Use of medicinal plants for headache, and their potential implication in medication-overuse headache: Evidence from a population-based study in Nepal

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Abstract

Background: In Nepal, traditional treatment using medicinal plants is popular. Whereas medication-overuse headache is, by definition, caused by excessive use of acute headache medication, we hypothesized that medicinal plants, being pharmacologically active, were as likely a cause.

Methods: We used data from a cross-sectional, nationwide population-based study, which enquired into headache and use of medicinal plants and allopathic medications. We searched the literature for pharmacodynamic actions of the medicinal plants.

Results: Of 2100 participants, 1794 (85.4%) reported headache in the preceding year; 161 (7.7%) reported headache on ≥15 days/month, of whom 28 (17.4%) had used medicinal plants and 117 (72.7%) allopathic medication(s). Of 46 with probable medication-overuse headache, 87.0% (40/46) were using allopathic medication(s) and 13.0% (6/46) medicinal plants, a ratio of 6.7:1, higher than the overall ratio among those with headache of 4.9:1 (912/185). Of 60 plant species identified, 49 were pharmacodynamically active on the central nervous system, with various effects of likely relevance in medication-overuse headache causation.

Conclusions: MPs are potentially a cause of medication-overuse headache, and not to be seen as innocent in this regard. Numbers presumptively affected in Nepal are low but not negligible. This pioneering project provides a starting point for further research to provide needed guidance on use of medicinal plants for headache.

Keywords
Herbal medications, pharmacodynamic activity, overuse, South-East Asia region, Global Campaign against Headache

Background

It has been assumed that medication-overuse headache (MOH) is less of a problem in highly rural poor countries because of the lack of access to pharmaceuticals (1). However, in a large epidemiological study in Nepal, the prevalence of probable MOH (pMOH, defined as the association of headache on ≥15 days/month with overuse of acute medication) was higher than reported in Europe (2,3).

In such countries, there is often strong reliance on alternative and complementary practitioners, and the use of plants for medicinal purposes is common (4,5). If these medicinal plants (MPs) have properties that

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make them active against acute headache, might their overuse also generate MOH? Studies to answer this are lacking, but the question is of interest also in the Western world, where the use of MPs is increasing (6), with a widespread belief that they are “harmless remedies without side effects” (7). At the same time, MOH is the type of headache associated with the highest cost per person in Europe (8).

In a pioneering project, we used data from a large population-based survey from Nepal to test the hypothesis: “Medicinal plants, being pharmacologically active, are as likely as other medications to cause MOH”. Our public-health objectives were:

- to establish the proportion of Nepalese adults using MPs against headache
- to assess the associations of such usage with demographic factors and disease attributes (symptom burden)
- to identify the MPs used
- to make a systematic listing of their pharmacological effects on the CNS
- to ascertain whether and to what extent they might be implicated in MOH causation

**Methods**

**Design of the epidemiological study**

This methodology has been described in detail previously (9). In summary, in a cross-sectional, population-based survey, trained health workers visited 2210 households selected randomly from 15 representative districts out of 75 in Nepal (2,9,10). One adult was randomly selected from each household, with 2100 agreeing to participate in a structured interview. The participation proportion was >99% (2). All data were collected during May 2013.

**Instruments**

The structured Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation (HARDSHIP) questionnaire was culturally adapted and translated into Nepali (9). HARDSHIP included demographic factors (age, gender, household consumption and altitude and urbanicity of dwelling) as well as indices of symptom burden (headache frequency, duration and intensity) and use of allopathic medication(s). Queries concerning MPs were added (2): Participants were asked whether they had used any herbal therapies specifically to relieve headache (not taken regularly to prevent headache), their names, if so, and on how many days they had been used during the preceding month.

**Diagnosis**

We specifically identified participants who reported headache on ≥15 days/month, and, among these, any who were using medications and/or MPs for acute headache. We diagnosed overuse in those who reported: a) Use on ≥15 days/month of either one type of MP or simple analgesics only; or b) use on ≥10 days/month of (i) more than one type of MP; (ii) any other acute medication (such as opioids, ergots or triptans); (iii) a combination of analgesics in different classes or of analgesics with other medications; or (iv) a combination of MPs and analgesics (2).

Migraine or tension-type headache (TTH) were diagnosed according to ICHD-3 beta criteria (11) in those with headache on <15 days/month. Further information on the methodology has been published elsewhere (2).

**Plant identification**

Two Nepalese botanists living in Norway were consulted to correct any local plant names that were misspelled in the data and to identify the genus and species of each plant from its local name(s) and description. Synonyms were searched for at www.efloras.org (12).

**Literature search**

We searched Micromedex and PubMed for reports of any pharmacological effects of the MPs on the CNS. Each plant’s botanical name was used as a search term, with the Medical Subject Heading (MeSH) term “central nervous system” added in the PubMed search. When there were fewer than three matches with the additional search term, only the plant name was used. In cases where we only had the plant-genus, “species” was added as a third search term in cases where there were >150 matches. We also looked for the plants in the encyclopaedia Plants and people of Nepal (13). When the plant names identified by the botanists gave no or few (<3) results, synonyms were searched for. We also looked for potential information sources in the reference lists of relevant articles.

We separated the potential effects of the plants on the CNS into (a) antioxidative effects, (b) anti-inflammatory or immunological effects (anti-inflammatory, pro-inflammatory, immunosuppressive, immunomodulatory effects, or influences on nitric oxide/inducible nitric oxide synthase), (c) effects on receptors, transmitters or synapses in the CNS, (d) effects on vasculature (constrictor or dilator), and (e) other effects.
Data management and statistical analyses

The outcome variables “use of medicinal plant” and “use of allopathic medications” during the preceding month for treatment of headache were categorized as “yes” or “no” and presented as numbers and percentages. Users of both MPs and allopathic medications were included in both categories. Proportions of participants using MPs or allopathic medications, with 95% confidence intervals (CIs), were estimated for any headache, migraine and headache on ≥15 days/month. The independent variable “age” was categorized into five groups (18–25, 26–35, 36–45, 46–55 and 56–65 years). Household consumption per year in United States dollars (USD) (at the time of study: 1 USD ≈ 100 Nepalese rupees) was used as an indicator of participants’ economic status, and categorized into three groups: Poorest (<950 USD/year), poor (950–1200 USD/year), and intermediate and above (>1200 USD/year). This gave the best split in numbers, while taking some account of Nepal’s absolute poverty line (nationally, USD 225 for an individual in 2013, but varying between locations; in Kathmandu, it was USD471 (14)). Our measure of consumption was based on households rather than individuals, and therefore set at a higher level. Dwelling was categorized as urban or rural, and altitude as low (<1000 m) or high (≥1000 m).

The symptom burden of headache was measured by frequency (headache days/month [d/m]), attack duration (hours) and headache intensity. While the first two of these were collected as continuous data, we categorized them so as to yield the best split in numbers between the categories. Thus frequency was categorized into four groups for any headache (<1, 1–2, 3–14 and ≥15 d/m), three for migraine (<1, 1–2 and 3–14 d/m) and two for headache on ≥15 d/m (15–20 and > 20 d/m). Duration was categorized into three groups: For any headache and migraine as <4, 4–12 and > 12 hours, and for headache on ≥15 d/m as <48, 48–144 and > 144 hours. We calculated proportion of time in ictal state (pTIS; %) from frequency and mean headache duration, and categorized it, again to give the best split in numbers, into four groups (<1, 1–3, 3.1–10 and >10%) for any headache and migraine, and three groups (<60, 60–80 and >80%) for headache on ≥15 days/month. Intensity was categorized as “not bad”, “quite bad” and “very bad” (equating to “mild”, “moderate” and “severe”).

