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Lead Encephalopathy Due to Traditional Medicines

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Abstract

Traditional medicine use is common in developing countries and increasingly popular in the western world. Despite the popularity of traditional medicines, scientific research on safety and efficacy is limited. However documented fatalities and severe illness due to lead poisoning are increasingly recognized to be associated with traditional medicine use. As society becomes more globalized, it is imperative for pharmacists and health care providers to learn about the safety of traditional medical practices. The information presented educates and alerts pharmacists and health care providers about the potential of traditional medicines to cause lead encephalopathy. Case reports were located through systematic literature searches using MEDLINE, CINAHL, AMED, CISCOM, EMBASE and The Cochrane library from 1966 to the February 2007. Reference lists of identified articles and the authors' own files were also searched. Inclusion criteria were cases of human lead encephalopathy associated with traditional medical practices. There were no restrictions regarding the language of publication. Data were subsequently extracted and summarized in narrative and tabular form. We found 76 cases of lead encephalopathy potentially associated with traditional medicine. Ayurvedic medicines were associated with 5 cases (7%), Middle eastern traditional medicines with 66 cases (87%) and 5 cases (7%) with other traditional medicines. Of the 76 cases, 5% were in adults and 95% were in infants and young children. Of the 4 adult cases, at least one was left with residual neurological impairment. In infants and young children, among 72 cases 8 (11%) were fatal, and at least 15 (21%) had residual neurological deficits. Traditional medicine users should be screened for lead exposure and strongly encouraged to discontinue metal-containing remedies. Therefore, the United States Food and Drug Administration and corresponding agencies in other countries should require and enforce heavy metal testing for all imported traditional medicines and "dietary supplements".

Keywords

Lead encephalopathy; traditional medicines; CAM; herbal medicines; folk medicine; herbal medicines

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Introduction

The World Health Organization's definition of traditional medicine encompasses health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied solely or in combination to treat, diagnose and prevent illnesses or maintain well-being [1]. Traditional medical systems have a unique and distinctly different set of beliefs and practices compared to western biomedicine related to pathophysiology, diagnosis, and therapeutics. In western countries, adaptations of traditional medicine are termed “Complementary and Alternative Medicine” (CAM). This paper uses the terminology “traditional medicine”.

Traditional medicine use is popular in all regions of the developing world and its use is rapidly increasing in the western world [1-4]. Traditional medicine is a vital yet often neglected part of healthcare in the developing world. At least two in three people in developing countries rely on traditional medicine, which offers them the most affordable and accessible form of primary health care [1]. Despite the popularity of traditional medicines, scientific research on safety and efficacy is limited. While some scientific evidence exists regarding their benefits, many key questions remain unanswered [5-7]. Are these therapies safe? Do they work for the diseases or medical conditions for which they are recommended? Also unregulated or inappropriate use of traditional medicines and practices can have negative or dangerous effects.

Well-designed scientific studies addressing these issues have only begun in the last 10-15 years. Although traditional medicines are widely considered to be safe, evidence from many countries on almost every continent suggests that unregulated use of heavy metals, especially lead, in traditional health practices may constitute a serious public health problem. Specifically, traditional health practices have become an important cause of lead poisoning. In this article, we focus on the most serious consequence of lead poisoning, encephalopathy, which is particularly concerning because of its potential to be fatal especially in infants and young children. As society becomes more globalized, it is imperative for pharmacists and health care providers to learn about the safety of traditional medical practices. The information presented educates and alerts pharmacists and other health care providers about the potential of traditional medicines to cause lead encephalopathy.

Lead Poisoning and Lead Encephalopathy

To better understand lead encephalopathy associated with traditional medicines, a brief update on lead toxicity is presented. Lead is a xenobiotic metal, and therefore, normal blood lead levels do not exist. Due to the worldwide use of lead in numerous products including paint, fuel and pipes, all persons have some detectable amount of lead in their bodies. Fortunately, the average blood lead levels in countries that have eliminated leaded gasoline have dropped sharply in recent years [8,9]. Currently, background blood lead levels in the U.S. are less than 5 µg/dL. Ideally, levels, should be below 10 µg/dL, especially for children in whom the U.S. Centers for Disease Control defines levels ≥ 10 µg/dL as poisoning. Clinical adult lead poisoning is usually defined as a blood lead level ≥ 40 µg/dL, however, numerous studies have demonstrated pathophysiologic changes below these respective levels in both adults and children [10,11]. Blood protoporphyrins are also useful as secondary diagnostic tools in lead toxicity because heme-based enzymes are impaired by lead. Protoporphyrin elevation lags behind the rise in blood lead; and after the cessation of exposure, protoporphyrin elevation takes longer to resolve. In general, free erythrocyte protoporphyrin (also measured as zinc protoporphyrin) reflects the last 6-8 weeks of exposures and normally is less than 35 µg/dL.

