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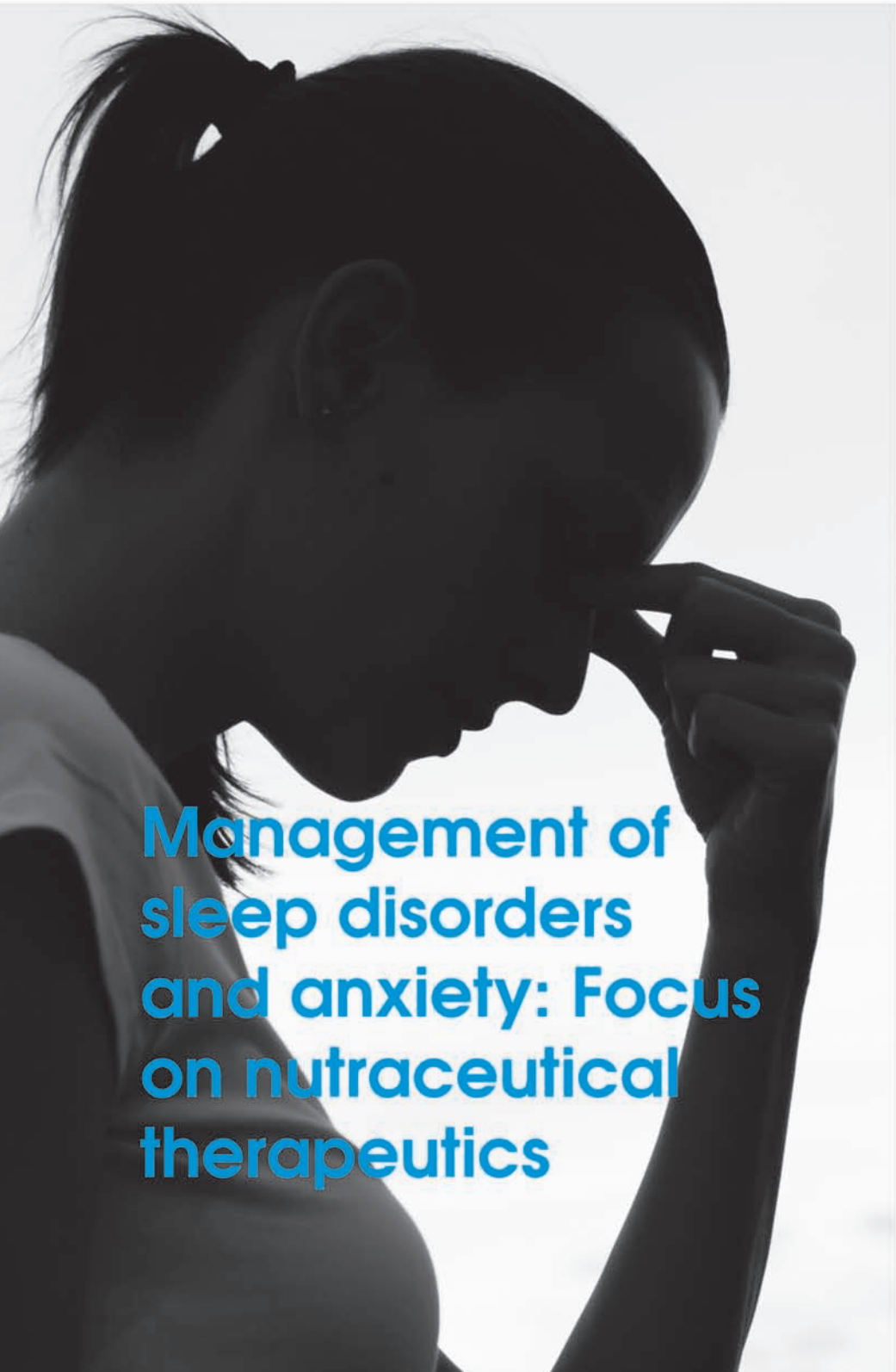

Management of sleep disorders and anxiety: Focus on nutraceutical therapeutics

Volume 31
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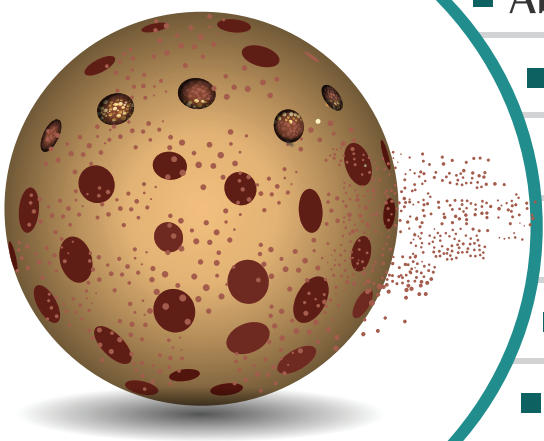

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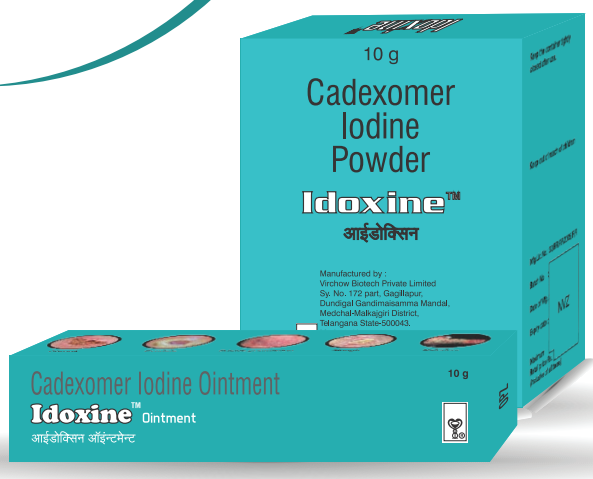

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1. Sundberg J. Poster presentation. The European Wound Management Association Conference, Milan Italy 1997
2. Sandoz H (UK), Swanson T et al. Wounds international 2017; available from https://www.woundsinternational.com/resources/details/biofilm-based-wound-care-with-cadexomer-iodine-made-easy.
3. Leaper DJ, Durani P. Int Wound J 2008;5:361–368.

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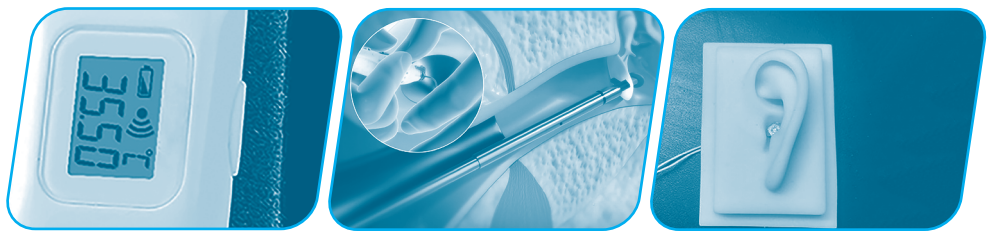

MEDICINE UPDATE
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EDITORIAL

Chronic endometritis: A persistent problem in Obs & Gynae

Dr. Mirudhubashini Govindarajan
FRCS(C), FICOG
Clinical Director
Womens Center and Hospital, Coimbatore

Chronic endometritis (CE) is defined as a persistent, long term infection of the endometrium resulting primarily in a local inflammation. It is a low grade inflammation with no systemic inflammatory signs or symptoms such as fever, pelvic pain, significant discharge. This chronic infection can result in a range of reproductive disorders - from repeated implantation failures (RIF) to recurrent early pregnancy losses, preterm labour, preterm prelabour rupture of the membranes (PPROM) and chronic deciduitis. The reported prevalence of CE ranges from 8% to 72% in women of reproductive age. Several micro-organisms such as *E. coli, Streptococcus, Enterococcus, Staphylococcus*, Mycoplasma spp, Urea plasma urealyticum, *Gardnerella vaginalis, Proteus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Corynebacterium, Yeasts* (*Saccharomyces* and candida spp), and *Mycobacterium tuberculosis* can be found in endometrium in patients of CE.