We used bivariate and multivariate logistic regression analyses (with odds ratios [OR] and adjusted odds ratios [AOR], each with 95% CIs) to investigate the associations of plant or medication use on the one hand, in all headache, migraine and headache on ≥15 days/month, and demographic variables and indices of headache burden on the other. These variables were entered as covariates in the multivariate logistic regression analyses, although, for frequency and duration, pTIS was excluded, and, for pTIS, frequency and duration were excluded.

In view of the number of analyses, we considered p < 0.02 to be statistically significant. Two-tailed p-values were calculated. All data were analysed with SPSS 21.0 software (IBM Corp., Armonk, NY, USA).

Results

Participants

A total of 2100 adults aged 18–65 years were included in the nationwide study; their sociodemographic characteristics have been presented previously (206). Here we analyze data of 1794 participants (85.4%) who reported headache during the preceding year. Their mean age was 36.1 ± 12.6 years, and male/female ratio was 1:1.6.

Use and overuse of medicinal plants and allopathic medications

Of these 1794 participants, 185 (10.3%) also reported use of MP(s) for headache at least once in the preceding month, while 912 (50.8%) had used allopathic medication(s) during the preceding month and using MP(s), 40 (34.2%) met our criteria for overuse. Of the 28 with headache on ≥15 days/month and using MP(s), six (21.4%) met our criteria for overuse. Of the 28 with headache on ≥15 days/month and using MP(s), six (21.4%) met our criteria for overuse. Three of these also reported use of allopathic medication(s), one on 15 days/month and therefore meeting our criteria for overuse of these also.

Plant identification

From the 73 local plant names reported, the botanists were able to identify or partially identify 45 plants (61.6%) and unable to identify 28. Of the 45, five were identified only by their genera, three were given only probable identities, and one was only partly identified (Herbal products Vicks). The identities of two others – “banphool” and “ketaki” –
Table 1. Use of medicinal plants and allopathic medication at least once in the preceding month among participants with any headache according to demographic factors and symptom burden (N = 1794).

| Medicinal plants | Ethnobotany in the Nepal Himalaya. | Allopathic medication |
|------------------|-----------------------------------|-----------------------|
| Variable         | N | n (%) | OR (95% CI) | p | AOR* (95% CI) | p | N | OR (95% CI) | p | AOR* (95% CI) | p |
| Yes              | 1794 | 185 (10.3) | – | – | – | – | 912 (50.8) | – | – | – | – |
| Age (in years)   |          |               | | | | | | | | | |
| 18–25            | 426 | 28 (6.6) | Reference | – | Reference | – | 205 (48.1) | Reference | – | Reference | – |
| 26–35            | 581 | 58 (10.0) | 1.6 (0.9–2.5) | 0.057 | 1.6 (0.9–2.6) | 0.055 | 307 (52.8) | 1.2 (0.9–1.6) | 0.14 | 1.2 (0.9–1.6) | 0.20 |
| 36–45            | 358 | 46 (12.8) | 2.1 (1.3–3.4) | 0.003 | 2.0 (1.2–3.6) | 0.006 | 173 (48.3) | 1.0 (0.8–1.3) | 0.96 | 0.9 (0.7–1.3) | 0.58 |
| 46–55            | 258 | 30 (11.6) | 1.9 (1.1–3.2) | 0.023 | 1.6 (0.9–2.9) | 0.078 | 138 (53.5) | 1.2 (0.9–1.7) | 0.17 | 1.2 (0.8–1.7) | 0.34 |
| 56–65            | 171 | 23 (13.5) | 2.2 (1.2–3.9) | 0.008 | 1.9 (1.1–3.5) | 0.037 | 89 (52.0) | 1.2 (0.8–1.7) | 0.34 | 1.0 (0.7–1.4) | 0.91 |
| Gender           |          |               | | | | | | | | | |
| Male             | 689 | 82 (11.9) | Reference | – | Reference | – | 306 (44.4) | Reference | – | Reference | – |
| Female           | 1105 | 103 (9.3) | 0.8 (0.6–1.1) | 0.081 | 0.8 (0.6–1.1) | 0.11 | 606 (54.8) | 1.5 (1.31.8) | <0.001 | 1.3 (1.1–1.6) | 0.014 |
| Household consumption (USD/year) |          |               | | | | | | | | | |
| <950             | 686 | 76 (11.1) | 1.1 (0.8–1.5) | 0.60 | 0.9 (0.6–1.3) | 0.67 | 355 (51.7) | 1.1 (0.9–1.3) | 0.65 | 1.0 (0.8–1.3) | 0.97 |
| >950             | 387 | 51 (13.2) | 1.9 (1.1–3.2) | 0.002 | 2.0 (1.3–3.0) | 0.002 | 278 (71.8) | 5.0 (3.3–6.6) | <0.001 | 4.3 (3.5–9.9) | <0.001 |
| Duration (in hours) |          |               | | | | | | | | | |
| Urban            | 686 | 36 (5.2) | Reference | – | Reference | – | 299 (43.6) | Reference | – | Reference | – |
| Rural            | 1108 | 149 (13.4) | 2.8 (1.9–4.1) | <0.001 | 2.6 (1.8–3.9) | <0.001 | 613 (55.3) | 1.6 (1.3–1.9) | <0.001 | 1.7 (1.4–2.1) | <0.001 |
| Household altitude |          |               | | | | | | | | | |
| <1000 m          | 845 | 63 (7.5) | Reference | – | Reference | – | 393 (46.5) | Reference | – | Reference | – |
| >1000 m          | 949 | 122 (12.9) | 1.8 (1.3–2.5) | <0.001 | 1.5 (1.1–2.2) | 0.015 | 519 (54.7) | 1.4 (1.2–1.7) | 0.001 | 1.1 (0.9–1.4) | 0.34 |
| Headache burden indices |          |               | | | | | | | | | |
| Frequency (days/month) |          |               | | | | | | | | | |
| <4               | 590 | 43 (7.3) | Reference | – | Reference | – | 183 (31.0) | Reference | – | Reference | – |
| 4–12             | 466 | 47 (10.1) | 1.4 (0.9–2.2) | 0.11 | 1.2 (0.7–2.1) | 0.50 | 227 (48.7) | 2.1 (1.6–2.7) | <0.001 | 1.6 (1.2–2.1) | 0.001 |
| >12              | 738 | 95 (12.9) | 1.9 (1.3–2.7) | <0.001 | 2.2 (0.9–5.4) | 0.080 | 502 (68.0) | 4.7 (3.7–6.0) | <0.001 | 2.5 (1.8–3.4) | <0.001 |
| Intensity        |          |               | | | | | | | | | |
| Not bad          | 373 | 32 (8.6) | Reference | – | Reference | – | 130 (34.9) | Reference | – | Reference | – |
| Quite bad        | 901 | 83 (9.2) | 1.1 (0.7–1.7) | 0.72 | 0.9 (0.6–1.4) | 0.68 | 451 (50.1) | 1.9 (1.5–2.4) | <0.001 | 1.3 (1.1–1.7) | 0.047 |
| Very bad         | 520 | 70 (13.5) | 1.7 (1.1–2.6) | 0.025 | 1.1 (0.7–1.8) | 0.76 | 331 (63.7) | 3.3 (2.5–4.3) | <0.001 | 1.7 (1.3–2.4) | 0.001 |
| Proportion (%) of time in ictal state |          |               | | | | | | | | | |
| <1               | 785 | 58 (7.4) | Reference | – | Reference | – | 264 (33.6) | Reference | – | Reference | – |
| 1–3              | 217 | 29 (12.3) | 1.8 (1.1–2.9) | 0.022 | 1.8 (1.1–3.0) | 0.021 | 118 (53.9) | 2.3 (1.7–3.1) | <0.001 | 2.2 (1.6–3.0) | <0.001 |
| 3–10             | 403 | 49 (12.2) | 1.7 (1.2–2.6) | 0.007 | 1.7 (1.1–2.7) | 0.013 | 252 (62.5) | 3.3 (2.6–4.2) | <0.001 | 3.0 (2.3–3.9) | <0.001 |
| >10              | 387 | 51 (13.2) | 1.9 (1.1–3.2) | 0.002 | 2.0 (1.3–3.0) | 0.002 | 278 (71.8) | 5.0 (3.3–6.6) | <0.001 | 4.3 (3.5–9.9) | <0.001 |

AOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval. N = total number within subsample; n = number within subsample responding positively.

*Adjusted for age, gender, household consumption, dwelling, altitude, headache frequency (F), attack duration (D), intensity and proportion of time in ictal state (pTIS) (for F and D, pTIS was excluded; for pTIS, F and D were excluded). p-values are two-tailed, and emboldened when significant (<0.02).

Four of the local plant names were applied to mixtures of different species, two were identified with more than one probable botanical name, two were used for more than one species and two for the same species as two others. Zandu balm was an exception, since this was found to contain both exact species and a mix of different species in a genus. Taken together, there were 60 species (four of them uncertain because of uncertain identifications by the botanists and six without definite confirmation by the botanists) and five genera identified from the 47 local plant names.
We reviewed 191 publications or encyclopaedias in the literature search. Of the 60 species, 49 were identified pharmacodynamically. Of the five genera, only two were identified pharmacodynamically since there were few studies on the genera as a whole. We found only one randomized controlled trial (RCT) relevant to use for headache, which was of low quality. No meta-analyses were found. The remainder of the studies found were animal, in vitro, or case studies (Table 4).

Of the 60 species, 37 (61.7%) were shown in the literature to have antioxidative effects, 27 (45.0%) to have anti-inflammatory or immunosuppressive effects, and 23 (38.3%) to have effects on receptors, transmitters or synapses in the CNS (Table 4). Of the five genera, two were shown to have anti-inflammatory or immunosuppressive effects and one to have effects on receptors, transmitters or

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### Table 2. Use of medicinal plants and allopathic medication at least once in the preceding month among participants with migraine according to demographic factors and symptom burden (n = 728).

| Variable                              | Medicinal plants                      | Allopathic medication                          |
|---------------------------------------|---------------------------------------|-----------------------------------------------|
|                                       | Bivariate analyses                    | Multivariate analyses                          |
|                                       | OR (95% CI) p                          | OR (95% CI) p                                  |
|                                       | AOR* (95% CI) p                        | AOR* (95% CI) p                                |
|                                       | n (%)                                 | n (%)                                         |
|                                       | Bivariate analyses                    | Multivariate analyses                          |
|                                       | OR (95% CI) p                          | OR (95% CI) p                                  |
|                                       | AOR* (95% CI) p                        | AOR* (95% CI) p                                |
|                                       | n (%)                                 | n (%)                                         |
| Yes (in years)                        |                                       |                                               |
| 18–25                                 | 153 (5.9)                             | Reference                                     |
|                                       |                                       | Reference                                     |
|                                       |                                       | OR (95% CI) p                                  |
|                                       |                                       | p                                             |
| 18–25                                 |                                       |                                               |
| 26–35                                 | 241 (12.0)                            | 2.2 (1.1–4.8)                                 |
|                                       | 0.048                                 | p                                             |
|                                       |                                       |                                               |
| 36–45                                 | 158 (13.9)                            | 2.6 (1.2–5.8)                                 |
|                                       | 0.021                                 | p                                             |
| 18–25                                 |                                       |                                               |
| 36–45                                 |                                       |                                               |
| 46–55                                 | 101 (15.8)                            | 3.0 (1.3–7.1)                                 |
|                                       | 0.012                                 | p                                             |
| 46–55                                 |                                       |                                               |
| 56–65                                 | 75 (12.0)                             | 2.1 (0.8–5.7)                                 |
|                                       | 0.11                                 | p                                             |
|                                       |                                       |                                               |
| Gender                                |                                       |                                               |
| Male                                  | 249 (14.1)                            | Reference                                     |
|                                       |                                       | Reference                                     |
|                                   |                                       | OR (95% CI) p                                  |
|                                   |                                       | p                                             |
| Female                                | 479 (10.4)                            | 0.7 (0.5–1.1)                                 |
|                                       | 0.15                                 | p                                             |
|                                      |                                       |                                               |
| Household consumption (USD/year)      |                                       |                                               |
| <950                                  | 277 (11.6)                            | Reference                                     |
|                                       |                                       | Reference                                     |
| >950                                  | 162 (12.3)                            | 1.1 (0.6–2.0)                                 |
|                                       | 0.63                                 | p                                             |
|                                      |                                       |                                               |
| Dwelling                              |                                       |                                               |
| Urban                                 | 261 (5.0)                             | Reference                                     |
|                                       |                                       | Reference                                     |
|                                       |                                       | OR (95% CI) p                                  |
|                                       |                                       | p                                             |
| Rural                                 | 467 (15.4)                            | 3.5 (1.9–6.4)                                 |
|                                       | <0.001                                | p                                             |
|                                      |                                       |                                               |
| Household altitude                    |                                       |                                               |
| <1000 m                               | 287 (21.3)                            | Reference                                     |
|                                       |                                       | Reference                                     |
| >1000 m                               | 441 (14.5)                            | 2.2 (1.3–3.6)                                 |
|                                       | 0.004                                 | p                                             |
|                                      |                                       |                                               |
| Headache burden indices               |                                       |                                               |
| Frequency (days/month)                |                                       |                                               |
| <1                                    | 235 (9.8)                             | Reference                                     |
|                                       |                                       | Reference                                     |
|                                       |                                       | OR (95% CI) p                                  |
|                                       |                                       | p                                             |
| 1–2                                   | 226 (13.7)                            | 1.5 (0.8–2.6)                                 |
|                                       | 0.19                                 | p                                             |
| 1–2                                   |                                       |                                               |
| 3–14                                  | 267 (12.1)                            | 1.2 (0.7–2.1)                                 |
|                                       | 0.51                                 | p                                             |
| 3–14                                  |                                       |                                               |
| Duration (in hours)                   |                                       |                                               |
| <4                                    | 148 (8.1)                             | Reference                                     |
|                                       |                                       | Reference                                     |
|                                       |                                       | OR (95% CI) p                                  |
|                                       |                                       | p                                             |
| 4–12                                  | 225 (11.6)                            | 1.5 (0.7–3.0)                                 |
|                                       | 0.28                                 | p                                             |
| 4–12                                  |                                       |                                               |
| >12                                   | 355 (13.2)                            | 1.7 (0.9–3.4)                                 |
|                                       | 0.11                                 | p                                             |
| >12                                   |                                       |                                               |
| Intensity                             |                                       |                                               |
| Not bad                               | 60 (4.7)                              | Reference                                     |
|                                       |                                       | Reference                                     |
|                                       |                                       | OR (95% CI) p                                  |
|                                       |                                       | p                                             |
| Quite bad                             | 354 (11.3)                            | 1.8 (0.6–5.2)                                 |
|                                       | 0.29                                 | p                                             |
| Very bad                              | 314 (13.1)                            | 2.1 (0.7–6.1)                                 |
|                                       | 0.17                                 | p                                             |
| Proportion (%) of time in ictal state  |                                       |                                               |
| <1                                    | 263 (9.1)                             | Reference                                     |
|                                       |                                       | Reference                                     |
|                                       |                                       | OR (95% CI) p                                  |
|                                       |                                       | p                                             |
| 1–3                                   | 83 (13.3)                             | 1.5 (0.7–3.3)                                 |
|                                       | 0.28                                 | p                                             |
| 3.1–10                                | 248 (14.5)                            | 1.7 (1.0–2.9)                                 |
|                                       | 0.061                                | p                                             |
| >10                                   | 134 (10.4)                            | 1.2 (0.6–2.3)                                 |
|                                       | 0.67                                 | p                                             |
| AOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval. N = total number within subsample; n = number within subsample responding positively.
*Adjusted for age, gender, household consumption, dwelling, altitude, headache frequency (F), attack duration (D), intensity and proportion of time in ictal state (pTIS) (for F and D, pTIS was excluded; for pTIS, F and D were excluded). P-values are two-tailed, and emboldened when significant (<0.02).

