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REVIEW ARTICLE

NIGHTMARES AS AN ADVERSE DRUG REACTION

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Abstract

Nightmares also categorized as fighting dreams suddenly awake the sleeper from Rapid Eye Movement (REM) sleep. Nightmares can be caused by improper food intake, alcohol withdrawal, digestive or nervous disorders and drug induced (mainly due to the drugs which affect the neurotransmitters). Some of the drugs that can induce nightmares are Beta blockers, Statins, Anti depressants, Anti epileptics, Sedative hypnotics, General anesthetic agents, anti histamines, endocrinal agents etc., The exact mechanisms involved for these drug induced nightmares is not clear. The occurrence of these nightmares due to the intake of various drugs is rare and in all these cases drug withdrawal is beneficial.

Introduction:-

Sleep is defined as unconscious condition of mind and body characterized by closed eyes which help to restore our body energy. Sleeping plays an important role in memory and learning process. Sleeping period may differ based on age (K Sembulingam and PremaSembulingam, 2012)[7].

There are two phases of sleep:
1. Rapid eye movement sleep [REM]
2. Non Rapid Eye Movement Sleep [NREM].

NREM sleep is again divided into four stages, which are
1. Stage-I: stage of Drowsiness
2. Stage-II: Stage of light sleep
3. Stage -III: stage of medium sleep
4. Stage -IV: Stage of deep sleep (K Sembulingam and Prema Sembulingam, 2012)[7]

Dreams occur during last stage of REM sleep but not in NREM Sleep. Dreaming is an epiphenomenon and a series of physiological episodes which include ideas, emotions, thoughts, and images that appear involuntarily in the brain at various phases of sleep. Dreams can be of various forms which are pleasant dreams and fighting dreams (Sarita Goyal et al., 2013) [12]. Nightmare is also known as a dream anxiety disorder. These are dysphoric dreams having nocturnal episodes including anxiety and fear with vivid, negative emotions in the mid night of rapid eye movement. Night terror is another word similar to nightmare characterized by automatic discharge, more fear with anxiety than in nightmares. It is also known as pavor nocturnes (Dennis F Thompson and Dana Reid Pierce, 1999) [3].

The term nightmare arise from 13th century which is collected from night and mare which means a female affected by an evil characterized by suffocation by the sleeper as they ride on the chest. Nightmare is also categorized as

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fighting dreams which suddenly awakes up the sleeper from rapid eye movement sleep (Maria E Møller et al.,2016) [9].

Nightmare is caused by improper food intake, digestive disorders or nervous disorders, alcohol withdrawal, drug induced. Drugs which effect the neurotransmitters cause nightmares (examples: gabaminergic, adrenergic, cholinergic, dopaminergic, B-blockers, Statins, erythromycin) (K Sembulingam and PremaSembulingam, 2012) [8].

According to International classification of sleep disorder, sleep disturbance is distinguished as psychiatric illness, dyssomnia, parasomnia, sleep wake transition disorder. ICSD-2 categorized nightmares as a parasomnia. The assessment of parasomnia is awakening the sleeper from the sleep and asks to recollect the dream. Nightmares can be recollected (SaritaGoyal et al., 2013) [12]. Nightmares is commonly affecting 4% of adult population, frequently nightmares are often observed in post-traumatic stress disorder, in about 10% of schizophrenic patients and personality disorder in half of the patients. Nightmares can also be an indication for early onset of psychiatric disorders (Stephaine Rek et al., 2017) [13].

Nightmares are categorized in to various types:
1. Nightmares without any clinical signs of psychopathology (idiopathic).
2. Nightmares along with other disorders like PTSD, anxiety, stress, substance abuse, and other psychiatric illness.
3. Drug induced nightmares (examples: acetylcholine, norepinephrine, serotonin, dopamine, R-suppressing agents).

Pathophysiology of nightmares is not clear (R. Nisha Aurora, M.D. et al., 2010) [11].

