Antidepressant-induced reduction in betel-quid use in patients with depression

A pioneer clinical study

Chung-Chieh Hung, MDa,b, Chien-Hung Lee, PhDc, Chia-Min Chung, PhDd, Srinivasan Nithiyanantham, PhDd, Hsien-Yuan Lane, MD, PhDa,b,e, Ying-Chin Ko, MD, PhDd,e,f

Abstract
Betel-quid is commonly used around the world and is listed as a Group I carcinogen. Prior research has suggested a possible association between antidepressants and betel-quid use. We aimed to clarify the effects of antidepressant therapy in betel-quid chewers in the population of patients with depression.

We enrolled 204 patients with depressive disorders, collected their demographic information, and administered the Substance Use Severity Rating Scale for alcohol, cigarettes, and betel-quid and the Hamilton Depression Rating Scale. We compared betel-quid and non-betel-quid chewers and examined the effects of antidepressant therapy on betel-quid abstinence after previous exposure to betel-quid.

Patients with depression were reported a higher prevalence of 26% betel-quid chewing habits and patients who chewed betel-quid showed more severe depressive symptoms. After antidepressant therapy, the addictiveness of betel-quid was significantly reduced by 4 times.

This was a pioneering study showing that antidepressants could be a candidate for betel-quid cessation therapy. Future clinical trials are needed to verify their efficacy in reducing consumption for betel-quid addiction treatment.

Abbreviations: BQ = betel quid, HAMD = Hamilton Depression Rating Scale, MANOVA = multivariate analysis of variance, MAOA = monoamine oxidase A, NDRI = nor-epinephrine dopamine reuptake inhibitors, SNRI = serotonin norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, SUSRS = substance use severity rating scale.

Keywords: abstinence, addiction, antidepressant, betel-quid, depression

1. Introduction
The Betel-quid (BQ) is a chewing mixture of dried or fresh ingredients from the areca catechu nut, with or without tobacco.

Since 1985, its addictive properties have been reported by the International Agency for Research on Cancer. BQ has been listed as a Group 1 carcinogen in humans, either with or without tobacco.

BQ chewing is a strong social bonding and cultural practice among individuals in SouthEast Asia, India, and South Pacific countries such as Papua New Guinea. An estimated 600 million people chew BQ worldwide, making it the fourth most popularly accepted psychoactive substance used in daily life.

The prevalence of BQ use in the general population is around 10% worldwide. An investigation has revealed the current prevalence of BQ chewing to be 10.7% in men and 2.5% in women in Taiwan. Regarding symptoms of abuse in Taiwan, higher incidences of dependence (46.1%), craving (40.5%), and tolerance (27.1%) than average are reported. Based on research into worldwide BQ chewing from a study of six Asian countries, in specific groups, such as Hunan men (a province of China), Malaysian women, and the Indonesian and Nepalese populations, the incidence of BQ dependence even exceeds that of alcohol dependence. However, the severity of BQ dependence and the resulting psychiatric problems are rarely studied.

MAO-A catalyzes the deamination of biogenic amines in the blood or synapses and regulates the levels of dopamine, serotonin, norepinephrine, and catecholamine. Literature indicated the mechanisms affected by the active ingredients of BQ may interact with antidepressants. Areca nut regulates the expression of monoamine oxidase- A (MAO-A) Xp 11.3. In human study, our team has investigated that the MAO-A are associated with high exposure betel quid use. Besides, another
literature has also detected that the ingredient of BQ stimulating
the levels of monoamines (serotonin and dopamine) by the
experimental design of MAO inhibition in rats.\textsuperscript{[13]}

The duration of untreated depression (DUD) might be related
with more severe depressive symptoms of the BQ chewers. Since
they probably tended to had longer DUD because the first
depressive episode under the condition of poor adherence and
cooperation with medical treatment. The previous study shows
that DUD is associated with the disability and outcome of the
depressive disorders.\textsuperscript{[14]}

Prior research suggests a possible association between
antidepressant mechanisms and BQ.\textsuperscript{[12]} However, few studies
have examined the relationship between BQ use and depressive
disorders. The comparison of the contributing risks to depressive
disorders between BQ chewers and non-BQ chewers is important
for better understanding. The association between antidepres-
sants and BQ dependence might indicate a potential future
cessation treatment. Our study examined the association between
severity of BQ use, depressive symptoms and the potency of BQ
abstinence under antidepressant therapy in patients with
depressive disorders.