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**Literature search**

We reviewed 191 publications or encyclopaedias in the literature search. Of the 60 species, 49 were identified pharmacodynamically. Of the five genera, only two were identified pharmacodynamically since there were few studies on the genera as a whole. We found only one randomized controlled trial (RCT) relevant to use for headache, which was of low quality. No meta-analyses were found. The remainder of the studies found were animal, in vitro, or case studies (Table 4).
Synapses in the CNS (Table 4). Fifteen species (25.0%) were mentioned in the literature as used against headache (Table 4). Serious adverse events (SAEs) affecting the CNS or resulting in death were reported for seven species (coma, loss of consciousness, seizures, paralyses, death) (Table 4). In addition, *Allium sativum* L. (garlic) has been shown to have anticoagulant properties resulting in bleeding (18). Respiratory and cardiac arrest have also been reported after ingestion of *Azadirachta indica* A. Juss (18), as has disseminated intravascular coagulopathy after ingestion of *Syzygium aromaticum* (L) Merrill & Perry (199).

Systemic bioavailability is implied by these pharmacodynamic properties. This is a key issue. We did not collect data on routes of administration to avoid overloading the already-long enquiry. While the literature indicates that many preparations of these MPs would be applied topically, others are taken orally and some are prepared for inhalation. Table 4 lists only the routes of administration potentially relevant to MOH causation.

**Associations according to headache type**

**Any headache.** We found somewhat greater use of allopathic medications (AOR 1.3), but not of MPs, among

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Table 3. Use of medicinal plants and allopathic medication at least once in the preceding month among participants with headache on $\geq 15$ days/month according to demographic factors and symptom burden ($n = 161$).

| Variable                        | Medicinal plants | Allopathic medication |
|---------------------------------|------------------|-----------------------|
|                                 | Bivariate analyses | Multivariate analyses | Bivariate analyses | Multivariate analyses |
|                                 | N    | n (%) | OR (95% CI) | p     | AOR* (95% CI) | p     | N    | n (%) | OR (95% CI) | p     | AOR* (95% CI) | p     |
| Yes                             | 161  | 28 (17.4) | – | – | – | – | 117  | (72.7) | – | – | – | – |
| Age (in years)                  |      |          |              |      |      |      |      |      |              |      |      |      |
| 18–25                           | 29   | 3 (10.3) | Reference | – | Reference | – | 17   | (58.6) | Reference | – | Reference | – |
| 26–35                           | 51   | 10 (19.6) | 2.1 (0.5–8.4) | 0.29 | 2.4 (0.6–10.6) | 0.23 | 38   | (75.5) | 2.1 (0.8–5.4) | 0.14 | 1.5 (0.5–4.6) | 0.47 |
| 36–45                           | 34   | 9 (26.5) | 3.1 (0.8–12.9) | 0.12 | 2.6 (0.6–12.0) | 0.21 | 24   | (70.6) | 1.7 (0.6–4.8) | 0.32 | 1.4 (0.4–4.5) | 0.58 |
| 46–55                           | 29   | 5 (17.2) | 1.8 (0.4–8.3) | 0.45 | 2.4 (0.5–12.6) | 0.29 | 22   | (75.9) | 2.2 (0.7–6.8) | 0.17 | 1.6 (0.5–5.6) | 0.47 |
| 56–65                           | 18   | 1 (5.6) | 0.5 (0.1–5.3) | 0.57 | 0.6 (0.1–6.7) | 0.67 | 16   | (88.9) | 5.6 (1.1–29.3) | 0.039 | 7.8 (1.2–50.6) | 0.029 |

Gender                           |      |          |              |      |      |      |      |      |              |      |      |      |
| Male                            | 44   | 10 (22.7) | Reference | – | Reference | – | 26   | (59.1) | Reference | – | Reference | – |
| Female                          | 117  | 18 (15.4) | 0.6 (0.3–1.5) | 0.28 | 0.5 (0.2–1.6) | 0.25 | 91   | (77.8) | 2.4 (1.2–5.1) | 0.019 | 1.8 (0.7–4.7) | 0.21 |

Household consumption (USD/year) |      |          |              |      |      |      |      |      |              |      |      |      |
| $<950$                          | 59   | 10 (16.9) | Reference | – | Reference | – | 41   | (69.5) | Reference | – | Reference | – |
| $\geq950$                       | 59   | 13 (22.0) | 1.4 (0.9–3.2) | 0.11 | 1.2 (0.7–2.1) | 0.50 | 41   | (69.5) | 0.5 (0.2–1.6) | 0.25 | 1.2 (0.5–2.9) | 0.75 |

Dwelling                        |      |          |              |      |      |      |      |      |              |      |      |      |
| Urban                           | 54   | 5 (9.3) | Reference | – | Reference | – | 42   | (77.8) | Reference | – | Reference | – |
| Rural                           | 107  | 23 (21.5) | 2.7 (0.9–7.5) | 0.060 | 2.1 (0.7–6.5) | 0.20 | 75   | (70.1) | 0.7 (0.3–1.4) | 0.18 | 0.7 (0.3–1.7) | 0.39 |

