REPORTS OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

The following reports, 1–4, were presented by S. Bobby Mukkamala, MD, Chair:

1. URINE DRUG TESTING

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
REMAINDER OF REPORT FILED
See Policies H-95.985 and D-120.936

INTRODUCTION

Over the past two decades, the rate of opioid prescribing, especially for patients with chronic non-cancer pain, has increased dramatically. It is estimated that between 9.6 and 11.5 million Americans are currently being prescribed long-term opioid therapy.[1] The overall increase in prescribing has been associated with a parallel increase in unintentional overdoses and deaths from prescription opioids.[2] In 2014, a total of 47,055 drug overdose deaths occurred in the United States; 61% of these involved some type of opioid, including heroin. Overdose deaths from heroin have quadrupled in recent years, and the majority of past year users of heroin report they used opioids in a nonmedical fashion prior to heroin initiation; hence, the availability of pharmaceutical opioids is relevant to the national heroin use and overdose death epidemics. In the most recent available report, benzodiazepines were involved in 31% of the opioid-related overdoses.[3] Despite clinical recommendations to the contrary, the rate of opioid and benzodiazepine co-prescribing also continues to rise.[3-5]

Identifying patients at risk for drug misuse is a challenge. There is no definitive way for physicians to predict which of their patients will develop misuse problems with controlled substances. Because of this, deciding which individual patients to evaluate with drug testing is an arduous task and in its place “universal precautions” have been recommended by some authors so that drug testing becomes a standard process when patients are receiving chronic opioid therapy.[6]

Urine is the most commonly used biological fluid or specimen used for drug testing. It is non-invasive to collect, a more than adequate volume is usually available, it is easier to process than other matrices,[7] and the time during which most analytes can be detected after exposure is sufficiently long (1-3 days for most).[8] This report therefore focuses on urine drug testing (UDT) and not on the testing of alternative specimens such as oral fluid, blood/serum, hair, or other body tissues or fluids (see Appendix). It is important to emphasize that drug testing can identify the presence or absence of a substance in the tissue or body fluids of an individual and can therefore confirm recent substance use (the undesired use of an unauthorized substance or the failure to adhere to use of a prescribed agent). UDT addresses use, but cannot diagnose, rule out, or rule in substance use disorder or addiction. Cases of non-use can indicate diversion but cannot provide proof of such behavior.

A large national diagnostic laboratory recently published an analysis of more than 3 million urine specimens obtained as part of physician monitoring for prescription drug misuse in 2015.[4] This analysis revealed a 54% rate of drug misuse based on UDT. Among those patients with abnormal findings, 45% had a similar class, non-prescribed, or illicit drug(s) detected; 23% had a different class, non-prescribed, or illicit drug(s) found; and 32% had at least one prescribed drug that was not detected. Benzodiazepines, followed by opioids, were the most common non-prescribed agents found in UDT samples. These results highlight the lack of patient adherence to recommended treatment plans for controlled substances and the potential for harmful drug combinations.[4] A sub-analysis of more than 150,000 specimens for controlled substances and illicit drugs detected heroin in 1.56% of the samples (age range 18 to 65+), underscoring the increasing threat of heroin use in the United States.[9] The concurrent use of benzodiazepines among heroin users was nearly 30%, mostly in a nonmedical fashion.

Accordingly, UDT is currently considered the most objective tool for monitoring and documenting treatment adherence to prescribed controlled substances and signs of drug misuse. When utilized properly, it is an objective indicator clinicians can employ within the confines of a patient-physician relationship along with other risk mitigation tools such as prescription drug monitoring programs (PDMPs) to help guide pain management strategies

while balancing patient needs, safety, and reducing risk.[10] UDT in its clinical applications is not intended to stigmatize or penalize patients, but to monitor for signs of misuse, provide clinically useful information, and promote honest dialogue so that a change in therapy or intervention can be introduced if (or when) needed.[11]

Outside of pain management practice, and the treatment of anxiety disorders or attention deficit hyperactivity disorder (ADHD), UDT is used in addiction medicine to detect unauthorized use of potentially addictive substances. It is also used in quasi-clinical physician health programs and related programs to monitor the status of continuous abstinence from alcohol and other drugs and the ongoing recovery in health care professionals who are receiving or have received treatment for a substance use disorder.

Evidence suggests that combining UDT with other risk mitigation strategies such as pill counts, treatment agreements, and patient education can reduce substance misuse by at least 50%.[10] The Council on Science and Public Health initiated this report to promulgate UDT as a medical management tool that can be used to better serve patient populations.

CURRENT AMA POLICY

AMA Policy H-95.985, "Drug Screening and Mandatory Drug Testing," states that physicians should be familiar with the strengths and limitations of drug screening techniques and programs and it lists several other details of drug testing that this report will update and clarify. Policy H-95.984, "Issues in Employee Drug Testing," advocates for education of physicians and the public regarding drug testing and supports the monitoring of evolving legal issues surrounding the testing of employees. These policies highlight that employment/workplace-related drug testing and clinical drug testing have different aims, ask different questions, and may use different testing methodologies.

METHODS

English-language articles were selected from a search of the PubMed database through August 5, 2016 using the search terms "urine drug testing" and "opioids," and "urine drug testing" and "controlled substances." Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society websites were conducted to identify clinical guidelines and position statements.

FORENSIC VERSUS CLINICAL URINARY DRUG TESTING

Historically drug testing has been forensic in nature and has assumed most donors will provide a negative specimen. In patient-centered UDT in a clinical setting, the majority of specimens provided are expected to be positive for a broad range of drugs that are prescribed for medical purposes which adds to the complexity of the testing and the interpretation of data. Most UDT today that involves drug testing laboratories includes elements of both forensic drug testing and clinical drug testing. Drug testing in clinical settings also includes toxicology testing, usually in hospital emergency departments or emergency psychiatry settings, used to help accurately diagnose possible drug poisoning or overdose. Clinical drug testing is often inaccurately labeled as "toxicology testing" involving "tox screens" when the goal of testing is not to identify a case of acute poisoning but is to assist in treatment planning for a chronic disease, such as chronic non-cancer pain or addiction.

Forensic Urine Drug Testing

In forensic drug testing, results are meant to stand up to legal challenges and meet the rules of evidence in legal proceedings. Chain-of-custody procedures, secure storage of samples, and stringent method validations are utilized with the aim of minimizing or eliminating false positive results, and rigorous laboratory certification programs are used to assure quality. The personnel running the tests in a forensic UDT laboratory usually have training in chemistry or forensic science and they understand chain-of-custody and medicolegal requirements.

Federally Regulated UDT. Mandatory guidelines for federal workplace UDT exist and are regulated by the Substance Abuse and Mental Health Services Administration (SAMHSA); only SAMHSA-certified laboratories can perform workplace drug testing on federal employees. The list of drugs tested under the federal program (often referred to as the SAMHSA-5 or federal-5) is limited and includes only five classes of drugs: amphetamines, marijuana, cocaine, opiates (natural opiates such as codeine and morphine, a metabolite of heroin, but not other synthetic opioids such as oxycodone, hydrocodone, buprenorphine and methadone), and phencyclidine (PCP) (see

Table 1). The SAMHSA-5 derives from Congressional legislation mandating drug testing of interstate truck drivers and other commercial vehicle operators; its finite group of analytes is also referred to as the DOT-5, for the U.S. Department of Transportation which regulates commercial vehicle use across state lines.

Federally regulated testing follows a screen-and-confirm paradigm in which lower cost, less specific, and often less sensitive screening methodologies are initially used and more costly, more sensitive, and more specific methods are used to confirm positive screening results. Positive test results based on immunoassays (IA) are only considered presumptive because of cross reactivity and differing sensitivity and specificity (see below). Presumptive positive results must be confirmed using definitive chromatography-mass spectrometry methods and all confirmed results must be evaluated by Medical Review Officers (MROs), who serve as a common point of contact between all participants in a UDT. MROs are licensed physicians who have expertise in drug disposition, training in drug collection procedures and the federal program, and have passed a certification exam.[12]

The concentrations required to generate a positive test result vary for each analyte, but are high (in order to minimize false positive results) compared to clinically-relevant concentrations for the prescription drugs included. The federal UDT program, does, however, set a standard for analytical quality, procedure, and measurement in forensic laboratories as well as in clinical laboratories.

Nonregulated Forensic UDT. Many states and private employers have adopted drug-free workplace programs that include UDT similar to the SAMHSA program. A multitude of other UDT applications exist including pre-employment testing, for-cause testing (in response to on the job impairment or after a workplace accident), reasonable suspicion testing, random workplace testing, return to work testing, school testing, sports testing, as well as testing in the criminal justice system, testing in child custody cases, Department of Transportation testing for required occupations, testing in the military (which is the model for the use of drug testing to prevent drug use),[7] and medical examiner (post-mortem) testing. Most of these testing applications have a testing panel that is broader than the SAMHSA-5 and can therefore include additional analytes such as oxycodone, oxymorphone, and other opioids, benzodiazepines, barbiturates, stimulants, anabolic steroids, emerging designer drugs such as synthetic cannabinoids and cathinones, and others.

Clinical Urine Drug Testing

Clinical drug testing is part of the medical evaluation within an established patient-clinician relationship. It is used for diagnosis, treatment monitoring, or the promotion of long-term recovery from a substance use disorder and in other clinical settings such as pain management.[7] The goal of clinical UDT is to meet the standards of medical practice, not the legal requirements of forensic testing. UDT can improve a clinician's ability to manage therapy with controlled substances and assist in, but not make the diagnosis of, a substance use disorder or addiction. Personnel running the testing in a clinical setting have a broad spectrum of laboratory training, often as a medical technologist, but do not usually have chain-of-custody or evidentiary training. Although most dedicated toxicology testing laboratories started as forensic in nature, some now specialize in testing and interpreting clinical and pain management samples and better understand the needs of physicians and their patients.[13,14]

URINE DRUG TESTING METHODS

The U.S. Food and Drug Administration (FDA) classifies laboratory developed tests, including point-of-care (POC) UDT testing devices, as waived, moderate, or high complexity under the Clinical Laboratory Improvement Amendments (CLIA).[15,16] Waived tests are typically easy to use and pose no reasonable risk if performed incorrectly. Once a CLIA certificate of waiver is obtained, the device or test must be used exactly according to manufacturer's instructions. Moderate and high complexity tests carry a significantly increased risk of inaccurate results, require specialized personnel who have been trained to run the instrumentation, use complex methodologies with multiple steps, and require certification with CLIA.[15,16]

Quality Assurance

Laboratory accreditation programs ensure the integrity of analytical results by providing laboratories a set of standards. The standards guarantee that tests are subjected to rigorous quality assurance criteria, are delivered in a manner that promotes proper interpretation, and are performed by qualified individuals. There are several voluntary accreditation programs including CLIA, SAMHSA, the College of American Pathologists (CAP), The American

Society of Crime Laboratory Directors (ASCLAD), New York State Department of Health (NYSDOH), and International Organization for Standardization/International Electrotechnical Commission (ISO/IEC). Each accreditation program has requirements specific for the focus of the laboratory services whether it be medical testing, workplace drug testing, or some other application.

Laboratories typically develop their own testing methods with rigorous quality controls. Most accreditation programs have proficiency testing that is a peer-based competency evaluation program to ensure accurate and reliable test results. The National Institute of Standards and Technology and the Department of Justice recently established the Organization of Scientific Area Committees (OSAC) in order to support the development and promulgation of forensic science standards and guidelines. The Toxicology Subcommittee focuses on standards and guidelines related to the analysis of biological samples for alcohol, drugs, or poisons, and the interpretation of these results.[17] As clinical UDT is a combination of both forensic and medical requirements, there are currently no standards specifically for its application, but accreditation programs for pain management are likely forthcoming.[18]

Requirements for laboratory directors vary depending on the type of testing and the accreditation body, but most require at a minimum a doctoral degree in a physical science, certification from a major body, and a degree of laboratory experience.[18] The qualifications and competency of individuals in UDT laboratories are evaluated by three major certification bodies: the American Board of Clinical Chemistry, the National Registry of Certified Chemists, and the American Board of Forensic Toxicology. Both personnel at the director level and technical personnel have annual continuing education requirements depending on certification/licensure and laboratory accreditation requirements.