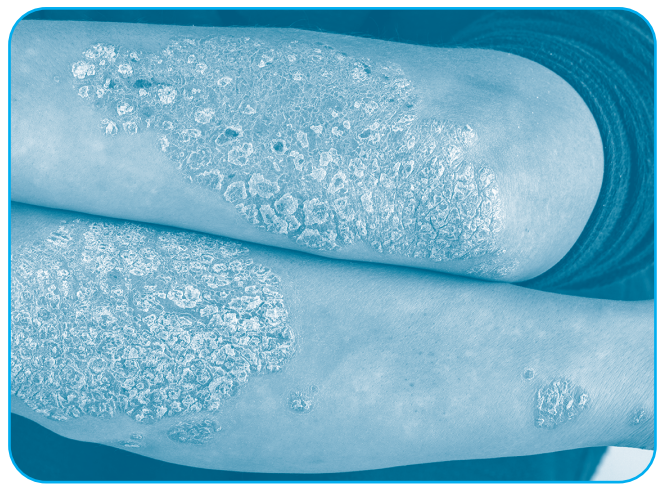
Chronic endometritis is clinically asymptomatic. However, occasionally symptoms such as abnormal uterine bleeding, pelvic pain, dyspareunia, leucorrhea, pelvic discomfort, spotting are reported along with complaints of hypomenorrhoea, secondary amenorrhoea and infertility. Histopathologically, it is characterized by superficial endometrial edema, abnormal increase in stromal cell density, asynchronous maturation of stroma and endometrial invasion by epithelial plasma cells, elevated inflammatory cytokines, such as TNF-α, IL-1 and IL-6, in menstrual blood. Inflammation associated with CE adversely affects pregnancy outcomes, causing miscarriage and preterm birth. The reported prevalence of CE in infertile women is 2.8–56.8%, 14–67.5% in women with RIF, and 9.3–67.6% in women with recurrent pregnancy loss. The risk factors associated with occurrence of CE are previous history of prolonged menstrual bleeding episodes, an abortion history, and a history of fallopian tube obstruction.

SECTION 1

GLOBAL UPDATE

EFFICACY OF COMBINATION THERAPY OF METHOTREXATE AND OTHER ORAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS IN PSORIASIS

The cornerstone in the treatment of immune-mediated inflammatory diseases (IMIDs) such as psoriasis is the oral conventional synthetic DMARDs (csDMARDs). Methotrexate (MTX), a synthetic folic acid analog, is the most commonly used csDMARDs in treatment of psoriasis. Its mode of action is through competitive inhibition of dihydrofolate reductase and aminoimidazole-carboxamide-ribonucleoside (AICAR) transformylase (ATIC). As MTX exhibits its anti-inflammatory and anti-proliferative properties, it has been used in a variety of skin disorders, including psoriasis, dermatomyositis, cutaneous sarcoidosis pityriasis rubra pilaris, chronic urticaria (CU), blistering disorders, localized scleroderma, atopic dermatitis (AD). It has been reported that MTX is important in treatment of psoriasis. However, the combination of MTX and other oral DMARDs or biologics can also be attempted. Hence, a systematic review was conducted with the purpose of evaluating efficacy and safety of the combinational use of MTX and other oral DMARDs in the treatment of psoriasis. A literature search was performed through Medline (PubMed), Embase, Web of Science, and the Cochrane Library.



The results of this review were:

- The combination treatment with MTX and other oral DMARDs demonstrated good efficacy and tolerability in psoriasis.
- No significant increase in adverse events were observed during combination therapy with MTX and other oral DMARDs

Conclusively, combination therapy with MTX and csDMARDs exhibits excellent effectiveness in treatment of patients with psoriasis with an inadequate response to oral DMARD monotherapy.

Source: Hsieh TS, Tsai TF. Combination Therapy for Psoriasis with Methotrexate and Other Oral Disease-Modifying Antirheumatic Drugs: A Systematic Review. *Dermatol Ther (Heidelb)*. 2023.

ROLE OF MYCOPHENOLATE MOFETIL IN THE TREATMENT OF BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is one of the most common autoimmune blistering disease which is treated by systemic glucocorticoids. However, systemic glucocorticoids are associated with numerous side-effects hence mycophenolate mofetil (MMF) can be used in BP as a steroid-sparing alternative. In line with this, a study was conducted to examine the efficacy and safety of MMF in patients with BP (n= 26). In this study, analysis of patients with BP treated with MMF alone (monotherapy; n=12) or in combination with prednisone (dual therapy; n=14) was done.

The results of the study were:

- There was complete improvement in BP in patients treated with MMF monotherapy (100%) in mean time period of 0.8 months
- Complete control of disease amongst both the groups was achieved in 5. 6 months and in 96. 2% of patients (25/26)
- Amongst the 26 patients, 46.2% patients were reported to experience disease remission with no subsequent flares for up to 15 months after MMF was discontinued
- There were no serious side effects

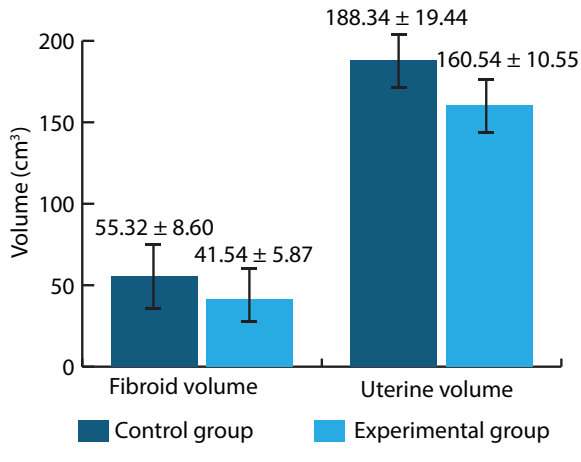
Hence, it was concluded that MMF is a safe and effective treatment for BP with improvement and complete response in most patients and remission in few patients.

Source: Liang S, Cohen J, Soter N. The Use of Mycophenolate Mofetil in the Treatment of Bullous Pemphigoid. *J Drugs Dermatol*. 2022 Feb 1;21(2):151-155.

EFFECTIVENESS AND SAFETY PROFILE OF MIFEPRISTONE COMBINED WITH ULTRASOUND- GUIDED RADIOFREQUENCY ABLATION IN TREATING PATIENTS WITH UTERINE FIBROIDS

A total of 130 patients with uterine fibroids were included with the aim to evaluate the efficacy and safety of oral administration of mifepristone combined with ultrasound-guided radiofrequency ablation in treating patients with uterine fibroids, as well as alterations of inflammatory cytokines including procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), and tumor necrosis factor-alpha (TNF-α), adhesion molecules including monocyte chemotactic protein 1 (MCP-1) and soluble intercellular adhesion molecule 1 (sICAM-1), and growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), transforming growth factor-β (TGF-β), and TGF-β receptor. Among 130 patients, 65 received ultrasound-guided radiofrequency ablation alone (control group) and the remaining women were given oral administration of mifepristone combined with ultrasound guided radiofrequency ablation (experimental group).