Household altitude              |      |          |              |      |      |      |      |      |              |      |      |      |
| $<1000$                         | 69   | 12 (17.4) | Reference | – | Reference | – | 50   | (72.5) | Reference | – | Reference | – |
| $\geq1000$                      | 92   | 16 (17.4) | 1.0 (0.4–2.3) | 1.0 | 0.9 (0.3–2.2) | 0.74 | 67   | (72.8) | 1.1 (0.5–2.1) | 0.30 | 1.2 (0.5–2.6) | 0.72 |

Headache burden indices         |      |          |              |      |      |      |      |      |              |      |      |      |
| Frequency (days/month)          |      |          |              |      |      |      |      |      |              |      |      |      |
| 15–20                           | 99   | 24 (24.2) | Reference | – | Reference | – | 73   | (73.7) | Reference | – | Reference | – |
| $>20$                           | 62   | 4 (6.5) | 0.2 (0.1–0.7) | 0.007 | 0.4 (0.1–1.6) | 0.18 | 44   | (71.0) | 0.9 (0.4–1.8) | 0.70 | 0.2 (0.1–0.7) | 0.010 |

Duration (in hours)              |      |          |              |      |      |      |      |      |              |      |      |      |
| $<48$                           | 56   | 9 (16.1) | Reference | – | Reference | – | 31   | (55.4) | Reference | – | Reference | – |
| 48–144                          | 50   | 15 (30.0) | 2.2 (0.9–5.7) | 0.091 | 2.6 (0.9–7.5) | 0.089 | 40   | (80.0) | 3.2 (1.4–7.7) | 0.008 | 2.6 (1.0–6.9) | 0.053 |

Intensity                       |      |          |              |      |      |      |      |      |              |      |      |      |
| Not bad/quite bad              | 62   | 9 (14.5) | Reference | – | Reference | – | 41   | (66.1) | Reference | – | Reference | – |
| Very bad                        | 99   | 19 (19.2) | 1.4 (0.6–3.3) | 0.45 | 1.5 (0.6–4.0) | 0.43 | 76   | (76.8) | 1.7 (0.8–3.4) | 0.14 | 1.3 (0.6–3.1) | 0.49 |

Proportion (%) of time in ictal state |      |          |              |      |      |      |      |      |              |      |      |      |
| $<60$                           | 64   | 14 (21.9) | Reference | – | Reference | – | 46   | (71.9) | Reference | – | Reference | – |
| $60–80$                         | 45   | 11 (24.4) | 1.2 (0.5–2.8) | 0.75 | 1.3 (0.5–3.4) | 0.61 | 30   | (66.7) | 0.8 (0.3–1.8) | 0.56 | 0.7 (0.3–1.7) | 0.68 |
| $>80$                           | 52   | 3 (5.8) | 0.2 (0.1–0.8) | 0.023 | 0.2 (0.1–0.9) | 0.041 | 41   | (78.8) | 1.5 (0.6–3.5) | 0.39 | 0.8 (0.3–2.2) | 0.71 |

AOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval. $N = $ total number within subsample; $n = $ number within subsample responding positively.

*Adjusted for age, gender, household consumption, dwelling, altitude, headache frequency (F), attack duration (D), intensity and proportion of time in ictal state (pTIS) (for F and D, pTIS was excluded; for pTIS, F and D were excluded). $p$-values are two-tailed, and emboldened when significant ($<0.02$).
| Formulation | Used for headache (source and level of evidence (15)) | Assumed pharmacodynamic mechanisms on CNS | Reported adverse events on CNS (serious: SAEs [including death]; non-serious: NSAEs) |
|-------------|-----------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------|
| *Abelmoschus moschatus* Medik* (component of Navaratna oil) | Topical (13) No data | Antioxidative (16) | SAEs: Death (18–20); coma (18,19); seizures (18) NSAEs: Fever, reduced mental status (18) |
| *Abrus precatorius* L. (Rato gerdji) | Oral/topical (13) (Level V) (15) | Immunostimulating (17); receptors (17) | |
| *Aconitum ferox* Wall. Ex. Ser. (Bikma herbal) | Oral/topical (13,18,21) No data | Other (18,22–26); Receptors (27,28) | SAEs: Death, paralysis (18); muscular fasciculations, tonic-clonic seizures (18,25) NSAEs: Paresthesias, pain, severe headache, restlessness, apprehension, confusion, incoordination, miosis, mydriasis, diplopia, blurred vision, yellow-green vision (18) |
| *Acorus calamus* L. (Bojo) | Oral/parenteral/topical (13,18) (Level V) (18) | Other (29,30) | SAEs: None reported (18) NSAEs: None reported (18) |
| *Allium sativum* L*** (Garlic) | Oral/topical (13,18) (Level V) (31) | Antioxidative (18,32–35); anti-inflammatory (36–38); receptors (33,35); other (31,39); antiapoptotic (35,36) | SAEs: None reported on CNS (18) NSAEs: Headache, fatigue, vertigo (18) |
| *Allium wallichii* Kunth**** (Garlic) | Oral (13) No data | Antioxidative (40) | No data |
| *Aloe vera* L. Burm. f. (Aloe vera herbal) | Oral/topical (13,18,41) No data | Antioxidative (42–45); anti-inflammatory (18,43,46); other (42,47) | SAEs: none reported (18,41) NSAEs: none reported (18,41) |
| *Artemisia indica* Willd. (Titepati leaves) | Oral/topical (13) (Level V) (48) | Antioxidative (49); immunostimulating (50); receptors (51) | No data |
| *Azadirachta indica* A. Juss. (Neem leaves) | Oral/topical (13,18) (Level V) (13) | Antioxidative (52); anti-inflammatory (53,54); receptors (55); antiapoptotic (52,53) | SAEs: Death, Reye-like syndrome, altered consciousness, seizures, decreased responsiveness (18) NSAEs: Lethargy (18) |
| *Brassica napus* L. (Mustard paste) | No data No data | No data | No data |
| *Calotropis gigantea* L. Dryand (Aank) | Inhaled/oral/topical (13) No data | Receptors (56) | No data |
| *Centella asiatica* L. Urb. (Gortapre) | Oral/parenteral/topical (13,18) (Level V) (13) | Antioxidative (57–61); anti-inflammatory (18,62); receptors (63–66); antiapoptotic (62) | No data |

(continued)
### Table 4. Continued.