Lead is toxic to the hematopoietic, renal, reproductive, cardiovascular and peripheral and central nervous systems. Symptoms of lead toxicity in adults, if present, are non-specific and vary greatly among individuals and also with the chronicity of exposure. Symptoms in adults

may begin with blood levels as low as 40 µg/dL, but usually with levels exceeding 50-60 µg/dL. Common complaints include abdominal pain, arthralgia and myalgia. Significant anemia is usually a sign of more chronic poisoning. From a neurological perspective, the earliest symptoms of lead toxicity in adults include fatigue, headache, sleep disturbance, irritability, malaise and decreased libido. Frank adult lead encephalopathy is currently uncommon, and usually requires blood lead levels exceeding 150 µg/dL, but can occur with levels as low as 90-120 µg/dL. Children are at much greater risk for developing lead encephalopathy at lower lead levels (>70-90 µg/dL).

Clinically, lead encephalopathy can present in acute or chronic forms. In acute lead encephalopathy the patient presents with headache, vomiting, ataxia, convulsions, paralysis, stupor and coma [12,13]. In chronic lead encephalopathy, the patient presents with loss of memory, behavioral abnormalities, depression, ataxia, seizures, drowsiness, restlessness and loss of sensory perception [12,13]. Chronic neurocognitive signs can be observed at lower lead levels than those associated with frank encephalopathy. Chronic adult neurotoxicity is often marked by neurocognitive and neuropsychiatric effects such as irritability, malaise, decreased libido, and impairment of short- and long-term memory [14]. Children's greater sensitivity to lead is important with regard to chronic neurobehavioral effects such as subtle impairments in learning, IQ decrements, and worse outcomes on socio-behavioral endpoints [14,15]. Lead encephalopathy can be lethal, and among survivors it can result in severe neurological deficits.

With regard to traditional medicines, gastrointestinal absorption of lead is the relevant route. Under normal circumstances, the gut absorbs around 15 percent of ingested lead, but absorption is increased in children, pregnant women, and in the presence of deficiencies of iron, calcium or zinc. Once absorbed, lead is distributed widely throughout the body, where it exists in three major compartments or pools: blood, bone, and soft tissues. Lead also readily crosses the blood-brain barrier, and is transferred across the placenta and into breast milk. The half-life in blood is of the order of weeks, while in most soft tissues the half-life is measured in months. Bone is the major endogenous storage site of lead, with a half-life of 5–15 years. Excretion of lead is primarily renal.

Methods

Case reports of encephalopathy were located through systematic literature searches using MEDLINE, CINAHL, AMED, CISCOP, EMBASE and The Cochrane library from 1966 to the February 2007 using the terms – encephalopathy, traditional medicines, CAM, herbal medicines, folk medicine, herbal medicines. Reference lists of identified articles were reviewed as well as authors' own files. Inclusion criteria were human cases of lead encephalopathy associated with the use of traditional medicine, alternative or complementary medical practices. There were no restrictions regarding the language of publication. These data were subsequently extracted and summarized in narrative and tabular form.

Results

We identified 76 reported cases of lead encephalopathy associated with traditional health practices. Table 1 summarizes the results based on the type of traditional medicines and whether they are adult or pediatric cases. The vast majority of cases were infants and young children. Cases were associated with traditional medicines from Indian subcontinent, China, Middle East and Latin America. For each traditional medical system, a brief description and its potential to cause lead poisoning precedes the description of lead associated encephalopathy cases.

Lead Encephalopathy Associated With Traditional Medicines from Indian Subcontinent

a) Ayurveda is a traditional medical system that has been practiced primarily in the Indian subcontinent for more than 2000 years. Ayurveda utilizes diet, herbal remedies, and massage, emphasizing the use of body, mind, and spirit in disease prevention and treatment.

