

The Safety of Chinese Herbal Medicine: A Pilot Study for a National Survey

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ABSTRACT

Objectives: The aim of this study was to establish the feasibility of conducting a national safety survey involving patients of herbalists monitoring and reporting adverse events associated with the routine practice of Chinese herbal medicine.

Methods: In June 2004, 549 herbalists who were members of the UK Register of Chinese Herbal Medicine were invited to ask 10 consecutive patients to participate in the survey. Consenting patients returned their baseline survey forms direct to the research center. Four (4) weeks later, patients were sent a follow-up questionnaire in which they reported adverse events that they perceived were caused by the Chinese herbal medicine over the previous 4 weeks. The data were analyzed with regard to types and frequencies of adverse events as well as potential risk factors using multilevel logistic regression and taking into account the clustering of patients with practitioners.

Results: Of the 161 responding practitioners of Chinese herbal medicine, 71 agreed to participate, comprising 13% of the total membership. A total of 194 patients returned baseline questionnaires, an average of 2.7 patients per practitioner, and 144 (74%) patients completed the 4-week follow-up questionnaires. A total of 20 patients, who were treated by 14 of the herbal medicine practitioners, reported 32 adverse events associated with Chinese herbal medicine over the 4-week period (14% of patients, 95% confidence interval [CI]: 9%–20%). No serious adverse events were reported. The most commonly reported adverse events were diarrhea, fatigue, and nausea. When controlling for potential confounders, patients consulting for Chinese herbal medicine for the first time were more likely to report an adverse event than were those who had consulted repeatedly (OR 3.03; 95% CI: 1.03–8.89, $p < 0.02$).

Conclusions: In this pilot study, the recruitment rate was low, with only 13% of practitioners participating and only 27% of potential patients returning consent forms, raising questions about potential bias. This research has provided some useful data that will assist in the initiation of future studies.

INTRODUCTION

More than 80% of the world's population seek out herbal medicines to cure their illnesses, and annual sales in Europe and the United States exceed \$8.¹ As Chinese herbal medicine becomes increasingly practiced in the West,² there has been a parallel surge in the number of reports of adverse events appearing in the literature along with more urgent

questions about the safety of Chinese herbal medicine,³ highlighting the need for better research evidence. Reports in medical journals have tended to concentrate on individual adverse events, some of which have been idiosyncratic and others caused by inadequate standards of herb supply, (including adulteration) and preparation. National media coverage has tended to feature these individual cases. There remains a lack of knowledge about the incidence of adverse

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events, in particular, the type and frequency of the adverse events associated with the everyday practice of Chinese herbal medicine.

In this context, a preliminary literature review was conducted searching for population-based studies of adverse events associated with Chinese herbal medicine. Both the English and Chinese literature were searched, and using the following resources: Index Medicus, MEDLINE,[®] EMBASE, Chinese Biomedical Literature Database CBM, and Chinese Evidence-Based Medicine/Cochran Centre Database CEBM/CCD, the National Research Register NRR, and Cochran Library CL. The search period was from 1990 to July 2004. The search was conducted using the following terms: Chinese herbs, herbal medicine, adverse events/effects, safety, side effects, risks, toxicity, interaction, complications, drug interactions, survey, audit, case-series, cohorts, surveillance, reviews, and pharmacovigilance. For inclusion in this review, studies were required to have systematically collected data on adverse events associated with Chinese herbal medicine and to have a defined size of the patient or practitioner population as a denominator to estimate incidence figures for risks.