| Formulation | Used for headache (source and level of evidence (15)) | Assumed pharmacodynamic mechanisms on CNS | Reported adverse events on CNS (serious: SAEs [including death]; non-serious: NSAEs) |
|-------------|--------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------|
| Cheilanthes albomarginata C.B. Clarke (Rani sini herbal) | Oral/topical (13) | No data | Antioxidative (67); anti-inflammatory (67) | No data |
| Colebrookea oppositifolia Sm. (Dursur) | Intranasal/oral/parenteral/topical (13) | (Level V) (13) | Receptors (68) | No data |
| Curcuma longa L. (Turmeric herbal) | Oral/Parenteral (18) | No data | Antioxidative (18,69–72); anti-inflammatory (18,69–71,73–77); receptors (78–81); other (69,82–85); vascular (77) | SAEs: None reported (18,41,86) NSAEs: None reported (5,41,86) |
| Curcuma zedoaria (Christm.) Roscoe* (component of Navaratna oil) | No data | No data | Antioxidative (87) | No data |
| Cymbopogon pendulus (Nees ex Steud.) W. Watson (Lemon grass) | No data | No data | No data | No data |
| Cyperus rotundus L.* (component of Navaratna oil) | Oral (13) | No data | Antioxidative (88,89); anti-inflammatory (89,90); receptors (91,92); other (93); antiapoptotic (89) | No data |
| Eclipta prostrata L.* (component of Navaratna oil) | Oral/topical (13) | No data | Antioxidative (94); receptors (94); other (95) | No data |
| Elettaria cardamomum L. (Aalainch) | Oral (18,41) | No data | Antioxidative (18,96); anti-inflammatory (97,98); other (99) | SAEs: None reported (18) NSAEs: None reported (18) |
| Eucalyptus globulus Labill.* (component of Zandu balm, from "Herbal products Vick") | Oral/parenteral/topical (18,41) | No data | Antioxidative (18); anti-inflammatory (18); receptors (100) | SAEs: Loss of consciousness, hypoventilation, convulsions (101,102) NSAEs: Ataxia, CNS depression (101) |
| Gaultheria fragrantissima Wall.* (component of Zandu balm, from "Herbal products Vick") | Topical (48) | (Level V) (48) | Antioxidative (103,104) | No data |
| Helianthus annuus L. (Sunflower) | No data | No data | Antioxidative (105); anti-inflammatory (105) | No data |
| Hibiscus rosa-sinensis L.* (component of Navaratna oil) | Oral/topical (13) | No data | Antioxidative (106); receptors (107) | No data |
| Hordeum vulgare L.* (Jamara) | Oral/topical (18) | No data | Antioxidative (18); other (108) | SAEs: None reported (18) NSAEs: None reported (18) |
| Inula cappa (Buch.-Ham. ex D.Don) DC. (Dwareko jaro) | Oral/topical (13) | (Level V) (2) | Anti-inflammatory (109,110) | No data |
| Lilium polyphyllum D. Don* (component of Navaratna oil) | No data | No data | No data | No data |
| Lygodium japonicum (Thumb.) Sw.** (Pinase) | Topical (13) | No data | Anti-inflammatory (111) | No data |
| Lysimachia alternifolia Wall.** (Pinase) | Inhaled (13) | No data | No data | No data |

(continued)
Table 4. Continued.

| Formulation                                                                 | Used for headache (source and level of evidence (15)) | Assumed pharmacodynamic mechanisms on CNS | Reported adverse events on CNS (serious: SAEs [including death]; non-serious: NSAEs) |
|----------------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------|----------------------------------------------------------------------------------|
| *Mentha arvensis* L* (component of Navaratna oil)                          | Intranasal/oral/topical (18,41)                         | Antioxidative (112,113); anti-inflammatory (113,114); receptors (113,115,116); other (114) | SAEs: None reported (41) NSAES: None reported (41)                                 |
| *Mentha spicata* L. (Menthol oil)                                         | Oral (13)                                               | Oxidative (110)                          | No data                                                                            |
| Micromeria biflora (Buch.-Ham. Ex. D. Don) Benth,** (Pinase)              | Inhaled/oral/topical (13)                              | No data                                 | No data                                                                            |
| *Myrica esculenta* Buch.-Ham. Ex. D. Don (Kafal ko bokra)                 | Oral/topical (13,18)                                   | Antioxidative (117); anti-inflammatory (118) | No data                                                                            |
| *(Neo)picrorhiza scrophulariiflora* (Pennel) D.Y. Hong (Kurki)            | Oral/topical (13)                                      | No data                                 | No data                                                                            |
| *Nyctanthes arbor-tristis* L. (Parijaat leaves)                           | Oral/topical (13)                                      | Antioxidative (119); immunostimulating (120–122); anti-inflammatory (123); other (124) | No data                                                                            |
| *Ocimum tenuiflorum* L. (Tulsi leaves/Kapoor*, ingredient in Banphool oil [translation not approved by botanists]) | Oral/topical (13,48)                                   | Antioxidative (125); anti-inflammatory (18); receptors (126–129)                 | No data                                                                            |
| *Ophiocordyceps sinensis* (Berk.) G.H. Sung, J.M. Sung, Hywel-Jones & Spatafora (mushroom) (Yarsagumba) | No data                                               | Antioxidative (130,131); anti-inflammatory (132); immunostimulating (132); other (132) | No data                                                                            |
| *Parmelia perlata* (Huds.) Ach. (component of Navaratna oil)              | No data                                                | No data                                 | No data                                                                            |
| *Phyllanthus emblica* L* (component of Navaratna oil/Aamla, which is also a component of Banphool oil, and in monotherapy) | Oral (13)                                             | Antioxidative (133–137); anti-inflammatory (135–137); receptors (138); other (135,137,138) | No data                                                                            |
| *Plumbago zeylanica* L. (Chitum)                                          | Oral/topical (13)                                      | Anti-inflammatory (139,140); receptors (141)                                       | No data                                                                            |
| *Rubus ellipticus* Sm. (Ainselu root)                                      | Oral/topical (13,18)                                   | Antioxidative (142,143)                  | No data                                                                            |
| *Sweertia angustifolia* Buch.-Ham. Ex D. Don** (Chiraito)                 | Oral (13)                                              | Antioxidative (145); anti-inflammatory (146,147)                                  | SAEs: None reported (144) NSAES: No data                                           |
| *Sweertia chirayita* Buch.-Ham. ex D. Don** (Chiraito)                    | Oral/topical (13), (Level V) (144)                     | Antioxidative (145); anti-inflammatory (146,147)                                  | SAEs: None reported (144) NSAES: No data                                           |
| *Syzygium nervosum* A Cunn, ex DC. (Kyamuna ko munto)                    | No data                                                | Antioxidative (148)                     | No data                                                                            |
| *Terminalia chebula* Retz. (Harro)                                         | Oral/topical (13)                                      | Antioxidative (149,150); other (150)                                                | No data                                                                            |
| Formulation                        | Used for headache (source and level of evidence (15)) | Assumed pharmacodynamic mechanisms on CNS | Reported adverse events on CNS (serious: SAEs [including death]; non-serious: NSAEs) |
|-----------------------------------|------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------------------|
| *Triticum aestivum* L. * (Jamara) | Topical (18)                                         | Receptors (151)                        | SAEs: No data NSAEs: Transformation of episodic into daily headache (152) |
| *Vitex negundo* L. * (Simali)     | Inhaled/oral/topical (13)                           | Antioxidative (153,154); anti-inflammatory (154,155); receptors (155) | No data |
| *Zanthoxylum armatum* DC. * (Timur)| Oral/topical (13)                                     | Antioxidative (156,157); anti-inflammatory (158,159) | No data |
| *Zea mays* L. * (Jamara)           | No data                                              | Antioxidative, antiapoptotic (160)     | No data |
| *Zingiber officinale* Roscoe * (Ginger) | Oral/topical (13,41)                           | Antioxidative (162,163); anti-inflammatory (162,164–168); receptors (169–171); other (172) | SAEs: None on CNS (161) (RCT) NSAEs: None on CNS (161) (RCT) |
| Genera with uncertain translations |                                                      |                                        |                                                                                  |
| *Ageratum sp.* *(Bherapate herbal)* | No data                                              |                                        |                                                                                  |
| *Cotoneaster sp.* *(Ghareko jaro or Ghare herbal)* | No data                                              |                                        |                                                                                  |
| *Hedyotis sp.* *(Nimaniko jadhibuti)* | No data                                              |                                        |                                                                                  |
| *Mentha sp.* L. * (component of Zandu balm from “Herbal products Vick”/Satva Pudina*; component of Banphool oil [translation not approved by botanists]*) | No data                                              |                                        |                                                                                  |
| *Piper sp.* *(Pepper)*            | No data                                              | Anti-inflammatory (173); receptors (173) | SAEs: Coma (18) NSAEs: Ataxia, confusion, vertigo, CNS depression (18) |
| Species with uncertain translations |                                                      |                                        |                                                                                  |
| *Asparagus racemosus* Willd.*** *(Satawari [participants called it Sartawa]*) | Oral (13,18)                                         | Antioxidative (175,176); receptors (176–179) | SAEs: None reported (18) NSAEs: None reported (18) |
| *Ipomoea carnea* Jacq. *(Ajamari jhar [participants called it Ajawane]*) | Topical (13)                                         | Antioxidative (180); anti-inflammatory (180); other (180) | No data. |
| *Justicia adhatoda* L. *(Asurako or Asuro)* | Oral/topical (13)                                     |                                        |                                                                                  |
| *Paris polyphylla* Sm.*** *(Satuwa [participants called it Sartawa]*) | Oral/topical (13)                                     |                                        |                                                                                  |
| Translations not approved by the botanists |                                                      |                                        |                                                                                  |
| *Convolvulus pluricaulis* Choisy* *(181) (component of Banphool oil (182)) | No data                                              | Anti-inflammatory (183,184); receptors (185,186); other (184,187–190) | No data |
| *Nardostachys grandiflora* D.C.* *(181) (component of Banphool oil (182)) | No data                                              |                                        | No data |