Approximately 80% of India's one billion population is estimated to currently use Ayurveda [16]. It is also used extensively elsewhere in the Indian subcontinent and among expatriate South Asian communities worldwide. Additionally, Ayurveda's popularity in western countries has increased. In the U.S., Ayurvedic remedies can be obtained from ethnic markets, Ayurvedic practitioners, health food stores, and the Internet.

Analytic studies have found metals in 30-65% of Ayurvedic products sold outside the United States [17,18], and 20% of those sold in Boston [19,20]. Most recently, Ayurvedic medicines containing toxic metals have been documented in the Chicago, Houston, New York and Canadian markets [21-23]. Over 80 cases of lead poisoning associated with use of Ayurvedic medicines (most without frank encephalopathy) have been described in the literature. In general, Ayurvedic-associated intoxications, compared to occupational lead poisoning, present after a longer period of exposure with higher blood lead levels and more hematopoietic toxicity (more basophilic stippling, lower hemoglobin and higher protoporphyrin levels) [24]. Of these more than 80 cases of lead poisoning at least five have resulted in encephalopathy. Four cases were recorded in adults and 1 case in a preterm infant. Of the four adult cases, all eventually developed anemia with basophilic stippling, and two were taking the same medication, *Mahayogaraj – gugul*. At least two recovered completely (Boxes 1,2) [25,26] and one had residual neurological impairments. This latter case was reported without clinical details in a case series of Ayurvedic lead poisonings by the U.S CDC [18]. He was evaluated and treated by one of the authors, and his neurological presentation and course are described below (Box 3).

Box 1

Ayurvedic Case Report from India [25]

Patient: 41 year old Asian Indian man with hypertension.

Presenting symptoms: Memory loss, anorexia, anhedonia

History of Medication: The patient was consuming ayurvedic medicines (mahayogaraj – gugul) for more than 6 months for his hypertension. The patient was not on any other prescription drugs and had no significant history of occupational or avocational lead exposure.

Clinical signs and symptoms: Memory loss, mild disorientation, weakness in the limbs with bilateral hypertonic and hyper reflexia, upgoing plantars and spastic gait.

Blood lead level: 161 µg/dL.

Blood film: Anemia with basophilic stippling

MR Imaging: Bilateral focal hyper intensities observed in parasagittal occipital lobes and similar lesions in temporal, parietal and frontal regions.

Diagnosis: Chronic Lead encephalopathy.

Therapy: Chelation therapy and discontinuation of Ayurvedic medicine.

Outcome: Patient recovered clinically and lesions on MR imaging resolved.

Box 2

Ayurvedic Case Report from New Zealand [26]

Patient: 51 year old New Zealand woman who recently returned from three year stay in India.

Presenting symptoms: Nausea, vomiting, abdominal pain and myalgia.

Past medical history: She had dengue fever and was taking Ayurvedic medicines for 10 months.

Clinical signs and symptoms: The patient was anemic and showed memory loss, disorientation, loss of sensory perception and tender abdomen.

Blood lead level: 69.3 µg/dL

Blood film: Normochromic anemia with prominent basophilic stippling.

Diagnosis: Chronic Lead encephalopathy.

Therapy: Discontinuation of Ayurvedic medicine.

Outcome: Patient clinically well and blood lead levels dropped to 20 µg/dL after 5 months.

Box 3

Adult Encephalopathy with Residual Impairment [18]

Patient: A 62 year old Asian Indian man with arthritis.

Presenting symptoms: Status epilepticus.

History of Medication: The patient was consuming ayurvedic medicines (Mahayogaraj – gugul) for more than 6 years for his arthritis. The patient was not on any other prescription drugs. occupational or a vocational lead exposures

Clinical signs and symptoms: Anemic patient in status epilepticus.

Blood lead level: 89 µg/dL FEP: 487 µg/dL

Blood film: anemia with prominent basophilic stippling.

Diagnosis: Acute and chronic Lead encephalopathy.

Therapy: He improved after multiple courses of chelation and chronic anti-convulsant therapy, but had residual anoxic brain damage due to periods of status epilepticus.