Types of Urine Drug Tests

Immunoassays. Many UDTs are grounded in IA biology and technology. IAs are based on competitive binding and use antibodies (ABs) to detect the presence of drugs, drug metabolites, or drug classes. In IAs, a known amount of labeled drug/metabolite is added to a specimen. Any drug/metabolite in the specimen will compete with the labeled drug/metabolite for binding with an AB. The amount of labeled antigen-AB complex remaining in the specimen is determined by the amount of drug/metabolite present in the specimen competing for the binding site.[15] IAs can use enzymatic, chemiluminescent, fluorescent, or colorimetric labeling for detection.

Many IA-based UDTs are designed to detect a specific drug or a class of drugs as either present or absent based on a designated cutoff, or threshold concentration for detection. A negative result could mean that no drug is present, or that the drug concentration is below the threshold. The results of these kinds of tests are considered presumptive; their results can represent either true or false positives, or true or false negatives.

IA UDTs include waived, moderate, and high complexity laboratory tests under CLIA. Many of these tests are available as commercial kits that contain reagents, calibrators, and controls. Urine samples can be analyzed via IA tests at the POC or can be sent to a laboratory where the IA test is performed by laboratory personnel. Methods and instructions differ in complexity and detail, some with many intricate steps and others with one step. The CLIA-waived IA tests include the POC devices described below. Some moderate and high-complexity IA instrumented devices have been adapted for use in larger medical practices and hospital laboratories, but rigorous and costly CLIA certification requirements have limited the implementation of the instruments in these settings.[15,18] Some clinical entities such as methadone clinics (federally-licensed Opioid Treatment Programs or OTPs), large pain clinics, and outpatient or residential addiction treatment facilities may have the economies of scale to purchase their own analyzers, obtain CLIA certification, and use these instruments on-site.

The main advantage of IA UDT is its ability to rapidly detect the presence of substances in urine. One major disadvantage is the limited range of drugs that the assays are able to detect. Because an AB is used for detection, there must be an AB developed specifically for the drug, metabolite, or class of drug. This requirement restricts the number of compounds that can be screened for based on IA. Most commercial IAs include only the SAMHSA-5 panel of drugs, which limits their clinical utility (even if a physician is not aware of this limitation). Some specialized IAs include semisynthetic and synthetic opioids, benzodiazepines, and other drugs. IAs are typically designed to have a high sensitivity (the ability to detect) balanced with lower degrees of specificity (the AB only binds to the target),[15] but the performance characteristics and limitations of the IA UDT vary between tests. Information supplied by the manufacturer should be given appropriate attention; the sensitivity and selectivity can affect the rate of false positive and false negative results and the designated threshold (being too high) could be

clinically irrelevant. Home UDT kits available for retail purchase and used by individuals outside of health care settings use IA methods.

Another confounding variable among IAs is cross-reactivity. Some compounds, despite no structural similarities to the target analyte, may bind to the AB and generate a false positive result. An extensive list of cross-reacting drugs for IAs exists that can cause false positive results (see Table 2).[15,19-22] Other medications and dietary supplements a patient is taking can significantly impact test results. Additionally, some IAs rely on the ability of an AB to bind to a class of drugs and a lack of cross-reactivity among important members of the class can result in false negative results. For example, many opioid IAs react to the natural opiates codeine and morphine, but may not react with the semisynthetic opioids hydrocodone or oxycodone. In hospital or clinic settings, a physician may order a drug test for opiates, and what is tested for by the IA methodology is only the natural opiates; the clinician may be unaware that in the context of drug-testing, the word "opiates" refers only to the natural compounds such as codeine, morphine, and the metabolites of heroin, without testing for "opioids." Many primary metabolites may not be reactive with IA UDTs as well. It is essential to understand the limitations of a specific IA test in this regard.

Unique challenges are associated with IA results for a drug class. IA UDTs do not unequivocally identify which member of a drug class is present in a positive specimen. Even if an IA is labeled "morphine" it may still produce a positive result for any number of opioids, including heroin (and multiple opioids). Conversely, IAs to detect benzodiazepines can have considerable variability in class cross-reactivity depending on which molecule the IA AB is based on. For example, test information may state that the IA will cross-react with alprazolam. A specimen from a patient taking alprazolam containing predominately the major urinary metabolite (α-hydroxyalprazolam) will return a false negative result. Benzodiazepine IAs have very high rate of false negative results and require knowledge of the metabolic pathways of the drugs to properly interpret their results.[23-25] Challenges are also found in the testing of stimulants. Many over the counter products contain sympathomimetics which will generate a false-positive result on an IA for stimulants when the clinician is looking for adherence to psychostimulant therapy or is attempting to detect unauthorized use of methamphetamine or psychostimulants. Prescription drugs such as bupropion, fluoxetine, and others can also produce false-positive IA results for stimulants (see Table 2).

Physicians and other prescribers typically utilize IA-based tests as an initial screening test (i.e., qualitatively positive or negative) in opioid-based pain management monitoring programs. Another issue in the clinical use of IA testing is whether confirmation of results is necessary. In some situations the results of an IA UDT may be sufficient, given an understanding of the possible high rates of false positive and false negative results. However, many organizations, including the Federation of State Medical Boards, recommend definitive identification of positive screening results.[26] The definitive identification of IA-based presumptive results requires more sophisticated technology for confirmation. Gas or liquid chromatography-mass spectrometry (GC-MS or LC-MS), discussed below, is the standard method of confirming preliminary (screening test) results generated via IA. Without understanding the limitations of testing devices or the laboratories conducting the testing, presumptive UDT testing may not be useful. Testing devices are on a continuum from less expensive/less sensitive and specific (e.g., POC devices) to more expensive/more sensitive and specific (confirmatory testing). Clinicians must be reminded that most drug tests they order are IA tests; actions they take in the care of their patient and treatment plan decisions should not be made based on a non-confirmed result from a presumptive test.

Point-of-Care Devices. POC tests are typically non-instrumented IA devices (strips, dipcards, cups with imbedded test strips) that can be used in the clinic (at the "point of" care). Testing can therefore occur outside of a laboratory and is not subject to any accreditation standard. These tests are typically granted CLIA-waived status, they lack quality assurance and quality control, and ensuring the integrity of materials following transportation or storage is largely unregulated. Test results are subjective in nature, usually based on a color-changing dye. POC tests are typically performed by health care workers who have many other office-related duties and who are not specifically trained in drug testing. Although POC tests seem simple and are comparatively affordable, they still require proficiency in execution and good laboratory practice is required to obtain reliable results. Product-use instructions and related information accompanying the test device are important to read and understand, and are often not followed.[27] Choosing a device that includes reliable customer support is beneficial. Some instrumented benchtop and small floor POC devices have the capability to link with electronic health records. These devices are of moderate complexity and require certification with CLIA,[15] can be expensive, and usually contain the SAMHSA-5 routine drug panel. They do, however, eliminate the visual interpretation and decision-making associated with the use of non-instrumented devices.

Understanding the limitations of a POC device is important. IA-based POC devices are presumptive, qualitative, variable, have limited sensitivities, offer limited testing menus, cannot distinguish between members of a drug class, and cannot differentiate a drug from its metabolite.[7,28] The possibility of cross-reactivity with other prescription, over-the-counter, and dietary supplement medications exists, which increases the probability of false positive and false negative results. Many POC IA products have not been optimized for use in a medical setting and are designed with federally-regulated UDT in mind.[15] Threshold concentrations and the drug targets may provide inadequate results for clinicians. The device information provided by the manufacturer includes often-unread advice that presumptive positive IA results must be confirmed with definitive testing, which is not a requirement for clinical UDT, but could be required based on the conditions of the CLIA waiver.[13] IA-based POC devices do, however, offer rapid results within minutes and can allow physicians to make presumptive in-office clinical decisions, if needed, before results are confirmed. This type of POC test can be useful as long as clinicians are well informed of the limitations.

Analytical Methods (GC-MS, LC-MS, LC-MS/MS). The current gold standard in UDT is separation of a specimen using GC-MS, LC-MS, or LC tandem mass spectrometry (LC-MS/MS). Separation via chromatography allows each compound in the specimen to be isolated and enter the mass spectrometer individually. The mass spectrometer provides a unique identifying fingerprint for each molecule. The use of GC- or LC-MS depends on the compounds being detected; volatile, nonpolar compounds are more suited for GC (often parent drugs). Chromatography-mass spectrometry is considered high complexity testing, is subject to FDA guidelines, and requires CLIA certification to operate.

GC- or LC-MS can be used for confirmatory testing after IA. Recently, LC-MS/MS has been used as a screening method[7] to identify many unique drugs and/or metabolites from different classes of drugs (see Table 1), for example opioids (natural, semi-synthetic, and synthetic), benzodiazepines, and stimulants in lieu of IA. Although LC-MS/MS is a more sophisticated technique than GC- or LC-MS, it can separate and identify many drugs from many classes in a single analysis from a single specimen. With this advantage, a test profile or panel can include many different analytes and detect relatively low concentrations of drug or metabolite from low volumes of starting material and be ideal for an analytical qualitative screening method. More sensitive quantitative GC-MS and LC-MS analytical methods that are drug class specific can then be used for confirmatory testing if desired. There are limitations, however, with MS technology; the greater the number of analytes included in an analysis, the lower the sensitivity of the assay; and not all substances are capable of detection–the structure of the drug or its metabolites must be known, therefore, some emerging drugs of abuse and designer drugs remain a challenge for MS detection.

Other reasons that these analytical methods may be necessary include the specific identification of a drug; IA can provide information about the class of a drug only. Additionally, a number of drugs, such as tramadol, carisoprodol, and designer drugs such as synthetic cathinones and cannabinoids, are not readily detected using IA and require chromatography testing. Sometimes specialty analytical testing is necessary, for example only GC-MS with a chiral column will be able to distinguish between d-methamphetamine (the illicit drug of abuse) and l-methamphetamine (the compound in Vick's inhalers). Chromatography-MS tests also can aid in validating disputed test results. Analytical methods also are quantitative methods, allowing the amount of drug excreted in urine to be quantified with the use of calibration curves and reference standards. Although this can be useful for gauging adherence, quantitative GC-MS, LC-MS, or LC-MS/MS data cannot be used to verify dosage exposure.[7] POC testing has a high rate of false positive and negative results, which is not a concern with GC-MS, LC-MS, or LC-MS/MS. Chromatography-MS instrumentation is relatively expensive, reading and interpreting mass spectrum data requires expertise, and the cost for a test is variable depending on the testing panel chosen.

TESTING: WHY, WHO, WHEN, AND WHAT

While UDT is an objective means to detect the use of nonprescribed or illicit drugs, the design of the testing program (including the clinical questions to ask and answer), the patient population to test, the frequency of testing, and the drug test panel are all determined by the ordering clinician and should be patient-centered.[29] One of the most common failings of UDT in clinical practice is its application only to high risk patients or those who are suspected of drug misuse.[30] Despite the objective evidence UDT can provide as a clinical tool and recommendations for its use as a risk mitigation strategy, UDT is underutilized and misapplied, and a lack of understanding exists that functions as a barrier for introducing successful testing programs into clinical care.[31-38]

Why Test?