(continued)
females than males (Table 1). There were no clear associations with age or household consumption.

Higher proportions of participants with any headache used MPs (AOR 2.6) and allopathic medications (AOR 1.7) in rural areas than urban (Table 1). Associations with high altitude, apparent in bivariate analysis, lost significance in multivariate analysis.

Increasing headache frequency (from 1 to \( \leq 15 \) days/month) was clearly associated with increasingly probable use of allopathic medication(s) (from 32.4% to 72.7%, a factor of 2.2; AOR 1.8–2.3), but, for MPs, this was so only for frequency \( \geq 15 \) days/month (from 7.3% to 17.4%, a factor of 2.4; AOR 2.0; Table 1). Long-duration (AOR 2.5) and severe headache (AOR 1.7) were each associated with increased use of allopathic medication(s), but not (in multivariate analyses) of MPs (Table 1). Participants with pTIS \( \geq 1% \) were more likely to have used allopathic medication(s) (AOR 2.2–4.4); a similar trend for MPs became clearly significant only when pTIS exceeded 3% (AOR 1.7–2.0; Table 1).

**Migraine.** There were no clear associations with age, gender or household consumption.

A higher proportion of participants with migraine used MPs (AOR 3.4) in rural areas than urban, but for allopathic medications this association just lost significance in multivariate analysis (AOR 1.5; \( p = 0.021; \) Table 2). Associations with high altitude, apparent in bivariate analysis, once more lost significance in multivariate analysis. High frequency (AOR 3.2) and pTIS \( \geq 1% \) were associated with more probable use of allopathic medications (AOR 2.2–4.4) but not of MPs (Table 2).

**Headache on \( \geq 15 \) days/month.** Only one association was clear: Less use of allopathic medication(s) (AOR 0.2) in very high-frequency headache (\( > 20 \) days/month) (Table 3). A similar trend for MPs (AOR 0.2) did not survive multivariate analysis. A trend away from use of MPs (AOR 0.2) with very high pTIS (\( > 80\% \)) was discernible but did not meet our significance threshold (\( p > 0.02; \) Table 3).

**Are medicinal plants as likely as other medications to be associated with headache on \( \geq 15 \) days/month?** As noted earlier, of 912 participants with headache and using allopathic medication(s), 117 (12.8%) reported headache on \( \geq 15 \) days/month, 40 of these (34.2%) meeting our criteria for overuse; of 185 using MP(s), 28 (15.1%) reported headache on \( \geq 15 \) days/month, six (21.4%) meeting our criteria for overuse. The difference between these proportions was not significant (\( p = 0.259 \) [chi-squared]). Of the 46 with headache on \( \geq 15 \) days/month and overuse, 87.0% (40/46) were using allopathic medication(s) and 13.0% (6/46) were using MPs (Table 2).

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**Table 4.** Continued.

| Formulation | Used for headache (level of evidence (15)) | Assumed pharmacodynamic mechanisms on CNS | Reported adverse events on CNS (serious: SAEs [including death]; non-serious: NSAEs) |
|-------------|-------------------------------------------|-------------------------------------------|----------------------------------------------------------------------------------|
| **Pandanus fascicularis** Lam. (181) (Ketaki (191)) | No data | Antiinflammatory (192) | No data |
| **Santalum album** L. (181) (component of Banphool oil (182)) | No data | Other (193) | SAEs: CNS depression, seizures, coma (18) NSAEs: None reported (18) |
| **Syzzygium aromaticum** L. Merrill & Perry (component of Banphool oil (182)) | Oral/topical (18) | Antioxidative (194,195); anti-inflammatory (18); receptors (196); other (197,198) | SAEs: Coma, seizures (199) NSAEs: Slight CNS depression (200) |
| **Terminalia bellirica** (Gaertn.) Roxb. (181) (Barro (181), component of Banphool oil (182)) | No data | Antioxidative (201,202); anti-inflammatory (203,204); receptors (205) | No data |

NSAEs: non-serious adverse events; RCT: randomised controlled trial; SAEs: serious adverse events.

*Not in monotherapy.

**Two or more different species have same local name.

More than one possible botanical name.
using MP(s), a ratio of 6.7:1, somewhat higher than the overall usage ratio of 4.9:1 (912/185) (again not significant: \( p = 0.262 \)).

**Discussion**

The study found that a considerable minority (10.3%) of people with headache in Nepal had used MPs as treatment for it during the preceding month, although a much higher proportion (50.8%) had used allopathic medication(s). As might be expected, use of each was more likely (MPs: 17.4%; allopathic medication(s) 72.7%) among those with headache on \( \geq 15 \) days/month. Among those with migraine in particular, use of MPs was positively associated with both rural (AOR 3.4) and high-altitude (AOR 1.9) dwelling.

Use of MPs for headache is therefore common, although less so than use of allopathic medications. Use of MPs is especially common among those with headache on \( \geq 15 \) days/month, again less so than allopathic medications. Both MPs and allopathic medications were overused, according to our definitions, in association with headache on \( \geq 15 \) days/month.

However, answers to the questions of whether MPs might be implicated in MOH causation, raised by our fifth objective, and, if so, whether they are as likely to cause MOH as allopathic medications, raised in our starting hypothesis, depend on evidence not only of use, overuse and association but also of a potential causal mechanism. We note, before further consideration of these, that diagnosis of MOH is presumptive, even with allopathic medications: the diagnostic criteria of ICHD-3 beta for practical reasons omit evidence of causation, relying on “Not better accounted for by another ICHD-3 diagnosis” (11). In epidemiology, this last criterion cannot be reliably applied, hence the term “probable MOH”.

With this caveat, we address these questions.