Box 4 highlights the dangers of lead-containing Ayurvedic medications in pregnant women [27]. The mother, a recent South Asian immigrant to Australia, had been using Ayurvedic medicines for years. An Ayurvedic doctor in India had prescribed the medicines for a gastrointestinal complaint. The mother was found to have a high blood level of lead (107 µg/dL) at 24 weeks gestation with normal blood film. At 30 weeks gestation she went into *status epilepticus* and delivered an infant with high blood levels of lead and congenital lead encephalopathy.

b) Ghasard: *Ghasard* is a traditional medicine commonly used by people from Indian subcontinent. It is a brown powder that is mixed in liquid and given to infants to ease digestion and prevent constipation. A case of death secondary to seizures from lead encephalopathy was reported in a 9-month-old boy following use of *Ghasard* [28]. The boy had been given several traditional medicines from the Indian subcontinent by his parents since age two months. At 8

months, the boy became less responsive, lethargic, stopped crawling, and refused bottle-feeding and developed tremors. At 9 months, the infant seized and shortly thereafter became apneic. The boy died two days later, and autopsy revealed severe lead poisoning with high lead concentrations in the blood and other tissues and lead lines observed on radiographs of long bone. All three medications given to the infant contained lead, with the highest concentration, 1.6% lead by weight, found in the *Ghasard* [28].

Box 4

Case Report in a Pregnant Woman from Australia and Preterm Infant Delivered by Her [27]

Patient: A 24 year old pregnant woman (at 30th week of gestation).

Presenting symptoms: Abdominal pain, disorientation, progressive confusional state culminating in seizures.

History of Medication: The patient is a recent immigrant from India to Australia and was consuming ayurvedic medicines periodically over the course of the past 9 yrs before this episode.

Clinical signs and symptoms: The patient showed progressive confusional state culminating in seizures.

Blood lead level: 107 µg/dL

Blood film: anemia with prominent basophilic stippling.

Diagnosis: Chronic Lead encephalopathy.

Therapy: Chelation and Discontinuation of ayurvedic medicine.

Outcome and findings in the infant: The patient was put on chelating therapy immediately and after 36hrs the woman had an ante- partum hemorrhage and after induction of labor she gave birth to a female baby by vaginal delivery.

Apgar scores were 4 and 6. The infant presented with signs and symptoms of bilateral diaphragmatic palsy and was intubated. The blood film showed Heinz bodies and lead concentration in cord blood was around 140 µg/dL and radiographs of the long bones showed an increase in the bone density adjacent to the metaphyses. The baby was chelated immediately and blood lead levels dropped. The baby had delayed milestones with peripheral weakness and bilateral wrist drop.

Lead Encephalopathy Associated With Traditional Middle Eastern Medicines and Health Practices

Many case reports and case series of lead encephalopathy have been reported in association with use of traditional Middle Eastern medicines and health practices. Documented case reports and series are described below.

“*Surma*” or “*kohl*” is a black lead-containing substance used in Middle Eastern countries and the Indian subcontinent, both as a teething powder (believed to produce strong gums and teeth) and as an eye cosmetic. It is also believed that application of *Surma* to the conjunctiva will help provide relief from the glare of the sun and has a role in strengthening the eyes.

Additionally, a popular custom is to apply *Surma* to children in order to protect them from being cursed by an “evil eye”. *Surma* preparations may contain up to 84% lead by weight [29]. In Kuwait, acute lead encephalopathy has been described following the use of *Surma* in 20 patients aged 1-18 months [30]. Their blood levels ranged from 60 to 257 µg/ dL. Two

patients died before starting treatment. Of the 18 patients who received chelation therapy, only 15 survived. Finally, at least four of the surviving patients had residual neurologic impairments.

“*Saoott*” or “*cebagin*” is another Middle Eastern traditional remedy used as a teething powder. Among six children with lead poisoning, two Saudi Arabian infants aged 10 and 12 months presented with acute lead encephalopathy. All of these children were reportedly prescribed *Saoott* by a traditional healer [31]. Analysis of *Saoott* demonstrated 51% lead content. Additionally, other local teething powders and eye cosmetics also contained lead, with the content ranging up to 88%.

