Review Article

Thyroid dysfunction and addictive disorders

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Various psychoactive substances including alcohol, tobacco, opioids interact with the hypothalamo-pituitary-thyroid axis (HPTA). Not only these psychoactive substances can lead to changes in the functioning of the HPTA, they can also bring about structural changes to the thyroid gland as well. Additionally, the pharmacological agents used in the treatment of addictive disorders also have clinically meaningful interaction with the thyroid disorders.

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The key endocrinal functions of the thyroid gland are the net result of the auto-regulatory mechanism that comprises of a very sensitive feedback control system involving the triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH). The major regulation of the thyroid function is through the hypothalamo-pituitary-thyroid axis (HPTA). The HPTA is known to be highly susceptible to modulation via changes in the homeostasis that is induced by various chemicals including the psychoactive substances. Our current review will address the current state of evidence regarding the interaction of various thyroid disorders with psychoactive substances.

Alcohol & Thyroid Disorders :

There has been evidence from both animal and human studies that shows that alcohol use disorders and thyroid dysfunction. Animal-based studies done on adult mice[1] have shown that exposure to alcohol for 4 weeks resulted in decreased thyroid hormone release to cold exposure and also increased TRH mRNA expression in the paraventricular nucleus of the hypothalamus. Another study[2] also showed that alcohol-laden diet when provided to adult mice resulted in lower levels of fT3 (free T3), fT4 (free T4) and basal TSH levels.

Human studies have also replicate these findings. Studies have shown that exposure to alcohol resulted in decrease in the levels of T3 and T4 in the peripheral circulation[3]. The studies have also reported normalization of the thyroid levels post- treatment and abstinence in patients with chronic use, but with re-lowering of the thyroid hormone levels after relapse[4]. The peripheral thyroid levels are also decreased during the state of alcohol withdrawal and abstinence. The studies have observed a degree of association between the severity of alcohol withdrawal and thyroid levels. This becomes clinically important considering the fact that hypothyroid state can worsen dysphoria in withdrawal and can result in relapse[5].

- **Various psychoactive including alcohol, tobacco, opioids interact with HPTA.**
- **Additionally, the drugs used in the treatment of addictive disorders also have significant interaction with the thyroid disorders.**
- **Therefore, the evaluation and management of such disorders need to explore cautiously and thoroughly.**

Considering studies that have been done on patients with alcohol withdrawal, the findings have been conflicting. More number of studies has reported euthyroid state in withdrawal than the other way round[6]. However, studies reporting abnormality generally reported a decrease in the T4 levels with gradual normalization over the next 2-4weeks[7]. Alcohol is also known to pose a direct toxic effect on thyroid cells resulting in decrease in the size of thyroid gland. This effect is more dependent upon the duration of alcohol use rather than the peak levels of alcohol[7].

Alcohol use has shown a consistent association with attenuation of the TSH levels in response to secretion of thyrotropin-releasing hormone (TRH)[8]. This phenomenon has been seen across various time-frames and some studies have also found a positive correlation between severity of withdrawals in abstinence and blunting of TSH response. Efforts to identify the putative mechanisms behind this phenomenon have led to exploration of the genetic mechanisms[9] and the role of the cirrhosis of liver[10]. However, results in both cases have not been encouraging.

Alcohol use shares an intriguing relationship with thyroid cancers. Number of studies have been published that shows a decrease in the incidence of thyroid cancers in patients with alcohol use[11]. The putative mechanism behind this could be due the suppression of TSH which is known to play a proliferative effect on the follicular cells

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of thyroid. However, when adjusted for comorbid tobacco use, which has been a persistent confounding factor also being associated with decreased thyroid cancer, the protective effect of alcohol use seems to become insignificant.

Among the various drugs used in the treatment of alcohol use disorders, Disulfiram, a deterrent agent which prevents patients from drinking, has prominent anti-thyroid action. Disulfiram has a chelating action by forming complexes with iodine resulting in a relative iodine deficiency[12]. Among the anti-craving agents; Naltrexone, an opioid antagonist has a clinically insignificant thyroid stimulating action[13]. Baclofen, which is a GABA-B agonist is known to attenuate the TSH release in response to TRH[14]. Acamprosate, an N-Methyl-D-aspartate (NMDA) receptor antagonist, used as an anti-craving agent, also doesn't have any interaction with thyroid hormones[7]. Benzodiazepines like diazepam, chlordiazepoxide or lorazepam has a relatively inert relationship with thyroid hormones[15].