Standard methods of adherence monitoring for prescribed substances, for example, self-reporting[8,39-41] and monitoring of symptoms or patient behaviors,[42] are unreliable for controlled substances. As noted above, a high rate of substance misuse occurs in the patients receiving prescriptions for controlled substances. Seminal studies[43-45] evaluating the use of UDT in patients with chronic pain revealed that approximately 50% of UDTs yielded appropriate results; the others showed illicit drugs and/or nonprescribed medications, absence of prescribed opioid(s), and/or specimen adulteration. In many cases, abnormal test results are not accompanied by behavioral clues or differences in other demographic or clinical variables.[44] UDT is objective and an abnormal result is the most frequently detected signal of opioid misuse. It is similarly useful in managing patients prescribed benzodiazepines or psychostimulants. UDT plays an important role in providing a more complete diagnostic picture for clinicians.[46] As noted earlier, the identification of a drug or metabolite in a UDT provides evidence of exposure to that drug and information about recent use of drugs, but it can only provide this information if the substance is present in the urine at levels above the threshold of detection. UDTs cannot identify the presence of a substance use disorder or the presence of physical dependence.[7] Before implementing UDT, physicians should understand the question they want to answer, understand the advantages and limitations of the testing technology and the interpretation of data, and ensure that the cost of testing aligns with the expected benefits for their patients.

Whom to Test?

Practice guidelines on pain management intended to promote safe and competent opioid prescribing recommend various measures to mitigate risk including UDT, but some disagreement persists on who should be subjected to routine UDT and its frequency.[7,26,29,47-51]

UDT can be useful in many medical specialty practices including but not limited to palliative medicine,[52] psychiatry,[7] geriatrics,[53] adolescent medicine,[54] addiction medicine,[29] and primary care.[55,56] The routine use of UDT in pain medicine[57] is recommended in several clinical guidelines.[21,26,48,58-60] As stated previously, UDT utilized in emergency settings is typically intended to diagnose acute drug poisonings or make immediate treatment decisions as opposed to chronic care situations. An American College of Emergency Physicians policy does address the use of UDT in the context of psychiatric patients.[61] Although medically appropriate opioid use in pregnancy is not uncommon, there has been a renewed focus on maternal opioid dependence, opioid exposure during pregnancy, and the increase in infants born with neonatal abstinence syndrome.[62-69] UDT can aid in obtaining a complete picture of drug exposure. Two studies in the Kaiser Health System involving nearly 50,000 obstetric patients demonstrated improved maternal and fetal outcomes when treatment for substance use disorders were linked with prenatal visits and UDT allowing for resources to be appropriately allocated for postnatal care.[70,71] The American Society of Addiction Medicine (ASAM) supports the use of UDT during pregnancy.[7,66] The American Congress of Obstetricians and Gynecologists (ACOG) also supports the use of UDT during pregnancy when substance use is suspected, but not during routine well care visits.[72-74]

Given the challenges inherent in deciding whom to test and the issues described in the paragraphs above on why to test, many clinicians have adopted recommendations to utilize “universal precautions” in opioid prescribing. This approach informs patients at the onset of a plan of care that the standard procedure for the clinician’s practice is to test *every* patient at the initiation of opioid therapy, and periodically on a random basis during the course of care. This avoids any patient feeling singled out and reduces the potential for stigma, discrimination, and clinical errors based on incomplete clinical information.

When to Test?

Although uniform agreement is lacking, an evolving consensus recommends testing new patients before prescribing controlled substances for a chronic disorder, in those seeking increased doses, in patients who resist a full evaluation, in those requesting specific controlled substances, in patients displaying aberrant behaviors, in pain management patients recovering from addiction, and special populations.[8,47,48] It is recommended that tests be administered at unscheduled and unpredictable times (random testing) so specimen donors are less likely to try to circumvent the test (see below).[7] Considerations about how often to test are influenced by concerns about cost and the proper stewardship of health care resources; both underutilization and overutilization of clinical drug testing are concerns. The recommended periodicity of testing in given clinical situations continues to be addressed. Currently, ASAM is developing a guideline for addiction medicine specialists engaged in varying levels of care (outpatient,

intensive outpatient/partial hospitalization, residential) and within various special populations (for example, health professionals or others in safety-sensitive occupations who are receiving addiction care). Other specialty societies have been encouraged to develop similar guidelines for their physician members and the populations they serve.

What to Test For?

Clinical drug testing should be individualized and not determined from a device, kit, or forced panel of drugs. It is important to know the clinical question to be answered to properly utilize UDT as a management tool. Although no device or testing panel may be ideal, any testing should be patient-centered. Testing should not be limited to only prescribed controlled substances; it is advantageous to include substances that have been problematic for that patient in the past if a history of drug misuse exists. Local patterns of substance misuse should be considered when designing the testing panel as well.[7]

The choice of drugs to include on a testing panel is complicated by the fact that many drugs and illicit substances are subject to misuse based on their "rewarding" properties and they may not be included in or detected on a standard drug test. Internet-based and other sources exist that are dedicated to informing users about chemistry, laws, laboratory tests, and how to evade detection of the most commonly tested substances. Additionally, there is a new and ever-evolving drug industry based on "designer drugs" which are being synthesized to evade existing drug tests and laws.[75]

INTERPRETATION OF UDT RESULTS

The valid detection period for drug exposure varies depending on the disposition characteristics of the drug, dose, and frequency of use. Specific characteristics of a urine sample include its appearance, temperature within 4 minutes of voiding, pH, creatinine concentration, and specific gravity.[8] The color of urine is based on the concentration of its constituents[8,76] and can vary based on medications, foods, or disease states; excess hydration can cause it to appear colorless. Concentrated urine specimens are usually more reliable than dilute specimens.

Manipulation/Adulteration, Specimen Validity Testing, Normalization, and Collection

One drawback of a urine specimen is that it is easy to tamper with. Collection in a medical setting is typically unmonitored and the potential for manipulation exists and should be considered. Dilution is usually done in an attempt to lower the concentration of illicit substance(s) below detection levels. Specimens that are excessively dilute will have low creatinine levels. Commercial "cleansing" beverages exist that when consumed in large volumes dilute urine and contain B vitamins to restore urine color.

Urine spiking with a specific substance is done to simulate adherence to medication taking and is not uncommon. For example, patients who know they will be subjected to adherence testing but who have not been taking the prescribed medication per instructions can add crushed drugs hidden under a fingernail to a urine specimen to generate a positive test result.[28] Diversion is sale or distribution of a prescribed medication to an unintended recipient. UDT cannot detect diversion, but a negative specimen may indicate diversion or some other maladaptive drug-taking behavior (i.e., periods of reduced medication use or abstinence followed by binging).[8] These behaviors can occur with buprenorphine prescribed for the treatment of opioid addiction, though the patient's aberrant behavior can be easily recognized when confirmatory testing data is interpreted and the relative amounts of parent compound and the primary metabolite, norbuprenorphine (if present) are evaluated.

Substitution is the switching of donor urine with drug-free synthetic urine, urine from another individual, or urine from an animal.[77] This is easily detected in many cases because house pets produce urine that has a very different pH from human urine. Test results are typically reported as "specimen incompatible with human urine" (or similar) when testing procedures include pH analysis.

Adulteration is the addition of oxidizing chemicals or other substances directly to the specimen that may interfere with the UDT. Some adulterants can be other drugs such as dextromethorphan or salicylates, which are known to cause false negative results with some IA UDTs; other adulterants are common household products or substances that are otherwise easily obtainable including salt, vinegar, bleach, soap, Visine®, glutaraldehydes, chromate-containing compounds, and sodium nitrate.[14] Being aware of this, many clinicians will not utilize any drug testing methodology that does not include testing for common commercially-available adulterants.

Most testing laboratories will perform specimen validity testing (SVT) on urine specimens.[78] SVT includes testing the specimen for creatinine, specific gravity, pH, nitrates, chromates, and other easy-to-obtain over-the-counter adulterant products, and assuring that values are consistent with those of normal human urine. Values outside of typical ranges may indicate the specimen has been tampered with or adulterants have been added.[14] Many laboratories will also normalize urine samples since urine drug concentrations vary significantly between individuals and can have an effect on UDT; if a urine specimen is dilute, a drug may be present, but below a measurable level. Normalization is a mathematical method using specific gravity or creatinine concentrations to adjust for dilution, thereby allowing the UDT results to be interpreted or compared. Often this can be useful when comparing serial analyte measurements or to minimize false negative results.[8,14]

To minimize specimen tampering many collection protocols require patients to leave outerwear and personal belongings in exam rooms, and to show pocket contents. Some relatively inexpensive POC collection devices (cups) incorporate validity testing such as temperature, pH, specific gravity, and oxidation and add an extra layer of assurance to specimen collection. Some testing laboratories will provide staff to physicians' offices to facilitate collections; third party collectors exist as well. Some third party vendors will send a single collector to a location and many third-party specimen collection sites exist for the employment drug testing market, for use by professional sports leagues for their testing protocols, or for monitoring programs for licensed health professionals, rather than for clinical drug testing. Once the specimen is collected, it should be refrigerated to minimize drug degradation, especially if testing is delayed. As noted, chain-of-custody handling of specimens between the site of collection and the laboratory bench are components of forensic and some employment-related testing, rather than clinical drug testing.

Interpretation of Results

Clinicians' predictions of UDT results are often inaccurate[21] and evidence suggests a majority of physicians have a poor understanding of how to interpret UDT results. Others may have a false sense of confidence about interpreting their patients' UDT results because they lack specific knowledge or don't fully understand the breadth of abnormal or unexpected toxicology findings that are possible.[10,33,79-81]

Unexpected findings are common in clinical UDT; results are much more than just a positive or negative result. There are complexities to consider in order to properly interpret UDT such as the type of assay, possible adulteration, detection time, detection thresholds, and therapeutic response. Therapeutic response can be variable and can be affected by drug potency, chemical properties, metabolism, dose, preparation, drug-drug or drug-herbal interactions, and the patient (diet, drug ingestion, weight, genetic makeup, disease state).[82,83] Appropriate interpretation of toxicology testing results requires a working knowledge of drug metabolism; although beyond the scope of this report, there are many intricate details involved in opioid pharmacokinetics and pharmacodynamics to consider.[82,83]

If POC devices are being utilized, consultation of product inserts is recommended and choosing devices with readily available customer support is advantageous. If a laboratory is used for UDT, then contacting the professionals at the laboratory, such as a toxicologists or laboratory director, is recommended whenever the clinician feels a need for guidance on interpretation of reported results. Additionally, physicians should be sure to obtain a full prescription and over-the-counter medication history (including dietary and herbal supplements), and use this information in the context of the UDT or provide this information to the testing laboratory since it could be relevant to interpreting UDT results.

CONCLUSIONS

UDT is an objective means to detect the use of nonprescribed or illicit drugs and to confirm the presence of prescribed drugs. The elements of the drug test such as the composition of the drug test panel (the list of analytes in a given test) and the testing method/technology should be determined by the ordering clinician. Therefore, it is important for physicians to understand the elements of UDT in order to make informed decisions. The value of UDT depends on clinicians appreciating the strengths and weaknesses of the test or the laboratory and their relationship with the laboratory. Understanding the drugs that are detected in IAs and those detectable only via confirmatory methods, cross-reactivity, and detection thresholds is critical, as is the fact that these parameters can change over time. Some clinicians have adapted the SAMHSA workplace drug testing model for clinical drug testing with success (IA screen with MS confirmation), but the range of analytes in the SAMSHA-5 itself is likely too narrow to

be of use in most clinical scenarios. Some laboratories offer LC-MS/MS UDT without IA and have been successful; other labs rely only on IA and find that acceptable for their clientele. Just as clinicians use HbA1c as an objective measure for the diagnosis of pre-diabetes, aberrant UDT results can be used as an objective measure[30] and used to motivate patient change and stimulate healthy physician-directed patient education. Although specific training and application to individual clinical management are outside of the scope of this report, the Council recommends the development of practical guidance to assist clinicians in implementing UDT in their practice and understanding how UDT results may affect patient management.

