

## EDITORIAL



## “Mind” in Betel-quid Use and Related Disorders

<sup>1</sup>Prashanth Panta, <sup>2</sup>Sachin C Sarode, <sup>3</sup>Gargi S Sarode, <sup>4</sup>Amol R Gadmail, <sup>5</sup>Shailesh M Gondivkar, <sup>6</sup>Shankargouda Patil

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Oral squamous cell carcinoma is characterized by a unique predisposing state called oral potentially malignant disorders (OPMDs). Wide variety of carcinogenic insult in the form of detrimental habits can contribute to the causation of variety of OPMDs.<sup>1,2</sup> One of the emerging carcinogenic insults is related to betel-quid (BQ) habit. Betel-quid is a potential mixture of a wide range of harmful carcinogenic compounds. It is among the most deleterious habits and a leading preventable cause of oral cancers, rampant in South Asia. In the step-by-step process of BQ abuse, the “mind” has a definitive role, and mind-body interventions may therefore, limit progression of BQ-associated conditions.

Betel-quid use disorder (BUD) is a condition characterized by prolonged use of BQ and individuals having at

least one type of quid per day for a minimum duration of 6 months are referred as “lifetime users.”<sup>3</sup> For “current users,” individuals must have used BQ within the preceding 12 months of presentation and “past users” are those who have not used BQ at least 12 months before the presentation.<sup>3</sup> Recently, the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria has shown that BUD is driven by an “addictive consumption,”<sup>3</sup> It was observed that moderate and severe BUD patients have shown the highest prevalence of OPMD, establishing a strong psychiatric basis for heavy BQ use.<sup>3</sup> Betel-quid use disorder may therefore, be considered as a “substance abuse condition” forming a high-risk intermediate in the development of OPMD.

Quality-of-life analysis in oral submucous fibrosis (OSF) patients revealed “psychological wellness” as the second most common affected factor.<sup>4,5</sup> Also many individuals consume more BQ when in distress and often consider it as “stress-relieving factor,” particularly seen in truck drivers and agriculture workers. We believe individuals under “work stress,” “life stress,” and/or depression start consuming BQ and slowly an addiction develops, making them continue the habit (i.e., craving), and a little later, the symptoms, such as “burning sensation and limited mouth opening” further increase the scores of stress and depression, which may also induce excess betel quid consumption (i.e., stress-induced eating). In time, this becomes a “vicious cycle” and due to the addictive nature of BQ ingredients, it is almost impossible to motivate patients to discontinue the habit and a potential psychiatric intervention is the need of the hour. In this context, we think both “addictive consumption” and “stress and depression scores” are deterministic in OPMD development in BQ users, dictating habit continuation at the grass root level.

We highlight that habit discontinuation is achievable with therapies like meditation that target and improve the mental condition. We hypothesize meditation technique (MT) in the management of addiction and craving

<sup>1</sup>Department of Oral Medicine and Radiology, MNR Dental College & Hospital, Sangareddy, Telangana, India

<sup>2,3</sup>Department of Oral Pathology and Microbiology, Dr. D. Y. Patil Dental College & Hospital, Dr. D. Y. Patil Vidyapeeth, Pune Maharashtra, India

<sup>4</sup>Department of Dentistry, Indira Gandhi Government Medical College & Hospital, Nagpur, Maharashtra, India

<sup>5</sup>Department of Oral Medicine and Radiology, Government Dental College & Hospital, Nagpur, Maharashtra, India

<sup>6</sup>Division of Oral Pathology, Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, Jazan University Jazan, Kingdom of Saudi Arabia

**Corresponding Author:** Prashanth Panta, Department of Oral Medicine and Radiology, MNR Dental College & Hospital Sangareddy, Telangana, India, Phone: +919701806830, e-mail: maithreya.prashanth@gmail.com

behavior in BQ users,<sup>6</sup> and the recent findings of Lee et al<sup>3</sup> have further strengthened our approach. Through functional connectivity studies using functional magnetic resonance imaging and diffusion tensor imaging, authors have also shown that long-standing BQ causes a disrupted coordination between prefrontal cortex and subcortical areas, indicating a poor white matter integrity.<sup>7</sup> These changes ultimately lead to declined inhibition control. The MT intervention, on the contrary, is a neuromodulatory approach operating precisely on the same circuitry (prefrontal cortex, anterior cingulate gyrus, and striatum) leading to induction of self-control and habit withdrawal.<sup>6,8</sup> Meditations have also shown to consistently reduce stress and depression scores.

In the past, numerous attempts were made to capture physical condition of patients with BQ habit, but only seldom authors have touched the subtle psychological dimension and new-age mind-body therapies like meditation. We believe that individuals with “moderate and severe BUD” (high-risk candidates) can be particularly targeted using MT, as they show the highest prevalence of OPMD.<sup>3</sup> Overall, MT is an important psychiatric treatment that can help manage “addictive phenomena in BQ chewers,” stress and depression, all of which are responsible for BUD, OPMD (e.g., OSF, leukoplakia), and future oral cancers at the grassroots level.

We also think that the synergistic effect of “stress-” and “BQ”-associated carcinogenesis cannot be underestimated, needing a deeper investigation. Stress and depression have been linked to cancers via the mechanisms of elevated inflammation and oxidative stress, decreased immune surveillance, and activated sympathetic nervous system.<sup>9</sup> Through the management of each of these pillars, MT may aid in the slowing down of “BQ-associated carcinogenesis” in OPMD users. “Inflammation” is strongly implicated in oral cancer and is influenced by the hypothalamic-pituitary-adrenal (HPA) axis triggered by psychosocial stress.<sup>10</sup>

At the molecular scale, the nuclear factor kappa B (NF- $\kappa$ B) activity is one among the key pathways induced by betel nut ingredients known to link “inflammation” and “oral cancer,” and a blockade of NF- $\kappa$ B significantly reduces cellular invasiveness in oral cancer.<sup>11,12</sup> In a systematic review on gene expression changes in meditation and related practices, the downregulation of NF- $\kappa$ B was defined as a consistent molecular signature.<sup>13</sup> In this context, meditation may also be applied as a promising supportive therapy for oral cancer patients.

Owing to the predominant psychiatric component underlying prolonged BQ use, we firmly believe that “mind” and its management through interventions like

“meditation” may play a pivotal role in the prevention and discontinuation of BQ habit, leading to an overall control of “BQ-associated conditions” and also in the event of oral carcinogenesis through different molecular mechanisms. This intervention will be acceptable and conceivable for Asian populations as meditation is an integral part of their religion.

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