Figure 1: Fibroid volume and uterus volume after treatment in experimental and control group among patients with uterine fibroids



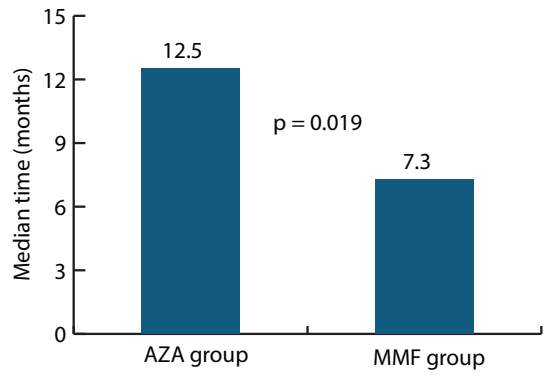
In comparison to the control group, experimental group exhibited statistical significant higher effective rate and smaller uterus and fibroids volume (Figure 1). There was statistical significant decrease in the levels of MCP-1, sICAM-1, VEGF, EGF, bFGF, TGF-β, TGF-β receptor, PCT, hs-CRP, and TNF-α in the serum in experimental group in comparison to control group. It can be concluded that oral administration of mifepristone combined with ultrasound-guided radiofrequency ablation is highly effective in treating patients with uterine fibroids as it could inhibit the expressions of inflammatory cytokines, adhesion molecules, and growth factors.

Source: Hou A, Yan Z, Zhang Y et al. Oral Administration of Mifepristone Combined with Ultrasound- Guided Radiofrequency Ablation in Treating Patients with Uterine Fibroids: Efficacy, Safety, and Alternations of Inflammatory Cytokines, Adhesion Molecules, and Growth Factors. *Journal of Nanomaterials*.2021.

COMPARATIVE EFFECTIVENESS OF AZATHIOPRINE AND MYCOPHENOLATE MOFETIL IN PATIENTS WITH PEMPHIGUS

One of the life-threatening auto-immune mucocutaneous disorders is pemphigus. The mainstay treatment of pemphigus is systemic corticosteroid as they can cause reductions in the mortality rate from <70% to >10%. There are various steroid sparing agents such as azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide, which can be used, among others as corticosteroids exhibit various side effects. Hence, this study was performed with the aim of comparing the effectiveness and safety profile of AZA and MMF as an accessory therapy with the corticosteroid prednisolone for the treatment of pemphigus. A total of 62 patients with pemphigus were enrolled and divide into two groups; 37 patients received prednisolone plus AZA as adjuvant therapy (AZA group) and 25 patients received prednisolone plus MMF as adjuvant (MMF group). The early end points were end of the consolidation phase (ECP) and late end points were complete remission (CR) on therapy, CR off therapy and immunological remission.

Figure 2: Median time to achieve complete remission (CR) on therapy in AZA and MMF groups among patients with pemphigus



Results of the study were:

- Both the treatment groups reached the ECP with AZA group at 88.2%; MMF group at 71.4%
- There were comparable results with respect to the median time taken to achieve this early end point (p= 0.362)
- On the other hand, the late end points such as CR on therapy was achieved with AZA at 73%; MMF at 72%
- The median time taken to achieve CR was significantly shorter for those on MMF than for those on AZA (Figure 2)
- Additionally, the cumulative steroid dose required for patients to achieve CR both on and off therapy was significantly higher in the AZA group than in the MMF group (p = 0.043 and p = 0.007 respectively)

Conclusively, MMF exhibits a shorter time to achieve CR on therapy and has a significantly higher steroid-sparing effect. However, AZA or MMF used in combination with corticosteroid is an effective beneficial therapy for treatment of pemphigus.

Source: Sukanjanapong S, Thongtan D, Kanokrungsee S, Suchonwanit P, Chanprapaph K. A Comparison of Azathioprine and Mycophenolate Mofetil as Adjuvant Drugs in Patients with Pemphigus: A Retrospective Cohort Study. *Dermatol Ther (Heidelb)*. 2020;10(1):179-189.

CLINICAL UPDATE

Management of sleep disorders and anxiety: Focus on nutraceutical therapeutics

INTRODUCTION

- Anxiety is an experience which we encounter in our daily life. It typically functions as an internal alarm that warns of potential danger and, in mild degrees, anxiety is serviceable to the individual.[1]
- However, these alarms can be false too which an individual with anxiety disorders may encounter. These false alarms may be intense, frequent, or even continuous that may lead to a state of dysfunctional arousal often leading to persistent sleep-wake difficulties.[1]
- It has been reported that stress and anxiety may cause sleeping problems or make existing problems worse.[2]
- Sleep is vital for almost each aspect of human life. Inadequate amount of sleep exerts an immense negative impact on health, increasing the risk of obesity, cardiovascular and metabolic disease, and mood and cognitive disorders, ultimately resulting in accelerated cellular senescence and overall aging.[3]
- Abnormal sleep patterns that interfere with physical, mental, and emotional functioning of an affected individual are characteristic features of sleep disorders. Stress or anxiety can cause a serious night without sleep, as do a variety of other problems.[2]
- Other common sleep disorders include sleep apnea (loud snoring caused by an obstructed airway), sleepwalking, and narcolepsy (falling asleep spontaneously). Restless leg syndrome and bruxism (grinding of the teeth while sleeping) are conditions that also may contribute to sleep disorders.[2]
- Sleep disturbances are reported to be highly prevalent in the general population, ranging from 15-25% in the United States, that they have been declared a public health epidemic.[3]
- Pre-existing medical and psychiatric conditions get exacerbated in presence of sleep disorders. There is a positive association between sleep disorders and rates of depression, anxiety, and impaired daytime functioning. They may also lead to poor occupational performance, motor vehicle accidents, cardiovascular and endocrine disorders, or heightened pain perception.[4]
- Of late, the workloads of healthcare workers during a pandemic involve exhausting shifts necessary to both manage the health emergency and overcome long-standing shortages of healthcare personnel, particularly nurses. This can cause negative outcomes for the safety of patients (in terms of mortality and morbidity) and health professionals (in lower job satisfaction, burnout and intention to leave).[5]

- This, in turn, negatively affects these workers' sleep quality, increasing the risk of distressed psychophysical health revealed in symptoms such as memory loss, low reactivity, irritability, worsening depression and suicidal tendencies.[5]

CATEGORIES OF SLEEP DISORDERS

The International Classification of Sleep Disorders, second edition (ICSD-2) subdivides sleep disorders into following categories:[6]

- Insomnias
- Sleep-related breathing disorders
- Hypersomnias of central origin related
- Circadian rhythm sleep disorders
- Parasomnias
- Sleep-related movement disorders
- Isolated symptoms, apparently normal variants, and unresolved issues
- Other sleep disorders.

Figure 1 depicts prevalence of different sleep disorders in general population.[7]

BURDEN OF NEUROPSYCHIATRIC DISORDERS

- It has been reported that prevalence of anxiety disorder is about 24% to 36% in subjects with insomnia and about 27% to 42% for those with hypersomnia.[1]
- With a 12-month prevalence of 10.3%, specific (isolated) phobias are the most common anxiety disorders, although persons suffering from isolated phobias rarely seek treatment[1]
- Panic disorder with or without agoraphobia (PDA) is the next most common type with a prevalence of 6.0%, followed by social anxiety disorder (SAD, also called social phobia; 2.7%) and generalized anxiety disorder (GAD; 2.2%).[8]
- Women are 1.5 to two times more likely to be diagnosed with anxiety disorder than men.[7]

Furthermore, it was observed that the relationship between anxiety and sleep is that sleep disturbance is a diagnostic symptom for some anxiety disorders, such as GAD and posttraumatic stress disorder (PTSD).[1]

RISKS OF PSYCHIATRIC DISORDERS IN THOSE WITH SLEEP DISTURBANCES

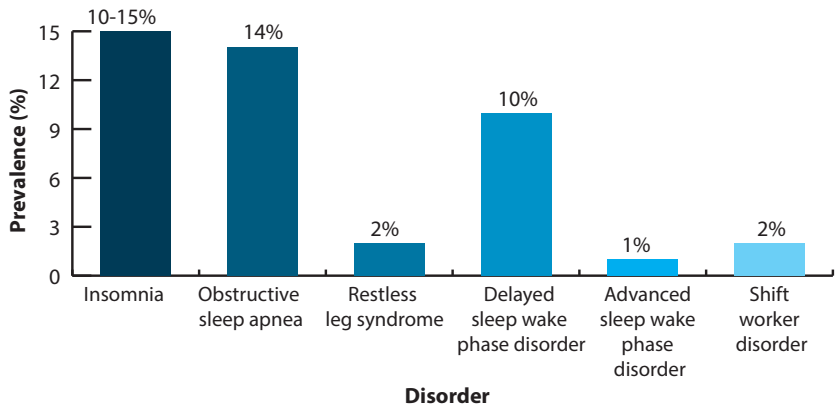
- Evidences have shown that the risks of psychiatric disorders in those with sleep disturbances are less well appreciated than the sleep disturbances associated with psychiatric disorders.
- However, the data that sleep disturbances are associated with an increased risk of developing psychiatric disorders has existed since the 1980s.[9]

Some of psychiatric disorders and their relation with sleep disturbances are briefed:[9]

A. Major depressive disorder

- Literature reports that those with insomnia and those with hypersomnia are roughly ten times as likely to have major depressive disorder (MDD) as healthy controls without sleep disorders.