2. Materials and methods

This study was approved by the China Medical University
Hospital Institutional Review Board (IRB). All the participants
gave written approval before the study. Our overall research flow
diagram was shown in Figure 1. Participants were recruited from
the psychiatric outpatient department of China Medical
University Hospital in Taichung, Taiwan between August
2014 and August 2015. We applied DSM-5 (The Diagnostic
and Statistical Manual of Mental Disorders Fifth edition)
criteria\textsuperscript{[15]} to select patients with current depressive disorders.
According to the DSM-5, this umbrella diagnosis includes major
depressive disorder, persistent depressive disorder, disruptive
mood dysregulation disorder, and other specified and unspecified
depressive disorders. Substance/medication-induced depressive
disorders were excluded to avoid confounds from other
substances or medications.

2.1. Measures of demographic information and clinical
characteristics

After the enrollment of eligible patients, we measured their
Substance Use Severity Rating Scale (SUSRS) scores for alcohol,
cigarettes, and BQ\textsuperscript{[16]} and their score on the Hamilton Depression
Rating Scale (HAM-D).\textsuperscript{[17]} Duration of antidepressant use was
retrospectively traced and was defined as the duration of
antidepressant dosing before this study. We included information
on the use of all kinds of antidepressants. Those who had lost
follow-up contact with the psychiatric service for at least 1 year
were classified as zero for antidepressant use during this time.

We also collected data on the type of antidepressant used,
including SSRIs (Selective Serotonin Reuptake Inhibitors), SNRIs
(Serotonin Nor-epinephrine Reuptake Inhibitors), and NDRIs
(Nor-epinephrine Dopamine Reuptake Inhibitors). Those that
did not fall into one of the above three groups, such as tricyclic
antidepressants, monoamine oxidase inhibitors, serotonin antag-
onists, reuptake inhibitors, and noradrenergic and specific
serotonergic antidepressants, were classified as “others.”

![Flow diagram of the study design.](image_url)
2.2. Comparisons between BQ and non-BQ chewers among patients with depression

We divided the patients into 2 groups: BQ chewers and non-BQ chewers. The BQ group consisted of all patients with a current or former habit of BQ chewing. In the non-BQ group, the patients had never chewed BQ. We compared the groups on age, education, employment, and their SUSRS scores for alcohol, BQ, and cigarettes, and their HAMD scores.

2.3. Follow-up measures in BQ chewers before and after antidepressant treatment

A trained psychiatrist or psychologist made telephone contact with the patients to follow up after antidepressant treatment. Their level and frequency of BQ consumption, SUSRS score for alcohol, BQ, and HAMD scores were collected as post antidepressant treatment measures.

2.4. Comparisons of the variables between antidepressant treatment and normal population without any intervention

We keep following up on the 20 patients who underwent the antidepressant treatment. We have collected another 18 subjects from the same hospital with BQ chewing habits without any antidepressant intervention in the past years. We obtained the information relating to the BQ chewing habits. The difference of their BQ chewing amount (quids/day), frequency (days/week), SUSRS and HAMD were compared.

2.5. Statistical analysis

The BQ and non-BQ chewing groups were compared on their clinical characteristics and associations. To carry out these analyses, the Student t test and Chi-squared test were employed. Multivariate analysis of variance (MANOVA) was applied to compare the intervention difference between the antidepressant treatment patients and natural BQ chewing cases.

3. Results

3.1. Demographic data and clinical characteristics of participants

We have collected the data from 204 patients with depressive disorders, in which the prevalence of BQ chewing was 26% (53 patients). The distributions of demographic and clinical characteristics in BQ chewing and non-BQ chewing groups are shown in Table 1. BQ chewing patients tended to be older (47 ± 11 years) and had higher SUSRS for alcohol (1.0 ± 2.7), cigarette (2.2 ± 2.8), and BQ (1.2 ± 2.7) consumption, and HAMD (13.2 ± 8.0), compared to their non-chewing counterparts (42 ± 14 years, 0.7 ± 0.6, 0.4 ± 1.4, 1.0 ± 2.1, and 10.3 ± 7.0) respectively.

