to resolve and took proper care. The review is a comparative study made between CES (Cranial Electrotherapy Stimulation) device and drugs used for such disorders and illness. The review gives a clear idea among CES and drugs, which one is more effective or are both helpful for treatment of such illness. Cranial electrotherapy stimulation (CES) is a U.S. Food and Drug Administration (FDA)-approved method for the treatment of depression, insomnia, and anxiety which consist of pulsed, low-intensity current that are applied to the earlobes or scalp. In spite of observational proof of clinical adequacy, its system of activity is to a great extent unknown. CES is known as a comparing and powerful treatment of various mind dysfunctions yet has its own specific benefits and hindrances, but might be effective if commonly known drugs are unable to cure the disorders. The drugs which are commonly used and studied are Benzodiazepines for insomnia, Doxepine for anxiety and Alprazolam for depression.

Keywords: *CES, anxiety, depression, insomnia.*

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INTRODUCTION:

Brain is the most delicate organ of our body known as the control centre, controlling functioning of voluntary and involuntary organ and organ system, and hence it is important for us to protect the brain. But various disorders and diseases might lead to improper functioning of the brain. The most common form of neurological disorders includes Insomnia, Anxiety and Depression.

- **Insomnia:** It is defined as the difficulty caused in sleep initiation causing an adverse effect on duration, consolidation, or quality.
- **Anxiety:** It is the fear, worry and extreme stressful condition.
- **Depression:** A mood disorder causing lack of interest and sadness.

In order to cure such disorders the most common form of treatment used are using medicines or the use of technology for treatment. The most common form of medicinal drugs use is Benzodiazepines for insomnia, Doxepine for anxiety and Alprazolam for depression. But the same disorders can be cured using modern technology called CES (cranial electrotherapy stimulation), a current stimulation device which helps in inhibiting the various causes of neurological disorders. Mental health issues are getting increased every year and it is affecting the daily life of patients and their family. About 3.8% of the total population is affected by depression; with 5% total are adults and 5.7% being adults above 60 years age. The average anxiety disorders from 1990-2017 percentage are about 6% in US [1]. Percentage of people in the U.S. who suffered from depression from 1990 to 2017 is about 4.5% [2]. During the pandemic the depressive and/or anxiety disorders showed a massive increment from 8.2% to 36.9% for anxiety and 6.6% to 30.2% for depression within a year [3].

Cranial Electrotherapy Stimulation (CES)

CES is a U.S. Food and Drug Administration (FDA)-approved method for treatment of insomnia, depression and anxiety which consist of pulsed, low-intensity current applied to the earlobes or scalp. It is a non-invasive therapeutic device that applies pulsed, alternating microcurrent (<1000 μA) penetrated through skin to the head via electrodes which are placed on the earlobes, zygomatic arches, mastoid processes or the maxillo-occipital junction. The U.S. Food and Drug Administration (FDA) permitted approval in year 1979 for the use of CES for mainly treatment of insomnia, depression, and anxiety [4]. In clinical populaces, CES has been utilized as an adjunctive treatment for a very long time problems including sleep deprivation, tiredness, post-horrendous pressure issue (stress) and tension. While the exact components basic putative CES consequences for clinical issues stay tricky, proposed impacts incorporate regulation of central and peripheral nervous systems, modifying resting state and limbic framework action, expanding cortical alpha-band action, and adjusting the arrival of synapses and downstream chemicals including catecholamines and glucocorticoids [5].

History

The primary CES gadget, the Somniatron, was created by the Soviet Union in the mid 1900s and conveyed 1-4 mA rotating current at 100 Hz by means of two electrodes appended to the eyelids [6]. The Somniatron was utilized to prompt absense of pain and provide rest in patients with sleep deprivation. In 1973, the principal CES gadget was showcased in the United States without formal administrative oversight, the Electrosone 50, for prompting unwinding and rest. The Electrosone conveyed substituting current at variable heartbeat recurrence (upto 4,000 Hz) with 2 mA to 8 mA force; the gadget was convenient and battery-worked, and terminals were put on the eyelids and mastoids [7].

From the 1980's through mid 2000's, a large number of the first CES gadgets were controlled as Class III gadgets by the United States Food and Drug Administration (FDA). All the more as of late, the FDA gave a last request (Docket No. FDA-2014-N-1209) to order CES gadgets promoted to regard tension or a sleeping disorder as Class II (extraordinary controls) clinical gadgets. In contrast, CES gadgets showcased to treat depression are delegated Class III clinical gadgets, requiring extra administrative oversight because of possible preposterous danger of sickness or injury (21CFR860.3). As a feature of the FDA guideline of CES gadgets, just authorized clinical professionals can arrange patient utilization of a CES gadget. Some available devices are as followed:

1. Alpha-Stim M (Electromedical Products International, Inc.)

a) Output: Bipolar asymmetric rectangular wave at 0.5, 1.5, and 100 Hz, up to 600 μA.
b) Electrodes: Ear clips.
c) URL: https://www.alpha-stim.com/product/alpha-stim-m-microcurrent-cranial-electrotherapy-stimulator/.