Only one study met the inclusion criteria, a 1996 survey of practitioners in Australia.⁴ In their survey 2795 practitioners of acupuncture and Chinese herbal medicine were invited to participate. Of these, 1100 completed their questionnaire, a response rate of 30% for “medical” practitioners and 50% for “non-medical” practitioners. These practitioners reported numerous adverse events arising from Chinese herbal medicines use, most commonly gastrointestinal symptoms, skin reactions, and severe fatigue. Practitioners reported that their patients experienced an average of one adverse event for every 8–9 months of full-time practice, or one adverse event for every 633 consultations. The mean reported adverse event rate of “nonmedical” practitioners was one half that of “medical” practitioners. Although this survey has provided the current authors the only data on incidence rates, it has two limitations. First, the survey asked for practitioners’ reports on adverse events rather than asking for patients’ reports, which is likely to lead to under-reporting.^{5,6} Second, the survey collected retrospective data from practitioners who were asked to report on adverse events over their lifetimes of practice, a less reliable approach than if the survey had been prospective.

The aim of the present study is to develop a program of research leading to an assessment of the frequency and type of adverse events associated with Chinese herbal medicine in routine practice. As a first step, a pilot study was conducted for a prospective national patient survey of adverse events. The primary objectives in this pilot study were as follows: to establish the willingness of practitioners and patients to participate; to assess response rates and the quality of data provided; to test procedures and documentation; to identify the most common adverse events for future re-

search; to obtain sufficient data to draw some preliminary hypotheses; and to provide a platform for the design of a full-scale prospective national survey.

METHODS

This pilot study was a prospective survey of patients who had been prescribed Chinese herbal medicine by qualified herbalists who were members of the Register of Chinese Herbal Medicine (RCHM). This organization is a self-regulating professional association representing practitioners of Chinese herbal medicine in the United Kingdom and has newly developed procedures for accreditation. The research methods were similar to those used in a recent study of acupuncture safety.⁷ Ethics approval for this study was given by the University of York’s Department of Health Sciences Research Ethics Committee.

Recruitment

In 2004, the 549 members of the U.K. Register of Chinese Herbal Medicine (RCHM) were invited to participate and to help recruit consenting patients >18 years of age who were able to read and write in English or Chinese. Practitioners were first asked if they would work with the investigators on this pilot patient survey and, if they agreed, they were sent letters with 10 Patient Information Leaflets and Consent Forms, which they were asked to hand out to their next 10 consecutive patients who were willing to consider receiving and completing a questionnaire 4 weeks later. National Health Service patients were excluded. Those patients willing to participate returned baseline data and their Consent Forms directly to the University of York. Four (4) weeks later these patients were sent a questionnaire from the University of York that asked detailed questions about their experiences of Chinese herbal medicine.

Data collection

Data were collected from responding practitioners, consenting patients at baseline, and patients at 4 weeks (details are provided in the box entitled Details on Data Collected). For the patients’ presenting conditions, we used the International Classification of Primary Care⁸ to code their primary presenting symptoms or problems. Some patients reported more than one problem; however, for consistency we coded only what they had listed first.

For this survey, adverse events were not defined but instead, but, to keep the questionnaire user-friendly patients were provided with a checklist of possible symptoms that was adapted from a previous survey.⁴ In contrast, “serious adverse events” were predefined as those that resulted in admission to the hospital or that were permanently disabling

Details on Data Collected

Responding practitioners provided data on gender, years of practice, where trained, whether they had National Health Service patients, whether they were willing to participate (and if not, their reason for not participating), and how many consultations they usually had per week.

At baseline, consenting patients provided data on gender, age, nationality, main problem or symptoms for which they were consulting, duration of their condition, whether they had consulted with their general practitioner (GP) or hospital specialist about their condition, who recommended them to consult their herbalist, whether the National Health Service was paying for their treatment, whether they had received Chinese herbal medicine before, the name of their herbal practitioner, and whether the study investigators could contact their herbalist in cases of a serious adverse event.

At the 4-week follow-up, patients provided data on how many consultations they had received, how many weeks they had taken Chinese herbal medicine, what type of Chinese herbal medicine they received (raw herbs, tablets, powders, etc), whether they had consulted with their GP or hospital specialist during the 4 weeks. Patients reported on what they perceived to be adverse events caused by the Chinese herbal medicine during previous 4 weeks.

