

## Betel, the Orphan Addiction

Melissa A Little<sup>1</sup> and Roger L Papke<sup>2\*</sup>

<sup>1</sup>Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee, USA

<sup>2</sup>Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville, FL, USA

### Abstract

Hundreds of millions of people worldwide are addicted to “betel nut” (areca), but unfortunately, to most people in Western nations, this addiction is perceived as little more than a curious Asian custom. Recent epidemiology has shown that betel use has concomitant health risks similar to tobacco use. This review discusses the magnitude of the problem, the need for increased public awareness, and the potential for developing programs to reduce the burden of this addiction on world health.

### Introduction

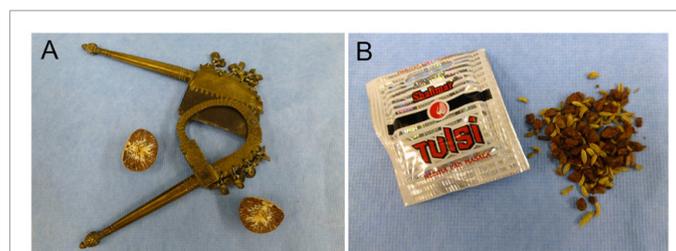
Strangely, it seems that a hundred years ago no one noticed or cared about the health hazards of smoking, even though for as long as there have been tobacco smokers there certainly must have been smoking-related deaths. Fortunately, in the past fifty years increased public awareness of the deleterious effects of tobacco smoke, whether first or second hand, has led to a decrease in the use of cigarettes by adults in America from 42.4% in 1965 to 17.8% in 2013 [1,2]. Fiscal and social factors, such as increased taxes and laws banning smoking in public areas, as well as a reversal in the media presentations, from ads for cigarettes to government-sponsored anti-smoking propaganda, have been instrumental in promoting this decrease, and those who have been able to quit, or were discouraged from acquiring the addiction, could expect, on average, an additional ten years of life [3]. However, as impressive as this decline in smoking has been, for tens of millions of Americans with a desire to quit smoking, the addiction remains insurmountable, even with the smoking cessation aids and programs currently available.

There are only two other drugs considered to be “addictive” that are more widely used than nicotine: alcohol and caffeine. However, there is virtually no public awareness or concern in Western nations about the fourth most widely used addictive substance, commonly known as “betel nut”, even though 300 to 600 million people worldwide are potentially addicted and at increased risk for oral disease and cancer [4]. Of course, for much of the Western world, the ignorance and indifference to this widespread addiction can be attributed to what Douglas Adams identified in his Hitchhiker novels as the closest thing to invisibility, the SEP (somebody else’s problem) field. For thousands of years the use of areca nut (betel) has been endemic throughout South Asia and the Pacific Islands. Curiously, although Europeans were quick to pick up the tobacco habit brought back by Sir Walter Raleigh, the Europeans who first explored and then exploited the nations of Asia were not prone to becoming habitual users of betel nut preparations.

The purpose of this review is to attempt to peek through the SEP field and encourage awareness of a problem of considerable scope and significance to world health. At present, however, the World Health Organization “have no activities on betel and no plans to promote activities in this field”, is according to Vladimir Poznyak, the head of the organization’s substance abuse unit (personal communication).

Our failure to appreciate this orphan addiction begins with a lack of understanding about what terms the “betel” or “betel nut” even refer to. The real drugs in “betel” come from the fruit of the palm *Areca catechu*, which, although commonly referred to as nuts, are technically drupes. The connection to “betel” comes from the common way in which pieces of areca nut are combined with other spices, flavorants, and sometimes

tobacco, and wrapped in leaves of the *Piper betle* vine, forming a packet known as a “betel quid”, which is then chewed. The main psychoactive ingredient of the areca nut is arecoline, which is known to be a muscarinic cholinergic agonist. Since arecoline is a weak base, another important ingredient in the betel quid that is required to alkalize the saliva and permit absorption is some form of slaked lime, often from burnt sea shells or coral. With the widespread use of areca in Asia, there are many regional differences in how the nut is prepared, variously from soft unripe fruit to hard dried nuts that would be impossible to chew and even require special cutters (Figure 1A) to prepare the pieces for the quid [5]. Often vendors in Asian markets sell prepared quids to the tastes of the local users. In Taiwan, where the quids are made from unripe nuts combined with betel flowers and/or leaves, as well as red lime paste, cardboard boxes of prepared quids are sold to motorists from glass-walled roadside booths in which the quids are prepared by scantily-clad women known as “Betel-nut girls”. In Taiwan the commercial value of areca nut production is greater than that of rice [6].



**Figure 1: A)** Traditional preparation of areca nut. A decorative guillotine-style betel nut cutter, probably from nineteenth century Rajasthan India, is shown with a sliced areca nut.

**B)** Twenty-first century areca preparation. A packet of Pan Masala, along with the contents of a similar packet, showing the brownish-red areca nut fragments as well as fennel seed and other ingredients used to flavor this brand of pan. All of the ingredients have been coated with an artificial sweetener, making this sort of product appealing to adolescents as well as adults.