2. Alpha-Stim 100 (Electromedical Products International, Inc.)

a) Output: Bipolar asymmetric rectangular wave at 0.5, 1.5, and 100 Hz, up to 600 μA.
b) Electrodes: Ear clips.

c) URL: http://alphachoices.com/as100.html.

3. Fisher Wallace Stimulator (Fisher Wallace Laboratories, Inc.)

a) Output: Symmetrical biphasic square wave at 15, 500, and 15k Hz, up to 4 mA.
b) Electrodes: Sponge electrodes, mounted on temples.
c) URL: https://www.fisherwallace.com/.

4. CES Ultra (Neuro-Fitness, LLC)

a) Output: Modified square wave at 100 Hz, up to 1.5 mA.
b) Electrodes: Woven electrodes with conductive gel, mounted on temples.
c) URL: https://www.cesultra.com/.

5. Caputron MindGear (Caputron Medical Products, LLC)

a) Output: Symmetrical biphasic square wave at 0.5 Hz, up to 1.5 mA.
b) Electrodes: Ear clips or self-adhesive electrodes for temples.
c) URL: https://caputron.com/collections/mind gear.

6. Neurocare NeuroMICRO (Neurocare, Inc.)

a) Output: Modified square DC biphasic pulses at 0.3, 8, and 80 Hz, at 12V.
b) Electrodes: Carbon electrodes with conductive gel, mounted on temples.
c) URL: http://neurocare.com/neuromicro-cranial-electrotherapy-stimulation/.

Mechanism: Conceptual Model

The basic point here is that we continue to present the fundamental CES [19] components to acquire a healthy degree of comprehension of the role of electrical boundaries ready to apply a great impact. The substance that executes a helpful impact is the 'flood of ionic charges' communicated in coulomb units for remedial adequacy. This 'flood of particles ionic charges' gives the (electrical) tweak units on cerebrum electric tissues. Along these lines, the best effect of any applied electrical flow is its capacity to deliver safe electrical powers following up on scalp locales to incite ionic stream streams from scalp through cerebrum tissues to make remedial ionic circuits. The quantity of Coulombs that communicate with disabled electrical properties of given neurons will characterize the unit of a restorative impact in the locale of interest.

The central issue here is that CES accomplishes cerebrum's biochemical resynchronizing impacts [4], [8];

- Builds transformation of amino acids.
- Particles shaping synapses.
- Rebalance synapses discharge.
- Recovers alpha and delta cerebrum waves.
- Raises blood levels of endorphins.
- Lessens fits and edema.
- Tonifies powerless muscles.
- Accomplishes deep relaxation.

CES sets up a perplexing helpful electric system affecting the impeded electrical resources of neurons of interest. Consequently dosimetric amounts are of basic significance in accomplishing an advantageous remedial impact. The essential issue here is that CES should satisfy the accompanying requirements [9]:

- It should have external electric flow extents characterized in miniature or milliampers units.
- It should depend on high frequencies having no abstract incidental effects.
- It should be of ideal planning composition to infused charge units.
- It should travel through an electric conductive medium to achieve an electric counterfeit circuit develop.
- It should have the required electrical boundaries precisely affecting electrical desynchronized properties of neuronal electric tissues.
- It should show the quantity of particular CES techniques expected to bring one's
- It should show the ideal electrical boundaries valuable for preventive requirements.

Thus, CES represents a fresh model of usage of electrotherapy that embraces biophysical mechanisms underlying electric resynchronizing modulation with four basic components:

- The magnitude (amplitude, density) of applied charges.
- The frequency of charge waves delivery.
- The cycling time of current application.
- The number of EEG electrode pairs applicable to regions of interest.

Anxiety:

A Comparative study of anxiety disorders treatment with Paroxetine in combination with cranial electrotherapy stimulation therapy. The goal was to investigate the extra impact of cranial electrotherapy feeling treatment in the treatment of tension problems using Alpha-Stim® device. The aftereffects of this review showed that a month and a half of joining paroxetine with day by day CES medicines, yielded critical improvement over paroxetine alone on the HAM-A scale from gauge to about a month and a half out [10].

In another study examination of the efficacy of CES for the treatment of anxiety and depression was done and ff the 115 subjects who were enrolled in the study, 108 subjects completed the study. There were 57 subjects in the active CES group and 51 subjects

in the sham CES group. Eighty-three percent (83%) of the active CES group had a decrease of ≥ 50% decrease in anxiety scores on Hamilton Anxiety Rating Scale (HAM-A) from baseline to endpoint of study [11].