Figure 1: Prevalence of different sleep disorders



Adapted from: Gupta R, Das S, Gujar K, *et al.* Clinical Practice Guidelines for Sleep Disorders. *Indian J Psychiatry.* 2017;59(Suppl 1):S116-S138.

- Moreover, a series of longitudinal studies indicate that having insomnia at one point in time considerably increases the risk for the subsequent development of new onset MDD.

B. Generalized anxiety disorder

- It is also reported that insomnia increases the risk for the subsequent development of anxiety disorders.
- Those with insomnia appear to have approximately doubled the risk of healthy controls.

C: Post-traumatic stress disorder

- It has been reported that pre-existing insomnia is a predisposing factor for the development of the PTSD syndrome following an extreme event.
- There is, however, also data available noted that sleep complaints occurring at 1 month or longer after trauma were significant predictors of the presence of a diagnosis of PTSD at 1 year post-trauma.

D. Schizophrenia

- Severe disturbance of sleep has been reported to occur prior to the development of episodes of acute psychotic decompensation in patients with schizophrenia.

E. Alcoholism

- There is a body of evidence suggesting that sleep difficulties are associated with increased risk of alcoholism.
- It is also demonstrated that sleep disturbances may increase the risks for alcoholism and may contribute to continued alcohol consumption among drinkers.
- Evidences suggest that those with insomnia are at increased risk for the development of subsequent alcohol use problems compared to those without disturbed sleep.[9]

PATHOPHYSIOLOGY OF ANXIETY-ASSOCIATED SLEEP DISORDERS

- Stress is a complex condition which is associated with emotional, cognitive, and biological factors. Excessive amount of stress causes long- and short-term disability in the various human systems, and activates the defense system of the central nervous system.

Sleep disorders are closely associated with significant medical, psychological and social disturbances

Adapted from: Han KS, Kim L, Shim I. Stress and sleep disorder. *Exp Neurobiol.* 2012;21(4):141-150.

- The stress responses are based on the type of stress and the individual's physiological responses. These latter responses consist of neuro-endocrine and behavioral responses, and include the changes in the activity and immune function of the hypothalamopituitary-adrenal (HPA) axis.
- In the beginning of sleep, the activity of HPA axis is suppressed continually. In the latter part of sleep, the HPA secretory activity increases so it is close to the maximum circadian rhythm immediately after waking up, and the prominent activity of the HPA axis and sympathetic nervous system influences the overall amount of rapid eye movement (REM) sleep.
- Thus, the increase of adrenocorticotrophic hormone (ACTH) in the morning is a decisive controlling factor that regulates the end of sleep. The fact that the beginning and end of sleep involve HPA axis activity, and the close temporal relationship between the axis and sleep provides a clue to identify the effects of the stress on sleep.[10]
- Dysfunctions of GABAergic (GABA, γ-aminobutyric acid) neurotransmitter systems have been implicated in anxiety disorders; however, it is one of the chief phenomenon in anxiety disorder patients relates to sleep alteration.[1]

In addition, other factors which may be responsible for sleep disorders are genetic and molecular

Genetic factors:[11]

- Apolipoprotein (Apo) E4, PER3 4/4
- HLA-DQB1*0602
- Homozygous Clock gene 3111C/C Clock and short (s-) allele of the 5-HTTLPR.

Molecular factors:[11]

- Wake-promoting chemicals like orexin, catecholamine, histamine
- Sleep promoting chemicals like GABA, serotonin, adenosine, melatonin, and prostaglandin D2.

RELATIONSHIP BETWEEN SLEEP COMPLAINTS AND ANXIETY DISORDER

- Anxiety disorders are considered as the most frequently occurring category of mental disorder in the general population. Sleep disturbance is considered as the second most common symptom of mental distress.[1]
- There is a positive correlation between all types of anxiety (generalized anxiety, obsessive-compulsive disorders, panic attack) and sleep disorders such as early insomnia, sleep interruption and low efficiency of sleep.

The EEG findings give different results according to the type of anxiety:

- Total sleep time reduction and low efficiency of sleep are features associated with generalized anxiety.
- In addition, sleep is unstable with numerous awakenings. Longer periods of stage 1 and 2 sleep are observed and slow wave sleeps as well as REM sleep time is reduced.[12]

There is a reduction in REM sleep latency in patients with obsessive compulsive disorders. Although sleep abnormalities observed in anxiety disorders differ from those observed in depressive disorders, none of these features can be considered specific of anxiety.[12]

CONSEQUENCES OF ANXIETY/SLEEP DISORDERS

It has been recognized that there is a positive association between psychopathology and poor sleep. Table 1 enumerates the clinical features of insomnia and anxiety.[13-15]

Generalized anxiety and sleep disorders may be the consequence of medical conditions, psychiatric conditions, concomitant medicine treatments or medicine withdrawal, substance abuse, stress and bad habits.[13-15]

MANAGEMENT

- The main focus of the treatment of GAD is reduction of the impairment that results from excessive anxiety and worry, and of the accompanying muscle tension, sleep disturbance, irritability, difficulty in concentrating and fatigue.
- Generalized anxiety disorders and associated insomnia should be managed with proper approach including pharmacotherapy and non-pharmacotherapy (Table 2).[11,16]
- It has been reported that anxiolytic drugs play an important role in the management of GAD, and their judicious use is an important part of the medical treatment of the disorder.[16]

Table 1: Clinical features of anxiety/sleep disorders

Chronic insomnia	Anxiety
• Severely reduced quality of life • Cognitive impairment • Physical complaints • Poor social functioning • Sleep-related breathing disorders • Restless legs syndrome (RLS) • Suicidal thinking • Completed suicides • Difficulty falling asleep • Nightmares • Excessive daytime sleepiness	• Apprehension • Subjective and physiologic manifestations of fear • Sweating, shakiness, dizziness, palpitations, mydriasis, tachycardia, tremor, gastrointestinal disturbances, diarrhea, and urinary urgency and frequency • Complaints of persistent nervousness, trembling, muscular tensions, sweating, light headedness, palpitations, dizziness, and epigastric discomfort

Adapted from: 1. Spiegelhalder K, Regen W, Nanovska S, *et al.* Comorbid sleep disorders in neuropsychiatric disorders across the life cycle. *Curr Psychiatry Rep.* 2013;15(6):364. **2.** Hombali A, Seow E, Yuan Q, *et al.* Prevalence and correlates of sleep disorder symptoms in psychiatric disorders. *Psychiatry Res.* 2019;279:116-122. **3.** Pharmacological Treatment of Mental Disorders in Primary Health Care. Geneva: World Health Organization; 2009. Chapter 6, Medicines used in generalized anxiety and sleep disorders. Available from: https://www.ncbi.nlm. nih.gov/books/NBK143206/. Accessed on: 22/1/22.