RECOMMENDATIONS

The Council on Science and Public Health recommends the following recommendations be adopted and the remainder of the report be filed:

1. That Policy H-95.985, "Drug Screening and Mandatory Drug Testing," be amended by addition and deletion as follows:

   Drug ~~Screening and Mandatory Drug~~ Testing

   The AMA believes that physicians should be familiar with the strengths and limitations of drug ~~screening~~ testing techniques and programs:

   1. Due to the limited specificity of the inexpensive and widely available non-instrumented devices such as point-of-care drug testing devices ~~screening techniques~~, ~~forensically~~ acceptable clinical drug testing programs ~~must~~ should include the ability to access highly specific, analytically acceptable ~~technically more complicated and more expensive~~ confirmation techniques, which ~~unequivocally~~ definitively establish~~es~~ the identities and quantities of drugs, in order to further analyze results from presumptive testing methodologies. Physicians should consider the value of data from non-confirmed preliminary test results, and should not make major clinical decisions without using confirmatory methods to provide assurance about the accuracy of the clinical data.

   2. Results from ~~such~~ drug testing programs can yield accurate evidence of prior exposure to drugs. Drug testing does not provide any information about pattern of use of drugs, dose of drugs taken, ~~abuse of or~~ physical dependence on drugs, the presence or absence of a substance use disorder, or about mental or physical impairments that may result from drug use, nor does it provide valid or reliable information about harm or potential risk of harm to children or, by itself, provide indication or proof of child abuse, or neglect or proof of inadequate parenting.

   3. Before implementing a drug testing program, physicians should: (a) understand the objectives and questions they want to answer with testing; (b) understand the advantages and limitations of the testing technology; (c) be aware of and educated about the drugs chosen for inclusion in the drug test; and (d) ensure that the cost of testing aligns with the expected benefits for their patients. ~~, and~~ Physicians also should be satisfied that the selection of drugs (analytes) and subjects to be tested as well as ~~and~~ the screening and ~~confirming~~ confirmatory techniques that are used meet the stated objectives.

   4. Since physicians often are called upon to interpret results, they should be familiar with the disposition characteristics ~~pharmacokinetic properties~~ of the drugs to be tested before interpreting any results. ~~and the use to which the results will be put.~~ If interpretation of any given result is outside of the expertise of the physician, assistance from appropriate experts such as a certified medical review officer should be pursued.

2. That our AMA, in conjunction with the AMA Opioid Task Force, develop practical guidance and educational materials to assist physicians with implementing urine drug testing as part of a risk mitigation strategy when opioid analgesics are prescribed for chronic use.

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Table 1. Drugs often included in urine drug testing (UDT) (adapted from[8]).

Drug/Drug Class	Drug or Metabolite Included in Testing
Amphetamines	Amphetamine[a]
	Methamphetamine[a]
	MDA[a]
	MDEA[a]
	MDMA[a]
	Phentermine
Barbiturates	Butalbital
	Phenobarbital
Benzodiazepines	Alprazolam
	Clonazepam
	Diazepam
	Flurazepam
	Lorazepam
	Nordiazepam
	Oxazepam
	Temazepam
Cocaine[a]	Benzoylecgonine[a]
Heroin	Heroin (diacetylmorphine)
	6-AM[a]
	6-acetylcodeine
Marijuana[a]	THCA[a]
Opioids	Buprenorphine
	Norbuprenorphine
	Codeine[a]
	Norcodeine
	Dihydrocodeine
	Fentanyl
	Hydrocodone
	Norhydrocodone
	Hydromorphone
	Meperidine
	Normeperidine
	Methedone
	EDDP
	Morphine[a]
	Oxycodone
	Noroxycodone
	Oxymorphone
	Tapentadol
	Tramadol
	O-desmethyl-tramadol
	N-desmethyl-tramadol
PCP[a]	PCP[a]
Carisoprodol	Carisoprodol
	Meprobamate
Anticonvulsants	Gabapentin
	Pregabalin

[a]Drugs/metabolites included in federally regulated SAMHSA UDT
6-AM=6-monoacetylmorphine;
EDDP=2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine;
MDA=3,4-methylenedioxyamphetamine;
MDEA=3,4-methylenedioxyethylamphetamine;
MDMA=3,4-methylenedioxymethamphetamine; PCP=phencyclidine;
THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid

Table 2. Compounds causing potential false positive results with immunoassay testing.

IA Test	Compound Causing a Potential False Positive		
Amphetamines	Amantadine Aripiprazole Benzphetamine Brompheniramine Bupropion Cathine Cloroquine Chlorpromazine Ciprofloxacin Clobenzorex Desipramine Dimethylamylamine Doxepin Ephedra Ephedrine Fenfluramine Fenproporex Fluorescein Fluoxetine Ginkgo	Isometheptene Isoxsuprine Labetalol m-Chlorophenylpiperazine (mCPP) MDA MDMA MDPV Mefenamic acid Mephentermine Metformin Methamphetaminea l-methamphetamine (Vick's Inhaler) Methylphenidate Metronidazole Ofloxacin Phenmetrazine Phenothiazines Phentermine	Phenylephrine Phenylethylamine Phenylpropanolamine Promethazine Propranolol Propylhexedrine Pseudoephedrine Pyrovalerone Ranitidine Ritodrine Salbutamol Selegiline Sodium Cyclamate Thioridazine Tolmetin Trazadone Trimethobenzamide Trimipramine Tyramine
Barbiturates	NSAIDS (ibuprofen, naproxen)	Phenytoin	Tolmetin
Benzodiazepines	Chlorpromazine Efavirenz Fenoprofen	Flurbiprofen Indomethacin Ketoprofen	Oxaprozin Sertraline Tolmetin
Buprenorphine	Codeine Dihydrocodeine	Morphine Methadone	Tramadol
Cocaine	Coca leaf tea[a] Ecgonine	Ecgonine methyl ester Tolmetin	Topical anesthetics containing cocaine[a]
Fentanyl	Trazadone	Risperidone	
Marijuana (THC)	Acetylsalicylic acid Baby wash/Soap Dronabinol[a]	Efavirenz Hemp-containing foods[a] NSAIDs (ibuprofen, naproxen)	Proton pump inhibitors (pantoprazole) Rifampin Tolmetin
Methadone	Chlorpromazine Clomipramine Cyamemazine Diphenhydramine	Doxylamine Phenothiazine compounds Olanzapine Quetiapine	Tapentadol Thioridazine Verapamil
Opiates	Dextromethorphan Diphenhydramine Doxylamine Heroin[a] Poppy seeds[a]	Procaine Quinine (tonic water) Fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin)	Ranitidine Rifampin Tolmetin Verapamil
Phencyclidine	Dextromethorphan Diphenhydramine Doxylamine Ibuprofen	Imipramine Ketamine Lamotrigine Meperidine	Mesoridazine Thioridazine Tramadol Venlafaxine, O-desmethyl-venlafexine
Tricyclic Antidepressants	Carbamazepine Cyclobenzaprine Cyproheptadine	Diphenhydramine Hydroxyzine	Promethazine Quetiapine

[a]Contain or metabolize to target analyte
Table information from[15,19-22]
MDA=3,4-methylenedioxyamphetamine; MDMA=3,4-methylenedioxymethamphetamine;
MDPV= Methylenedioxypyrovalerone; NSAIDS=non-steroidal anti-inflammatory drugs

Table 3. Common causes of false negative results with immunoassay testing.

Potential Causes of False Negative IA Test	Example
Lack of cross reactivity for the desired tested drug class	An IA targeted for natural opiates does not readily detect semisynthetic opioids such as oxycodone.
Drug metabolites do not cross react with IA	An IA detects alprazolam but does not reliably detect the predominant metabolite, α-hydroxyalprazolam. Opioid normetabolites are also a concern (e.g., norhydrocodone).
Threshold of IA is too high	Many IAs were developed for workplace UDT and have thresholds > 300 ng/mL (and as high as 2,000 ng/mL). A more appropriate threshold for clinical UDT is ≤ 100 ng/mL.
Specimen is dilute	Fluid intake can cause drug concentration to fall below the threshold concentration.
Adulterated or substituted specimen	Added adulterants can mask the presence of some drugs. Substituted specimens can contain urine from another person, animal, synthetic urine, or some other fluid.
Desired drugs not included in testing	Many commonly abused prescription drugs require separate IAs to detect and could be overlooked in a POC device (e.g., natural opiates, oxycodone, synthetic opioids, methadone, tapentadol, buprenorphine) and others may not be included in IA presumptive testing (e.g., carisoprodol).
IA=immunoassay; UDT=urine drug testing; POC=point-of-care testing	

APPENDIX - Alternative Specimens for Drug Testing

Although urine is the most common matrix used for drug testing, other matrices are available including oral fluid, blood/serum, breath, hair, nails, and sweat. Differences in the collection and interpretation for each specimen type as well as some strengths and weaknesses are associated with each matrix.[8,14]

Matrix	Detection Window	Collection	Interpretation	Strengths	Weaknesses
Oral Fluid	Acute use: ~4 hrs Chronic use: 24-48 hrs	Non-invasive; observed; non-standardized procedures; use of collection device highly recommended	Disposition of parent drug exceeds metabolites; drug concentrations 10-100x lower than urine	Harder to adulterate; use for shy bladder, renal impairment, suspected urine tampering	Some drugs a challenge (e.g. transdermal buprenorphine); sample volume could be hard to obtain; POC devices developed for forensic use and not recommended for clinical testing
Blood/ Serum	Limited to current drug use (hours)	Invasive; difficult to properly store and transport	Disposition of parent drug exceeds metabolites	Can detect low levels of drug (usually in a legal context)	Generally requires lengthy testing procedures; expensive
Breath	Limited to current drug use (hours)	Non-invasive	Limited to the evaluation of alcohol	Well correlated with blood alcohol levels	Most other drugs not sufficiently volatile for breath analysis
Hair	Weeks, months, years (depending on hair length)	Non-invasive; easy to collect; difficult to cheat; easy to store	External contamination possible; color bias; hair treatments may alter drug disposition; drugs may not be detectable for weeks following exposure; segmental analysis variable	Possible use for past drug use	Not all drugs equally incorporated; labor intensive sample preparation; low drug concentrations; expensive; not recommended for clinical testing

Matrix	Detection Window	Collection	Interpretation	Strengths	Weaknesses
Nails[84]	Fingernails: 3-5 months Toenails: 8-14 months	Non-invasive; nail clippings	Disposition of parent drug usually exceeds metabolites	Possible use for past drug use	Mechanisms of incorporation not fully understood
Sweat[85,86]	~1 week	Non-invasive; adherent patch	Less sensitive than urine	Extended detection time	Unreliable adherence so limited utility; rash; external contamination

2. NATIONAL DRUG SHORTAGES: UPDATE

Informational report; no reference committee hearing.

HOUSE ACTION: FILED

INTRODUCTION

Policy H-100.956, "National Drug Shortages," directs the Council on Science and Public Health (CSAPH) to continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates (HOD) on progress made in addressing drug shortages in the U.S. This informational report provides an update on continuing trends in national drug shortages and ongoing efforts to further evaluate and address this critical public health issue.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from September 2015 to August 2016, using the text term "drug shortages" combined with "impact," "crisis," "oncology," "chemotherapy," "antibacterial," "pediatric(s)," "nutrition," and "parenteral." Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP), Government Accountability Office (GAO), Pew Charitable Trusts, Generic Pharmaceutical Association, the Pharmaceutical and Research Manufacturers of America (PhRMA) and by direct contact with key FDA and ASHP staff who manage drug shortage issues on a daily basis.

BACKGROUND

The Council has issued six previous reports on drug shortages.[1-6] The findings and conclusions from these reports are summarized in CSAPH Report 2-I-15.[6] The remainder of this report will update current information on drug shortages since that report was developed.