There have been various trails that develop the treatment for nightmares. Pharmacological treatment for nightmare along with PTSD is Prozosin, α-1 noradrenergic antagonist which improves the day time symptoms of PTSD and reduces other sleep disturbance. Another most effective drug is serotonin potentiating non-SSRI agent (Trazadone and nefazodone) which showed moderate to large therapeutic effect on nightmares in a controlled trail. Various clinical trials are conducted to develop various agents but it does not show any therapeutic effects on nightmares. Benzodiazepines can be prescribed in PTSD but it doesn't show any effect on nightmares with PTSD, while it can decrease nightmares associated with REM sleep behavior disorders.

Cognitive behavioral therapy is an approach for nightmares; initially desensitization is applied by continuous exposure to fearful nightmare and habituation to emotional response by nightmares. Desensitization shows improvement in frequency of nightmares, sleep disturbance and symptoms of anxiety. Another approach is imagery rehearsal therapy to decrease the frequency and intensity of nightmares by repeating practicing dreams during day time. Exposure, Relaxation and Rescripting therapy shows a great efficacy in long term improvement of nightmares (Brant Hasler, MA and Anne Germain, PhD, 2009) [2].

Mechanisms involved in inducing nightmares:

Sleep is associated with the fields of neuropharmacology and psychopharmacology which includes events and mechanisms which are not yet explained clearly. Both these fields consider dreaming as a mysterious event in sleep that includes nightmares as a sub classification. From some drug studies, it has been shown that some drugs can cause disturbed dreaming due to a side effect of neuropharmaceutical action or as backlash withdrawal and results in the production of hyper-bizarre psychotic dreaming.

Dreaming contains activated dream contexts in a sequential manner being experienced. Brain sub-consciously attempts to disarm the fear filled elements present in these activated dream contexts. Failure of this mechanism results in reinforcement of more fearful memory or a memory with distress elements. These distress elements activate to cause a nightmare cycle. Imbalance of neurotransmitters may cause failure of this mechanism. This imbalance formed by neuropharmaceutical effects of drugs is termed as drug-induced nightmares.

Nightmares can be caused due to some mechanisms like faulty action of the drug to fit the nonsensical stream of neurological data into brain's compilation of expected physical action or reaction. Pharmacological disturbances of dreaming are rare but has proven phenomenon while drugs with neurological pharmacodynamics causes disturbed dreaming more likely.

Imbalances in neurotransmitter levels may cause disturbed dreaming. Excess of neurotransmitters with excitatory function may cause hyper activation of amygdala and resulting in increased fear expression while excess of neurotransmitter with inhibitory function results in disturbed dreaming by down regulating and blocking the fear extinction.

Hence, different drugs cause nightmares by affecting the concentration of neurotransmitters. Imbalance between these neurotransmitters result in fear-filled dreams also termed as nightmares (Issac Brenzer, 2011) [6].

Table 1:- Neurotransmitters and their effects on sleep.

Neurotransmitters	**Effect**
Acetylcholine	Promotes wakefulness and REM sleep
Dopamine	Increases waking and REM sleep
GABA	Increases sleep
Glutamate	Increases wakefulness and REM sleep inhibit NREM sleep
Norepinephrine	Inhibits sleep and increases wakefulness. In case of bilateral injection increases REM sleep
Serotonin	Increases wakefulness, decreases sleep

Nightmares can be produced due to the intake of drugs that affect the neurotransmitters like norepinephrine, serotonin and dopamine. Nightmares are also associated with the withdrawal of REM-suppressing agents and drugs which affect Gamma Amino Butyric Acid (GABA) and Acetylcholine. It is not clear that if there is any common pathophysiological process for different types of nightmares (Sarita Goyal et al., 2013) [12].

A cognitive model of recurrent nightmares:

Mainly observed in case of a traumatic event (post traumatic nightmares) or being chased or losing a relative (idiopathic nightmares). This model is proposed as recurrent nightmare which is represented in the memory as a fixed expectation pattern: a script. This script describes the sequence of events which allows variability. Dream memories include this script as an autobiographical memory. Nightmare script is an isolated highly distressing memory which can be clearly recalled after its occurrence.

