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Understanding Safety and Adverse Drug Events in Homeopathy: A Fair and Balanced Approach

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EDUCATIONAL OBJECTIVES

At the completion of this activity, the participant will be able to:

- Examine homeopathic principles and the FDA's risk-based regulations for homeopathic products
- Compare common homeopathic products, the symptoms for which they are used, and the likelihood of an adverse drug event based on dilutions
- Analyze Poison Control Center data to assess the safety of homeopathic products
- Identify appropriate uses and counseling points for homeopathic products

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Introduction

In the United States, "wellness" is a multitrillion-dollar industry.[1] The wellness industry encompasses alternative therapies such as specialized diets, complementary and alternative medicines, and homeopathy. Patients who are dissatisfied with their treatment or disenfranchised with the medical system often look elsewhere for solutions. Health care providers (HCPs) often worry that when people choose wellness products, they may gravitate away from evidence-based treatments.[1,2] Patients sometimes ask pharmacists questions about wellness products including homeopathy. Many pharmacists lack training in wellness approaches in general and homeopathy specifically, and cannot speak to safety or efficacy. This continuing education activity introduces homeopathy with an emphasis on safety.

The homeopathic product market has grown in the past 20 years. In 2018, American consumers spent $437 million on homeopathic products, with cold and flu ($174 million), pain relief ($85 million), and children's medicine ($87 million) the top sellers.[3,4] But HCPs frequently lack knowledge about homeopathy.[5] Homeopathy advocates cite its lack of adverse events (AEs), patient-centered approach, and low cost as reasons for its popularity. Critics say homeopathy is quackery that has no basis in science.[2] Which is it? Homeopathy—a system of traditional medicine that is recognized by the World Health Organization (WHO) and a distinct pharmacopeia in the United States—differs from conventional medicine significantly. Exploration of homeopathy's principles can help pharmacists assess its safety and efficacy and counsel patients knowledgably. TABLE 1 lists 11 commonly used homeopathic products.[2,6]

STAR*

If a patient asks you to explain homeopathy, what would you say?

***S = Stop; T = Think; A = Assess; R = Review**

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TABLE 1. COMMON HOMEOPATHIC PRODUCTS[2,6]

Homeopathic product	Typical target condition or symptom(s)
Allium cepa (onion)	Common cold and hay fever, especially when there is a thin, watery, and burning nasal discharge
Arnica (mountain daisy)	Orally: Shock and trauma from injury, pain, healing acceleration Topical gels, ointment, or spray: sprains, strains bruising on unbroken skin
Calendula (marigold)	Topical: Burn relief
Chamomilla (chamomile)	Irritability in infants, especially from teething or colic
Hypericum (St John's wort)	Injuries to the nerves or to highly enervated parts of the body (eg, fingers, toes, and back); shooting pain
Ignatia (St Ignatius bean)	Acute grief, anxiety, and depression
Magnesia phosphorica (phosphate of magnesia)	Cramps, including menstrual cramps
Nux vomica (poison nut)	Ailments exacerbated by conventional or recreational drugs; symptoms of overeating or from drinking too much alcohol
Pulsatilla (windflower)	A specific pattern of physical symptoms and psychological characteristics (warm-blooded tendencies, dislike of heat, quickly changing emotional state, and a strong tendency to want to please others)
Rhus tox (poison ivy)	Sprains and strains; flu or arthritis in people who experience rusty gate syndrome (pain when they start to move that improves over time)

The Basics of Homeopathic Medicine

The term "homeopathy" melds the Greek words "homoion" (similar) and "pathos" (disease). Homeopathy's advocates embrace 3 principles:

- The Law of Similars (also called, "like cures like")
- Minimum dose
- Single remedy

Homeopathic practitioners use infinitesimal doses of substances that in large doses would be toxic to stimulate a person's own healing responses. They propose that using infinitesimal quantities avoids undesirable AEs.[7]

Homeopathy emanated from German doctor Samuel Hahnemann's (1745–1843) observation that consuming Peruvian cinchona tree bark induced malaria-like symptoms but also cured malaria.[8] He extrapolated that observation to other substances and conditions. He concluded that animal, mineral, or plant substances that cause a particular symptom in healthy people would cure the same symptoms when administered in homeopathic doses and forms to ill people exhibiting those symptoms.[8] Accordingly, all homeopathic medicines are derived from natural animal, mineral, or plant substances and prepared using serial dilutions and precise succussions (vigorous shaking with directional strikes).[7]

Homeopathy was popular in the United States in the 19th century. By 1900, 22 homeopathic medical schools had produced more than 1000 homeopathic practitioners. The United States was also home to 100 homeopathic hospitals.[9] In the subsequent decades, practice of homeopathy dwindled and the majority of homeopathic colleges and hospitals disappeared by 1910. The last homeopathic hospital closed in the 1950s. Interest in homeopathy reignited in the 1970s, although fewer than 100 homeopathic practitioners (often called homeopaths) remained active at that time. In the next 10 years, that number grew to more than 1000.[10,11]