Patients reporting experiencing an adverse events during the 4 weeks provided data on the following: the adverse event itself, their herbal medicine, any conventional medical test, the severity of the adverse event, whether they stopped taking Chinese herbal medicine, whether the adverse effects returned if they take the Chinese herbal medicine again, whether they were taking any conventional medication concurrently, whether they would be willing to take Chinese herbal medicine again after the adverse event, how likely they thought the adverse event was caused by the Chinese herbal medicine, and how bothersome the adverse events were.

or life threatening,⁹ and patients could check relevant categories on the checklist. With the patients' permission, a follow-up of all serious events was planned, with a short telephone interview to clarify the details of the event.

Analysis

Using SPSS (SPSS, Inc., Chicago, IL) for analysis, an assessment was made of how representative the participating herbalists were compared to the RCHM membership as a whole. The demographics of the patients were noted and compared with data on general practitioners' (GPs') patients¹⁰ and the general population.¹¹ A comparison was also made of those patients who did and did not complete the 4-week follow-up questionnaires.

The incidence of adverse events associated with Chinese herbal medicine on a "per patient per 4 weeks" basis is reported. In a univariate analysis, characteristics of patients who reported experiencing adverse events were compared to characteristics of those who did not, using the *t* test, χ^2 test, or Fisher's Exact test. In a univariate analysis, odds ratios (OR) were estimated for patient variables that might predict the risk of adverse events. A multilevel logistic regression model, using Mplus software (Muthén and Muthén, Los Angeles, CA), was used in which potential confounders were controlled for while clustering of patients within practitioners was taken into account. Using this analysis, the effects at both the patient level (level 1, in multilevel modeling terms) and the practitioner level (level 2, in multilevel modeling terms) were considered.¹²

RESULTS

Practitioners

A total of 161 (29%) members of the RCHM responded to the letter, and 71 (13%) practitioners stated that they would agree to participate. However, patients of only 46 practitioners returned consent forms. Practitioners who responded but declined to participate reported that they were too busy ($n = 26$), were not in practice at present ($n = 23$), were away ($n = 15$), were seeing too few patients ($n = 13$), or gave other reasons ($n = 4$). Six unopened letters were "returned to sender."

Details of the participating practitioners are shown in Table 1. When comparing those who did with those who did not participate in the survey, similar proportions were found with regard to gender $\chi^2 = 0.12$, $df = 1$, $p = 0.73$, and significant differences with regard to training (Fisher's Exact test: $p = 0.004$). The majority of herbalists had <10 years of experience and were consulted by <10 herbal medicine patients per week.

Patients who responded at baseline

There were 194 patients responding at baseline who met the inclusion criteria. Of these, 152 (78%) were female and 42 (22%) were male. The mean age of our respondents was 45 years (SD 12.7, range 20–76 years). Table 2 compares demographic data on gender and age to data on patients of GPs from the General Household Survey¹⁰ and the general population from the UK Census.¹¹

The majority of patients (86%) were self-identified as British, of those remaining, only one patient stated that she was Chinese. Based on the International Classification of Primary Care,⁸ the main presenting symptoms or problems reported by patients as their reasons for consulting their practitioner of Chinese herbal medicine are shown in Table 3.

A total of 85 (44%) patients had had their symptoms for >5 years, and 76 (39%) patients had had their symptoms for 1–5 years. In all, 162 (84%) patients reported having already consulted their GPs or hospital specialists about their main problems or symptoms. A total of 71 (37%) reported that they were receiving Chinese herbal medicine for the first time. Responding patients reported the most common pathways to consulting practitioners of Chinese herbal medicine as self-referral (37%), via a family/friend/colleague (31%), or via a complementary practitioner (23%). National Health Service practitioners (GP, physiotherapist, hospital

specialist, or nurse) recommended Chinese herbal medicine to only 6% of patients.