Mechanism:

If the neutral or ambiguous dream elements are threatening and similar to nightmare script elements, nightmare script will be activated and due to highly visual mode of brain in REM sleep, nightmare script can be replayed resulting in the occurrence of recurrent nightmares. This process is mediated by emotional intensity of nightmares. Perceived similarity between dream elements and nightmare script is mediated by emotional intensity of nightmare.

Nightmare distress:

Recurrence of nightmare can be determined by distress caused by nightmares. This distress can be exacerbated by personality factor neuroticism, which is a tendency to experience negative emotions and/or anxiety/thrill. The intensity emotional distress of a nightmare is affected by the tendency to experience negative emotions. Hence, due to intense negative emotions and awakenings, an anxious person can be aroused from a chase; while a thrill-seeker may not be aroused to some extent and may stay dreaming. From this current model we can say that neuroticism affects both emotional intensity of nightmares and its evaluation afterwards (Victor I. Spoormaker, 2008) [15].

Model diagram:

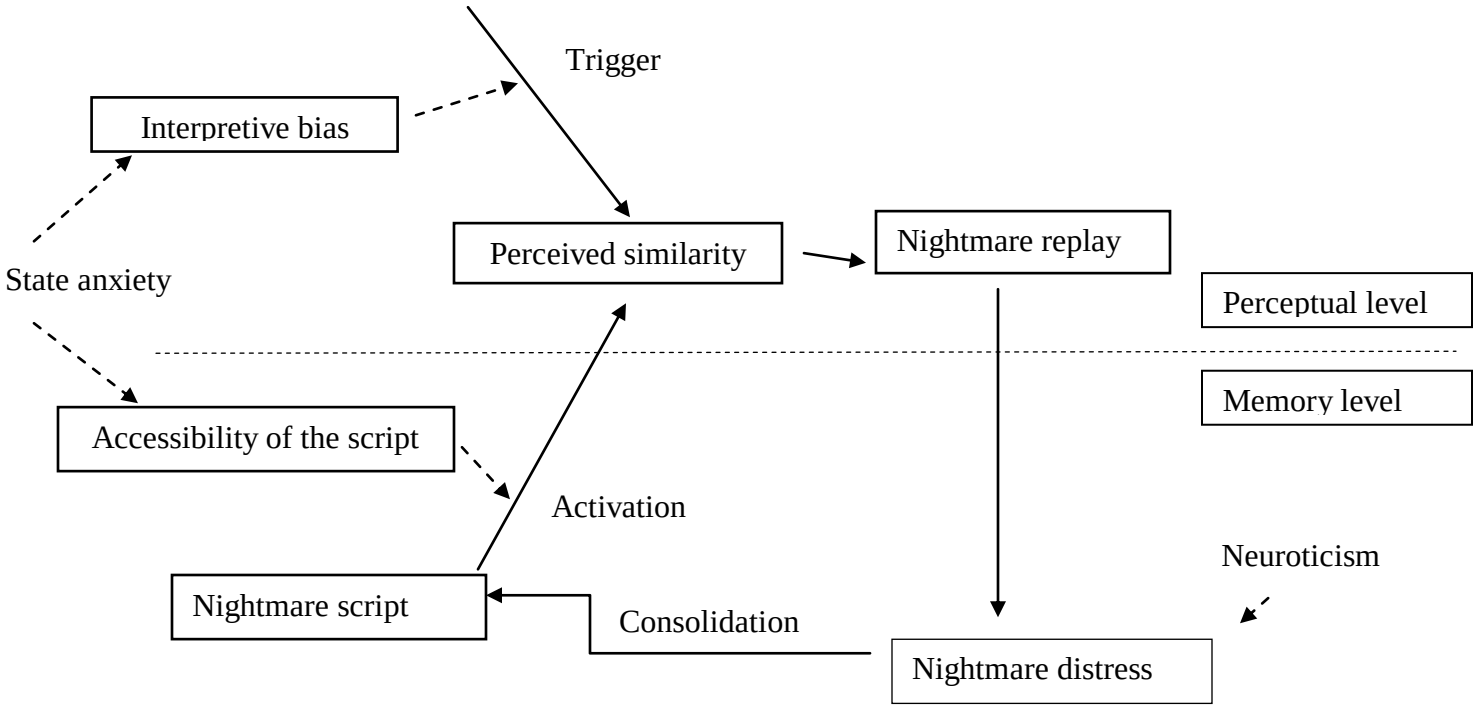

Fig 1:- A cognitive model of recurrent nightmares.

Drugs involved:
Antihypertensive agents such as β-blockers (propranolol, Atenolol, Betaxolol, Bisopropolol & Labetalol) can cause nightmares.

Hypolipidemic agents like simvastatin, pravastatin, Atorvastatin, are REM sleep suppressors & rarely cause nightmares.

Statins, HMG-COA (hydroxyl -3-methyl –glutaryl-co enzyme A) reductase inhibitors act by inhibiting HMG Co-A reductase there by inhibiting de-novo synthesis of cholesterol resulting in reduced serum cholesterol. Low serum cholesterol may cause psychiatric conditions (sleep disturbance)

Drugs used in Alzheimer's disease:
Pharmacological alteration of cholinergic activity in the Central nervous System (CNS) results in alteration of REM sleep. According to a hypothesis cholinergic neurons in the brain stem are excited to induce REM sleep. Hence cholinergic antagonists help to reduce REM sleep while cholinergic agents (Anticholinesterases) tend to induce it. Anticholinesterases have a tendency to cause nightmares.

Antidepressant agents:
Withdrawal of REM sleep suppressant agents like Chlomipramine is associated with intense visual dreaming and nightmares due to REM sleep rebound. Citalopram, SSRI produces nightmares by reducing REM sleep time.

Antiepileptic drugs:
Nightmares are also caused by the intake of drugs that affect Gamma Amino Butyric Acid (GABA) receptor (agonists, modulators and reuptake inhibitors).
For example: Valproic acid.

Sedative Hypnotic drugs:
Dreams and night terrors are seen due to increase in REM sleep with the intake of benzodiazepines (Diazepam) and Non-Benzodiazepine hypnotic (Zolpidem).

General Anaesthetic agents:
Drugs like Thiopental, Ketamine, and Midazolam are reported to cause nightmares.

Antihistamines: Histamine is a modulator for dreaming. Hence, antihistamine drug-Chlorpheniramine has also been reported to cause nightmares.

Antimicrobial and Immunosuppressive agents:
NREM sleep is increased in case of viral and bacterial infections. Erythromycin and Ciprofloxacin are reported to cause nightmares. Immunosuppressant-Gusperimus is also reported to induce nightmares.

Analgesic drugs:
Initial usage of opioid drugs like Morphine, Buprenorphine often reported vivid dreams. Non-opioid drug, Naproxen may affect dreams.

Endocrinal agents:
Larger doses of Testosterone and Dehydroepiandosterone (DHEA) may also cause nightmares.

Miscellaneous drugs:
Other drugs associated with the occurrence of nightmares are NMDA receptor antagonists (Dextromethorphan) and Nicotine receptor partial agonist (vareniciline).

Herbal drugs:
Ashwagandha is a well-known Ayurvedic drug to cause surreal dreams.

Some drugs suppress REM sleep which results in increased intensity of REM episodes that can be manifested as nightmares (examples: β-blockers induced nightmares by involving central adrenergic receptor &suppressing melatonin secretion). Night mares occur due to major life events & mental stress increases its frequency.

Another example is Reserpine induced nightmares although this drug increases REM sleep, nightmares are caused due to depletion of neurotransmitter, particularly dopamine. Dopamine receptor stimulation causes nightmares (examples: Dopamine agonist which are used to treat Parkinson's disease which is associated with nightmares) (Sarita Goyal et al., 2013) [12].