Table 2: Management of chronic insomnia

I. Non-pharmacological treatment
1. Sleep Hygiene • Educating the patients about lifestyle modifications like limiting the daytime naps • Avoiding late night dinner or evening intake of alcohol, caffeine, or smoking • Encouraging them to adopt a healthy diet • Exercise regime • Maintain a regular sleep and wake time schedules.
2. Sleep Restriction Therapy
3. Stimulus Control Therapy
4. Relaxation Therapy
5. Cognitive Behavioral Therapy for insomnia (CBTi)
II. Pharmacological management
1. Drugs acting on GABA-A receptors • Benzodiazepines (BZD) • Benzodiazepine receptor agonists (BzRA or non-BZD)
2. Drugs acting on Melatonin Receptors
3. Drugs acting as Orexin Receptor Antagonist
4. Drugs acting as Histamine-1 Receptor Antagonist
5. Off-label drugs • Antidepressants • Atypical antipsychotics • Anticonvulsants

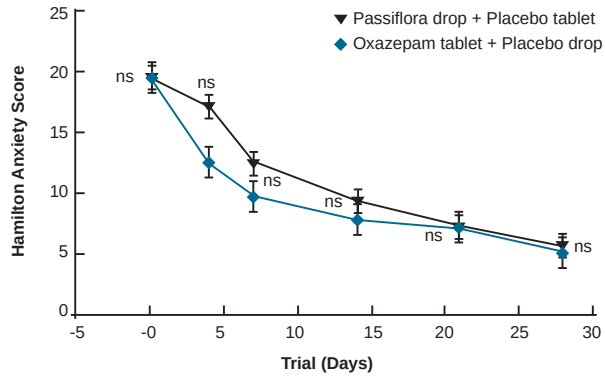
Adapted from: 1. Kaur H, Spurling BC, Bollu PC. Chronic Insomnia. [Updated 2021 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from:https://www.ncbi.nlm.nih.gov/books/NBK526136/. Accessed on: 14/1/2022. **2.** Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. *Sleep Med Rev.* 2000;4(3):263-276. .

- Each patient must be carefully evaluated for the severity and the chronicity of the symptoms before starting treatment.[16]
- The field of nutraceuticals fits apt for treating such disorders. The quality of being nontoxic, non-habit forming, and being practically more efficient has had made nutraceutical as an excellent option in the treatment of sleep disorders.[17]

PASSION FLOWER

- The *Passiflora incarnata L.*, also known as passion flower, is a perennial plant that can grow up to 10 m, with egg-shaped edible fruit.
- *Passiflora incarnata* is reported to be one of the best-documented species of the Passiflora genus with therapeutic properties.

Figure 2: Demonstrated effect of study treatments on anxiety



ns = non-significant

Adapted from: Akhondzadeh S, Naghavi HR, Vazirian M, *et al.* Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharm Ther.* 2001;26(5):363-7.

- The aerial parts of the plant, flowers, and fruits are used for medicinal purposes. They exert antihelmintic, antispasmodic, and anxiolytic effects.
- It can also be used as a remedy for burns, diarrhea, painful menstruation, hemorrhoids, in neurotic disorders, insomnia, to treat morphine dependence, and can be helpful in convulsions or neuralgia, too.
- Systematic review concludes that evidence from various randomized controlled trial, suggests that passion flower, may be helpful in treating symptoms in neuropsychiatric patients.[18]
- Passion flower is potentially effective in the treatment of anxiety.
- Data is available on the sleep-inducing effects of passion flower in cells and animals, suggesting that *Passiflora incarnata* extract might have potential for treating human insomnia.[19]
- A double-blind randomized trial compared the efficacy of *Passiflora incarnata* extract with oxazepam in the treatment of GAD. Findings of the study demonstrated that passiflora extract is effective in the treatment of systemic anxiety (Figure 2); additionally, there is a low incidence of impairment of work efficiency with Passiflora extract, as compared to oxazepam.[20]
- It is the chemical constituent flavonoid that is responsible for the anxiolytic activity of Passiflora. Mechanism of action of the flavonoids identified in *P. incarnata* is related to the modulation of

the γ-aminobutyric acid (GABA) system, because Passiflora flavonoids are partial agonists of $GABA_A$ receptors and inhibit the uptake of [3H]-GABA into experimental models cortical synaptosomes.[21]

- Details have shown that pharmacological effects of *Passiflora incarnata* are mediated via modulation of the GABA system including affinity to $GABA_A$ and $GABA_B$ receptors, and effects on GABA uptake.[22]
- It is well known that many patients have preoperative anxiety, which calls for the need to develop a drug (preferably given orally) for premedication that is a strong anxiolytic with minimal psychomotor impairment such as herbal medicines that includes Passiflora. A study had shown that administration of oral *Passiflora incarnata* as a premedication reduces anxiety without inducing sedation.[23]

MELATONIN

- Pineal gland secretes a hormone melatonin at night. This hormone has many physiological functions, the main one being to synchronise individuals' biological rhythms.
- Exogenous melatonin has the same chronobiotic action, even at small doses (0.125mg).
- Additionally, a sleep-inducing (soporific) action appears to occur in a dose-effect relationship. These effects of exogenous melatonin have interesting applications in psychiatric disorders in clinical practice.
- The French institute of medical research on sleep (SFRMS) appointed a group of experts who conducted a consensus conference to study the indications of melatonin and the conditions of its prescription.[24]
- In literature, exogenous melatonin proves to be useful among patients with a stabilized psychiatric disorder or in remission, to prevent relapse in case of associated complaints of insomnia, poor quality sleep or delayed sleep phase syndrome.
- In somatoform disorders, melatonin is a potential treatment option for painful symptoms in fibromyalgia, irritable bowel syndrome, functional dyspeptic syndrome and temporomandibular joint dysfunction.[24]
- A randomized double-blind placebo-controlled two-period two-treatment (melatonin and placebo) crossover study showed significant improvement in sleep quality with effective and well-tolerated melatonin supplementation in patients with traumatic brain injury (Table 3).[25]

MAGNESIUM

- Magnesium is one of the essential mineral for humans.
- Being the second most abundant intracellular cation, magnesium is involved in almost all major metabolic and biochemical processes.

Table 3: Effect of melatonin on anxiety/sleep quality in patients with traumatic brain injury

		Adjusted mean (95% CI)		
	No. of participants	**Melatonin treatment**	**Placebo treatment**	**p value**
Primary outcomes				
PSQI, global score	33	7.68 (6.34 to 9.02)	9.47 (8.13 to 10.81)	<0.0001
Sleep latency, minimum	31	1.37 (1.26 to 1.48)	1.42 (1.31 to 1.53)	0.23
Secondary outcomes				
Sleep efficiency	31	-3.22 (-3.61 to -2.82)	-3.54 (-3.94 to -3.13)	0.04
ESS, score	33	2.36 (2.00 to 2.73)	2.53 (2.17 to 2.90)	0.15
HADS anxiety, score	32	7.84 (6.23 to 9.45)	9.00 (7.39 to 10.61)	0.006
HADS depression, score	32	8.53 (6.93 to 10.13)	8.34 (6.75 to 9.94)	0.68
FSS, score	33	-4.18 (-4.74 to -3.62)	-3.73 (-4.28 to -3.17)	0.03

Abbreviations: PSQI- Pittsburg sleep quality index, HADS- Hospital anxiety depression scale, ESS- Epworth Sleepiness Scale, FSS- Fatigue severity scale

Adapted from: Grima NA, Rajaratnam SMW, Mansfield D, *et al.* Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. *BMC Med.* 2018;16(1):8.