CURRENT TRENDS IN DRUG SHORTAGES

The two primary data sources for information on drug shortages in the United States continue to be the Drug Shortage Resource Center maintained by ASHP in cooperation with the University of Utah Drug Information Service and the Drug Shortage Program at the FDA.[7,8] For a reminder on how the ASHP and FDA information and statistics on drug shortages are developed, see Table 1. The ASHP defines a drug shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent." The FDA defines shortages as a period of time when the demand or projected demand for a medically necessary drug in the United States exceeds its supply. Medically necessary drugs are defined by FDA as "any drug product used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other drug that is judged to be an appropriate substitute or there is an inadequate supply of an acceptable alternative."

Because their criteria differ (the main distinction being the FDA's definition of a "medically necessary drug"), the ASHP site lists more drug shortages than the FDA site.

American Society of Health-System Pharmacists

As of September 13, 2016, ASHP's Drug Shortage Resource Center identified 135 drugs in shortage, down from 180 at the same time in 2015. Among these drug shortages, 17 products were not commercially available at all.[8] Sixty-nine manufactured drugs have been discontinued since 2010, an increase of 9 from a year ago. The top active shortages by drug class remain central nervous system agents, electrolytes and nutritional components, antimicrobials, cardiovascular drugs, and chemotherapeutic agents. For a longitudinal view of new drug shortages on an annual basis, and the number of active drugs shortages quarterly, see the Appendix. Active shortages include both new and unresolved drug shortages. According to ASHP, the number of new shortages continues to decrease, while the number of active shortages has stabilized to a certain degree.

Food and Drug Administration

As of September 13, 2016, the FDA reported that 61 drugs were currently in shortage (compared with 67 one year ago), and 10 had been resolved.[8] The latter are closely monitored because they may be at risk for falling back into shortage. Based on passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, companies are required to notify FDA of a permanent discontinuance or an interruption in manufacturing of certain drug products six months in advance, or if that is not possible, as soon as practicable. The shortage notification requirement has apparently reduced the number of new shortages by allowing FDA additional time to work with manufacturers to prevent shortages. The FDA's drug shortages website lists drugs that meet these criteria, reflecting shortage information supplied by manufacturers.[8] A Final Rule published on July 27, 2015 provides further guidance on the notification process and adds biologic products to the requirements for notification about potential supply disruptions.[9]

Drug Shortages Metrics Reported by FDA. The FDA's third annual report on drug shortages (required by FDASIA) noted the following metrics during the first three quarters of calendar year 2015.[10]

- FDA was notified of 131 potential shortage situations by 47 different manufacturers, comparable to the numbers reported in 2014.
- 128 new drug shortages were prevented in the first three quarters of 2015, a 64% increase over the comparable time period for 2014.
- The review of 102 generic abbreviated new drug or supplemental applications was expedited, comparable to the numbers reported in 2014.
- 11 inspections were prioritized to address a drug shortage, comparable to the number reported in 2014.
- 11 fewer new drug shortages occurred in the first three quarters of 2015 (22) compared with the same period in 2014 (33).
- FDA exercised regulatory flexibility and discretion in 19 instances affecting 37 medically necessary products. Most of these involved measures to mitigate risks such as removing particulate matter, extra testing for quality, third-party oversight of production, provision of special instructions to prescribers and/or patients, or approval of foreign sources. With respect to the last of these mitigation strategies, the FDA now conducts regular virtual meetings with their international regulatory counterparts to share information on drug shortages and mitigation strategies impacting patients in other countries.

The FDA also has developed apps for both the iPhone and Android operating systems that provide access to drug shortage information as well as notifications about new and resolved drug shortages.

Reporting a Drug Shortage

Physicians can directly report a drug shortage via the ASHP drug shortage website. Physicians can directly report a drug shortage to the Center for Drug Evaluation and Research via email (drugshortages@fda.hhs.gov) or by phone at 240-402-7770.

GAO REPORT

In a follow-up to its 2014 report on drug shortages, the Government Accountability Office (GAO) evaluated trends in drug shortages from 2010-2015 in an effort to identify influential factors.[11] This evaluation confirmed that the FDA had prioritized 383 new, abbreviated, and supplemental drug applications to address drug shortages, mostly for

sterile injectable products. The use of this prioritization scheme was temporally associated with reductions in active and ongoing shortages. Analysis of selected categories (i.e., sterile injectable anti-infective and cardiovascular drugs) confirmed that shortages were strongly associated with previously identified key drivers, namely a decline in the number of manufacturers, existence of a generic product, and an emergent problem with manufacturing capability in at least one manufacturer that was sufficiently serious to cause a warning letter to be issued. Shortages were more likely to affect generic drugs with low profit margins, although drug price itself was not predictive in this study.

GENERIC PHARMACEUTICAL ASSOCIATION

Given that the majority of drug shortages involve generic products, the GPhA created a voluntary approach called the Accelerated Recovery Initiative in 2013 intended to accelerate the recovery of certain critical drugs in short supply.[4,12] This multi-stakeholder approach relies on voluntary, confidential communication between an independent third party (IMS Health) and pharmaceutical companies involved in the manufacturing of generic injectable drugs in shortage. Additionally, wholesalers, distributors, and the FDA can provide information to assist companies with making timely decisions to help avert or mitigate a shortage. While this program is apparently still operational, there are no publicly available reports evaluating its degree of success.[12]

CLINICAL IMPLICATIONS

Despite increasing success in preventing or mitigating drug shortages and an overall decrease in the number of new drug shortages, critical drug shortages continue to occur across multiple therapeutic categories. While the existence of a sole source manufacturer is a risk factor for shortages, it also has been the focus of some recent exorbitant drug price escalations. Reviews of shortages affecting the operation of emergency departments identified several intravenous formulations that remain in short supply and are affecting patient care including certain opioid analgesics, antiemetics, selected antimicrobials, benzodiazepines and other drugs used for rapid induction of anesthesia, electrolytes, and local anesthetics.[13,14] Shortages of various antidotes also have been noted, and the implications of drug shortages for pediatric patients, those with cardiovascular disease or those who are acutely ill have been studied.[15-18] In some cases, work-arounds have been successful in maintaining patient safety and achieving satisfactory clinical outcomes.[19]

SUMMARY

Manufacturers are notifying the FDA about potential disruptions in supply or shortages earlier than in the past and the FDA is expediting the review of new applications intended to address shortages. Accordingly, the total number of new drug shortages continues to decline and the extent of ongoing shortages has stabilized over the past two years. However, the drug supply for many acutely and critically ill patients in the United States remains vulnerable despite federal efforts.[20] Some progress is being made, but permanent solutions remain elusive and beyond the control of individual practitioners and the health care system.

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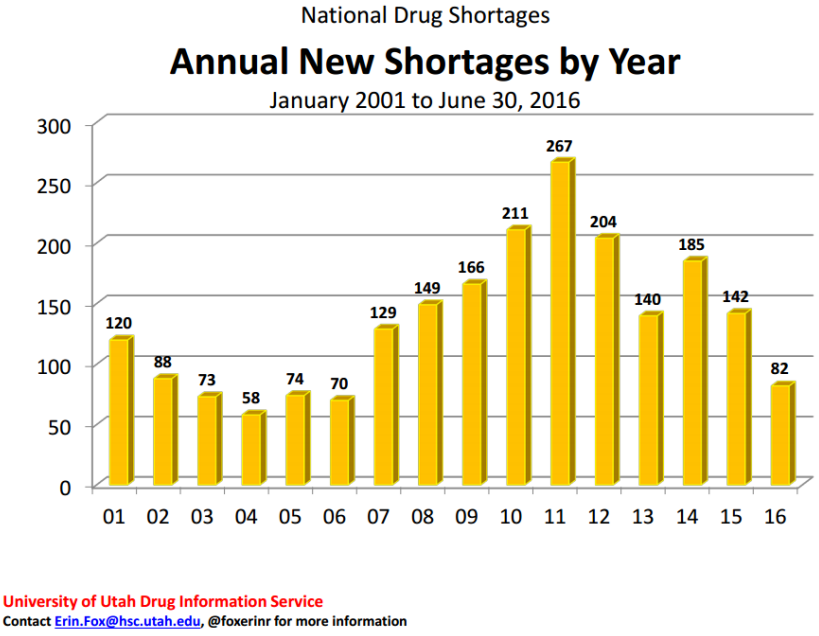
Table 1. Contrasting the FDA (CDER) and ASHP Drug Shortage Websites

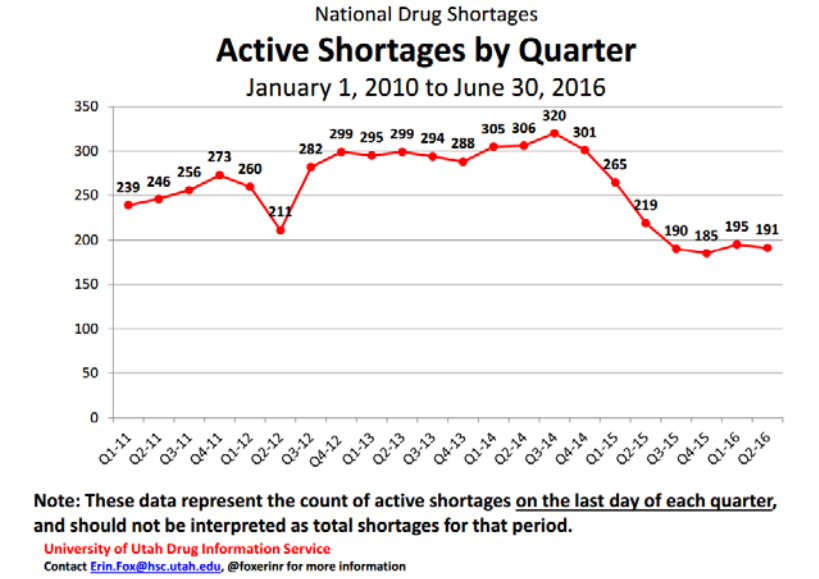
	FDA	ASHP
Purpose	Provides information obtained from manufacturers about current shortages, estimated duration, and discontinuations and provides information about FDA's and other stakeholders' roles in addressing and preventing shortages	Notification of new shortages and status of ongoing shortages; drug shortage management resources
Audience	Public	Healthcare practitioners
Scope of shortage list	All drugs are listed that are confirmed to be a national shortage by FDA. A shortage is considered to be the period of time when the demand for the drug within the United States exceeds the supply of the drug.[a]	All drug and biologic shortages reported and confirmed with manufacturer that are national in impact.
Source of shortage report	Manufacturers notify FDA of production disruption and voluntarily provide updates. Reports are also received from ASHP and from public via drugshortages@cder.fda.gov Note: Manufacturer-provided information represents shortage status at drug firm level.	Voluntary reports from practitioners, patients, pharmaceutical industry representatives and others Note 1: Information is updated based on release dates from manufacturers. Note 2: Reports reflect status at healthcare provider level.
Criteria for inclusion on list	Manufacturers cannot meet current market demand for the drug based on information provided by manufacturers and market sales research. Drug listed are defined as "medically necessary."	(1) Shortage is verified with manufacturers and (2) affects how pharmacy prepares or dispenses a product, or (3) requires use of alternative drugs, which may affect patient care.
Criteria for resolving shortage	One or more manufacturers are in production and able to meet full market demand.	All manufacturers of the drug restore all formulations and dosage sizes to full availability. Note: Products are listed despite partial or restricted availability as supply chain disruptions can result in intermittent shortages at the provider or patient level.
Reason for shortage	Provided by manufacturers using reasons required by legislation.[b] FDA encourages firms to provide additional information about reasons and other information which, if proprietary, is nondisclosable without the firm's permission.	Provided by manufacturer, if willing to disclose. Note: May differ from FDA's due to different sources of information and legislation requiring FDA to use specified reasons

Table 1. Contrasting the FDA (CDER) and ASHP Drug Shortage Websites		
Other information	Estimated duration, links to regulatory information such as recalls and Dear Healthcare Provider Letters	Estimated duration, list of available products, implications for patient care and safety, shortage management strategies, therapeutic alternatives

Notes:
[a] A separate shortage webpage for vaccines and some biologics is maintained by the Center for Biologics Evaluation and Research
[b] Categories include (a) requirement related to complying with good manufacturing practices; (b) regulatory delay; (c) shortage of an active ingredient

APPENDIX





3. GENOME EDITING AND ITS POTENTIAL CLINICAL USE

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED
REMAINDER OF REPORT FILED
See Policy H-480.945

BACKGROUND

The promise of gene therapy has increased substantially over the last decade due to rapid advancements in two technologies: DNA sequencing and genome engineering. Next-generation DNA sequencing techniques, reviewed by this Council in 2012, have allowed analysis of the genome and discovery of the genetic basis of disease with unprecedented speed and accuracy.[1,2] Concurrently, techniques have been discovered that allow modification of the genome with a level of efficiency and precision that had not previously been achieved.[3] One such technique, termed CRISPR-Cas9,[4] has triggered a surge of research efforts to harness it for correcting mutations that are disease-causing, and to understand how it could be used as a therapeutic intervention in individuals with disease.[5] Along with the scientific and medical advances in genome editing, ethical concerns also are evident, especially about the permanent editing of fertilized embryos, altering the genome of every differentiated cell that arises from that embryo and the offspring of that individual.[6]

The Council on Science and Public Health has initiated this report to inform physicians and the House of Delegates about the remarkable advances in genome editing seen in recent years and its potential clinical applications in gene therapy, as well as concerns about it and proposals to ensure its responsible use.