Discussion:-

Dreaming is a complex cognitive process in human central nervous system during sleep. It is to investigate a wide variety of variables including psychological, psychiatric, medical, sleep, behavioral and other factors. These factors contribute to night mare occurrence and severity. The established casual factors are Negative effect, Post- Traumatic Stress Disorder symptoms (PTSD) and stressful life events.

Some of the symptoms significantly experienced by the severity of night mares are: worry, depersonalization, paranoia and hallucination. The symptoms that remain even after controlling the causal factors is longer sleep duration which showed a strong and consistent association with night mare occurrence and increased amount of late night Rapid Eye Movement sleep (REM) (Stephaine Rek et al., 2017)[13].

Some of the drugs affecting neurotransmitters and REM sleep have been shown to cause nightmares. However, disordered dreaming and sleep disorder were commonly found in type-2 Diabetes mellitus. The type-2 DM patients who have the occurrence of bad dreams and poor sleep quality were associated with poor glycemic control & duration of disease.

Metformin is one of the oldest oral anti-diabetic drugs. It has an excellent profile of its efficacy & safety. Meanwhile, there were many reviews and meta-analysis for assessing metformin adverse effects. They mentioned

only a brief reviews and case reports showed a possible causality of metformin induced nightmares and abnormal dreams.

During night time, cerebral blood glucose levels play a major role in explaining the occurrence of nightmares and abnormal dreams. Nocturnal Hypoglycemia is clinically asymptomatic but in some individuals abnormal dreams and poor sleep quality are seen. In Nocturnal Hypoglycemia, some symptoms may provide another possible mechanism of abnormal dreams associated with metformin. The symptoms are absence of fatigue and Negative mood changes whereas the rare side effects of metformin may be night mares & abnormal dreams(Theo Audi Yanto et al.,2018) [14].

Montelukast is a leukotriene receptor antagonist used to treat Asthma. Sleep abnormalities including nightmares may be experienced by patients who are treated with montelukast. Some of the patients are using other drugs simultaneously. In this case, observed by Gloria Cereza et al., the only suspected drug is Montelukast, because nightmares were cured after stopping the Montelukast (dechallenge). After this they have done a rechallenge test and the patients were exposed again to these nightmares. Hence, the suspected drug reported as adverse drug reaction for nightmares was Montelukast (Gloria Cereza et al., 2012) [4].

Similar incidence was reported by Peter J H Smack Greegor in a case report regarding Atorvastatin inducing Nightmares. Dechallenge of the drug stopped the occurrence of nightmares. Nightmares are considered as occasional adverse effect of Statins (Peter J H Smak Gregoor, 2006) [10].

Nightmares are considered as 'highly probable' adverse drug reaction for Mitrazapine in a case report by Amit Dang et al., In this they mentioned that in a 2-year prescription monitoring conducted by Australian ADR Advisory Committee, only 14 events were spontaneously reported from almost 5,00,000 funded prescriptions. Sleep disturbances are extremely rare with Mitrazapine (Amit Dang et al., 2008) [1].

Gurvinder Arora et al., submitted a case report regarding the occurrence of nightmares on administering Citalopram 20mg for 5 days. Nightmares did not occur a day after dechallenge of this drug. Similar case has never been reported before (Gurvinder Arora et al., 2012) [5].

Maria E Moller et al., observed the occurrence of 3-7 nightmares per week in a female patient who is administered with Erythromycin 250mg 4 times a day. After a few days remission of nightmares is observed after stopping the treatment for 3weeks. The occurrence of nightmares with this Erythromycin is a rare phenomenon (Maria E Møller et al., 2016) [9].

Conclusion:-

Drug induced nightmares are mainly caused due to the intake of drugs that affect neurotransmitters like Serotonin, Adrenergic, GABA etc. These nightmares are rarely seen among the people and withdrawal of the drug stopped its occurrence.

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