Enactment of the Food, Drug, and Cosmetic Act (FD&C Act) in 1938 was a defining moment in medical history, establishing a requirement for the Food and Drug Administration (FDA) to approve all new drugs before they could be marketed; manufacturers had to prove each drug's safety before marketing it. It also prohibited false therapeutic claims for drugs.[12] Additional statutes gave the FDA jurisdiction over drug labeling and the Federal Trade Commission (FTC) jurisdiction over drug advertising.[13] An amendment to the FD&C Act in 1962 transferred authority for prescription drug advertising to the FDA. The FTC retained oversight of OTC drug and supplement advertising. Homeopathic drugs occupy a unique place in the regulatory framework: homeopathic products can make a therapeutic claim.[14] However, these drugs are not subject to the same level of premarket scrutiny by the FDA as conventional drugs (referred to as allopathic drugs by homeopaths, meaning they bear no connection to the nature of the symptoms they target).

Homeopathic drugs are listed in a pharmacopoeia all its own. Homeopathic monographs in the *Homœopathic Pharmacopœia*

of the United States (HPUS) delineate the exact steps necessary to prepare homeopathic products. The HPUS describes 2 types of dilution[15]:

- X dilutions: The original substance (1 part) is diluted with liquid (9 parts), providing a tincture with a 1 to 10 dilution, or 1X. The manufacturer repeats the process, diluting the 1X tincture with 9 parts of liquid and creating a more dilute tincture with a higher decimal designation (factor of 10) with each successive dilution (eg, 2X, 3X).
- C dilutions: The process begins by taking 1 part of the original substance and adding it to 99 parts diluent (water or alcohol), followed by succussion, which creates the 2C potency; then, 1 part of 2C is added to 99 parts diluents to make 3C. This process continues to make the common C-potencies stocked in community pharmacy practice: 6C, 9C, 15C, and 30C.

Manufacturers use various liquids for dilution, most often water, ethanol, or a water/ethanol mixture. If substances are insoluble, they triturate (crush or grind the substance) into a solid, usually lactose. They also use lactose for most solid remedies, spraying dried globuli (balls made of sugar) with the final liquid dilution and leaving it to dry. The HPUS indicates the globuli should range in size from 8 mm to 80 mm.[16]

The Homœopathic Pharmacopœia Convention of the United States (HPCUS) evaluates substances for inclusion in the HPUS (among other things). This group bases safe concentrations of commercially available products using toxicity data from available literature. They consider accidental ingestion of 30 mL or 16.2 grams of the substance by a 10-kg child. It is then translated into the equivalent dilution for that concentration. Then HPCUS increases the margin of safety by making the first safe OTC dilution 100 times less dilute than the lowest calculated concentration at which AEs might occur in a 10-kg child.[17]

HPUS defines standards for uniform product manufacturing, testing, and processing. Substances must meet 3 criteria to be included in the HPUS:

- The HPCUS has determined the drug to be safe and effective.
- The drug must be prepared according to the specifications of the General Pharmacy and relevant sections of the HPUS.
- The submitted documentation must be in an approved format as set forth in the relevant sections of the HPUS.
- Further criteria include references to the homeopathic substance's therapeutic effects.[16]

All homeopathic products are labeled in a standard way. For OTC products, the "Drug Facts" section on the label lists the ingredients (using the Latin binomial, the 2-term naming system that classifies species) and dilutions (eg, 6X, 6C, 30X, 30C). Homeopathic practitioners use low dilutions, such as 6X or 6C, for local symptoms and high dilutions, such as 30X or 30C, for generalized symptoms. To pharmacists trained in traditional medicine (allopathy), homeopathic dilution is counterintuitive because these substances are diluted beyond Avogadro's number (the dilution at which traditional chemists indicate no molecular trace of the original substance is present).[18] Homeopathy's advocates allege that if homeopathic products were only diluted at each step, skeptics would be justified in asserting that they cannot possibly work. They hypothesize that the succussion's impacted strikes at each step create nanoparticles that are the active principle.[18] Advocates' hypothesis is that using low-dose dilution and matching the medicine to the symptoms stimulates the body's own adaptive response. The infinitesimal amount of diluted active ingredient decreases the likelihood of AEs. Homeopaths indicate that in dilutions above 4C or 8X, the original substance's toxic properties have disappeared.[19]

Common Misconceptions

Patients may ask pharmacists for "something homeopathic for…" Often, patients mean that they are looking for natural or nonpharmaceutical products because they may erroneously believe that "homeopathic" is synonymous with natural or drug-free.[2] Homeopathy differs from herbal medicine, nutrition, vitamin therapy, or other forms of complementary and alternative medicines (CAM). The FDA and the FTC define homeopathy specifically according to the HPUS and the definition has specific repercussions in terms of regulatory oversight and advertising.