Depression:
A similar study performed for anxiety was done for depression, to examine the efficacy of CES for the treatment of depression. The active CES device was set to 100 µA, study was done by Hamilton Depression Rating Scale (HAM-D17) compared to the sham treatment at the endpoint of the 5 week study. There was a huge difference between the active and sham groups which was for depression from baseline to endpoint of study ($p<0.001$, $d=0.78$). The HAM-D17 scores decrease in the active group of 8.04 (14.5 to 6.47; 55.4%) was more than 2.3 times the mean decrease of 3.26 (13.22 to 9.96; 24%) on the HAM-D17 for the sham group (See Figure 2). Eighty-two percent (82%) of the active CES group had a decrease of ≥ 50% decrease in depression scores on the HAM-D17 from the baseline to the endpoint of study [11].

Another study by *Ronald R. et.al* was done on sheriff officers and efficacy was observed. Depression measures (BDI and BSI-D) were compared with sham treated patients. Beck Depression Inventory was used to measure depression, the active CES group had significantly lower depression scores on the BDI ($p<0.05$) and the BSI-D ($p< 0.01$) than the sham group [12].

Insomnia:
A study on efficacy of cranial electric stimulation for the treatment of insomnia was done for 5 days. The CES was set up at 100 µA and for 60 min, while a sham device identical to CES device but no current emitted which was measured on psychiatric impairment rating scale (PIRS). Fifty-seven (57) subjects volunteered and completed the study consisting 46 males and 11 females. From which 28 were active CES group and 29 were sham CES group. Over three-quarters of the subjects completed the full 5 CES treatments (N=44, 77%). The active CES group average about had 43 extra minutes total sleep time when it was compared with sham CES group subjects, an average of 19 minutes less sleep time was reported. A gender difference also emerged where men in the active CES group who completed 5 sessions of CES reported a significant improvement in total time slept at 2 points in the study, after the initial ($p=0.04$, $d=0.41$) and after the fourth ($p=0.03$, $d=0.49$) treatments as compared to men in the sham group. There were no significant changes among the females [13].

Advantages of CES:
When study regarding CES was done using Alpha-Stim SCS device with two electrodes attached to bilateral earlobes on 10 participators in order to measure its effect on wakefulness they showed significant reduction of sleep dormancies when measure with electroencephalography (ECG). When an open successive cohort study was performed it demonstrated significant enhancement in anxiety and depression symptoms of generalized anxiety order following 12 and 24 weeks of CES treatment with an original Nascence-Stim AID device with bilateral earlobe electrodes [5]. CES can also be used to significantly better the symptoms in cases with fibromyalgia, CES was found to be non invasive, effective, retain health benefits, accessible [14]. Another merit of using CES was that it's safe to use and doesn't retain any trouble to the health of the patient. It's simple to operate with and doesn't involve too much specifics and therefore comfortable. It's also plant to be movable; it was also found that CES helps to ameliorate memory, attention, mental clarity, enhanced literacy capability and vitality [15]. CES has been used as ancillary treatment for clinical diseases like wakefulness, depression, post traumatic stress complaint and anxiety [16].

Disadvantages of CES:
Vertigo, skin vexation and headaches are reported to be the most observed side goods of CES. Cases that use implanted leaders or defibrillators are advised not to conclude for CES remedy. Electric considerations of CES are limited to dosimetric expressions that produce trends for neuronal functional changes [17].

Drugs for treatment of mental disorders:

Anxiety: Alprazolam(XANAX**):**
Alprazolam was patented during the 1970s, having been created by J.B. Hester at Upjohn Company (later piece of Pfizer, Inc.). In 1981 it was approved by the U.S. Food and Drug Administration (FDA) for use in people experiencing from stress or from panic issue. It is taken orally, by and large as a tablet, and isS accessible in an extended-release formulation, enabling the medication to be made accessible to the body progressively in the wake of being taken and subsequently decreasing the frequency of organization [18]. Alprazolam isn't just the most generally recommended benzodiazepine, yet it is the most ordinarily prescribed psychotropic drug in the United States, representing in excess of 48 million remedies administered in 2013 [19], [20]. It is felt

that it works by improving the movement of specific neurotransmitters in the brain [21]. Alprazolam is widely processed in people and its metabolites are discharged principally in the urine. Subsequent to taking Xanax, the peak impacts of the medication are regularly felt inside one to two hours. As a halfway span drug, Xanax stays in an individual's framework for 12 to 15 hours. Xanax is administered in 0.25 mg, 0.5 mg, 1 mg, and 2 mg strengths.