Patients who completed the 4-week questionnaires

In all, 144 (74 %) of the 194 patients completed the 4-week follow-up questionnaires. These patients were reasonably similar to the patients who completed consent forms at baseline in terms of gender ($\chi^2 = 0.219$, $df = 1$, $p = 0.639$) and age ($t = 0.62$, $df = 192$, $p = 0.53$). Patients had consulted their herbal practitioner most commonly only once over the 4 weeks (30%), followed by twice (28%). Over the 4 weeks, 102 (74%) participating patients did not have contact with their GPs or hospital specialists about their main problems or symptoms.

Of the participating patients, 74% (101) had been taking Chinese herbal medicine for 4 weeks, 10% for 3 weeks, 12% for 2 weeks, and the rest for 1 week or less. Patients re-

TABLE 1. PRACTITIONER DATA, WITH COMPARISONS BETWEEN PARTICIPATING MEMBERS OF THE REGISTER OF CHINESE HERBAL MEDICINE AND MEMBERS NOT PARTICIPATING

<i>Characteristic</i>	<i>Participating practitioners</i>	<i>Nonparticipating practitioners</i>
Gender ($n = 540$)		
Female	34 (48%)	235 (50%)
Male	37 (52%)	234 (50%)
<i>Where trained ($n = 549$)</i>		
China	17 (24%)	105 (22%)
CICM	12 (17%)	26 (5%)
NCA	7 (10%)	23 (5%)
LSATCM (now University of Westminster)	6 (9%)	26 (5%)
LAOM	4 (6%)	36 (8%)
LCTA	4 (6%)	38 (8%)
Others	21 (30%)	224 (47%)
<i>Number of consultations/week</i>	<i>Participating practitioners ($n = 71$)</i>	
<10	37 (52%)	
10–20	19 (27%)	
20–30	8 (11%)	
30–40	4 (6%)	
>40	3 (4%)	
<i>Years of practice</i>	<i>Participating practitioners ($n = 71$)</i>	
<5	19 (27%)	
5–10	17 (24%)	
10–15	15 (21%)	
15–20	10 (14%)	
20–25	7 (10%)	
>25	3 (4%)	

CICM, College of Integrated Chinese Medicine; NCA, Northern College of Acupuncture; LSATCM, London School of Acupuncture and Traditional Chinese Medicine (now University of Westminster); LAOM London Academy of Oriental Medicine; LCTA, London College of Traditional Acupuncture.

TABLE 2. DEMOGRAPHIC DATA COMPARING SURVEY PATIENTS AT BASELINE WITH GP PATIENTS AND THE U.K. POPULATION

	<i>Chinese herbal medicine patients 2004 (%) (n = 194)</i>	<i>GP patients GHS^a 2002 (%) (n = 20,149)</i>	<i>General population, U.K. Census^e 2001 (%) (n = 58,789,194)</i>
Gender			
Male	21.6	43	48.7
Female	78.4	57	51.3
<i>Age (years)</i>			
18–24	4.6		8.4
25–34	19.1	14 ^b	14.3
35–44	26.3		14.9
45–54	27.3		13.2
55–64	14.4	16 ^c	10.6
65–74	7.7	22	8.4
75–84	0.5	25 ^d	5.6
85+	0		1.9
Average age	44.9	44.3	38.6

GP, general practice.

^a(General Household Survey, 2002).

^bPatients ages 16–44 years.

^cPatients ages 45–64 years.

^dPatients ages >75 years.

^e(U.K. Census 2001)

ported that they had been taking their herbal medicine as either an herbal powder (38%), tablets (23%), herbal tea or infusion (17%), raw herbs or decoction (10%), and herbal tincture (4%), or “others” (6%).