“*Bint al dahab*” is an Iranian folk remedy made by grinding rock into a powder and mixing it with honey and butter. This remedy is given to newborn babies for colic and for the early passage of meconium after birth. Acute lead encephalopathy was reported in 25 Omani infants living in the UK. In 20 of these cases, the poisoning followed the ingestion of *bint al dahab* and in three others was associated with the ingestion of unknown traditional medications [32]. The patients ranged in age from 1 to 8 months and were hospitalized. At discharge from the hospital, 56% of these children continued to exhibit residual neurologic impairment.

In Dubai, United Arab Emirates (U.A.E.) 19 cases of acute lead encephalopathy all presenting with convulsions were reported following the use of various traditional remedies [33]. The median blood lead level of these infants was 75µg/dL. The mean age was less than four months and notably, 7 cases were encephalopathic even though they had blood lead levels less than 70 µg/ dL. Despite treatment, including chelation, 13 infants remained neurologically impaired. In addition to *Surma*, other local practices found to be associated with lead poisoning and encephalopathies were *Santrinj* and *Bokhoor*. *Santrinj* is an amorphous red powder containing 98% lead oxide. Although used principally as a paint primer for metallic surfaces in Saudi Arabia and other Middle Eastern countries, it is also a home remedy for abscesses (“gum boils”) and teething. *Bokhoor*, on the other hand, is another traditional Middle Eastern practice where wood and lead sulphides are burnt to produce pleasant fumes to calm infants.

Lead Encephalopathy Associated With Traditional Latin American Medicines

Azarcon is a bright orange powder which is about 95% lead. *Greta* is a yellowish powder with similar lead content and is obtained through pottery suppliers. Both are commonly used in Latin American communities for treating ‘*empacho*’ or constipation. The belief is that the powders relieve obstruction of the gastrointestinal tract. Various cases of lead poisoning have been associated with these medications, including acute encephalopathy. In 1982, two siblings who were treated with *azarcon* in Mexico developed lead poisoning. The children subsequently presented to a San Diego hospital. The 15 month old infant had a blood lead level of 124 µg/ dL, while the 3 year old sibling died due to seizures [34-38].

Lead Encephalopathy Associated With Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is an ancient system of health care from China including herbal and nutritional therapy, acupuncture, massage, restorative physical exercises, and meditation. TCM practitioners use several different methods to classify traditional Chinese herbs: “The Four Natures”; “The Five Tastes”, and “The Meridians” [39-41]. Chinese traditional medicines are mixtures of herbs using standardized formulas and are manufactured both within and outside China.

Many Chinese traditional medicines have been tested and found to contain unacceptable concentrations of heavy metals, primarily mercury, lead, and arsenic [42,43]. Accordingly, numerous case reports and case series of lead poisoning have been associated with the use of these medicines. Yu *et al.* report a case of lead encephalopathy associated with use of herbal

medicine [44]. As most of the Chinese herbal medicines are mixtures of different herbs, associating a single herb with encephalopathy is not easy. However pharmacists and health care providers should be alert to the use of commonly used herbs which have potential to cause lead poisoning and possible encephalopathy. The herbal medicines implicated in known cases of lead poisoning are *Ba-Baw San* and *PO Ying Tan*.

Ba- Baw san is a commonly used Chinese herbal medicine for colic and pacifying young children. Cheng *et al* reported cases of lead exposure and poisoning associated with its use in young children [45]. The possible source of contamination is the unregulated use of lead and other heavy metals in the preparation of the medicine. An additional case of acute lead poisoning presenting with altered sensorium and high blood levels was reported in a 4-month-old infant who was taking several Chinese herbal medicines [46]. The analyses of 11 brands of these Chinese herbal medicines by flameless atomic absorption spectrophotometry revealed that one of the medicines, *Po Ying Tan*, had a mean lead content of 7.5 mg per unit dose [46].

Discussion

This article presents evidence from case reports and case series that lead poisoning and specifically, lead encephalopathy can result from the use of a wide variety of traditional remedies of diverse geographic and cultural origin. Additionally, documented fatalities and permanent deficits occurred among a subset of these cases. While the actual incidence of lead encephalopathy caused by traditional medicines is unknown, the results of the review provide significant insights about traditional medicine causes of lead encephalopathy. There are several distinct reasons for the presence of lead in certain traditional medicines. They include environmental contamination of medicinal herbs and plants, contamination during manufacturing and/or packaging, and the deliberate inclusion of lead as an ingredient. The latter has at least two explanations. First, systems like Ayurveda believe in that metals have a therapeutic role. Second, others may add lead to increase the weight of the product prior to sale.