Mechanism of action:
The specific mechanism of activity of alprazolam is unknown. Benzodiazepines bind to gamma aminobutyric acid (GABA) receptors in the mind and upgrade GABA-intervened synaptic inhibition; such activities might be answerable for the adequacy of alprazolam in pressure and frenzy problem [22]. Neurotransmission depends on excitatory and inhibitory signalling. γ-aminobutyric acid (GABA) type-A receptors (GABAARs) are individuals from the pentameric ligand-gated particle channel (PLGIC) The most common GABAARs in vivo are the α1β2γ2 receptors, which contain both GABA (β+/α-) and benzodiazepine (BZD, α+/γ-) restricting locales in the intersubunit points of interaction of the important subunits [23], [24]. The benzodiazepine restricting site is between the alpha-1 and gamma-2 subunit. Benzodiazepine restricting site seem to display coupling with GABA-A receptors, and this improves the impacts of gamma-aminobutyric acid (GABA) by expanding GABA proclivity at the GABA-A receptor [25]. The major inhibitory synapse GABA, when bound to the GABA-A receptor,intervenes the quieting or inhibitory impacts of alprazolam on the human sensory system. Alprazolam is quickly consumed after oral organization with a peak plasma concentration at 1 to 2 hours. The bioavailability of oral alprazolam midpoints 80 to 100%percent, Alprazolam is 80% bound to serum protein, principally egg whites [26].

Adverse effect:
Utilizing alprazolam can achieve an variety of incidental effects. Most alprazolam incidental effects are not life-threatening, but rather some might require clinical consideration [27].
Common side effects of alprazolam (Xanax) include:

- A Type of Abnormal Movement Disorder Called Dyskinesia
- Inconvenience Breathing
- Obstruction
- Pain with Menstruation
- Premenstrual Syndrome
- A Problem with Menstrual Periods
- Irritation of the Skin Due To an Allergy
- Joint Pain
- Muscle Pain
- Pain in the Arms or Legs
- Wooziness
- Trouble Sleeping
- Loss of Muscle Coordination

Uses:
This drug is used to treat the panic and stress associated with panic disorder. Alprazolam belongs to a class of drugs called benzodiazepines which act on the cerebrum and nerves (central nervous system) to produce a calming effect. It works by increasing the effects of a certain natural chemical in the body (GABA), it is utilized in the treatment of panic issue. Perspiring, breathing issue, weakness and numbness in hands are a portion of the indications of a panic disorder [28].

Depression: Doxepine (Silenor):
Introduction:
Doxepin is a tricyclic antidepressant that was FDA approved in 1969 to treat major depressive disorder and derived from dibenzoxepin, and it has activities and utilizations like those of amitriptyline. The more stamped narcotic properties of doxepin make it valuable in depressed patients with rest unsettling influences and in depression related with anxiety [29]. Significant depressive disorder influences more than 17.3 million Americans in the U.S. 75% of people who experience the ill effects of mental problems stay untreated, and around 1 million individuals end it all. Doxepin is a medicine utilized in the treatment of significant depressive disorder, anxiety, insomnia disorder, just as in the administration of skin pruritus [30]. Doxepin shows antagonist effects on alpha-adrenergic, muscarinic, and histaminic receptors. With such a wide assortment of receptors to obstruct, oral details of doxepin have been FDA approved to treat insomnia and anxiety, and effective plans have FDA approved to manage skin pruritus[31],[32].[4][5][6] Doxepin has proven to be an effective analgesic in treating neuropathic pain [33],[34]. Doxepin is displayed to repress the reuptake of noradrenalin and serotonin. The reuptake inhibition of dopamine is exceptionally weak. Doxepin's metabolite desmethyldoxepin (nordoxepin) has additionally stimulant impacts [35].

Chemistry
SINEQUAN (doxepin HCl) is a dibenzoxepin derivative and is the first of a family of tricyclic psychotherapeutic agents. Specifically, it is an isomeric mixture of: 1-Propanamine, 3-dibenz [b,e]oxepin-11(6H)ylidene-N,N-dimethyl-, hydrochloride [36].

Mechanism of action:
Silenor (doxepin) binds with high fondness to the histamine H1 receptor where it capacities as a main antagonist. The specific component by which doxepin applies its rest upkeep impact is obscure, however is accepted because of its hostility of the H1 receptor. The specific instrument by which doxepin applies its rest upkeep impact is obscure, however is accepted because of its threat of the H1 receptor. Inconstancy of doxepin plasma concentration may add to interindividual distinction in treatment reaction and secondary effect seriousness. An ideal scope of plasma convergence of TCA that relates well to treatment reaction has been characterized dependent on restorative medication checking. Depression appears to result from a compound unevenness and an absence of synapses in the cerebrum. The various classes of antidepressant medications have been defined to perform interesting components by focusing on various receptors and expanding the accessibility of synapses. Doxepin is in the tricyclic antidepressants (TCA) drug class; these specialists work by expanding the centralization of the synapse's serotonin (5-HT) and norepinephrine (NE) in the cerebrum. This activity draws out the accessibility of the synapses (5-HT and NE) inside the synaptic parted and upgrades their neurotransmission by forestalling their reuptake back into the presynaptic terminal.

Doxepin additionally shows adversarial properties in the focal sensory system by obstructing the accompanying receptors: histamine (H1), alpha-1 adrenergic, and muscarinic. It additionally represses sodium and potassium directs in cardiomyocytes [37], [38]. Adapted liver cell showing up-and-comer qualities associated with the digestion of the tricyclic doxepin.