Adverse events

A total of 20 patients, who were treated by 14 of the herbal medicine practitioners, reported 32 adverse events as-

TABLE 3. ICPC CATEGORIES FOR MAIN PROBLEM OR SYMPTOM REPORTED AT BASELINE BY PATIENTS SEEKING TREATMENT WITH CHINESE HERBAL MEDICINE (n = 194)

	<i>Categories</i>	<i>Number of patients</i>	<i>% of Total</i>
A	General	23	11.9
B	Blood	2	1.0
D	Digestive	24	12.4
F	Eye	8	4.1
H	Ear	3	1.5
K	Circulatory	5	2.6
L	Musculoskeletal	10	5.2
N	Neurologic	19	9.8
P	Psychologic	8	4.1
R	Respiratory	17	8.8
S	Skin	24	12.4
T	Endocrine, metabolic and nutritional	3	1.5
U	Urology	3	1.5
W	Pregnancy, childbearing and family planning	11	5.7
X	Female genital system	29	14.9
Y	Male genital system	4	2.1
Z	Social problems	1	0.5
	Total	194	100

ICPC, International Classification of Primary Care (see Ref. 7).

sociated with Chinese herbal medicine. This represents a rate of 14 patients per 100 over 4 weeks (95% CI: 9–20). The 32 adverse events are presented in Table 4; most commonly experienced were diarrhea, nausea, and fatigue. None of the adverse events reported were considered serious as previously defined.

Of these 20 patients, nine also reported taking prescribed conventional medication, and one had a blood test by her herbal practitioner to check her liver function. Four patients who experienced adverse events initially consulted with skin problems, four patients with female gynecologic problems, and three with digestive problems. Eight patients stopped taking Chinese herbal medicine after experiencing adverse events, 10 did not stop and it is not known whether the other two patients stopped. All patients who stopped taking their Chinese herbal medicine found that their adverse symptoms also stopped. Four of these patients reported a return of the adverse symptoms when they resumed taking their Chinese herbal medicine. Of these 20 patients, 16 reported that they would be willing to have Chinese herbal medicine again, whereas two would not and another two did not respond to the question. Seven (7) patients thought that Chinese medicine was “definitely” the cause of their adverse events, four “probably,” four “possibly,” and two “not likely,” and three did not know. Two found the adverse event “extremely bothersome,” four “very bothersome,” seven “bothersome,” five “a little bothersome,” and two did not answer this question.

Potential risk factors for adverse events

To identify which factors might help predict the risk of adverse events, as the dependent variable the report (or not) of an adverse event was used. Independent variables were used in the statistical model if they had p values of <0.25

in an exploratory univariate analysis, this cut-off being chosen to ensure that the statistical model included variables with a potential impact as predictors when controlling for confounding. On this basis, at the patient level the following were included: gender of patient (as a higher proportion of male subjects reported an adverse event, $p = 0.13$); consultation with a GP or specialist about a symptom or problem before this survey (a higher proportion had prior consultations, $p = 0.20$); first-time users of Chinese herbal medicine (a higher proportion were first-time users, $p = 0.05$); number of herbal medicine consultations in the 4-week survey period (a higher proportion had more than three consultations, $p = 0.21$); and whether there was a consultation with a GP or specialist within the 4-week survey period (a higher proportion of patients did not consult, $p = 0.04$). At the practitioner level, the model included the gender of the patients' herbalists (a higher proportion of patients with male herbalists reported adverse events, $p = 0.10$). Table 5 presents the relative risks as both unadjusted odds ratio (OR) from the univariate analysis and adjusted OR from the two-level logistic regression. Thus, when controlling for known confounding, it can be inferred that patients who took Chinese herbal medicine for the first time were significantly more likely to report adverse events (OR = 3.03, 95% CI: 1.03–8.89, $p = 0.02$).