Magnesium acts as a cofactor in following:

- Enzymatic reactions
- Primary functions including protein and nucleic acid synthesis
- Regulation of metabolic pathways
- Neuronal transmission, neuromuscular function
- Regulation of cardiac rhythm
- Magnesium is a naturally occurring calcium channel blocker which is involved in the maintenance of electrolyte balance (e.g., regulation of sodium–potassium ATPase activity), and plays a key role in membrane excitability.[26]
- Supplementation of magnesium appears to improve subjective measures of insomnia such as insomnia severity index (ISI) score, sleep efficiency, sleep time and sleep onset latency, early morning awakening, and likewise, insomnia objective measures such as concentration of serum renin, melatonin, and serum cortisol, in elderly people.[27]
- It is seen that magnesium supplementation brings significant improvement, both subjective and objective, to the patients who have insomnia. It has been demonstrated that after 8 weeks of magnesium supplementation, the patients had increased sleep time, as well as sleep efficiency.[28]

L-THEANINE

- L-theanine (γ-glutamylethylamide) is a unique non-protein amino acid which is found in green tea (*Camellia sinensis*), a widely consumed beverage associated with human health.
- Mechanism of action of L-theanine may be potentially mediated through glutamate receptors as the structure of L-theanine resembles that of L-glutamic acid, a possibility supported by its partial co-agonistic effect on the N-methyl-D-aspartate receptor.
- In daily life, L-theanine is a potential nutraceutical ingredient that mitigates and prevents stress-related psychic confusion in modern society.[29]
- In concordance to above, findings of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, suggest that supplementation of L-theanine may assist in the reduction of stress and anxiety in people exposed to stressful conditions.[30]

A study[31] was done to examine the effectiveness of L-theanine for patients with MDD. Results were as follows:

- Hamilton Depression Rating Scale (HAMD-21) score was reduced after L-theanine administration (p=0.007). This reduction was observed in unremitted patients (HAMD-21>7; p=0.004) at baseline.
- Anxiety-trait scores decreased after L-theanine administration (p=0.012) in the State-Trait Anxiety Inventory test.
- Pittsburgh Sleep Quality Index scores also decreased after L-theanine administration (p=0.030) in the unremitted patients at baseline.
- Regarding cognitive functions, response latency (p=0.001) and error rate (p=0.036) decreased in the Stroop test, and verbal memory (p=0.005) and executive function (p=0.016) were enhanced in the Brief Assessment of Cognition in Schizophrenia test after L-theanine administration.
- It was inferred that chronic (8-week) L-theanine administration is safe and has multiple beneficial effects on depressive symptoms, anxiety, sleep disturbance and cognitive impairments in patients with MDD.

CONCLUSION

Sleep is an important aspect to maintain healthy life. In modern society, sleeping disorders and anxiety are prevalent problems, and are major contributors to negative impact on health of an affected patient. Nutraceuticals are found to be effective in the treatment of sleep disorders. Nutraceuticals comprising of passion flower, L-theanine, magnesium and melatonin can act as potential therapeutic regime without any undesirable side-effects; suggesting that use of nutraceuticals is an effective and well-tolerated option for managing anxiety and insomnia.

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CLINICAL UPDATE

A 62-year-old POST-CABG patient associated with hypertension, reduce renal function (eGFR-60), hepatomegaly, prostatomegaly, hyperuricemia, degenerative arthritis, co-morbid anxiety and depression; successfully treated in combination with life style modification, bioactive compounds and few medications

CASE HISTORY

A 62-year-old obese male patient presented with complaints of chronic low back pain, difficulty in micturition, mild central chest pain, anxiety and low mood, sweating and tiredness. He had done Coronary Artery Bypass Graft (CABG) operation 10 years ago. After that he was fine for 7 years. His low back pain was started slowly when he lifts heavy objects and micturition problem gradually worsened.

On further enquiring, he had anxiety, low mood, sweating, and tiredness. He had a BMI of 37 KG/M^2. He had been advised to follow DASH diet and regular morning walk for 30 minutes with Structured Exercises Programme. Low back pain and difficulty in micturition bothered him very much.

CLINICAL EXAMINATION

- The patient was well-oriented to time, place and person
- Weight: 89 KG, Height: 157 CM
- BMI: 37 KG/M^2
- Waist circumference: 105 CM, neck circumference: 41 CM
- BP: 130/80 mmHg
- The remainder of the physical exam was unremarkable.

DIAGNOSTIC EVALUATION

- No h/o trauma, infection or inflammatory low back pain or unexplained weight loss
- ROM of Lumbar Spine:
  - » Forward flexion- moderately painful
  - » Extension- no pain.
- Straight leg raising test:
  - » RT 50 Degree
  - » LT Free.
- Schober's test and FABER Test: Normal.
- X-ray of L-S spine and both knee (Lat and AP view):
  - » Grade I Spondylolysthesis
  - » Grade II both knee OA change.
- Tingling Sensation of Rt lower limb: Rt sided lumber S_1 radiculopathy
- No saddle anesthesia or any kind of CAUDA EQUINA features.
- Obesity is determined as an important cause.

MANAGEMENT

He was advised to follow DASH diet, increase Aerobic Exercises under the guidance of Physical Therapy Specialist and maintain a healthy lifestyle measures. A plan on relaxation techniques, stress management and psychotherapy was considered for improvement of quality of life. He was also suggested to drink less water after 7 pm and regular deep breathing therapy on morning and evening daily. "Tab Cresvin beta -2 tab bd (2 tab 20 min before breakfast and 2 tab 20 min before dinner) for 3 months + Tab ibandronate (150) (once in a month) + Tab elemental calcium (500) daily + vitamin D3 (4000 IU) + [Tab telmisartan (40) + Tab metoprolol ER (50) combination (1 tab after breakfast) x 3 months]+[Tab escitalopram (5) + Tab clonazepam (0.5) combination for 15 days than Tab escitalopram(5) for 3 months.] +Tab methylcobalamine (1500 mcg) 1 Tab sublingually for 3 month + Tab Esomeprazole (40)-1 Tab ODAC× 3 months+ 2% diclofenac gel-to be apply locally × bd × continue for 3 months".

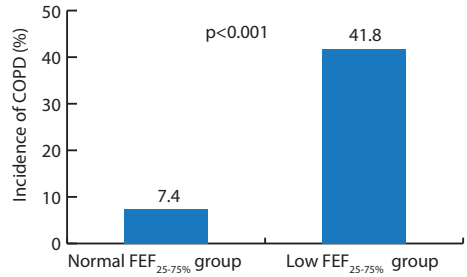
The patient responded well with the treatment and returned to Physical Medicine and Rehabilitation Outpatient Department at Bankura Sammilani Medical College and Hospital (BSMC&H) for follow-up three months later. There was marked improvement of all symptoms and patient felt more energized. Post-intervention BP was 130/80 mmHg and BMI was markedly decreased to 34 kg/m^2. He was advised to continue Bioactive Compounds (Tab Cresvin Beta) with other medications. He was also instructed to follow DASH diet, proper physiotherapy regime, lifestyle modification as far as possible.

Usefulness of $FEF_{25-75\%}$ values in predicting the risk of COPD development in patients with normal lung function

FORCED EXPIRATORY FLOW AT 25%-75% AND COPD: OVERVIEW

- Chronic obstructive pulmonary disease (COPD) affects large and small airways, with the majority of dysfunction occurring in airways less than 2 mm in diameter. Spirometry, with a focus on FEV_1, is used to identify airflow obstruction, predict COPD development [FEV_1/forced vital capacity (FVC) <0.7] and grade severity in COPD.[1,2]
- The FEV_1 in a healthy lung represents both passive and active lung and chest wall recoil. It also represents the resistance in both large and small airways. However, the use of FEV_1 alone may understate the severity of minor airway abnormalities in individuals with obstructed lung.[1]
- Forced expiratory flow rate between 25% and 75% ($FEF_{25-75\%}$) of the vital capacity represents the maximum mid-expiratory flow rate and it is more indicative of air movement through the medium-sized and small airways, particularly in individuals with normal FEV_1 and FEV_1/FVC; also, it is less effort-dependent.[2,3]
- Of late, $FEF_{25-75\%}$ is being considered the most sensitive indicator of airflow, particularly in peripheral airways where main airflow obstruction arises. Studies have demonstrated a reduction in $FEF_{25-75\%}$ in early bronchial impairment, which is usually associated with small airway disease.[2]
- However, because of its significant intra- and inter-user variability and broad range of suggested normal values, this parameter has proved challenging to employ clinically in the evaluation of early disease at the level of the individual patient.[1]