Of 60 plant species identified, 49 were pharmacodynamically active on the CNS, with effects (on CNS receptors, and anti-inflammatory and antioxidative actions) likely to be relevant in MOH causation. This is a revelation of some importance, since 8.8% of all adults aged 18–65 years in Nepal (10.3% of the 85.4% with headache) apparently use MPs for headache (although only 25.0% of these plants have been recognized in the literature as treatments used for headache, and, in a study of traditional use of MPs in Western Nepal, headache was not listed as an indication for any of the plants (207)).

The probably multiple mechanisms of MOH causation are still unclear. Every known drug used in acute headache treatment, with a range of pharmacological actions, can cause MOH when overused (208,209). The MPs used for headache by our study participants are highly pharmacologically active, many with actions similar to those of conventional medications for headache: *Inter alia*, anti-inflammatory, serotonergic and opioidergic properties, also seen in headache medications such as aspirin, NSAIDs, triptans and opioids. While we cannot (and do not) conclude that MPs are an actual cause of MOH, these findings are such that MPs, wherever they are used and overused, must be included among its potential causes.

It is worth observing that, while only six participants using MPs had headache on \( \geq 15 \) days/month and fulfilled our criteria for overuse, there is no accepted definition of overuse of MPs. We placed MPs on equal terms with other acute headache medication (2), so that use of MPs of a single type on \( \geq 15 \) days/month or of more than one type on \( \geq 10 \) days/month was deemed to be overuse. This said, our search of the literature indicated that many of the plants used for headache had multiple, independent pharmacological actions. This made it likely that each consisted of different active substances, and more logical, therefore, to use \( \geq 10 \) days/month as the overuse threshold regardless of how many types were consumed, increasing the number diagnosed as MP-overusers. However, we considered the conservative definition a better test of our hypothesis.

Use of MPs for headache escalated with headache frequency at the same rate as use of allopathic medication(s), more than doubling as frequency increased from 1 to \( \geq 15 \) days/month. As, probably, the most influential driver of medication overuse, increasing headache frequency appears to operate similarly on MPs and allopathic medications. However, people in ictal state for most of the time (pTIS > 80%) had, apparently, given up on MPs. This was not seen with allopathic medications. It is easy to speculate that people in this near-end state, with headache almost all of their time, find (or believe they find) greater benefit from allopathic medications, so that many switch allegiance. Since there was no sign of reduced use of MPs as pTIS increased up to 80%, there is no support for the alternative explanation—that risk of developing more frequent headache is higher in those who use allopathic medication(s) than in those using MPs. There are no other studies on MPs and headache to throw light on this question.

Other associations were, perhaps, of limited interest. Considerably higher proportions of participants with migraine used MPs in rural areas than urban (AOR 3.5), a finding that was not unexpected, and a reflection, probably, of urban/rural cultural difference driven, in part, by less-easy access in rural areas to health care. Association with high altitude lost significance in multivariate analysis because rural dwelling was itself strongly associated with higher altitude.
There were limitations in this study. First, even though there were 2100 participants overall, the sample size of those reporting headache on ≥15 days per month was only 161. This resulted in lower than ideal statistical power. A second limitation lay in language and plant identification. Since no data collected in the original survey related the local names of the MPs to the ethnicity of those using them, it was impossible for the botanists to identify all of them with their botanical names (more than 120 languages are spoken as mother tongue in Nepal (210)). In addition, no data had been collected on dosages or routes of administration, as already noted, or on whether the MPs were gathered by the participants themselves, prescribed by health workers or dispensed by traditional healers. Although this was information relevant to our public-health objectives, the original survey had deferred its collection to future studies (if warranted) to avoid overloading an already lengthy enquiry.

A third factor, also limiting but outside our control, was the lack of guiding evidence in the literature. Only one relevant RCT was found in the search for side effects and use against headache, and this was of low quality. It was impossible to establish whether the MPs are actually beneficial in acute headache. Additionally, there were no studies on the pharmacological effects on the CNS for a large proportion of the MPs, which left uncertainties about their possible actions.

Despite these limitations, a participation proportion of 99.6% in the original survey excluded participation bias (2), and the methodology for collecting the data was thoroughly considered (211). These were considerable strengths. This is the first large nationwide study to investigate the use of MPs for headache in Nepal. We assume it will be the starting point for multiple endeavours: Further studies on overuse of plants with pharmacological properties among people with headache disorders; RCTs on MPs used for headache to establish their effects, if any; basic research on the mechanisms that lead to MOH to test our hypothesis more decisively, and provision of guidance on the use and misuse of MPs for headache.

**Conclusion**

MPs are used as symptomatic treatments for headache by almost 9% of the Nepalese population aged 18–65 years, 15% of whom report headache on ≥15 days/month. Many of these MPs have pharmacodynamic properties similar to those implicated in MOH causation by allopathic medication overuse. On this accumulation of evidence, MPs, whenever used, should be considered at least a potential cause of MOH, perhaps no less than allopathic medications, although this is unproven. The six presumptive cases we identified in Nepal, in a sample of 2100 (0.3%), are, in public-health terms, a small but not negligible proportion. Given a global context in which herbal remedies are becoming increasingly popular, this evidence attaches considerable importance to further research on MOH in relation to MPs. This study provides a starting point, where none existed before.

**Public health relevance**

- Medicinal plants must be included among the potential causes of MOH.
- In Nepal, where use of medicinal plants is culturally entrenched, presumptive evidence suggests a small but nonetheless measurable impact at population level.
- In developed countries, where MOH is the headache with the highest cost per person, the use of medicinal plants is widely believed to be harmless, and increasing.
- For these reasons, further research and guidance on use of MPs for headache are needed.

**Abbreviations**

AE: adverse events; AOR: adjusted odds ratio; CI: confidence interval; CNS: central nervous system; D: duration; F: headache frequency (headache days); HARDSHIP: Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation; IRC-KUSMS: Institutional Review Committee of Kathmandu University School of Medical Sciences; MeSH: Medical Subject Heading; MOH: medication-overuse headache; MP: medicinal plant; NSAEs: non-serious adverse events; OR: odds ratio; pMOH: probable MOH; pTIS: proportion of time in ictal state; RCT: randomized controlled trial; SAEs: serious adverse events; TTH: tension-type headache; USD: United States dollar.

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Author contributions

All authors were involved in conception and design of this study. KM, AR, ML and TJS were responsible for data acquisition in the original population-based study. EOS planned and conducted the literature search and established the pharmacological properties of medicinal plants reportedly used by participants. KM and HIT performed the analyses. All authors contributed to interpretation of the data. EOS drafted the manuscript and TJS contributed to its revision. All authors reviewed it critically for intellectual content and all, other than KM, approved the final version of the manuscript.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: TJS is a Director and Trustee of Lifting The Burden. The authors declare no other competing interests.

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Availability of data and materials

The datasets used and analysed during this study are held securely at The Norwegian University of Science and Technology. They are still undergoing analyses. Once these are completed, the datasets will be available from the corresponding author for academic purposes.

Ethics and approvals

The study protocol was approved by the Regional Committee for Health and Research Ethics in Central Norway, the Nepal Health Research Council and the Institutional Review Committee of Kathmandu University School of Medical Sciences, Dhusitkel Hospital (IRC-KUSMS). Consents were taken according to requirements of IRC-KUSMS (2,10).

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