Adverse effects:
Doxepin is an unique antidepressant since it produces different adverse effects dependent on the receptor it antagonizes. Doxepin antagonizes three distinct receptors, which include: histamine, adrenergic, and muscarinic. Doxepin blocks histamine H1 receptor and causes sedation and sleepiness; consequently, FDA has endorsed low-portion doxepin, 3 mg, and 6 mg measurements to be utilized as a first-line specialist in quite a while with rest aggravations and sadness related with uneasiness. Appropriate instruction is important to keep patients from self-curing and ingesting too much of such pills. Doxepin additionally can possibly cause a huge expansion in weight and was evaluated in an investigation of 329 patients treated with doxepin and amitriptyline [39],[40]. [16][17][18] Ultimately, doxepin blocks muscarinic receptors and produces anticholinergic side results like dry mouth, blockage, dazedness, discombobulation, tachycardia, and delayed QT interval [41], [42]

Doxepin oral capsule might cause drowsiness. You shouldn't drive, use apparatus, or do different exercises that require sharpness subsequent to taking this medication until you know what it means for you. This drug can also cause other side effects like:

- drowsiness
- dizziness
- dry mouth
- blurred vision
- constipation
- trouble urinating
- nausea or vomiting
- upset stomach
- changes in how foods taste
- weight gain

Uses:
Doxepin is used to treat depression and tension.
Doxepin is in a class of prescriptions called tricyclic antidepressants. It works by expanding the measures of specific normal substances in the mind that are required for mental equilibrium.

Doxepin is likewise accessible as a tablet to treat sleep deprivation. This monograph just gives data about doxepin for gloom or tension. In the event that you are involving this drug for sleep deprivation, read the monograph entitled doxepin (a sleeping disorder) [43].

Insomnia: Benzodiazepines (Lorazepam, Diazepam, Midazolam)
Introduction: Benzodiazepines **(also called "benzos")** are a class of psychotropic drugs with narcotic sedative-hypnotic, anxiolytic, anticonvulsant, and muscle relaxant impacts. Benzodiazepines are among the most abused and misprescribed drugs in the world [44]. Despite repeated suggestions to restrict benzodiazepines to short-term use (2-4 month), specialists overall are as yet recommending them for months or a year [45]. Utilizing information investigation, specialists inferred that 12.5% of grown-ups in the U.S. utilized benzodiazepines, which extrapolates to around 30.5 million people. However, just 2.1% of U.S. grown-ups abused them (once), and just 0.2% met the standards for benzodiazepine use issues. Among benzodiazepine users, 17.1% abused them, and less than 2% had benzodiazepine use issues [46], benzodiazepines act on the GABA receptor and its

chloride channel, consequently hyperpolarizing the neuron. Consequently benzodiazepines share the mechanistic issues connected with GABA initiation and chloride levels and the unfavorable impacts related with phenobarbital, including respiratory and, all the more once cardiovascular depression [47]. The first benzodiazepine to be created was chlordiazepoxide (Librium), trailed by a huge assortment of specialists, including diazepam (Valium) and alprazolam (Xanax), every one of which has slightly various properties. Benzodiazepines work by upgrading the activity of the synapse gamma-aminobutyric corrosive (GABA), which restrains tension by diminishing specific nerve-drive transmissions inside the mind [48].

Mechanism of action:

Benzodiazepine receptor agonists (BZRAs) work through GABA receptors to advance rest by repressing brainstem monoaminergic excitement pathways, through help of VLPO inhibitory GABAergic projections to excitement focuses like the front nerve center TMN, the posterolateral hypothalamic hypocretin neurons, and the brainstem excitement areas. Mechanism of action appears to be via potentiation of gamma-aminobutyric acid (GABA)-receptor–mediated effects in CNS because it binds to the GABA binding site. Diazepam is metabolized to desmethyldiazepam (nordiazepam) and oxazepam [49]. Benzodiazepines, similar to alprazolam (Xanax), lorazepam (Ativan), clonazepam (Klonopin) and clonazepam) follow up on the focal sensory system (CNS) and mind. They are referred to pharmacologically as GABAergic specialists, narcotic hypnotics, or minor sedatives. GABA is the boss inhibitory synapse in the mammalian focal sensory system. Its job is in diminishing neuronal volatility and, in people; it is likewise liable for the guideline of muscle tone. Assuming your sensory system was a vehicle, GABA works similar as the "brakes". When the "vehicle" brings off speeding not too far off (edginess of the sensory system), GABA capacities as the "brakes" to quiet and dial it back. Benzodiazepines additionally tie to their own receptors (benzodiazepine receptors) that are arranged on the GABA-A receptor. Mix of a benzodiazepine at this site goes about as a sponsor to the activities of GABA, permitting more chloride particles to enter the neuron, making it significantly more impervious to excitation [50].