### Table 1

| Variables                  | BQ group (N=53) | Non-BQ group (N=151) | P value |
|----------------------------|-----------------|----------------------|---------|
| Continuous factor, mean±SD |                 |                      |         |
| Age (years)                | 47±11           | 42±14                | <.005   |
| Education (years)          | 4.2±5.8         | 4.6±6.3              | .32     |
| Alcohol SUSRS              | 1.0±2.7         | 0.4±1.4              | <.01    |
| Cigarette SUSRS            | 2.2±2.8         | 1.0±2.1              | <.01    |
| BQ SUSRS                   | 1.2±2.7         | 0.0±0.5              | <.01    |
| HAMD                       | 13.2±8.0        | 10.3±7.0             | <.01    |
| Categorical factor, %      |                 |                      |         |
| Employment                 | 58.5            | 51.3                 | .36     |

### Table 2

| Variables                  | Follow-up (N=20) | Lost follow-up (N=33) | P value |
|----------------------------|------------------|-----------------------|---------|
| Continuous factor, mean±SD |                  |                       |         |
| Age                        | 46±10            | 48±11                 | .18     |
| BQ                         | 39±44            | 31±55                 |         |
| Alcohol SUSRS              | 0.8±1.8          | 1.2±3.1               | .27     |
| Cigarettes SUSRS           | 1.9±2.4          | 2.4±3.0               | .23     |
| BQ SUSRS                   | 1.3±3.6          | 1.2±2.1               | .43     |
| HAMD                       | 15.5±7.7         | 11.9±7.9              | .06     |
| Antidepressant treatment   | 7.1±6.7          | 7.4±7.5               | .43     |
| Antidepressant Categories, %|                  |                       |         |
| SSRI                       | 6 (30)           | 11 (33.3)             | .68     |
| SNRI                       | 3 (15)           | 9 (27.3)              |         |
| NDRI                       | 5 (25)           | 6 (18.2)              |         |
| Others                     | 6 (30)           | 7 (21.2)              |         |

### Table 3

| Variables                  | Follow-up (N=20) | Lost follow-up (N=33) | P value |
|----------------------------|------------------|-----------------------|---------|
| Continuous factor, mean±SD |                  |                       |         |
| Age                        | 46±10            | 48±11                 | .18     |
| BQ                         | 39±44            | 31±55                 |         |
| Alcohol SUSRS              | 0.8±1.8          | 1.2±3.1               | .27     |
| Cigarettes SUSRS           | 1.9±2.4          | 2.4±3.0               | .23     |
| BQ SUSRS                   | 1.3±3.6          | 1.2±2.1               | .43     |
| HAMD                       | 15.5±7.7         | 11.9±7.9              | .06     |
| Antidepressant treatment   | 7.1±6.7          | 7.4±7.5               | .43     |
| Antidepressant Categories, %|                  |                       |         |
| SSRI                       | 6 (30)           | 11 (33.3)             | .68     |
| SNRI                       | 3 (15)           | 9 (27.3)              |         |
| NDRI                       | 5 (25)           | 6 (18.2)              |         |
| Others                     | 6 (30)           | 7 (21.2)              |         |

Prevalence of BQ chewing: 26%. All data are expressed in mean±standard deviation (SD). Abbreviation: BQ=Betel-Quid, HAMD=Hamilton Depression Rating Scale, SUSRS=Substance Use Severity Rating Scale.

3.2. Characteristics and comparisons between successfully retained BQ-chewing participants and lost to follow-up

As shown in Table 2, the characteristics of successfully followed-up BQ-chewing participants were as follows: age, 46 ± 10 years; SUSRS-alcohol, 0.8 ± 1.8; SUSRS-cigarettes, 1.9 ± 2.4; SUSRS-BQ, 1.3 ± 6.6; HAMD, 15.5 ± 7.7; and duration of antidepressant treatment, 7.1 ± 6.7 years than the patients were lost to follow-up (24 ± 10 and 15.5 ± 11.3 years, respectively). There is no significant difference between the retained and lost BQ chewers of 6 variables.

The successfully retained BQ chewers were treated with antidepressants in the following proportions: SSRIs, 30%; SNRIs, 15%; NDRIs, 25%; and others, 30%. Their counterparts who could not be followed up were treated in the following proportions: SSRIs, 33.3%; SNRIs, 27.3%; NDRIs, 18.2%; and others, 21.2%. There is no significant difference in the category of antidepressant used between the 2 groups.