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2006 and 2016 using the search terms “gene editing,” “genome editing,” and “CRISPR.” To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Genome editing information posted on the websites of the National Academies of Sciences, Engineering, and Medicine and the American Society of Human Genetics also was reviewed. Additional articles were identified by manual review of the references cited in these publications.

GENE THERAPY

The concept of gene therapy, broadly defined as the use of genes or other genetic sequences to counteract or replace malfunctioning genes that cause disease, arose decades ago. Yet it has been slow in becoming a widespread therapeutic option, due in part to the complex mechanisms required to deliver genetic material to the cell and drive appropriately timed therapeutic gene expression, while avoiding the disruption of endogenous cellular function.[7] The first successful attempt at gene therapy occurred in the early 1990s in two children with severe combined immune deficiency (SCID) caused by defects in the adenosine deaminase (ADA) gene. Normal copies of the *ADA* gene were inserted into their T-cells at repeated time points, resulting in sustained immune function.[8] Other gene therapy trials in the 1990s and 2000s were considered successful, but they were small, early-phase trials, and limited to only a few participants with very rare genetic diseases that were well characterized at the time. Challenges to using gene therapy more widely persisted, including the transient expression of genes inserted to the cell but not permanently into the cell’s genomic DNA (called “transgenes”), requiring continual therapy; limitations in the ability of viral vectors to deliver functional genes to cells; insertional mutagenesis, the propensity of genetic sequences to randomly insert into genomic DNA, causing mutations and resultant disease; and immune responses to the introduced foreign DNA.[7,9]

Nevertheless, research to overcome gene therapy barriers continued, and important successes have been realized. In 2015, it was reported that gene therapy was successful in several patients with Wiskott-Aldrich syndrome (WAS), a severe primary immunodeficiency caused by mutations in the *WAS* gene.[10] The trial was one of the first to use an engineered viral vector that could limit insertional mutagenesis and reduce associated complications. Other gene therapy successes have included the use of modified T-cells to treat relapses in acute lymphoblastic leukemia;[11] restoration of vision in patients with Leber congenital amaurosis, an inherited abnormality of the retina that causes

blindness;[12] and reduction of bleeding episodes in patients with severe hemophilia B.[13] Another milestone was achieved in 2012 with the approval by the European Medicines Agency (EMA) of the first gene therapy product available in Europe. Alipogene tiparvovec, marketed as Glybera, is designed for the treatment of the rare disease lipoprotein lipase deficiency.[14] This year, the EMA also approved Strimvelis, a gene therapy product for the treatment of ADA-caused SCID.[15,16] No human gene therapy products have been approved to date by the FDA, although development of products is underway in the biotechnology industry.[17]

Genome Editing

Progress in gene therapy is likely to accelerate with newly discovered techniques that allow for precise and permanent modification of the genome without the complications that accompany other gene therapy techniques. The risk for insertional mutagenesis is drastically reduced because the therapeutic genetic sequences used are engineered to insert into the cell's genomic DNA at precise locations.[7] Additionally, because the therapeutic sequence is inserted into the cell's genomic DNA rather than being expressed as a transgene, expression of it can be more tightly controlled.[7] Termed "genome editing" or "genome engineering," these techniques are being tested for gene therapy applications that could correct or inactivate disease-causing mutations, introduce protective mutations, insert functional genes, or disrupt foreign DNA (such as that present in viral or bacterial infections).[18]

HOW DOES GENOME EDITING WORK?

DNA Editing

The genome editing process is illustrated in the Figure (see page 14). It is dependent on an engineered DNA-cleaving enzyme (a nuclease) that is programmed to cut genomic DNA at specific locations. Four major classes of nucleases can be engineered for site-specific editing; of these four classes, the CRISPR-Cas9 class can be easily targeted to almost any location in the genome and carries out its nuclease activity most efficiently.[19] The Cas9 nuclease was first discovered in bacterial adaptive immunity experiments. Bacterial genomes carry DNA sequences called "clustered regularly interspaced short palindromic repeats" (or "CRISPR"), which are located in close proximity to the coding sequence of a CRISPR-associated ("Cas") DNA-cleaving enzyme. In bacteria, the CRISPR sequences act as guides for Cas9's nuclease activity, providing a defense mechanism against phage infection.[19] Further studies demonstrated that Cas9 could be engineered to cleave the DNA of many organisms' cells, including humans', at specific locations by providing it with the correct guide.[19,20]

Once Cas9 is engineered to cleave genomic DNA at a specific location, it can be inserted into the cell to carry out its nuclease activity. It finds the location it has been engineered to recognize and cuts both strands of the DNA (Figure). When the DNA strand is cut, the cell uses its own DNA repair mechanisms to attempt to repair the cut. Two different repair mechanisms result in different outcomes. In one mechanism, called non-homologous end joining (NHEJ), the two ends of the DNA strand that have been cut are directly rejoined.[18] However, this process is often inaccurate and results in the insertion or deletion of a small number of nucleotides, disrupting normal gene function (Figure). This is the genome editing mechanism used to inactivate a gene. By cutting a gene in its coding region and forcing repair through NHEJ, the small insertions or deletions that occur in the coding region suppress gene function or inactivate the gene altogether.[18] An example of the way in which this type of genome editing could be used therapeutically is in sickle cell disease.[3] Sickle cell disease is caused by mutations in the *HBB* gene, which render γ-globin dysfunctional. Functional γ-globin can be restored by upregulating the expression of the *HBG* gene. However, *HBG* is suppressed by the gene *Bcl11A*. By using genome editing to inactivate *Bcl11A*, *HBG* gene function is activated and γ-globin expression can be restored.[3]

The other repair mechanism used by cells after the DNA strand has been cut is called homologous recombination (HR). In HR, the cell uses a DNA fragment that exactly matches the sequences surrounding the cut as a template to direct repair (Figure). Genome editing takes advantage of the use of these DNA fragments to direct repair; an exogenous DNA fragment containing a new gene or a corrected sequence of nucleotides, along with sequences that match those surrounding the site of the DNA cut, is inserted into the cell along with Cas9.[18] When Cas9 cuts the DNA in the location it has been engineered to recognize, the cell uses the exogenous DNA fragments as a template to repair the cut (Figure). This is the genome editing mechanism that is used to correct a mutation or insert a functional gene. The exogenous DNA repair fragment can be engineered to carry a correction to a mutation or a new functional gene that will be incorporated into the genome. In the example of sickle cell disease discussed above, this

method could be used to either correct the mutation in the *HBB* gene, or insert a functional *HBB* gene in another location, restoring γ-globin expression.[3]

Delivery mechanisms

For genome editing to occur, the engineered nuclease has to be introduced into target cells. This can occur either *ex vivo* or *in vivo*. In *ex vivo* delivery, a portion of the cell population that is targeted for editing is removed from the body, undergoes genome editing, and then is returned to the host. In this mechanism, the engineered nuclease and DNA repair fragments (for HR editing) can be introduced into the cultured target cells through several methods, including electroporation, a pulse of electricity that briefly opens pores in the cell membrane to allow the nuclease and DNA repair fragments to enter; or non-pathogenic viruses that insert the nuclease and DNA repair fragments directly into the cell.[18] *Ex vivo* delivery results in high editing rates, and therefore is often used for gene therapy applications. However, because it is difficult for some target cell populations to survive manipulation outside of the body, *ex vivo* delivery is usually limited to tissues with adult stem cell populations that are amenable to culture and manipulation, such as those from the hematopoietic system.[18]

In *in vivo* delivery, the engineered nuclease and DNA repair fragments are delivered to targeted cells in their native environment within the body. This has been achieved by using non-pathogenic viral vectors with affinity for the target tissue; the viruses are packaged with the nuclease and the DNA repair fragments (for HR editing), which are deposited directly into the cell when the virus "infects" it.[18] *In vivo* delivery is preferred when the target tissue is not amenable to culture or manipulation outside of the body. It can also be used to efficiently target multiple tissue types, allowing for its therapeutic use in a wider range of diseases.[18] However, the viruses that can be used as vectors are sometimes limited in their affinity for multiple tissue types, and while they are non-pathogenic, the amount of virus necessary for use in therapeutic genome editing may induce an immune response.[18]

CLINICAL APPLICATIONS OF GENOME EDITING

The most immediate uses of genome editing have been in biomedical research settings. The relative ease of using the CRISPR-Cas9 system, as well as other programmable nucleases, has triggered the modeling of human disease and proof-of-concept studies in a number of species and in human cell lines.[21] A few experimental uses have progressed to early clinical trial stages in humans. Selected examples that are most promising for gene therapy are discussed in this section.

Monogenic Disorders

Nearly 8,000 diseases are monogenic, i.e., caused by mutations in single genes.[3] Many of these diseases are candidates for gene editing because, simplistically speaking, the modification needed is only in one gene. At this time, successful genome editing for several monogenic diseases has been achieved in model organisms. For example, in a mouse model of Duchenne muscular dystrophy (DMD), which mimics the human form of DMD with a mutation in the *dystrophin* gene, a viral vector was used to deliver Cas9 *in vivo* to mouse muscle cells.[22-25] The Cas9 was engineered to cut the *dystrophin* gene in two places flanking the mutation, thereby removing the mutation from the cells' genomic DNA, then the cut ends of *dystrophin* were repaired by the NHEJ mechanism.[22-25] The technique only partially restored Dystrophin protein function, but it was enough to restore partial muscle function in the mice. Particularly exciting was the finding that gene editing occurred in satellite cells, stem cells that are present in muscle, implying that the satellite cells could populate the muscles with cells carrying the partially repaired *dystrophin* gene.[25]

Preclinical studies using genome editing to correct the mutations that cause cystic fibrosis have also been promising. Organoids are small amounts of functional tissue derived from human stem cells. In intestinal organoid tissue derived from patients carrying mutations in the *CFTR* gene, which causes cystic fibrosis, the CRISPR-Cas9 system was used to correct the mutations through the HR mechanism.[26] The corrected *CFTR* was fully functional and was able to "rescue" the cystic fibrosis phenotype in the organoids.[26] Together with other experiments showing that cultured intestinal organoids can be transplanted into and become functional in the colons of mice,[27] this provides a potential strategy for gene therapy in patients with cystic fibrosis.