Side Effects of Benzodiazepines:

Common side effects among all BZDs incorporate drowsiness, torpidity, and weariness. At higher measurements, impeded engine coordination, wooziness, dizziness, slurred discourse, foggy vision, mind-set swings, and elation can happen, just as unfriendly or whimsical conduct in certain examples. BZDs are disposed of gradually from the body, so rehashed portions over a delayed period can bring about critical aggregation in greasy tissues. Subsequently, a few manifestations of overmedication (hindered reasoning, bewilderment, disarray, slurred discourse) can show up over the long run. Resistance, reliance, and withdrawal are unfriendly impacts related with long haul use [51], [52].

As a rule, when utilized as coordinated under management from a specialist, benzodiazepines are somewhat alright for brief periods of time. They are not, however, intended to be taken for longer than half a month to a couple of months all things considered. They are for the most part planned for the momentary help of indications that regularly require further mental or clinical intercession to be effectively made due. Tenacious sleep deprivation, for instance, might be brought about by a basic clinical or psychological wellness issue that can be dealt with securely with treatment or option pharmacological methods.

The most well-known side effects related with benzodiazepines are:

- Dizziness
- Sedation
- Weakness
- Unsteadiness
- Transient drowsiness commonly experienced during the first few days of treatment
- Depression
- Increased Anxiety
- Lack of motor control
- Blurred vision
- Slurred speech
- Slow breathing
- Muscle weakness
- Memory issues
- Conduct changes- for example, expanded danger risk, incoherence, particularly in more established individuals, hazard of reliance, particularly with long haul use. They cause essentially less respiratory wretchedness than barbiturates and, thus, are seldom deadly in an overdose.

Benzodiazepines used for what?

Benzodiazepines are used as a sleep aid and anti-anxiety medicine. They help treat symptoms such as decreased need for sleep, racing thoughts, unusual talkativeness, increased activity, agitation, or distractibility, which may be part of a manic or

hypomanic episode in people with bipolar disorder. There is a risk of addiction, so these medications are usually limited to short-term use for temporary relief of these symptoms.

Benzodiazepines may be used to treat:
- Alcohol withdrawal
- Anxiety
- As a muscle relaxant
- Panic disorder
- Seizures

CONCLUSION:

In India, during 2017 there were 197·3 million suffering from various mental disease among which depression and anxiety are the common. Mental disorders contributed 4·7% of the total DALYs in India in 2017, compared with 2·5% in 1990. Among the total depressive disorders (33·8%, 29·5–38·5), anxiety disorders (19·0%, 15·9–22·4) were the common [53]. Comparative studies of male and female, female were more. Through these studies it is observed that patient sufferers who got CES technology for mental health management got recovered fast as compared to the one with medicine. Looking both has various advantages and disadvantages. CES treatment is effective and also cheap but proper care and proper health care professionals are required for proper management and record purpose. On the contrary, medications for mental health may be effective but it's not 100% effective for every patient, as well as the cost of such medications is more if the disorders not manage properly. The adverse effects of drugs, its overdose might be an issue. As population of India is growing, the mental health issues are also getting increased due to various physical and mental factors. So technologies like CES might be a better option if compared to medicines for mild symptoms or for short term use. Yet CES is not universally accepted and its full recognition is not known to patients. It is still under better development and might be a better choice for mentally weak patients facing depression, insomnia and anxiety. The global cranial electrotherapy stimulation devices market is being aided by the growth of the neurological devices market, which reached a value of about USD 11.2 billion in 2020. The neurological devices market is further expected to grow at a CAGR of 7.8% in the forecast period of 2022-2027 to reach a value of approximately USD 17.5 billion by 2026.

REFERENCES:

[1] Share of the U.S. population with anxiety 2017. Statista n.d. https://www.statista.com/statistics/979919/percentage-of-people-with-anxiety-us/ (accessed January 18, 2022).

[2] Share of the U.S. population with depression 2017. Statista n.d. https://www.statista.com/statistics/979880/percentage-of-people-with-depression-us/ (accessed January 18, 2022).

[3] Infographic: Pandemic Causes Spike in Anxiety & Depression. Stat Infographics n.d. https://www.statista.com/chart/21878/impact-of-coronavirus-pandemic-on-mental-health/ (accessed January 18, 2022).

[4] Feusner JD, Madsen S, Moody TD, Bohon C, Hembacher E, Bookheimer SY, et al. Effects of cranial electrotherapy stimulation on resting state brain activity. Brain Behav 2012;2:211. https://doi.org/10.1002/brb3.45.

[5] Brunyé TT, Patterson JE, Wooten T, Hussey EK. A Critical Review of Cranial Electrotherapy Stimulation for Neuromodulation in Clinical and Non-clinical Samples. Front Hum Neurosci 2021;15.

[6] Guleyupoglu B. A Comprehensive View of Electrosleep: The History, Finite Element Models and Future Directions n.d.:70.

[7] Kirsch DL, Price LR, Nichols F, Marksberry JA, Platoni KT. Military service member and veteran self reports of efficacy of cranial electrotherapy stimulation for anxiety, posttraumatic stress disorder, insomnia, and depression. US Army Med Dep J 2014:46–54.