In the United States, the FDA distinguishes between official HPUS-listed ingredients and nonofficial ingredients. To be eligible for HPUS status, the product must be proven safe, effective, and prepared using HPUS standards. Homeopathic products can be over the counter (OTC) or prescription, depending on the target condition or the ingredient. Although homeopathic products must be manufactured using good manufacturing practices in the United States, they are not held to the rules for expiration dating, tablet imprinting, and determining identity of the product and strength. However, manufacturers must document stability data by assessing compatibility of ingredients and excipients and possible disintegration over a reasonable time period.[21] In 2016, the FTC issued a policy statement that they will enforce regulations related to OTC homeopathic prod-

PATIENT CASE 1

A patient approaches pharmacist Meghan with a bottle of cough syrup and asks if it is homeopathic. Meghan is about to say no, but hesitates, remembering that many people confuse the term "homeopathic" with "natural." She asks the patient, "What do you mean by "homeopathic?" The patient says that she is looking for something natural in it because she is pregnant. Meghan explains that the 2 terms are not synonymous, and explains how homeopathic products are made. She takes advantage of the opportunity to ask the patient to describe her symptoms. She follows the general process described in the *Handbook of Nonprescription Drugs*,[20] and asks:

- What specific symptoms the patient is experiencing
- How long she has had the symptoms
- The specific type of cough

She also screens for exclusions to self-treatment. In her discussion with the patient, Meghan learns that the cough is mild and most likely self-limiting, and that the patient is adamant that she needs "something" for her cough. Meghan shows the patient several products that are suitable for her cough. She also shows her how to find the National Drug Code (NDC) number indicating which products are homeopathic.

ucts more strictly to back up claims with scientific evidence. It clarified its stance in 2017. The FTC will also hold efficacy and safety claims for homeopathic products to the same standard as other products with the same claims.[22]

Understanding Homeopathy

Pharmacies and other brickfront and online stores carry a large array of OTC therapies, including homeopathic products. In 2012 (most recent data available), an estimated 5 million adults and 1 million children used homeopathic products in the United States.[23] Many pharmacies stock homeopathic products; therefore, pharmacists need information about them but are unlikely to have acquired such knowledge in formal education. Pharmacists can educate patients about homeopathic preparations' strengths and limitations. For example, patients should only use homeopathic products for minor, self-limiting conditions—never for serious or severe conditions.[24] Pharmacists need to know that mislabeling is a problem that confuses consumers and increases risk. They also need to examine data from poison control centers.

Numerous medical societies, health care agencies, and scientific bodies have denounced homeopathy as ineffective. In the United States, most federal websites that discuss homeopathy—including the National Institutes of Health's National Center for Complementary and Integrative Medicine—indicate little evidence supports homeopathy as an effective treatment for any specific health condition.[23] The California-based National Council Against Health Fraud has issued a position paper urging consumers not to purchase homeopathic products.[25] Globally, the Australian government has been perhaps the most aggressive in its condemnation of homeopathy, and has issued a statement indicating that after careful assessment, they could not find any health conditions for which reliable evidence of homeopathy's effectiveness exists.[26]

TABLE 2. REASONS CONSUMERS MAY SELECT CAM[27]

Conventional medication was ineffective
CAM allows consumers to be more actively involved in their health
Conventional treatments had unpleasant side effects
CAM emphasizes treating the whole person
Medical doctors communicated poorly, and desperation
Desperation; will try anything

CAM, complementary and alternative medicines.

It is difficult to establish precisely why patients choose homeopathic products, as few studies have addressed this question. One study examined 6 motivations for employing CAM, which are listed in TABLE 2.[27] It found that more than 50% of study participants concurred with all of these reasons, except "doctors communicated poorly" (40.1% concurred with this statement). The 2 top reasons were that CAM allows consumers to be more actively involved in their health and CAM emphasizes treating the whole person. It is probable that patients select homeopathy for the same reasons, embracing the idea that the body is able to heal itself using a nonspecific adaptive response.[2,27]

Homeopathic medicines' low cost and safety record may also be motivators. These products are comparatively inexpensive and generally regarded as safe. Additionally, numerous manufacturers and vendors including online outlets have encouraged use of homeopathic products. Unfortunately, not all manufacturers produce high-quality, adequately labeled products that conform to established industry guidelines.[28]

Safety of Homeopathy and Potential AEs

Safety of homeopathic products is of great interest, as safety is one of its primary and well-advertised selling points. Use of homeopathy is much more common in Europe, especially in Germany and France. Researchers in Germany examined that country's national health care database to study homeopathic remedies given orally and administered by subcutaneous injection (a method commonly employed in Europe but

TABLE 3. HOMEOPATHIC REMEDIES THAT CARRY PRECAUTIONS[14,34-36]

Homeopathic remedy	Source	Precaution
Apis mellifica	Venom of the common honeybee or a tincture made from the whole bee	Should be avoided by people who are allergic to beestings.
Arnica montana	Ragweed	Should be applied to intact skin to avoid absorption through open sores or broken skin. People who are allergic to ragweed and related plants should avoid arnica because it may precipitate an allergic reaction.
Homeopathic topicals	Various	Should be applied to intact skin to avoid absorption through open sores or broken skin.
Nux vomica	Nux vomica tree (*strychnos nux vomica*)	Contains the competitive glycine receptor antagonist strychnine, which causes muscular convulsions when undiluted. Taking nux vomica for longer than a week or in high amounts (30 milligrams or more) can cause severe adverse effects. Strictly contraindicated in people who are pregnant, breast-feeding, or have liver disease.