Other studies demonstrated successful proof-of-concept results using genome editing for the treatment of many other monogenic diseases, including hemophilia B, hereditary tyrosinemia, ADA-caused SCID, sickle cell disease,

and β-thalassemia.[3,18,19] The biotechnology company Editas has stated that it will begin a clinical trial in 2017 using CRISPR-Cas9 as a gene therapy mechanism to correct mutations causing Leber congenital amaurosis.[28]

Cancers

With more than 1.5 million cases of cancer diagnosed and half a million deaths from cancer each year,[29] the prospect of treating cancer using genome editing-based technologies is appealing. However, it is widely thought that direct repair of acquired or inherited mutations in cancer cells would not be effective.[18] Mutations in cancer cells give them a fitness advantage over non-cancerous cells, i.e., they divide quickly and do not respond to the cells' signals to halt growth or self-destruct. Even the most efficient genome editing could not repair every cancer cell present in a tissue or throughout the body, so cancer cells with repaired mutations would quickly be outcompeted by their non-repaired counterparts, rendering the therapy ineffective.[18]

Despite the inability to directly correct mutations in cancer cells, research has shown exciting results using engineered T-cells to harness the immune system's ability to fight cancer. T-cells are harvested from patients with certain types of cancer, engineered to express receptors that have specific and strong affinity for tumor antigens, and then infused back into patients, where they attack tumor cells.[30,31] This technique has been the most successful in trials for melanomas and leukemias and lymphomas of B-cell origin.[31]

Genome editing is now being explored as a technique to engineer T-cells that more stably and permanently express the receptors that target them to cancer cells. In June 2016, the National Institutes of Health approved a proposal to use the CRISPR-Cas9 system to edit T-cells from patients with one of three cancer types: multiple myeloma, sarcoma, or melanoma.[32] The genome editing will include inserting a gene that helps the T-cells better recognize cancer cells, inactivating a gene that interferes with the recognition process, and inactivating a gene that allows cancer cells to prevent T-cell attacks.[32] Recruitment could begin late in 2016, once FDA and institutional review board approval are granted.[33] Another trial using genome-edited T-cells is set to begin this year in China in patients who have metastatic non-small cell lung cancer and for whom chemotherapy, radiation therapy, and other treatments have failed. In that trial, CRISPR-Cas9 will be used to inactivate the gene that encodes PD-1, which normally acts as a check on the cell's capacity to launch an immune response.[34]

Non-Genetic Disorders

In addition to the use of genome editing to correct diseases caused by genetic mutations, it also is being investigated for use in treating infectious diseases and a variety of other health conditions. For example, the discovery that patients who carry mutations disabling the HIV receptor CCR5 are nearly completely resistant to HIV infection provided the basis for a genome editing-based clinical trial for treating HIV. A small, early-phase clinical trial removed T-cells from patients with HIV, used an engineered nuclease to mutate the *CCR5* gene, and then transplanted the edited T-cells back into the patients.[3,18,35] Preliminary results showed that in the majority of patients receiving the edited T-cells, HIV DNA levels in the blood decreased, and in one patient, HIV was undetectable.[35] Unlike the fitness disadvantage that directly edited cancer cells have when compared to their non-edited counterparts, T-cells with the edited *CCR5* gene have a fitness advantage over the non-edited T-cells; in the trial, the edited T-cell population had lower rates of cell death than did non-edited T-cells, suggesting that they are more stable.[35] Complete removal of the virus will be challenging, however, and will depend on extremely efficient delivery and editing strategies;[18] phase II trials are now ongoing to test such strategies. Similar genome editing mechanisms have also shown promising results in treating hepatitis B virus infection.[36,37]

Genome editing also is being explored as a therapy to reduce cardiovascular disease risk. The gene *PCSK9* was recently discovered as a modulator of LDL cholesterol function. People carrying dominant gain-of-function mutations in *PCSK9* have highly elevated LDL level and premature coronary heart disease, and those carrying homozygous loss-of-function mutations have a nearly 80 percent reduction in LDL level with no apparent adverse clinical consequences.[38,39] PCSK9-targeting monoclonal antibodies are currently being tested in clinical trials as LDL-lowering therapies.[40] Genome editing of *PCSK9* has been tested in the pre-clinical setting. A viral vector was used for *in vivo* delivery of Cas9, engineered to introduce mutations in the *PCSK9* gene using the NHEJ mechanism, to liver cells of mice.[41] Editing occurred in more than half of the liver cells, and resulted in a 35-40 percent reduction in total cholesterol and reduced LDL plasma fractions.[41] This study has contributed to the notion that the future of cholesterol management may first be a bi-weekly or monthly intervention using PCSK9-inhibitor antibody drugs,

then eventually become a one-time intervention that permanently and selectively modifies the genome to inactivate *PCSK9* and thereby reduce cholesterol.[42]

CONSIDERATIONS BEFORE CLINICAL USE

The pace of exploration of genome editing as a potential tool for gene therapy has been rapid in recent years. However, translation of applications to the clinic will require the careful consideration of a number of factors, including the safety of the technology, its possible use in editing the germline, and high costs that could result in access problems and health disparities.

Safety

The specificity of engineered nucleases, i.e., their ability to cut DNA at precisely targeted positions and avoid cutting at non-targeted locations, will be a key factor in the translation of this mechanism of gene therapy into clinical practice. Genetic modifications resulting from genome editing are permanent, so off-target modifications could create cells with functional impairment or even oncogenic potential. CRISPR-Cas9 genome editing appears to result in only rare instances of off-target modification; one study estimated that one error in 300 trillion base pairs could occur, and given that the human genome is only 3 billion base pairs, that equates to one off-target modification per 100,000 cells.[43] However, more sophisticated methods are needed for evaluating the likelihood of off-target modification for each potential clinical use, and studies are ongoing to develop ways of preventing off-target modification.[44,45] Clinical use of genome modification would not be appropriate without mechanisms to ensure that off-target modifications are extremely rare and result in negligible clinical consequence.[18,46]

Another safety concern lies with using viral vectors as delivery mechanisms. Adeno-associated virus (AAV) vectors are approved for clinical use,[47] and have high delivery efficacy for a number of tissue types. But AAV vectors pose some challenges. In some cases, nucleases packaged within AAV vectors are constitutively active, increasing the chances of off-target modification.[18]Also, many people who have been naturally exposed to AAV have developed immunity to it, so it may not be an appropriate delivery mechanism for them.[18] Immunotoxicity also may occur upon exposure to certain engineered nucleases, including Cas9, since they are microbially derived.[48] Alternative delivery systems, including lipids and nanoparticles, are being explored to avoid the potential for immunotoxicity.[49,50]

Germline Editing

The most ethically-fraught conversations about genome editing center on the use of the technology to modify the genome of germline cells (eggs and sperm) or early-stage embryos. Such editing would result in permanent modifications to the individual arising from the germline cells or embryo, and would permanently change the gene pool since those modifications would be passed on to future generations. Conversations about these issues took on new urgency when researchers in China demonstrated that CRISPR-Cas9 could be successfully used to edit the genome of early-stage human embryos.[51] The embryos used in the study were genetically incapable of maturing into viable zygotes, and important limitations in the efficiency of CRISPR-Cas9 in human embryos were discovered, but the study nonetheless illustrated the application of genome editing to human embryos before ethical standards for its use have been widely promulgated. Further evidence that genome editing is close to being used in human embryos comes from a study that used CRISPR-Cas9 to induce genome modifications in one-cell stage embryos of cynomolgus monkeys, resulting in live births.[52] Cynomolgus monkeys are so genetically close to humans that they are often used to model human disease. The genome-edited animals are now being studied to determine the efficiency of the editing and potential health consequences stemming from it.[52]

Several organizations, including the National Academies of Sciences, Engineering, and Medicine (NASEM) and the American Society of Human Genetics (ASHG), have convened expert working groups to study the issue and define principles by which germline editing should or should not occur. Discussions center on the use of genome editing to treat or cure diseases for which no other equally effective therapy exists, and what types of disorders are sufficiently debilitating that extreme measures like genome editing are needed. The case for germline editing is most compelling when both parents are homozygous for a disease-related gene variant; however, that is a rare occurrence.[53] Another question that arises is whether genome editing has any value over preimplantation genetic diagnosis, which allows prospective parents who carry heritable disease-causing genes to select embryos lacking those genes.[54] Genome editing for complex polygenic diseases is likely not possible because those genes usually have very weak effects on their own and are often involved in a variety of physiological functions, some of which may be beneficial.[53,54]

Discussions also focus on the potential for non-medical use of germline editing, such as for selecting desirable traits, and the autonomy of parents to make genetic modifications in their offspring, who themselves are not able to consent.[53]

NASEM, along with the Royal Academy and the Chinese Academy of Sciences, held a summit late in 2015 during which a committee of scientific and ethics experts discussed genome editing and developed conclusions about its use.[55] The consensus conclusions support preclinical research on genome editing, as well as its use in somatic gene therapy concordant with regulatory law. However, the committee does not support clinical use of germline editing until "(i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application."[55] The committee will complete a comprehensive study of the scientific underpinnings of human genome editing technologies, their potential use in biomedical research and medicine, including human germline editing, and the clinical, ethical, legal, and social implications of their use by late 2016.[56]

Similarly, ASHG has convened a Workgroup on the Implications of Genome Editing to craft policy on genome editing; in addition to ASHG, the Canadian Association of Genetic Counselors, International Genetic Epidemiology Society, National Society of Genetic Counselors, and Association of Genetic Nurses and Counselors (United Kingdom and Ireland) participated in the Workgroup.[57] It developed a draft policy outline that supports research into the use of germline editing as long is does not culminate in a human pregnancy, and believes that clinical application should not proceed unless, at a minimum, there is "a) a compelling medical rationale, b) an evidence base that supports its clinical use, c) an ethical justification, and d) a transparent public process to solicit and incorporate stakeholder input."[57] ASHG has solicited member comments on the draft policy and will finalize it in the coming months.

The AMA Code of Medical Ethics contains similar sentiments regarding gene therapy and genetic engineering. Opinion 7.3.6, "Research in Gene Therapy & Genetic Engineering," states that genetic manipulation should be reserved for therapeutic purposes, and that efforts to enhance "desirable" characteristics are contrary to the ethical tradition of medicine. It sets out a number of conditions that should be met before physicians engage in research involving gene therapy or genetic engineering, including evidence that the intervention will be safe and effective, that no other suitable or effective therapies are available, and that it is restricted to somatic cells. The full opinion is in the Appendix. The Council believes that the principles set forth in Opinion 7.3.6 should guide AMA policy on genome editing.

Costs and Health Disparities

As is the case for many expensive therapies, access problems are likely to occur if genome editing-based gene therapies become viable clinical options. Use of the first gene therapy product approved by the EMA, Glybera, has been limited to only one patient because it carries a price tag of more than $1 million. It was covered by the patient's insurance company, but only after her physician worked intensely to obtain authorization.[16] It is not known what the cost of the newly EMA-approved gene therapy Strimvelis will be, but its manufacturer, GlaxoSmithKline, has stated that it will be "significantly less" than the $1 million mark.[16] According to the manufacturer of Glybera, UniQure, the high cost of gene therapy drugs is based on the substantial development costs, the fact that the market for the rare diseases they treat is exceptionally small, and in Glybera's case, that it is administered only once, rather than repeatedly over a period of time.[58] Compared to the $250,000 per year average cost of other orphan drugs that treat rare diseases, a one-time dose of a $1 million drug could be considered cost-saving. However, that cost is so high that it is unlikely patients who need the therapies could afford them, or that insurance companies would authorize payment. This undoubtedly would create health disparities issues, in which only the wealthiest patients, or those fortunate enough to have coverage through insurers who will approve the therapy, could have access to it. Although Glybera and Strimvelis are based on transgene expression rather than permanent genome modification, it is reasonable to assume that genome editing-based gene therapies would have similarly expensive development processes, leading to high costs for patients.