Figure 1: Incidence of COPD in a normal FEF25-75% group and a low FEF25-75% group[2]



- Small airway disease, a key component of COPD, is eventually caused by remodeling of the airways, mucus plugging, and immune cell infiltration induced by cigarette smoking. Emerging evidences suggest that individuals with COPD typically experience diminished $FEF_{25-75\%}$. It is now being posited that $FEF_{25-75\%}$ may indicate COPD earlier than other indicators like FEV_1, D_{LCO}, and FVC.[2]

Table 1: Outcomes of the lung function test based on the FEF25-75% z-score[2]

Variables	Normal FEF25-75%	Low FEF25-75%	p-value
FEV1 (L)	2.6±0.6	2.2±0.6	<0.001
FEV1 (% predicted)	109.8±16.2	93.5±11.2	<0.001
FVC (L)	3.3±0.8	3.0±0.8	0.007
FVC (% predicted)	99.7±14.3	92.7±10.0	<0.001
FEF25-75% (L/sec)	2.4±0.8	1.6±0.5	<0.001
FEF25-75% (% predicted)	93.0±23.4	58.7±10.0	<0.001
FEV1/FVC	78.6±4.7	73.6±2.9	<0.001

- In this context, a study[2] was conducted to evaluate the efficacy of $FEF_{25-75\%}$ as an early indicator for the diagnosis of COPD.

STUDY OBJECTIVE

- To determine whether $FEF_{25-75\%}$ can be an early predictor of COPD.[2]

METHODOLOGY

- Observational cohort study
- A total of 307 patients (age >40 years) without COPD and with normal pulmonary function test (PFT) results
- Baseline FEV_1, FEV_1/FVC, FVC, and $FEF_{25-75\%}$ values were obtained for all patients
- $FEF_{25-75\%}$ z-score < −0.8435 was considered low
- Normal $FEF_{25-75\%}$ group: n= 216
- Low $FEF_{25-75\%}$ group: n= 91
- Follow-up PFTs at intervals between 6 months and 1 year.[2]

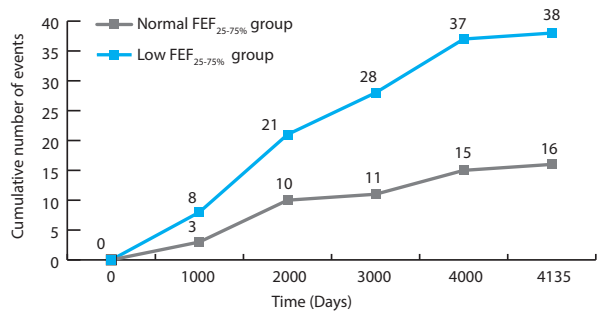
RESULTS

- Among 307 individuals who underwent the 10-year follow-up, 54 patients (17.6%) developed COPD
- When compared to the normal $FEF_{25-75\%}$ group, the low $FEF_{25-75\%}$ group had a considerably greater incidence of COPD (7.4% vs. 41.8%; p<0.001, respectively) (Figure 1)
- FEV_1, FEV_1/FVC, and FVC values in the low $FEF_{25-75\%}$ group were all considerably lower in comparison to the normal $FEF_{25-75\%}$ group when baseline PFT findings between the normal and low groups were compared (Table 1)
- The results of the multivariate analysis showed that the major factors for the development of COPD were age, smoking status, FEV_1/FVC z-score, and $FEF_{25-75\%}$ z-score (Table 2)
- The low $FEF_{25-75\%}$ group was shown to significantly increase the probability of developing COPD in the multivariate analysis (HR, 3.308; 95% CI, 1.650–6.632)
- When compared to the normal $FEF_{25-75\%}$ group, the cumulative development of COPD in the low $FEF_{25-75\%}$ group was noticeably higher (Figure 2).

Table 2: Major factors contributing to the development of COPD[2]

	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Low FEF25-75%	5.665	3.156–10.166	3.308	1.650–6.632
Age (years)	1.038	1.009–1.068	1.088	1.050–1.128
Smoking status				
Occasional smoker	2.242	0.968–5.195	4.586	1.913–10.993
Long-term smoker	2.003	1.118–3.586	2.179	1.115–4.258
PFT				
FEV1/FVC z-score	0.284	0.182–0.444	0.452	0.219–0.936
FEF25-75% z-score	0.366	0.256–0.523	0.453	0.267–0.766

Figure 2: Cumulative development of COPD in normal FEF25-75% versus low FEF25-75% groups[2]



CONCLUSION

Findings of the study suggested that $FEF_{25-75\%}$ value in patients with normal lung function could be used as a valuable indicator for the development of COPD. Clinicians should carefully monitor patients presenting with low $FEF_{25-75\%}$ values who are susceptible to COPD, even if they have normal lung function.[2]

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SECTION 3

MEDICAL QUIZ

Q1. Which of the following conditions may cause genu recurvatum?

a. Osteoarthritis
b. Scoliosis
c. Marfan syndrome
d. Reumatoid arthritis

Q2. Which of the following factors is a risk factor for the development of haematologic malignancies?

a. Regular exercise
b. Exposure to ionizing radiation
c. Consumption of high-fat diet
d. None of the above

Q3. Which of the following causes of proteinuria occurs due to overflow of protein, rather than glomerular or tubular injury?

a. Lupus nephropathy
b. Multiple myeloma
c. Focal segmental glomerulosclerosis
d. Membranous nephropathy

Q4. Which of the following conditions is commonly associated with splinter hemorrhages?

a. Aortic stenosis
b. Pulmonary hypertension
c. Venous insufficiency
d. Infective endocarditis

SECTION 4

EVENTS UPDATE

14th INTERNATIONAL CONFERENCE ON PULMONARY & RESPIRATORY MEDICINE

Date: 21-22 August 2023
Venue: Dubai
Website: https://pulmonology.conferenceseries.com/

4th INTERNATIONAL CONFERENCES IN LUNG DISEASE & RESPIRATORY HEALTH

Date: 27-28 September 2023
Venue: Prague, Czech Republic
Website: https://lungdiseases.conferenceseries.com/

THE 2023 GOLD INTERNATIONAL COPD CONFERENCE

Date: 13-14, November 2023
Venue: Philadelphia
Website: https://www.goldcopdconference.com/

INTERNATIONAL CONFERENCE ON PERSONALIZED APPROACH TO SEVERE ASTHMA

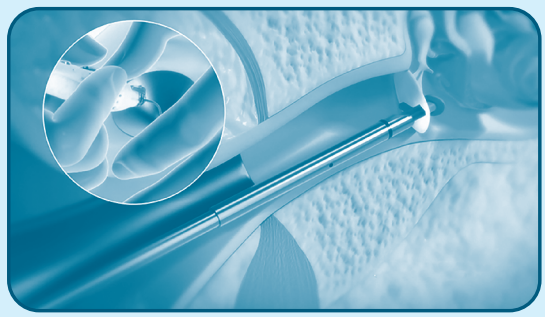
Date: 18-19, December 2023
Venue: Istanbul, Türkey
Website: https://waset.org/personalized-approach-to-severe-asthma-conference in-december-2023-in-istanbul

SECTION 5

TECH UPDATE

REVOLUTIONIZING PEDIATRIC EAR TUBE PLACEMENT WITH THE HUMMINGBIRD DEVICE

A Minnesota-based medtech company has developed the Hummingbird Tympanostomy Tube System (TTS), a breakthrough pediatric technology that allows for in-office ear tube placement. Traditionally, ear tube placement requires general anesthesia, which can be distressing for children and parents. The Hummingbird TTS eliminates the need for general anesthesia by utilizing only a local anesthetic. The FDA cleared Hummingbird TTS combines the steps and tools required for traditional procedures into a single device, allowing for incision and tube placement in one pass. The procedure, conducted in the doctor's office, takes approximately five minutes, and parents can remain with their child for added comfort. A recent multicenter study demonstrated that ear tube placement with the Hummingbird device, performed on awake young children using a topical anesthetic, was safe, successful, and well tolerated. Children recover quickly and can resume normal activities immediately following the procedure. This innovative technology provides a significant advancement in pediatric care, reducing surgical trauma and improving the overall experience for both children and parents.