rarely used in the United States). They found 486 reports of adverse reactions with 46 classified as serious among the 303 million doses administered; 27% were related to the delivery method (eg, redness and swelling at the injection site).[29]

One patient population that often needs OTC relief but may not be able to take conventional medication is pregnant women. Ethics guidelines prevent researchers from conducting randomized, controlled studies in pregnant women, so no safety research exists. The French use homeopathy often and 94.5% of France's pharmacists report, based on experience, they would recommend use in pregnant women.[30]

Academic and public health researchers from Florence, Italy, who were interested in integrating complementary medicine into mainstream medicine reviewed data from 1970 to 1995.[31] They associated homeopathic medicines with a higher incidence of AEs than placebo. However, most effects were mild and transient. The researchers concluded that homeopathic drugs recommended by homeopathic specialists were safe. They stated, "because minimum doses are used (in homeopathic medicines), they could also be suitable for pregnant women, newborns and children." They warned that risk was highest when patients failed to switch from homeopathic cures to traditional medicine when necessary.[31]

No medication or remedy is completely safe for all patients all the time. Homeopathic advocates indicate that they administer infinitesimal homeopathic doses, which minimizes the risk of AEs.[31] The Consumer Healthcare Products Association—a national trade association representing leading manufacturers and marketers of OTC medicines, dietary supplements, and consumer medical devices—indicates that homeopathic medicines are considered safe for use in adults and children based on the presence of infinitesimal amounts of active ingredients.[32,33] Returning to our introductory sentence—that no medication or remedy is completely safe for all patients all the time—pharmacists need to remember that homeopathic remedies cross the line to "unsafe" when patients use them for anything but mild, self-limiting conditions.

The WHO reports that homeopathic remedies rarely cause AEs, especially when they are produced using good manufacturing practices, have concurrent quality assurance monitoring, and are labeled appropriately.[5] A 2009 WHO technical document, *Safety Issues in the Preparation of Homeopathic Medicines (2009),* indicates that many people believe homeopathic remedies are benign and present no major safety concerns based on their very high dilutions (ie, undetectable or unquantifiable concentrations in final products), and notes that not all homeopathic products are dilute.[5] Production aberrations could create potential safety hazards, as could use of compromised materials. Source materials include minerals, plants, insects, fungi, bacteria, viruses, and animal tissues. Diluting source materials that are impure or contaminated (or adulterated)—even at concentrations that exceed Avogadro's number—could potentially introduce contamination and compromise safety.[5]

It is critical to differentiate dietary supplements from homeopathic medicines because they are often mistaken for each other. Consumers need to read and follow homeopathic product label instructions. As homeopathic medicines can be purchased OTC, accurate and understandable labeling is crucial. Vulnerable populations (eg, older adults, pregnant women, children, and immunocompromised individuals) and consumers who need serious acute or chronic medical care need consultation and referral to a conventional health care provider.

TABLE 3[14,34-36] lists certain homeopathic remedies that carry precautions despite their extreme dilution. Pharmacists should also note that solid oral dosage forms often contain lactose, and may be contraindicated in lactose-intolerant individuals.[2]

PATIENT CASE 2

Joe Dearborne is a 64-year-old man with longstanding hypertension and diabetes. Despite his complete adherence to his medications, he continues to have periodically elevated blood pressure readings. He has a terrible cold, and he says he started taking a homeopathic product that his daughter picked up for him last week. He says that the product is "itty-bitty" pellets that come in a small blue tube. He has been taking the remedy for 3 days, and he says that starting on the second day, he developed gastrointestinal discomfort. He wants to know if it is from the homeopathic product.

Meghan starts her question by asking if he has any allergies. He says that he had a rash at one point from lisinopril. She asks if he is allergic to anything else. He says, "You mean like beesting and milk?" She says, "Yes, exactly." He reveals that he is allergic to both. Meghan educates him that many solid homeopathic dosage forms are made with lactose, and it is probable that is what is causing his problem. They discuss alternative options to provide some relief.

Homeopathic remedies are no substitute for appropriate, evidence-based medical care. The *New England Journal of Medicine* noted a specific concern about uptake of homeopathy: some patients may rely on inert homeopathic remedies when conventional treatments would be more effective. The author cited an incident in which an ostensibly homeopathic nasal spray contained high doses of zinc gluconate. The word "ostensibly" applies here because the product, although labeled as a homeopathic product, did not meet the exact definition of homeopathy. Its intranasal use was linked to anosmia (loss of smell) that could be permanent, resulting in its removal from the market.[14]

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★ What are homeopathic aggravations, and when might symptoms suggest referral to a traditional health care provider?