DISCUSSION

This pilot study has been a first step in exploring some of the issues that arise when undertaking a survey of patients' experiences of adverse events; the population sampled was patients who were consulting practitioners of Chinese herbal medicine in the United Kingdom. The main

TABLE 4. FREQUENCY AND TYPE OF ADVERSE EVENTS REPORTED AS ASSOCIATED WITH CHINESE HERBAL MEDICINE ($n = 144$)

<i>Adverse events</i>	<i>Number of adverse events reported</i>	<i>Reported adverse event rate/100 patients over 4 weeks</i>	<i>95% CI</i>
Diarrhea	6	4.2	1.8–8.8
Fatigue	4	2.8	1.1–6.9
Nausea	4	2.8	1.1–6.9
Abdominal pain	4	2.8	1.1–6.9
Headache	3	2.1	0.7–5.9
Emotional disturbance	2	1.4	0.4–4.9
Bloating	2	1.4	0.4–4.9
Respiratory disturbance	1	0.7	0.1–3.8
Constipation	1	0.7	0.1–3.8
Skin reaction	1	0.7	0.1–3.8
Palpitations	1	0.7	0.1–3.8
Others	4	2.8	1.1–6.9
Total	32	22.2	16.2–29.7

CI, confidence interval.

TABLE 5. CHARACTERISTICS OF PATIENTS REPORTING ADVERSE EVENTS ASSOCIATED WITH CHINESE HERBAL MEDICINE (n = 144)

	<i>Number of patients reporting an adverse event over 4 weeks/total reporting</i>	<i>Unadjusted relative risk, odds ratio (95% CI), and p value (univariate analyses)</i>	<i>Adjusted relative risk, odds ratio (95% CI), and p value (logistic regression)</i>
<i>Patient-level variables (level 1)</i>			
Male patients	7/30	2.36 (0.85, 6.58)	2.16 (0.67, 6.96)
vs.			
Female patients	13/114	<i>p</i> = 0.13	<i>p</i> = 0.10
Prior consultation with GP or specialist	19/120	4.33 (0.55, 33.99)	4.75 (0.53, 42.65)
vs.			
No prior consultation with GP or specialist	1/24	<i>p</i> = 0.20	<i>p</i> = 0.92
First time taking Chinese herbal medicine	11/51	2.56 (0.98, 6.71)	3.03 (1.03, 8.89)
vs.			
Took Chinese herbal medicine before	9/93	<i>p</i> = 0.05	<i>p</i> = 0.02
Three consultations or less involving treatment of Chinese herbal medicine	6/26	2.12 (0.73, 6.17)	1.32 (0.78, 2.22)
vs.			
More than three consultations involving treatment of Chinese herbal medicine	14/113	<i>p</i> = 0.21	<i>p</i> = 0.85
Contact with GP or specialist during the 4 weeks	9/36	2.76 (1.04, 7.35)	2.19 (0.70, 6.86)
vs.			
No contact with GP or specialist during the 4 weeks	11/102	<i>p</i> = 0.04	<i>p</i> = 0.91
<i>Practitioner-level variables (level 2)</i>			
Patients with male practitioners	12/65	2.26 (0.83, 6.13)	2.44 (0.77, 7.74)
vs.			
Patients with female practitioners	7/77	<i>p</i> = 0.10	<i>p</i> = 0.07

CI, confidence interval; GP, general practitioner.

finding from this study is that there are several potential sources of bias that may compromise the usefulness of the methods and the validity of the preliminary data. At the level of the practitioner, a major potential source of response bias arises from the disappointingly low response rate. Of the 549 members of the Register of Chinese Herbal Medicine, the largest and most developed self-regulating professional association in the United Kingdom, only 161 (29%) of the herbal practitioner membership responded, and only 71 (13%) agreed to participate in this herbal safety study. Even if the response rates had been improved on (for example by following up nonresponding practitioners with another letter or phone call), this methodology would probably have not sufficiently raised the response rate to a more acceptable level.

A number of reasons may account for this low practitioner response rate. Practitioners themselves reported that their most common reason for not participating was because they were too busy or were not in practice at the time. Perhaps the extra work required of practitioners for a research study may have been considered to be too great a burden. The steady stream of negative publicity about Chinese herbal medicine, much of it related to poor-quality herbs and inappropriate prescribing, may have led to a protective concern about the future role of the profession. Furthermore, there is some skepticism about research in all complementary medical professions, compounded by concerns relating to unforeseen and problematic consequences of research in general. Most members of the RCHM are also practicing acupuncturists, which may explain why they were treating on average <10 herbal medicine patients per week. These and probably other reasons together led to a response rate well below the 30% achieved in a similar survey of acupuncture practitioners.⁷ The current results cannot be extrapolated with any confidence to herbalists with different professional affiliations, backgrounds, or levels of experience, because this survey involved only patients of members of the RCHM.