3.3. Differences in BQ use and HAMD scores before and after antidepressant treatment

We followed up with 20 patients from the BQ-chewing group (response rate: 40%). After antidepressant therapy, we found that the mean level of BQ use in this group fell from 39±43 to 4±6 quids/day, the frequency of BQ consumption fell from 5.3±3 to 0.7±1.1 days/week, SUSRS scores for BQ fell from 1.3±3.6 to 0.3±0.8, and HAMD scores fell from 15.5±7.7 to 2.4±2.5.
We observed a BQ chewing prevalence of 26% in male patients diagnosed with depressive disorders according to the DSM-5. This was higher than the average prevalence in Taiwan and even worldwide. We observed a BQ chewing prevalence of 26% in male patients who were diagnosed with depressive disorders according to the DSM-5. We found that the difference of intervention group BQ chewing amount 2.6 quids/day, frequency 0.4, SUSRS (BQ) 0.1, and HAMD 1.3. Statistical significance existed in the interaction $P$ value in the reduction of BQ consuming amount, frequency, SUSRS and HAMD.

### 3.4. Comparisons of the variables between antidepressant treatment and normal population without any intervention

The 20 depressive patients with BQ chewing followed for the consecutive 2 years and collected another 18 participants with mild anxious or depressive symptoms who did not receive any antidepressant intervention. The results were demonstrated in Table 4. We have calculated the difference of BQ consuming amount (quids/day), chewing frequency (days/week), SUSRS (BQ) and HAMD before and after the observation period. We found that the difference of intervention group BQ chewing amount 39.2 quids/day, frequency 4.8 days/week, SUSRS (BQ) 2.3, and HAMD 11.8 while the counterpart was revealed as the difference of BQ chewing amount 2.6 quids/day, frequency 0.4, SUSRS (BQ) 0.1, and HAMD 1.3. Statistical significance existed in the interaction $P$ value in the reduction of BQ consuming amount, frequency, SUSRS and HAMD.

### Table 4

| Variables    | Before | After | Difference | $P$ value | Before | After | Difference | $P$ value | Interaction $P$ value |
|--------------|--------|-------|------------|-----------|--------|-------|------------|-----------|----------------------|
| Amount       | 44.5 (49.3) | 5.3 (6.0) | −39.2       | .008      | 43.7 (46.5) | 41.1 (46.6) | −2.6        | .089      | .004                 |
| Frequency    | 5.7 (1.6)  | 0.9 (1.1) | −4.8        | <.001     | 5.3 (2.5)  | 4.9 (2.9)  | −0.4        | .238      | <.001                |
| SUSRS        | 2.7 (5.2)  | 0.3 (0.5) | −2.3        | .079      | 1.0 (0.7)  | 0.9 (0.7)  | −0.1        | .163      | .05                  |
| HAMD         | 14.9 (6.6) | 3.1 (2.6) | −11.8       | <.001     | 6.1 (5.2)  | 4.7 (5.3)  | −1.3        | .004      | <.001                |

BQ = Betel-quid, HAMD = Hamilton Depression Rating Scale, SUSRS = Substance Use Severity Rating Scale.

paired t test $P$ value.

Interaction $P$ value = Intervention*$t$ effect.
design. In the follow-up contact by telephone, poor motivation in the participants might have contributed to recall bias. The high drop-out rate (33 of the 53 initial cohort patients chewing BQ) deserved alert of the substantial risk of bias, though the drop-out and the retained group patients did not differ significantly in the 6 measured variables (Table 2). The high drop-out rate also described the nature of the poor motivation of the study cohort. This might also contribute to useless counseling and psychotherapy for the abstinence of BQ addiction. The fact that the available patients with a clinical depression diagnosis had already undergone continuous antidepressant therapy may also have influenced our findings.

5. Conclusion

Patients with depressive disorders had an elevated prevalence of BQ chewing (26%). The present study was a first step towards understanding a possible correlation between the severity of depressive symptoms, signs and substance use of BQ in a clinical setting. Antidepressant treatment reduced the clinical severity of BQ use, as measured by the amount and frequency of consumption and SUSRS (BQ) scores. Depressive symptoms, as measured by HAMD scores, were also significantly reduced. A more powerful study design, such as a randomized clinical trial, may in the future allow verification of the relationships between BQ use, depressive symptoms, and antidepressant use. The novel findings of our study were antidepressant might be the therapeutic agent for the BQ addiction patients, mainly via the MAO-A pathway. This study provides preliminary data and requires replication in larger trials.

Srinivasan Nithiyanantham orcid: 0000-0001-9217-1269.