Aggravations

When discussing the safety of homeopathic remedies, it is critical to understand "aggravations." The very idea of "like cures like" means that the remedy can cause the symptoms. Homeopaths allege that when they administer a remedy that works, symptoms may worsen for a few hours to a few days. This is called "aggravation," and practicing homeopaths also refer to it as "artificial disease" that activates the body's own healing processes. In most cases, the aggravation is unnoticeable, but homeopaths estimate that roughly 25% of patients will experience perceptible symptoms.[2,37]

Homeopaths contend that people unfamiliar with homeopathy may misconstrue aggravations to be AEs. Generally, if original symptoms worsen slightly and then resolve, homeopaths will call it an aggravation. Different or severe symptoms may indicate an AE. A systematic review attempted to quantify and validate aggravations.[37] The review looked at 24 trials of homeopathic products and determined that aggravations were rare, with patients treated with placebo or homeopathic remedies experiencing similar rates of aggravation (50 vs 63, respectively). The authors report that they could find no definitive evidence that homeopathic aggravations exist.[37]

A 2016 meta-analysis attempted to distinguish between and establish rates of AEs and aggravations associated with homeopathic remedies.[38] These statisticians included 41 randomized controlled trials (N = 6055); 28 trials reported AEs, and 5 trials reported aggravations. They used the Common Terminology Criteria for Adverse Effects to approximate AEs, and found that 68% of AEs were mild (grade 1), 25% were moderate (grade 2), and 6% were severe or medically significant (grade 3). (Note that no grade 4 [life-threatening] or grade 5 [lethal] events were reported.) Using the same scale, they classified homeopathic aggravations as mild in 98% of reports and significant or severe in 2% (all severe asthma attacks). AEs and aggravations were associated with both complex (containing more than 1 homeopathic constituent) and single remedies of low and high dilutions. Findings from this meta-analysis suggest that patients treated with homeopathy and placebo or conventional medicine experience AEs at similar rates. The study limitations acknowledge that homeopaths may have underreported AEs based on the belief that homeopathy is natural and does not cause AEs. The heterogeneity between studies and lack of standard reporting procedures and terminology used to describe "harm" complicated the analysis.[38]

A 2017 systematic review included 54 studies examining homeopathic products with concentrations higher than 11X (because a 12X serial dilution of 1:100 starting solution is regarded as equivalent to the "Avogadro limit" for molecular detection).[39] Results showed a small, statistically significant, effect of non-individualized homeopathic treatment. The analysts indicated the finding was not robust to sensitivity analysis when they restricted data to 3 trials that presented the most reliable evidence.[39]

Another group of analysts re-examined the data, excluding

all studies that failed to report AEs numerically and another study that examined a questionable homeopathic intervention.[40] They reviewed data from 1528 patients. Their results indicated 795 patients receiving homeopathic treatment reported 75 AEs (9.4%). For comparison, 733 patients receiving placebo reported 73 AEs (10%). The frequency of adverse reactions between homeopathic treatment and placebo treatment was similar.[40]

Homeopathy-Related AEs

In recent years, the FDA has publicized results of several events associated with homeopathic products. Reports of possible belladonna toxicity from teething tablets surfaced in 2016, prompting the FDA to issue a warning letter to the manufacturer.[41] Reports indicated that children taking the product had developed symptoms consistent with toxicity from belladonna (also called deadly nightshade, a substance that contains the anticholinergic atropine). The FDA inspected the manufacturer's laboratories and tested its products. It found detectable amounts of belladonna alkaloids in select bottles of teething product that exceeded the label claim of a 12X dilution significantly.[41] At a 12X dilution, even the FDA's highly sensitive testing methods should not have detected any belladonna.[41] The bottles also contained variable and inconsistent amounts of caffeine and scopolamine[41-43]:

- Atropine undetectable to 50-1100 nanograms (0.00005 mg-0.00011 mg)
- Caffeine undetectable to 1-5.7 nanograms (0.000001 mg-0.0000057 mg)
- Scopolamine undetectable to 0.1-53 nanograms (0.0000001 mg-0.000053 mg)

Inconsistent levels of belladonna were attributed to a faulty manufacturing process. The agency's letter to consumers further warned that "homeopathic teething tablets containing belladonna pose an unnecessary risk to infants and children and [the FDA] urges consumers not to use these products…" The manufacturer issued a voluntary national recall of all its homeopathic teething tablets and gel.[44,45]

Anyone can report adverse reactions or quality problems to MedWatch, the FDA Safety Information and Adverse Event Reporting Program, online, or by mail or fax. The FDA Adverse Event Reporting System (FAERS) is an interactive database that aggregates the raw data obtained from the reporting individual's information. The system has some limitations (eg, reports are not verified by medical personnel, may be duplicates or incomplete, and do not establish causation).[46] Additionally, the definition of homeopathics in FAERS is inexact and may include some CAM products. A search for "homeopathics" in the FAERS database public dashboard on October 17, 2020, revealed 1428 total reports filed since 1998; in that same time frame, the total number of reports for all products was 20,292,362. Of the 1428 associated with homeopathy, 1156 were reported as serious, with 38 reports of death.[46] It is notable that in 2016, individuals filed 276 reports, with 77% associated with the baby teething product discussed above and 1 death (unconfirmed) in an infant associated with that product. When using this site, it is impossible to retrieve case specifics and again, reports have not been review by medical experts or sorted for duplicates.

The 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System indicates that calls concerning potential poisonous exposures to homeopathic products are rare. It reports the following figures[47]:

- Of all human exposures reported in 2018, dietary supplements, herbals, and homeopathic products collectively represented 2.68% of the 2,541,958 reports.
- Dietary supplements, herbals, and homeopathic products collectively represented 4.16% of pediatric exposures.
- Homeopathic products were not associated with fatalities.