\*Corresponding author: Roger L. Papke, Ph.D, Professor, Department of Pharmacology & Therapeutics, University of Florida College of Medicine, Gainesville, FL, USA; E mail: [rlpapke@ufl.edu](mailto:rlpapke@ufl.edu)

Received August 27, 2015; Accepted August 28, 2015; Published August 31, 2015

Citation: Little MA, Papke RL (2015) Betel, the Orphan Addiction. J Addict Res Ther 6: e130. doi: [10.4172/2155-6105.1000e130](http://dx.doi.org/10.4172/2155-6105.1000e130)

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Historically, betel use cut through all levels of Asian society and was very common amongst the nobility. As recently as 1998, Queen Elizabeth II was presented with a silver betel nut box by the Sultan of Brunei [7]. Presently, though, betel use in Asia is generally inversely related to level of education and income [6,8]. Additionally, just as machine-made cigarettes increased the accessibility of tobacco, in recent decades areca nut preparations have become widely available, especially in India, in convenient foil packets sold as Paan Masala / Supari mix (Figure 1B) or as Gutka, which is a combination of both smokeless tobacco and areca nut pieces. Both whole areca nuts and inexpensive packets of Paan Masala are readily available in the United States for sale on eBay. Such worldwide accessibility permits areca nut users to maintain their habit even should they immigrate to countries such as the U.S., the U.K., or Australia, where fresh areca preparations would not be available. Of course, traveling with them are all of the health risks associated with their addiction.

Just like the addicting properties of areca, the concomitant health hazards have likewise been affected by the “somebody else’s problem” effect. Nonetheless, evidence is mounting regarding increased risk of oral diseases such as oral sub mucous fibrosis [9-12] and cancers [13-18]. As a result, betel quid has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004) [19]. While these associations are irrefutable, the economic impacts of these health consequences to the developing nations of Asia has never been assessed but are doubtless considerable.

As noted above, although people of European descent have been exposed to areca nut use for centuries, and both the raw and processed nuts are available cheaply to anyone with a computer, areca nut addiction has remained largely restricted to peoples of Asian decent. Westerners often describe a highly aversive reaction to their first use of betel [20-22]. For any user, the most obvious and immediate reaction to areca is the copious production of almost asphyxiating amounts of saliva. Pigments from the nut combine with the alkalized secretions to produce brilliant red spittle that must be either expectorated or swallowed. Many walls in poorer neighborhoods in India carry the marks of this phenomenon. For some people, the effects that follow are disorienting or debilitating, probably associated with muscarinic effects in the brain. Habitual Asian users are more likely to report mild euphoria or stimulant effects like strong coffee. In India betel has long been considered an aphrodisiac.

Most of the research on areca use has been limited to epidemiological and biological investigations. However, there is a growing body of research focusing on the behavioral and psychosocial factors that lead individuals to initiate and/or maintain areca use. Recently, researchers have begun exploring the psychology of areca addiction. There is growing support for areca (betel) addiction [23-25], although it is unclear what threshold signifies dependence. The stimulant and anxiolytic effects of areca have been associated with escalation of use and dependency [23,27-29]. However, disentangling the independent effects of areca addiction is challenging, given that many users concomitantly use tobacco [19,30,31]. In a multi-country study, researchers found that areca dependence ranges from 12.5% to 92.6% for tobacco free users and 47.9 to 99.3% among tobacco added users [32]. Other studies have found similarly high rates of dependence among tobacco-added users [25]. Further support for areca addiction can be found in reports from areca users trying to quit undergoing withdrawal symptoms that are similar to nicotine withdrawal [27]. Additionally, researchers have begun to explore reasons why people use areca [24,33]. The most strongly endorsed reason people reported

for using areca was because of the way it made them feel [24]. This growing body of research suggests that in order to promote cessation, the stimulating effects of areca use must be addressed either through pharmacotherapy or behavioral interventions.

Given that areca users experience many of the same patterns of dependence and withdrawal symptoms experienced by tobacco users, researchers have begun to compare these two groups to see if similarities could be found which would inform the development of areca cessation behavioral interventions. Researchers have found that both sorts of users express a desire to quit and intend to quit; however, most do not have plans for when or how to quit [34], suggesting that, similar to smokers, users may be in need of assistance in planning and carrying out their quit attempt [34]. Counseling techniques such as motivational interviewing or cognitive-behavioral therapy, which have been widely used to help people stop smoking [35,36], could be a good starting point for the development of areca cessation interventions. Of course, in nations such as India and Taiwan, where betel use is high and undoubtedly is already presenting a burden on the national health care systems, public awareness programs could also be implemented to encourage cessation and discourage acquisition of the habit.

Another approach for treating areca dependence could be in pharmacotherapy. Pharmacotherapy has been successful in promoting tobacco cessation. It is unknown whether any of the pharmacotherapies that have proven effective in aiding tobacco cessation could prove helpful for areca users. However, it has recently been discovered that arecoline functions as a partial agonist for the nicotinic receptor subtypes most closely linked to nicotine dependence [37], making such crossover therapeutics an attractive possibility. While this nicotinic activity may not be the basis for the short-term reinforcing effects of betel use, it would be consistent with changes in the meso-limbic reward pathways; similar to what occurs in smokers that leads to dependence and withdrawal [38,39]. For a habituated betel user, the reported anxiolytic effects of the drug may be due to the alleviation of withdrawal.

The global health burden associated with areca use worldwide necessitates attention towards this addictive behavior. Given that it has been demonstrated that users do indeed become dependent [23-25], and that a substantial portion of the areca users have the desire to quit [34], it seems to be an addressable problem.

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Citation: Little MA, Papke RL (2015) Betel, the Orphan Addiction. *J Addict Res Ther* 6: e130. doi: 10.4172/2155-6105.1000e130

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