Another source of response bias arises because only 2.7 patients per practitioner completed the baseline consent form. This could be caused by practitioners not handing out all 10 forms as requested, for the same sorts of possible reasons discussed above. Alternatively, it could be the result of patients taking the documentation home and then not completing and returning it. Another concern is that only one patient identified herself as Chinese, a much lower proportion than we would have expected, which again calls into question how representative the sample was. The 4-week follow up questionnaire achieved a reasonable response rate of 74%.

With only 144 patients participating in this survey, the data on safety must be interpreted with caution. However, some preliminary data on their experiences of the types and frequencies of adverse events that they associated with taking Chinese herbal medicine have been established. Al-

though no serious adverse events were reported, a much larger sample size would have been required to draw conclusions about the incidence of rarely occurring events. With regard to nonserious adverse events, some tentative conclusions can be inferred. For example, of the 144 patients, 20 patients reported 32 adverse events over 4 weeks. This represents a rate of 14 adverse events per 100 patients over 4 weeks. This represents an average, for the 20 patients, of 1.7 adverse events each. The most common events reported were diarrhea, fatigue, and nausea. When interpreting these data, potential reporting bias must be borne in mind. It is possible that patients may have under-reported adverse events, perhaps because of very positive experiences with Chinese herbal medicine or because of concerns about protecting their practitioners. In a somewhat different context, it has been found that users of herbal medicines are less likely to report adverse events associated with their use of herbal medicine to their GPs than when the events are associated with their use of pharmaceutical medication.¹³ It is also possible that patients may have over-reported adverse events, particularly because the 4-week questionnaire had a checklist that was designed for ease of use with checkmark boxes. Despite these concerns, the data on adverse events reported here should be useful in taking forward research in this area.

Some of the factors that might have contributed to these experiences of adverse events have also been explored. However, the data are limited to some extent by the nature of the study design. For example, the precise herbs that made up the prescriptions, which commonly have a range of different herbs, are not known. Statistical associations between individual herbs and adverse events would have been difficult to infer, in part because of the small sample size and in part because of potential herb-herb interactions. Another complication relates to potentially complex interactions between herbs and prescribed medication.¹⁴ In this survey, nine of the 19 patients who experienced adverse events were also taking prescribed medication. Concurrent medication was asked about only from those patients reporting adverse events, and therefore one cannot know whether prescribed medication is a predictor of adverse events. In the statistical modeling the only potential risk factor that was found to be associated with a higher adverse event rate was first-time use of Chinese herbal medicine (adjusted OR = 3.03, $p = 0.02$). It makes sense that users who dislike or react badly to the herbs would tend to discontinue use, resulting in a selection process whereby ongoing patients are the ones who tolerate the herbs better or who perhaps experience benefits that outweigh negative experiences.

The patients who responded at 4 weeks were found to be representative in terms of age and gender compared to those who consented only at baseline. Participating patients were more likely to be women (78%), which can be explained only in part by the fact that women tend to consult their GPs more often than do men.¹⁰ In the current survey the mean

age was 46 years and, compared to the Census data,¹¹ a relatively higher proportion of individuals between the ages of 25 and 54 years tend to consult herbalists. The three most common reasons for consulting practitioners of Chinese herbal medicine were female gynecologic problems, digestive problems, and skin problems. Typical characteristics of patients were that they most commonly had their primary problems for >5 years, had consulted their GPs or hospital specialists before they consulted herbal medicine practitioners, had taken Chinese herbal medicine before, and had self-referred or been recommended to Chinese herbal medicine practitioners by family members, friends, or colleagues. Patients who were consulting herbal practitioners for the first time made up a relatively large proportion (37%) of the patient sample, considerably larger than the 11% found in the survey of acupuncture patients.⁷ It would be useful to explore the reasons for this difference.