A total of 7883 (0.3%) reports mentioned homeopathic products specifically (an additional 1968 reports mentioned either a dietary supplement or homeopathic product that was unknown).[47]

Poison Control Centers employ pharmacists and physicians to write potential poison exposure guidelines. These health care providers constantly add products to the database. Toxicologists develop and review proposed algorithms, which undergo strict peer review. They will recommend 1 of 3 actions: stay home, call or visit a primary care provider, or go to the emergency department immediately. Poison Control Centers (1-800-222-1222) are available 24 hours a day and they have recently developed an app (triage.webpoisoncontrol.org/#!/exclusions) that lets people start the screening process online; it also allows people to try the app and see how it works.[48] The American Association of Poison Control Centers coordinates the nation's 55 poison centers. These centers offer free, confidential, expert medical advice. PoisonHelp.org is an online primary resource and helps reduce costly hospital visits through in-home treatment. Individuals can text "POISON" to 797979 to save the poison control contact information in a smartphone.[49]

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★ What are some reasons why a manufacturer might want to include the word "homeopathic" on a product's label?

Regulations in Homeopathy

The regulatory process for homeopathy was reviewed earlier but some products use the term homeopathic when they should not. Regulation of homeopathic medications differs from regulation of legend (prescription) drugs and OTC products. The FDA provides oversight for herbs, supplements, and vitamins. Companies that manufacture these products do not need FDA approval to market them but they cannot make specific medical claims under the Dietary Supplement Health and Education Act of 1994. They must adhere to good manufacturing practices employing reliable processes that meet quality standards. The FDA monitors dietary supplements after they are marketed. If the FDA finds a product to be unsafe, it can take action (ie, penalize the manufacturer or distributor, issue a warning, or recall the product).[50]

PATIENT CASE 3

Lisa is a middle-aged woman who comes to the pharmacy with a brown bag full of her mother Eloise's medications, including her supplements and all of her OTC products. She asks Meghan to review all of them. She says that Eloise has been declining mentally lately and she thinks that she may have overdosed on one of these products. She is particularly concerned about 2 products: an herbal supplement that her mother started last week to improve cognition and a homeopathic product that her mother takes periodically for pain. Although she suspects these 2 products, she says that she is stopping all medication, including her mother's antihypertensives, inhalers for chronic obstructive pulmonary disease, and secondary prevention for breast cancer.

Meghan starts the process by separating the medications into prescription medications, OTC medications, herbals, and homeopathic products. She also reviews Eloise's fill/refill history and sees that she has not had her inhaler filled as often as she should have. She suspects that undertreated COPD is probably affecting Eloise's cognition. She also accesses the American Association of Poison Control Centers' new app with Lisa, and they start the screening process. Ultimately, they connect with a poison control pharmacist and learn that neither the herbal nor the homeopathic product have been associated with reports of declining cognition.

Meghan and Lisa agree that (1) Eloise needs better supervision of her medicine, especially her inhaler and (2) Eloise needs to be seen at her pulmonologist's office for reassessment. They decide to meet again with Eloise present after she sees the pulmonologist. At that meeting, Meghan will help her organize her medication, review inhaler technique, and look for ways to simplify her medication regimen.

For true homeopathic products, the FDA enforces criteria promulgated by the HPUS. Again, homeopathy's oversight process dates to the 1938 FD&C Act, which regulates homeopathy as a form of OTC medicine (with a very few prescription-only exceptions).[20] The HPUS allows homeopathic label claims based on provings (experiments in healthy volunteers that establish indications). As an aside, Hahnemann's term "Pruefung" means "test"; the English translation to "proving" implies that the process provides proof (often misconstrued to be scientifically-based evidence). In actuality, provings elicit a substance's therapeutic potential and are not constructed as a trial designed to determine statistically significant evidence.[2] Bona fide homeopathic medicines are prepared in FDA-inspected manufacturing facilities. Each product must conform to HPUS specifications. Production facilities should be sterile, dust-free environments, and 2 employees should verify each step. Homeopathic medicines have designated NDC numbers. Consumers can find the HPUS NDC number on the single ingredient products' labels.[51]

Some manufacturers make products, allege they can be used for chronic conditions such as hypothyroidism or attention-deficit/hyperactivity disorder in children, and label them as homeopathic. Chronic conditions are inappropriate for self-care or homeopathic remedies. Homeopathic organizations that strictly adhere to the HPUS monitor the marketplace for such fraudulent homeopathic claims and mislabeling of products. They petition the FDA to remove these products when they identify them. The zinc-containing cold product discussed above was a hybrid of full-strength zinc and a 10% homeopathic dilution of zinc (ie, the homeopathic ingredient also contained measurable amounts of zinc). The active ingredient was full-strength zinc, delivered directly to the nasal passages by nasal spray. By including a homeopathic dilution, the manufacturer was able to make a health-related label claim. This product should not have been labeled as homeopathic.[52]