[8] Gilula MF, Kirsch DL. Cranial Electrotherapy Stimulation Review: A Safer Alternative to Psychopharmaceuticals in the Treatment of Depression. J Neurother 2005;9:7–26. https://doi.org/10.1300/J184v09n02_02.

[9] Yakov N. Cranial Electrotherapy Stimulation (CES) in Neuropsychiatry: Definition & Insights from Electric Learning Paradigms' n.d.

[10] Ling L, Jun H. A Comparative Study of Anxiety Disorders Treatment with Paroxetine Associated with Cranial Electrotherapy Stimulation Therapy 2016. https://www.semanticscholar.org/paper/A-Comparative-Study-of-Anxiety-Disorders-Treatment-Ling-Jun/da3d121a96b26d6754af8c7e9758aa76970d83a1 (accessed January 17, 2022).

[11] Barclay TH, Barclay RD. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. J Affect Disord 2014;164:171–7. https://doi.org/10.1016/j.jad.2014.04.029.

[12] Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clin Psychol

Rev 1988;8:77–100. https://doi.org/10.1016/0272-7358(88)90050-5.
[13] Lande RG, Gragnani C. Efficacy of cranial electric stimulation for the treatment of insomnia: A randomized pilot study. Complement Ther Med 2013;21:8–13. https://doi.org/10.1016/j.ctim.2012.11.007.
[14] Shekelle P, Cook I, Miake-Lye IM, Mak S, Booth MS, Shanman R, et al. The Effectiveness and Risks of Cranial Electrical Stimulation for the Treatment of Pain, Depression, Anxiety, PTSD, and Insomnia: A Systematic Review. Washington (DC): Department of Veterans Affairs (US); 2018.
[15] Krause B, Kadosh RC. Can transcranial electrical stimulation improve learning difficulties in atypical brain development? A future possibility for cognitive training. Dev Cogn Neurosci 2013;6:176–94. https://doi.org/10.1016/j.dcn.2013.04.001.
[16] Lee IH, Seo EJ, Lim IS. Effects of aquatic exercise and CES treatment on the changes of cognitive function, BDNF, IGF-1, and VEGF of persons with intellectual disabilities. J Exerc Nutr Biochem 2014;18:19–24. https://doi.org/10.5717/jenb.2014.18.1.19.
[17] Yakov N. Cranial Electrotherapy Stimulation (CES) in Neuropsychiatry: Definition & Insights from Electric Learning Paradigms' n.d.
[18] alprazolam | Description, Uses, & Side Effects | Britannica n.d. https://www.britannica.com/science/alprazolam (accessed January 17, 2022).
[19] Ait-Daoud N, Hamby AS, Sharma S, Blevins D. A Review of Alprazolam Use, Misuse, and Withdrawal. J Addict Med 2018;12:4. https://doi.org/10.1097/ADM.0000000000000350.
[20] Schatzberg AF, Nemeroff CB. The American Psychiatric Association Publishing Textbook of Psychopharmacology. American Psychiatric Pub; 2017.
[21] Alprazolam: Uses, Dosage, Side Effects. DrugsCom n.d. https://www.drugs.com/alprazolam.html (accessed January 17, 2022).
[22] Niravam (Alprazolam): Uses, Dosage, Side Effects, Interactions, Warning. RxList n.d. https://www.rxlist.com/niravam-drug.htm (accessed January 17, 2022).
[23] Scott S, Aricescu AR. A structural perspective on GABAA receptor pharmacology. Curr Opin Struct Biol 2019;54:189–97. https://doi.org/10.1016/j.sbi.2019.03.023.
[24] Olsen RW. GABAA receptor: Positive and negative allosteric modulators. Neuropharmacology 2018;136:10–22. https://doi.org/10.1016/j.neuropharm.2018.01.036.
[25] Sigel E, Ernst M. The Benzodiazepine Binding Sites of GABAA Receptors. Trends Pharmacol Sci 2018;39:659–71. https://doi.org/10.1016/j.tips.2018.03.006.
[26] George TT, Tripp J. Alprazolam. StatPearls, Treasure Island (FL): StatPearls Publishing; 2022.
[27] Patterson E, MSCP, NCC, July 16 Lpcl updated on, 2021. Alprazolam Effects | Short Term, Long Term & Side Effects. DrugAbuseCom n.d. https://drugabuse.com/benzodiazepines/xanax/effects-alprazolam-use/ (accessed January 17, 2022).
[28] Alprazolam Oral: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD n.d. https://www.webmd.com/drugs/2/drug-8171-367/alprazolam-oral/alprazolam-extended-release-oral/details (accessed January 17, 2022).
[29] Marsh W. Doxepin. In: Enna SJ, Bylund DB, editors. XPharm Compr. Pharmacol. Ref., New York: Elsevier; 2007, p. 1–5. https://doi.org/10.1016/B978-008055232-3.61649-6.
[30] Almasi A, Meza CE. Doxepin. StatPearls, Treasure Island (FL): StatPearls Publishing; 2022.
[31] Wu J, Chang F, Zu H. Efficacy and safety evaluation of citalopram and doxepin on sleep quality in comorbid insomnia and anxiety disorders. Exp Ther Med 2015;10:1303–8. https://doi.org/10.3892/etm.2015.2686.
[32] Kouwenhoven TA, van de Kerkhof PCM, Kamsteeg M. Use of oral antidepressants in patients with chronic pruritus: A systematic review. J Am Acad Dermatol 2017;77:1068-1073.e7. https://doi.org/10.1016/j.jaad.2017.08.025.
[33] Wörz R, Berlin J. [Treatment of chronic pain syndromes with antidepressants.]. Schmerz Berl Ger 1989;3:1–7. https://doi.org/10.1007/BF02527466.
[34] Casale R, Symeonidou Z, Bartolo M. Topical Treatments for Localized Neuropathic Pain. Curr Pain Headache Rep 2017;21:15. https://doi.org/10.1007/s11916-017-0615-y.
[35] Eschler DC, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. J Drugs Dermatol JDD 2010;9:992–7.
[36] Sinequan (Doxepin): Uses, Dosage, Side Effects, Interactions, Warning. RxList n.d.