Opioids and Thyroid Disorder :

The relationship between consumption of opioid derivatives and thyroid function remain intriguing. Animal studies have reported that administration of morphine can reduce TSH release immediately after its administration. However, the effects seem to disappear when we consider chronic administration of morphine[16]. Studies based on human subjects have however shown inconclusive trends. Some of the studies have shown a decrease in the TSH, T3, T4 levels after administration of morphine[17], while others have reported decrease in TSH only[18]. Some other studies have again shown al T3 increase and total T4 decrease[19]. There has been a case report of patients developing hypothyroidism being on methadone maintenance[20]. Opioid agonists like methadone[21] and heroin[22] are also known to increase the levels of thyroid binding globulin (TBG) which results in the level of fT3.

A study done on Swiss-Webster mice showed that T4 administration led to up-regulation of opioid receptors and decrease in pain threshold, but led to decrease in the duration of analgesia from morphine[23]. Even in human subjects this effect attains clinical significance as long term treatment of chronic pain with opioids can lead to inhibition of hypothalamic-pituitary function which can result in alteration of pain perception[24].

Nicotine and Thyroid Disorders :

Nicotine use is known to have a very weak pro-thyroid effect in euthyroid patients. One pathway of causing this is via the increase in sympathetic stimulation, which also results in thyroid stimulation[25]. The mechanism behind this maybe a direct stimulatory action on the thyroid gland[25]. But, since smoking has not been found to be a risk factor for either non-toxic or toxic multinodular goiter, the effect size of this stimulation remains questionable in clinical scenario. However, in hypothyroid patients, nicotine can reduce thyroid secretion and augment the clinical presentation. Nicotine use, alternatively is considered as a significant risk factor for patients with Graves' hyperthyroidism, and the risk becomes even more significant with patient s with ophthalmopathy[26]. Though the mechanism behind this association is not very clear, probably, nicotine induces change in the structure of the thyrotropin receptors, which leads to the production of thyrotropin-receptor stimulating antibodies that react strongly with retro-orbital tissue. Smoking also has been found to cause increase in the concentrations of serum thyroglobulin and thicyanate in fetus, if the mother had a history of smoking[27]. Other studies have demonstrated higher T4 and lower TSH levels in fetus delivered by smoking mothers[28]. Nicotine exposure while lactation has also been shown to cause neonatal hypothyroidism, which can be reversed by smoking cessation[29].

Among the drugs used to treat nicotine dependence, both bupropion and varenicline has a relatively thyroid neutral profile. However, product monographs for varenicline does mention about rare occurrences of thyroid disorders.

Other Psychoactive Substances and Thyroid Disorders :

The interaction of thyroid disorders with other substances use disorders have been relatively less studied. Studies conducted on patients with cannabis use disorders failed to show any clinically significant changes in thyroid functions[30,31]. The effects of cocaine use has been very similar to hyperthyroid state as both can lead to features like increased energy, psychomotor activation, diaphoresis, hyperthermia, and cardiovascular arousal. Cocaine withdrawal also shares its features with hypothyroidism (eg- anergia, depression, psychomotor retardation, hypersomnia, and weight gain). However, attempts to understand any potential relationship between the disorders has been less rewarding. While some patients with cocaine use presented with bluting of TSH release in response to TRH, other did not shown any significant alterations in thyroid functions[32]. However, there has been some speculation that hypothyroid state can have a predisposing role to develop cocaine addiction[33], though further research in this area is warranted. Toluene, which is among the active substance in inhalants, has also been reported in the literature as being associated with hypothyroidism, which is usually reversible after cessation of sniffing[34,35].

Thyroid function is also interfered by medicines used for management of addictive disorders in a clinically significant manner. These interactions need to be looked out for in clinical practice. Table 1 summarizes the information on various clinically significant pharmacological agents that can be encountered while treating patients with addictive disorders.

Table 1 — *Clinically significant interactions of select pharmacological agents used in management of addictive disorders^ on thyroid functioning*

Mechanism of interaction	Drugs	Clinical Relevance
Inhibition of T4/T3 secretion	Lithium	Significant
Stimulation of T4/T3 secretion	Naltrexone	Insignificant
Chelating action causing relative iodine deficiency	Disulfiram	Significant
TSH suppression	Carbamazepine Oxcarbazepine	Significant
Displacement of thyroxine from thyroxine binding globulin	Phenytoin Nonsteroidal anti-inflammatory medications	Significant
Increased hepatic metabolism of levothyroxine	Phenobarbitol Phenytoin Carbemazepine	Significant
Increased thyroxine binding globulin levels	Methadone Morphine	Significant
Blunted TSH response to TRH	Baclofen Cocaine	Insignificant

^Including co-occurring mental disorders

Conclusion :

The evaluation and management of various co-occurring medical disorders is of paramount importance. Our current understanding of the two disorders warrants the need to explore for the co-occurrence of thyroid disorders and addictive disorders as this has multiple meaningful interactions.

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