The FDA has repeatedly decided that risk-based monitoring is the best way to regulate homeopathic medicines (and OTC products), which means they increase monitoring when any signal indicates there may be a problem. The FDA's Center for Drug Evaluation and Research issued a draft guidance on drug products labeled as homeopathic in 2017, and, in October 2019, issued a revised draft. The new guidance would reclassify all homeopathic drugs as unapproved "new drugs," thus making them subject to withdrawal from the marketplace. The guidance, which is not legally binding, prioritizes certain homeopathic products that are higher risk[53]:

- Products associated with injury report that, after evaluation, raise potential safety concerns
- Products that contain or allege to contain ingredients associated with potentially significant safety concerns

- Products that contain or claim to contain ingredients associated with potentially significant safety concerns, particularly when those ingredients are concentrated or in low dilution presentations (eg, infectious agents, controlled substances, multiple ingredients that could be synergistic, or those that could be toxic)
- Products for routes of administration other than oral and topical
- Products for vulnerable populations, such as those with compromised immune systems, infants and children, older adults, and pregnant women
- Products intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions
- Products deemed adulterated under the FD&C Act

Labels and Advertising

US law considers drug labels a form of advertisement and, as such, the FTC has jurisdiction over homeopathic labeling content. In November 2016, the FTC clarified the level of scientific proof needed to support marketing claims on homeopathic labels after determining that homeopathic products' efficacy statements may be misleading. A product's claim can no longer be "based only on the theories of homeopathy from the 1700s that are not accepted by most modern medical experts. To be non-misleading, the product and the claims must also comply with the requirements for homeopathic products and traditional homeopathic principles."[54] Clarifying labeling statements are required to comply with the FTC truth-in-labeling policy.[54]

In 2017, the FTC issued a policy statement claiming that they will now enforce laws related to OTC homeopathic products more strictly. They indicated they would require manufacturers to substantiate claims with scientific evidence, and hold efficacy and safety claims for homeopathic products to the same standard as other products with the same claims.[55]

Homeopathy in the Pharmacy

The community pharmacist may be the sole HCP who has contact with people who are considering self-medication with homeopathic remedies.[2] Homeopathy is only appropriate for self-limiting conditions and must never replace needed conventional treatment.

The United Kingdom Royal Pharmaceutical Society issued guidance to pharmacists in 2015, and it covers key points that can be applied regardless of geography[56]:

- Pharmacists who sell homeopathic products must be competent in the subject matter and be able to discuss homeopathic products' safety, effectiveness, and formulation with patients.
- Pharmacists should never recommend or sell homeopathic products for serious medical conditions.
- Pharmacists must encourage patients to continue taking prescribed conventional medication when they take a homeopathic product.
- Pharmacists should screen patients for serious, underlying, or undiagnosed medical conditions and refer them as appropriate.

Pharmacists can take other steps when they have questions about homeopathic products. They can consult the label and contact the product's manufacturer. Reliable manufacturers collect information, including the product name, lot number, and patient history related to the AE. US law requires manufacturers to have safety committees that review data and classify AEs using an objective classification (surely, probably, possibly, or not at all) to categorize potential AEs. They communicate with the consumer, provider, poison center, and the FDA.

Homeopathy can help pharmacists start informative conversations and identify patients' unmet needs. Discussion must be nonjudgmental and fact based. Pharmacists should remind and encourage patients to tell their HCPs about all medicines, including homeopathic and other natural products.

Pharmacists must assess the pros and cons of homeopathic product use with an appreciation of the patient's unique circumstances and belief system. If patients present with potential AEs, establishing causality is complicated. Pharmaceutical care principles still apply, and pharmacists need to follow the same process of questioning and elimination of possible causes as they would if a traditional medicine is involved. Serious symptoms require emergency care. If the homeopathic product is suspect, discontinue it and any possible offending agent and refer the patient to immediate medical care.

Many people believe that because homeopathic preparations tend to be safe, they are harmless. Pharmacists need to remember that a treatment's value depends not just on risks but also by its effectiveness. People need to employ risk–benefit analysis. Even if a treatment is safe, the risk–benefit analysis cannot be positive if it does not work. Alternatively, treatments that have significant AEs weigh in with a positive risk–benefit if they save lives.[2]

Conclusion

The Washington Post ran an opinion piece by Nikki Stamp, a surgeon, in February 2020, that discussed various wellness products with an emphasis on those supported by no or bad "science." Dr Stamp concludes, "To truly ensure people's safety, medicine must of course denounce dangerous, unnecessary and expensive snake oil, but it must also turn our attention inward and provide care that people need and want, communicated with compassion and supporting their autonomy. If we are to ensure that people are protected against medical half-truths and harmful remedies, my profession must move far away from the patriarchal practices that have alienated so many. Medicine has helped create this problem, and we must do better to be its solution."[1] Pharmacists can learn a lesson from this quote. To truly help people, we have to be tolerant, appreciate patient autonomy, and educate them about every product's strengths and limitations.