https://www.rxlist.com/sinequan-drug.htm (accessed January 18, 2022).
[37] Feighner JP. Mechanism of action of antidepressant medications. J Clin Psychiatry 1999;60 Suppl 4:4–11; discussion 12-13.
[38] Kołodziej M, Majewska M, Krajewska A, Szponar J. [Prolonged toxic coma and anisocoria secondary to doxepin, lorazepam and phenobarbital poisoning--case study]. Przegl Lek 2012;69:624–6.
[39] Vande Griend JP, Anderson SL. Histamine-1 receptor antagonism for treatment of insomnia. J Am Pharm Assoc JAPhA 2012;52:e210-219. https://doi.org/10.1331/JAPhA.2012.12051.
[40] Yeung W-F, Chung K-F, Yung K-P, Ng TH-Y. Doxepin for insomnia: a systematic review of randomized placebo-controlled trials. Sleep Med Rev 2015;19:75–83. https://doi.org/10.1016/j.smrv.2014.06.001.
[41] Feighner J, Hendrickson G, Miller L, Stern W. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. J Clin Psychopharmacol 1986;6:27–32.
[42] Feighner JP, Cohn JB. Double-blind comparative trials of fluoxetine and doxepin in geriatric patients with major depressive disorder. J Clin Psychiatry 1985;46:20–5.
[43] Baker B, Dorian P, Sandor P, Shapiro C, Schell C, Mitchell J, et al. Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. J Clin Psychopharmacol 1997;17:15–21. https://doi.org/10.1097/00004714-199702000-00004.
[44] admin. Introduction to Benzodiazepines. PsychDB 2017. https://www.psychdb.com/meds/benzos/home (accessed January 18, 2022).
[45] Ashton H. The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry 2005;18:249–55. https://doi.org/10.1097/01.yco.0000165594.60434.84.
[46] Abuse NI on D. Research suggests benzodiazepine use is high while use disorder rates are low. Natl Inst Drug Abuse 2018. https://www.drugabuse.gov/news-events/science-highlight/research-suggests-benzodiazepine-use-high-while-use-disorder-rates-are-low (accessed January 18, 2022).
[47] Bermak J, Johnstone T, Gee K. Benzodiazepines. In: Fink G, editor. Encycl. Stress Second Ed., New York: Academic Press; 2007, p. 310–6. https://doi.org/10.1016/B978-012373947-6.00422-0.
[48] benzodiazepine | drug | Britannica n.d. https://www.britannica.com/science/benzodiazepine (accessed January 18, 2022).
[49] Morin CM, Benca RM. Chapter 45 - Insomnia: nature, diagnosis, and treatment. In: Montagna P, Chokroverty S, editors. Handb. Clin. Neurol., vol. 99, Elsevier; 2011, p. 723–46. https://doi.org/10.1016/B978-0-444-52007-4.00004-7.
[50] Mechanism of Action. Benzodiazepine Inf Coalit n.d. https://www.benzoinfo.com/mechanism-of-action/ (accessed January 18, 2022).
[51] Charles E. Griffin III. Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects. Ochsner J 2013;13:214.
[52] Fox C, Liu H, Kaye AD, Manchikanti L, Trescot AM, Christo PJ. Clinical aspects of pain medicine and interventional pain management: a comprehensive review. Paducah KY ASIP Publ Antianxiety Agents 2011:543–52.
[53] Sagar R, Dandona R, Gururaj G, Dhaliwal RS, Singh A, Ferrari A, et al. The burden of mental disorders across the states of India: the Global Burden of Disease Study 1990–2017. Lancet Psychiatry 2020;7:148–61. https://doi.org/10.1016/S2215-0366(19)30475-4.