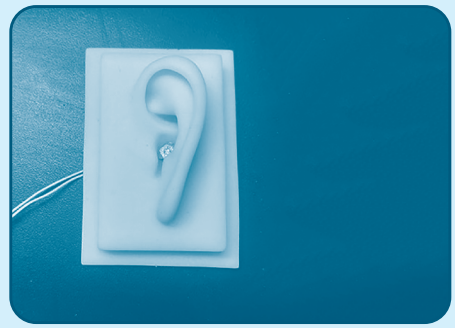
Source: Hummingbird Device for Ear Tube Placement: Interview with Steve Anderson, CEO of Preceptis Medical. Available at: https://www. medgadget.com/2021/03/hummingbird-device-for-ear-tube-placement-interview-with-steve-anderson-ceo-of-preceptis-medical.html. Accessed on 24/07/2023.

BLUETOOTH WEARABLE BABY THERMOMETER: AN ACCURATE AND PAINLESS METHOD TO MEASURE INFANT'S TEMPERATURE

An axillary baby thermometer was designed to measure the temperature levels around the clock without causing baby discomfort. The continuous temperature monitor which is present in the thermometer display baby's current temperature and send a reading every 90 seconds to your bluetooth-enabled iOS or android device. It is ideall for infants/children between the ages of 6 months and 3 years. This app sends an alert notification if the temperature exceeds a certain level. In comparison to other non-invasive methods of temperature measurement it has various advantages sush as precise and accurate temperature readings.

Source: MobileHealth's Bluetooth Wearable Baby Thermometer Measures Your Baby's Temperature Accurately and Painlessly. Available at: https://www.medgadget.com/2017/02/mobilehealths-bluetooth-wearable-baby-thermometer-measures-babys-temperature-accurately-painlessly.html. Accessed on 24.07.2023

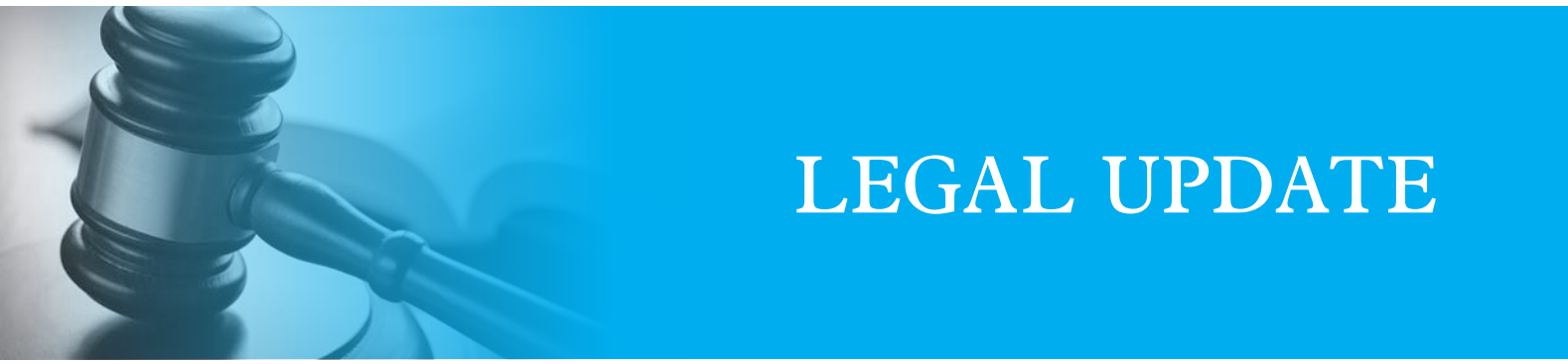
HEARING THE FUTURE: BATTERY-FREE DEVICE PAVES THE WAY FOR ARTIFICIAL COCHLEA DEVELOPMENT



A team of scientists at Huazhong University of Science and Technology has developed a battery-free device with potential applications in creating an artificial cochlea for individuals with hearing loss. Herein, the scientists incorporated barium titanate nanoparticles coated with silicon dioxide into a conductive polymer to construct a piezo-triboelectric material with a sponge-like consistency. When sound waves interact with the material, the nanoparticles move and generate an electrical charge. This self-powered technology eliminates the need for an external power source, such as a battery, which can result in bulky or replaceable devices. The device is designed to produce an optimal electrical signal at 170 hertz, which is within the range of an adult's voice, maximizing its usefulness. Initial tests involved playing music through the device within a model ear and converting the resulting electrical signal into a new music file. The recognizable playback of the music file indicates that the device accurately converts sounds into electrical signals.

Source: Battery free device acts as artificial cochlea. Available at: https://www.medgadget.com/2021/11/battery-free-device-acts-as-artificialcochlea.html. Accessed on 24/07/2023.

SECTION 6



LEGAL UPDATE

Digital health regulation and its associated legal challenges

INTRODUCTION

Digital health is defined by WHO as the "a broad umbrella term comprising of eHealth, as well as emerging areas, such as the utilization of advanced computing sciences in 'big data', genomics and artificial intelligence". Healthcare digitization comprises of two components such as medical data digitization including electronic health records and delivering healthcare services by using technology such as telemedicine, providing medical care to patients without physical access to a healthcare facility.[1] Healthcare is evolving with the digital revolution. With the development of artificial intelligence products, all the aspects of healthcare are covered. Artificial Intelligence can harness data generated in digital healthcare and help in better diagnosis, treatment selection, and prediction of clinical outcome. Increased presence of AI solutions in digital healthcare enhances issues of certainty, explainability and fairness.[2] There is an increasing toll of cyber attacks on hospitals and healthcare institutes. Therefore, there is a growing concern for privacy. Digital health in India is governed by scattered current legal and regulatory landscape.[1]

INDIAN POLICIES AFFECTING HEALTHCARE DIGITIZATION

Type of policy[1]	Title of policy[1]	Description[1]
Regulations	The Clinical Establishments (Registration and Regulation) Act	Regulate clinical establishments in India Aims to ensure uniformity and quality in the healthcare service received across the country.
	DNA Technology (Use and Application) Regulation Bill	Regulates the use and application of DNA technology for the purpose of establishing identity of missing persons, offenders, under trials and unknown deceased persons
	Digital Personal Data Protection Bill (DPDP Bill)	Data only used for lawful purposes Strengthens the state's role in the data economy and consequently increases the state's power for surveillance without any checks and balance Places few restrictions on the government's use of personal data
Law	The Drugs and Cosmetics Act ("D&C Act")	Regulate the manufacturing, import, sale, and distribution of drugs in India Outline the drugs that can be sold only through prescriptions issued by registered medical practitioners and those that can be sold over the counter Impacts e-Health and m-Health platforms
	Information Technology Act and Rules (IT Act)	Govern the key element such as the constant exchange of information between the patient and the service provider Consent is required under the Data Protection Rules
	The Information Technology Reasonable security practices and procedures and sensitive personal data or information Rules ("Data Protection Rules")	
	The Medical Devices Rules ("MDR")	Comprehensive quality requirements to be followed by marketers, importers, manufacturers, and sellers of notified medical devices
National Standards	The Information Technology (Intermediaries Guidelines) Rules ("Intermediary Guidelines")	Providing access to a communication system over which the information is hosted or stored

TO CONCLUDE

With the advent of digital health avenues, there is a growing necessity to manage the medico-legal challenges that comes along with it. Hence, these should be addressed with the evolution of digital health in India.

REFERENCES

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2. Cummins N, Schuller BW. Five Crucial Challenges in Digital Health. *Front Digit Health*. 2020;2:536203.

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