Of the 76 cases, 72 (95%) occurred in infants and young children. Of the 4 adult cases, at least one was left with residual neurological impairment. Among the affected infants and young children, 8 cases (11%) were fatal, and at least 15 others (21%) had residual neurological deficits. The fact that children were affected more frequently and more severely than adults is not surprising given children's greater susceptibility to lead, and their lower threshold for the development of encephalopathy. For example, the incomplete development of the blood- brain barrier most likely results in a greater distribution of lead to the brain in young children. Additionally, for nutritional and developmental reasons, children also absorb a higher proportion of ingested lead. Epidemiological studies of traditional medicine use and lead toxicity in the United States and abroad are warranted, and should prioritize children and pregnant women.

The reports of lead encephalopathy identified and presented here are likely to be only the “tip of the iceberg” for several reasons. These cases are a subset of the much larger universe of reported lead poisonings due to traditional medicines that cause intoxication, but did not result in frank encephalopathy. Secondly, many of cases of possible lead encephalopathy related to traditional medicine use are never reported for the following reasons:

1. Relatively few clinicians are familiar with traditional medicines and health practices.
2. Patients are usually unaware that they are being exposed to metals or other toxins.
3. The signs and symptoms of lead encephalopathy are often non-specific.

4. Patients often do not discuss with their clinicians the use of traditional medicines and clinicians rarely ask their patients about this information.

There are multiple reasons why traditional medicine use may not be disclosed to clinicians. (Box 5) [47]. By understanding and breaking down these communication barriers, providers can better ascertain their patients' traditional medicine use. When herbal remedy use has been established, there are several extensive, evidence-based resources on the efficacy, safety, pharmacodynamics, mechanism of action, adverse effects, and potential drug-herb interactions (Box 6).

Box 5

Most Common Reasons Cited by Patients for Not Revealing Their CAM Use to Medical Practitioners

Their doctor never asked them about it.

It wasn't important for their doctor to know.

It was none of their doctor's business.

Their doctor would not understand.

Their doctor would disapprove.

Their doctor would discourage them.

Their doctor might not continue as their provider.

Adapted from Eisenberg [47].

Box 6

Sources of Information About Herbal Medicines

- Natural Standard (www.naturalstandard.com)
- Natural Medicines Comprehensive Database (www.naturalmedicines.com)
- Consumer Labs (www.consumerlab.com)
- NCCAM website (nccam.nih.gov)
- Cochrane Database Reviews
- CAM on PubMed
- UpToDate.

We believe our findings have several implications for clinicians and public health officials. Clinicians evaluating and treating patients with encephalopathy should consider lead poisoning from traditional medicine use in the differential diagnosis. A thorough history of herbal and supplement use should be taken at the same time as the standard medication history. A history of herbal medicine intake should be aggressively pursued in the setting of unexplained neurologic complaints and blood lead testing should be done promptly. Users of traditional health practices should be screened for lead exposure and strongly encouraged to discontinue metal-containing remedies. Additionally, regarding broader prevention efforts, public health and community organizations should consider issuing advisories to users of potentially harmful traditional remedies, encouraging them to consult their physicians about lead screening. Finally, the United States Food and Drug Administration and corresponding agencies in other countries should require and enforce heavy metal testing for all exported and imported

traditional medicines. The new FDA guidelines regulating the quality of dietary supplements [48] is a welcome step in this direction and should encourage regulatory authorities in other countries to formulate rules and enforce them.

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Table 1
Cases of Lead Encephalopathy Associated with Traditional Medicines by Type of Medication

Traditional Medical System	Cases of Lead Encephalopathy N (%)	N (%) Pediatric Cases within CAM System or Medication
Ayurveda	5 (7%)	1 (20%)
Ghasard	1 (1 %)	1 (100%)
Traditional Middle Eastern Practices	66 (87%)	66 (100%)
Azarcon and Greta	2 (3%)	2 (100%)
Traditional Chinese Medicine	2 (3%)	2 (100%)
Total	76 (100%)	72 (95%)