To take this research forward, a major reconsideration of the survey design may be necessary. Several strategies exist for estimating the impact of adverse reactions in a population, including cohort studies such as this one, case-control studies, and spontaneous reporting schemes.¹⁴ The cohort strategy has limitations in terms of identifying the incidence of rare adverse events, and an infeasibly large sample size may be required to ensure a reasonably accurate estimate. Given that metabolic idiosyncratic reactions have been predicted to occur at a rate of 1 in 10,000,¹⁵ then according to Henley's Rule of Threes,¹⁶ to have a 95% probability that no serious adverse event occurs in n treatments, a survey sample size needs be three times n . On this basis, if a national survey with a sample size of 30,000 patients monitored over a predefined period had no reported serious adverse events, then one could estimate with 95% probability that no serious adverse event would occur in a sample of 10,000 patients. However this number raises daunting logistic problems. Case-control studies could be used to track whether a particular herb or prescription caused a particular disease or reaction; however, a suspect herb must be the impetus for such a study, and it is difficult to establish appropriate controls. Spontaneous reporting such as "yellow card" schemes may be useful in providing early signals that an individual herb may be causing an adverse event. However for Chinese herbal medicine, this is complicated by herb-herb interactions and herb-drug interactions, as well as the inherent limitations to such schemes when used on a voluntary basis.¹⁷ None of these accepted strategies for pharmacovigilance can be easily applied to the field of herbal medicine.

From this pilot study, it appears that there continues to be a place for further research, but not along the lines originally conceived. Potential bias within this design would undermine the value of the data if it were collected in a large-scale study aimed at determining the incidence of both serious and nonserious adverse events. More in-depth research should be conducted, with the focus on nonseri-

ous adverse events associated with the routine practice of herbal medicine. For this purpose, quantitative methods with a feasible sample size would suffice. A number of possible research directions could be identified. For example, future research could explore in more depth the characteristics of the more common adverse events, in particular the severity and duration of impact and the role of interactions, both between herbs and prescribed medication. It is also of interest why 80% of patients (16 of 20) who experienced adverse events continued to be willing to undergo treatment with Chinese herbal medicine. This was the case despite more than half of the patients believing that their adverse events were definitely or probably caused by taking their herbal medicines. There is also a useful role for more qualitative methods. For example, in-depth interviews could explore how patients weigh the perceived costs of adverse events with the perceived benefits of Chinese herbal medicine. In this regard, one could adapt the methodology used by Cassidy in her research into what acupuncture patients value about their treatment,¹⁸ eliciting equivalent data from patients consulting for Chinese herbal medicine.

CONCLUSIONS

This pilot study, which was planned as a first step toward collecting data on patients' experiences of adverse events associated with the routine practice of Chinese herbal medicine in the United Kingdom, has demonstrated that the study design may be compromised by the potential response bias resulting from low response rates from practitioners (13%) and return rate of consent forms from patients (27%). The reasons for this require further investigation. It was found that patients, once recruited, responded well at 4 weeks, with a response rate of 74%. The preliminary conclusions from this study are that diarrhea, fatigue, and nausea are the most common adverse events associated with Chinese herbal medicine. These reactions were not sufficiently negative to discourage most patients from seeking further treatment with Chinese herbal medicine. There were no reports of serious adverse events.

This pilot study has highlighted potential weaknesses in this methodology if used as a full-scale national survey of adverse events. Primarily the issue of response bias needs to be addressed. Nonetheless the need to conduct such a survey remains compelling, as only in this way can one estimate the current public health risks associated with Chinese herbal medicine when provided by self-regulated practitioners in routine practice. Future research in this area, if properly conducted, will inform policy developments in the field and potentially support current moves, such as in the United Kingdom, toward statutory regulation of adequately trained practitioners of Chinese herbal medicine.

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