References

[1] International Agency for Research on Cancer. Tobacco Habits Other Than Smoking: Betel-quid and Areca-nut Chewing; and Some Related Nitrosamines. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 1985; 37. Available at: http://monographs.iarc.fr/EN/GMonographs/vol1-42/mono37.pdf. Accessed October 23-30, 1984.
[2] International Agency for Research on Cancer. Betelquid and areca-nut chewing and some areca-nut derived nitrosamines. Paper presented at the IARC Monogr Eval Carcinog Risks Hum 2004; 85. Available at: http://monographs.iarc.fr/EN/GMonographs/vol85/mono85.pdf. Accessed October 11-18, 1984.
[3] International Agency for Research on Cancer. A review of human carcinogens: personal habits and indoor combustions. Paper presented at the IARC Monogr Eval Carcinog Risks Hum 2012; 100E. Available at: http://monographs.iarc.fr/EN/GMonographs/vol100E/mono100E.pdf. Accessed September 29-October 6, 2009.
[4] Lee CH, Ko AM, Warnakulasuriya S, et al. Intercountry prevalences and practices of betel-quid use in south, southeast and eastern Asia regions and associated oral preneoplastic disorders: an international collaborative study by Asian betel-quid consortium of south and east Asia. Int J Cancer 2011;129:1741–51.
[5] Nelson BS, Heishober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. Ann Emerg Med 1999;34:238–43.
[6] Shanran RN, Mehrotra R, Choudhury Y, et al. Association of betel nut with carcinogenesis: revisit with a clinical perspective. PLoS One 2012;7:e42759.
[7] Pickwell SM, Schimelpfening S, Palinkas LA. ‘Betel mania’. Betel quid chewing by Cambodian women in the United States and its potential health effects. West J Med 1994;160:326–30.
[8] Gupta PC, Ray CS. Epidemiology of betel quid usage. Ann Acad Med Singapore 2004;33:31–6.
[9] Lee CH, Ko AM, Yen CF, et al. Betel-quid dependence and oral potentially malignant disorders in six Asian countries. Br J Psychiatry 2012;201:383–91.
[10] Lee CH, Chiang SL, Ko AM, et al. Betel-quid dependence domains and syndrome associated with betel-quid ingredients among chewers: an Asian multi-country evidence. Addiction 2014;109:1194-204.
[11] van Amsterdam J, Talhout R, Vleeming W, et al. Contribution of monoamine oxidase (MAO) inhibition to tobacco and alcohol addiction. Life Sci 2006;79:1969–73.
[12] Chen PH, Tu HP, Wang SJ, et al. Monoamine oxidase A variants are associated with heavy betel quid use. Addict Biol 2012;17:786–97.
[13] Khan S, Abbas G, Ahmed FS, et al. Effect of dichloromethane fraction of Areca catechu nut on monamines associated behaviors and tyramine pressor sensitivity in rodents. Pak J Pharm Sci 2014;27:303–7.
[14] Gho L, Gotelli S, Cerretti A, et al. Duration of untreated depression influences clinical outcomes and disability. J Affect Disord 2013;175:224–8.
[15] American Psychiatric AssociationDiagnostic and Statistical Manual of Mental Disorders (Fifth ed.). Washington, DC: American Psychiatric Association; 2013.
[16] WHO Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Geneva: World Health Organization; 1994.
[17] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[18] Chung CM, Kuo TM, Chiang SL, et al. Antidepressants in association with reducing risk of oral cancer occurrence: a nationwide population-based cohort and nested case-control studies. Oncotarget 2016;7:11687–95.
[19] Saija A, Princi P, De Pasquale R, et al. Arecoline, but not haloperidol, induces changes in the permeability of the blood-brain barrier in the rat. J Pharm Pharmacol 1990;42:135–8.
[20] Molinengo L, Cassone MC, Orsetti M. Action of arecoline on the levels of acetylcholine, norepinephrine and dopamine in the mouse central nervous system. Pharmacol Biochem Behav 1986;24:1801–3.
[21] Little MA, Pokhrel P, Murphy KL, et al. Intention to quit betel quid: a comparison of betel quid chewers and cigarette smokers. Oral Health Dent Manag 2014;13:512–8.
[22] Moss J, Kawarmoto C, Pokhrel P, et al. Developing a betel quid cessation program on the Island of Guam. Pac Asia Jq 2013;6:144–50.
[23] Osborne PG, Ko YC, Wu MT, et al. Intoxication and substance use disorder to Areca catechu nut containing betel quid: a review of epidemiological evidence, pharmacological basis and social factors influencing quitting strategies. Drug Alcohol Depend 2017;179:187–97.
[24] Lee CH, Ko AMS, Yang FM, et al. Association of DSM-5 betel quid use disorder with oral potentially malignant disorder in 6 betel quid endemic asian populations. JAMA Psychiatry 2018;75:261–9.