ADDITIONAL RESOURCES	
Homeopathic Pharmacopoeia of the United States	hpus.com
National Center for Complementary and Integrative Health	nccih.nih.gov
FDA Drug Products Labeled as Homeopathic Guidance for FDA Staff and Industry	www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-products-labeled-homeopathic-guidance-fda-staff-and-industry

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POSTTEST QUESTIONS

1. **A practicing homeopath describes why infinitesimal doses of arnica (mountain daisy) are used in homeopathy for pain, injury, and healing a celebration. He explains that mountain daisy, when given orally and its full strength, causes pain, injury, and delayed healing. Which principle of homeopathy does this describe?**
   A. The Law of Similars
   B. Minimum dose
   C. Single remedy
   D. Aggravation

2. **A patient who has difficulty limiting her dietary intake consults with the homeopath and a remedy that consists of Nux vomica (poison nut). Which of the following statements is TRUE regarding Nux vomica (poison nut)?**
   A. This product will not have a National Drug Code (NDC) on the label.
   B. This product will be labeled with the words "poison nut" only.
   C. This product is usually used for irritability in infants.
   D. This product is used in homeopathy, but not in liver failure.

3. **Over a period of 2 weeks, the FDA receives 57 reports from parents of patients or health care providers who have used a homeopathic remedy for itching in children. All of the patients report that they have developed an itchy, red, weeping rash. The FDA initiates an investigation. What is this an example of?**
   A. Mislabeling
   B. Adulteration
   C. Risk-based monitoring
   D. Provings

4. **After investigating the situation described previously in question 3, the FDA's laboratory analyst finds a substance in the product that may have been introduced in the manufacturing process and is known to cause rash. What is this an example of?**
   A. Mislabeling
   B. Adulteration
   C. Risk-based monitoring
   D. Provings

5. **Sophia, an elderly woman who has no chronic conditions, begins taking a 12X homeopathic product for occasional gastrointestinal upset. Shortly after she begins taking it, she says that in addition to an upset stomach, she now has several bouts of mild dizziness 4 or 5 times a day. She asks you if you think that the homeopathic product could be causing the dizziness. Why is it unlikely that the homeopathic product is related to dizziness?**
   A. You suspect that her occasional gastrointestinal upset is probably associated with recent events in her life, and the dizziness probably is, too.
   B. This product is for gastrointestinal upset; if it were to cause adverse effects, they would be gastrointestinal in nature and severe in onset.
   C. Randomized controlled trials of this product would have reported dizziness as an adverse effect and included it on the label.
   D. At 12X dilution, this product exceeds the Avogadro limit for molecular detection, and probably will not cause adverse effects.

6. **Several years ago, the FDA asked the manufacturer to voluntarily remove zinc-containing nasal products from the market after numerous reports of anosmia. The FDA's laboratory reported finding concentrations of zinc that were considerably higher than those that would be acceptable under a definition of "homeopathic." Which of the following statements is TRUE?**
   A. Zinc is a natural product, and thus the manufacturer labeled it appropriately as "homeopathic" according to the Homœopathic Pharmacopœia of the United States (HPUS).
   B. According to the HPUS, any products containing plant, animal, or mineral substances that cause a particular symptom in healthy people are homeopathic.
   C. This product should not have been labeled as homeopathic because it was not as dilute as the definition of homeopathic requires.
   D. It is permissible for this product to be labeled as homeopathic provided that one ingredient in the bottle is actually diluted in accordance with HPUS.

POSTTEST QUESTIONS (continued)

7. **In the 2018 Annual Report of the American Association of Poison Control Centers, data indicated that 2.68% of the approximately 2,000,500 reports were associated with homeopathic products. What is one limitation to the data?**
   A. An additional 1968 reports mentioned either a dietary supplement or a homeopathic product that was not identified.
   B. Neither pharmacists nor physicians were involved in the review process at various Poison Control Centers across the country.
   C. Poison Control Centers only accept reports from licensed health care providers so the data are probably underreporting the problem.
   D. There are no limitations to this data as the data were collected by people trained in analysis of poison control reports.

8. **Which of the following is the MOST appropriate advice to give to a patient starting a homeopathic product?**
   A. "We stock several over-the-counter medications that can lower your blood pressure and decrease your reliance on prescription drugs."
   B. "If your symptoms worsen or do not improve over the next several days, seek advice from a traditional health care provider."
   C. "While you are taking this homeopathic medication, you can discontinue any prescription medications for similar problems."
   D. "I do not know why you would want to try this medication. Everybody knows it is quackery."

9. **Which of the following would be an appropriate use for a homeopathic product?**
   A. Thyroid disease
   B. Hypertension
   C. Diabetes
   D. Cold symptoms

10. **Which of the following patients is most likely to be interested in homeopathic products?**
    A. A patient who is newly diagnosed with cancer and has not started treatment
    B. A patient who has started a traditional medication and is optimistic it will work
    C. A patient who has an excellent rapport with her primary care provider and specialist
    D. A patient who reports that conventional medication has not helped

INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Pharmacists, please go to **www.pharmacytimes.org/go/homeopathy-aes** to access the online version of this activity.

Pharmacy technicians, please go to **www.pharmacytimes.org/go/homeopathy-aes-techs** to access the online version of this activity.

Click "Proceed," then complete the online pretest.

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