CONCLUSIONS

The last few years have seen unprecedented progress in the development of genome editing mechanisms and their potential applications for gene therapy. While most research is at the preclinical stages, a small number of clinical trials in humans have begun, with others planned for the near future. Much work remains to ensure the safety and

effectiveness of genome editing, and questions remain about the appropriate use of germline editing. The Council supports continued research into the clinical applications of genome editing, but urges caution and thoughtful consideration before clinical germline editing is undertaken. The Council also urges continued work to develop international consensus standards for permissible therapeutic uses of germline editing.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report be filed.

1. That our American Medical Association (AMA) encourage continued research into the therapeutic use of genome editing.

2. That our AMA urge continued development of consensus international principles, grounded in science and ethics, to determine permissible therapeutic applications of germline genome editing.

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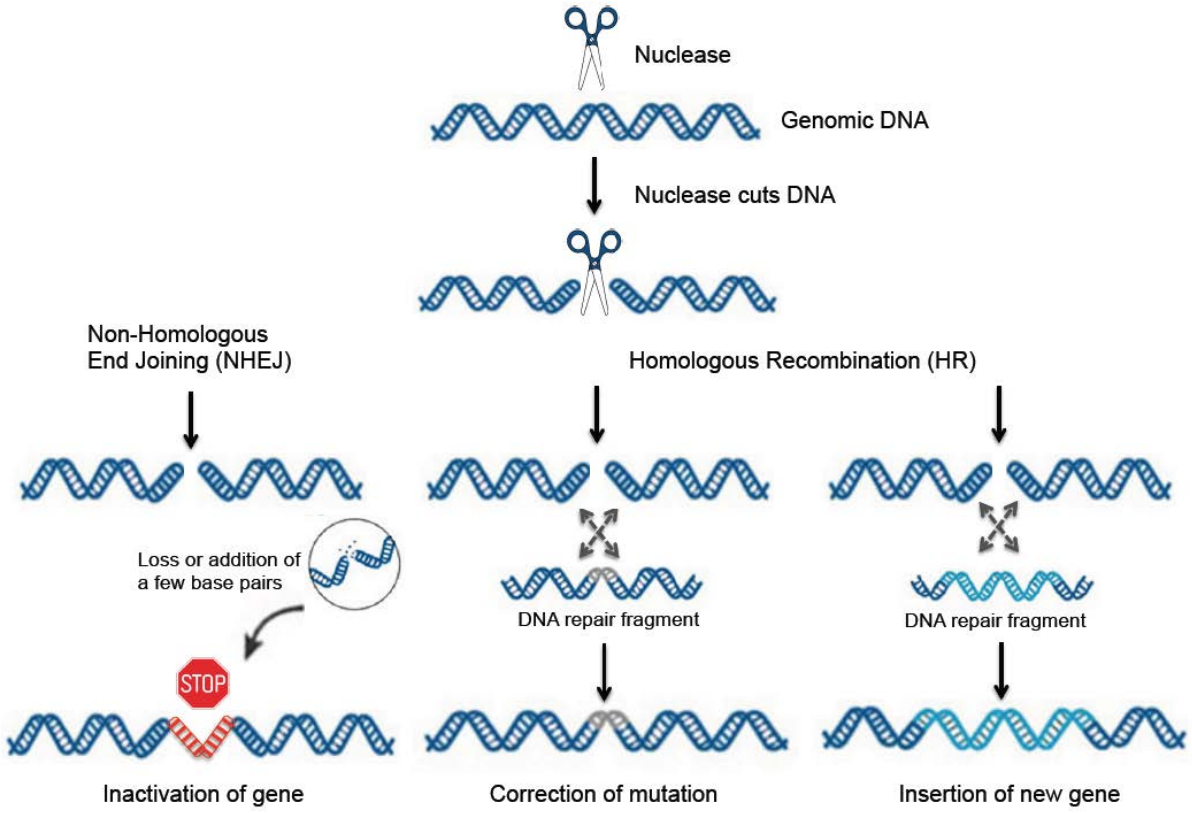
Figure. The genome editing process.



A nuclease engineered to cleave genomic DNA at a precise location is inserted into the cell. Once the DNA is cut, the cell uses either non-homologous end-joining (NHEJ) or homologous recombination (HR) to repair the cut. In NHEJ, the two ends of the DNA strand that have been cut are directly rejoined, but this process results in the insertion or deletion of a small number of nucleotides, disrupting normal gene function. In HR, an exogenous DNA fragment containing a new gene or a corrected sequence of nucleotides, along with sequences that match those surrounding the site of the DNA cut, is inserted into the cell. The cell uses the exogenous DNA fragment as a template to repair the cut, incorporating the sequence present into the genomic DNA, correcting a mutation or inserting a functional gene. (Figure adapted from http://www.calyxt.com/technology/targeted-genome-editing/.)

APPENDIX - AMA Code of Medical Ethics, 7.3.6, Research in Gene Therapy & Genetic Engineering

Gene therapy involves the replacement or modification of a genetic variant to restore or enhance cellular function or the improve response to nongenetic therapies. Genetic engineering involves the use of recombinant DNA techniques to introduce new characteristics or traits. In medicine, the goal of gene therapy and genetic engineering is to alleviate human suffering and disease. As with all therapies, this goal should be pursued only within the ethical traditions of the profession, which gives primacy to the welfare of the patient.

In general, genetic manipulation should be reserved for therapeutic purposes. Efforts to enhance "desirable" characteristics or to "improve" complex human traits are contrary to the ethical tradition of medicine. Because of the potential for abuse, genetic manipulation of nondisease traits or the eugenic development of offspring may never be justifiable.

Moreover, genetic manipulation can carry risks to both the individuals into whom modified genetic material is introduced and to future generations. Somatic cell gene therapy targets nongerm cells and thus does not carry risk to future generations. Germ-line therapy, in which a genetic modification is introduced into the genome of human gametes or their precursors, is intended to result

in the expression of the modified gene in the recipient's offspring and subsequent generations. Germ-line therapy thus may be associated with increased risk and the possibility of unpredictable and irreversible results that adversely affect the welfare of subsequent generations.

Thus in addition to fundamental ethical requirements for the appropriate conduct of research with human participants, research in gene therapy or genetic engineering must put in place additional safeguards to vigorously protect the safety and well-being of participants and future generations.

Physicians should not engage in research involving gene therapy or genetic engineering with human participants unless the following conditions are met:

(a) Experience with animal studies is sufficient to assure that the experimental intervention will be safe and effective and its results predictable.

(b) No other suitable, effective therapies are available.

(c) Gene therapy is restricted to somatic cell interventions, in light of the far-reaching implications of germ-line interventions.

(d) Evaluation of the effectiveness of the intervention includes determination of the natural history of the disease or condition under study and follow-up examination of the participants' descendants.

(e) The research minimizes risks to participants, including those from any viral vectors used.

(f) Special attention is paid to the informed consent process to ensure that the prospective participant (or legally authorized representative) is fully informed about the distinctive risks of the research, including use of viral vectors to deliver the modified genetic material, possible implications for the participant's descendants, and the need for follow-up assessments.

Physicians should be aware that gene therapy or genetic engineering interventions may require additional scientific and ethical review, and regulatory oversight, before they are introduced into clinical practice.

4. HORMONE THERAPIES: OFF-LABEL USES AND UNAPPROVED FORMULATIONS (RESOLUTION 512-A-15)

Reference committee hearing: see report of Reference Committee K.

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
REMAINDER OF REPORT FILED
See Policies H-150.989, D-120.937 and D-120.969

INTRODUCTION

Resolution 512-A-15, "Off-Label Use of Hormone Therapy," introduced by the Women Physicians Section and referred by the House of Delegates asked:

> That our American Medical Association work with national health care organizations to advocate on behalf of the public and our patients on the appropriate evaluation and treatment of hormone deficiencies, as well as the side effects from use of hormone therapy without objective evidence to guide treatment, especially when given to promote weight loss or a general feeling of well-being.

Hormone therapy is the treatment of diseases or conditions with hormones that are derived from endocrine glands or substances that simulate or modulate hormonal effects.[1] The most common uses of U.S. Food and Drug Administration (FDA) approved hormone therapies include replacement during menopause, oncology therapies, and for endocrine or genetic disorders. Although oral contraceptives are a common use of hormones, their primary use for the prevention of pregnancy is not considered a therapy. Over the past several years there has been a large expansion in the use of hormones for off-label uses such as "well-being," anti-aging, low libido and sexual dysfunction and other conditions in the absence of an evidence base to guide treatment (e.g., human chorionic gonadotropin (hCG) for weight loss).[2] Clinicians prescribing hormone therapies off-label are found in primary care clinics or practices, hospital settings, specialty practices, and "commercial wellness clinics." Products being

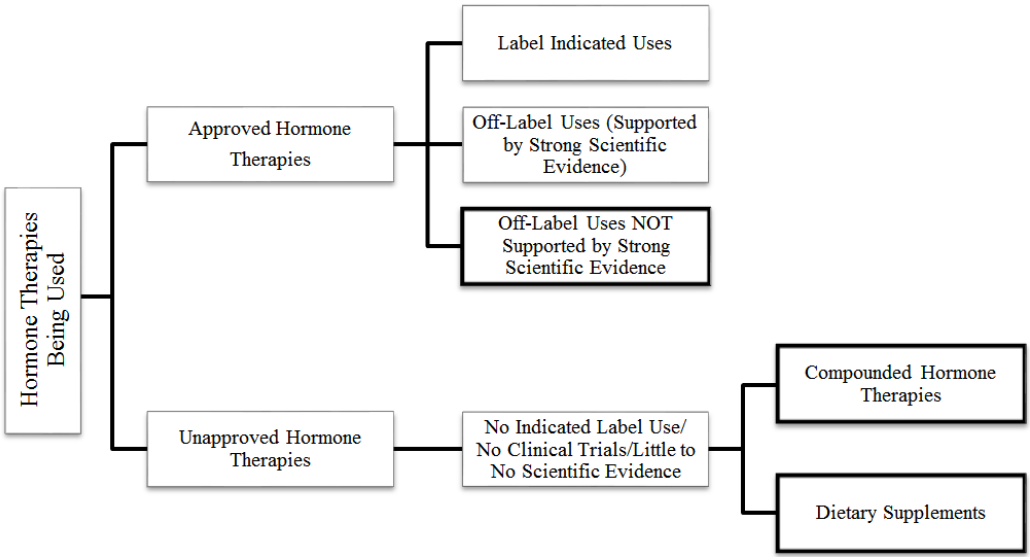
prescribed include both FDA-approved pharmaceuticals and unapproved hormones, including compounded preparations.

Recently, the pursuit of individual health and well-being has been put in the spotlight and become an evolving trend. The global wellness industry is now a $3.4 trillion market, more than 3-fold larger than the worldwide pharmaceutical industry.[3] In the U.S., the sale of compounded hormone therapies is estimated at $1.5 billion, with continued growth projected over the next several years.[4]

Females, males, children, transgender individuals, and athletes are all recipients of hormone therapies. These therapies can be categorized as follows (see Figure 1):

- Use of approved drugs according to a labeled indication
- Off-label use of FDA-approved hormone therapies supported by scientific evidence
- Off-label use of FDA-approved hormone therapies in the absence of scientific evidence
- Widespread use of unapproved hormone therapies, including compounded hormone therapies. While subject to some FDA regulation, hormone-containing dietary supplements can also be considered in this category.

Figure 1**.** Flow chart of hormone therapy uses (bold boxes indicate the focus of this report).



CURRENT AMA POLICY

Current AMA Policy H-120.988, "Patient Access to Treatments Prescribed by Their Physicians," supports the decision-making authority of a physician and the lawful use of FDA-approved drug products for an off-label indication when such use is based upon sound scientific evidence or sound medical opinion. Policy D-120.969, "FDA Oversight of Bioidentical Hormone (BH) Preparations," is a set of directives urging stronger FDA oversight over bioidentical hormones; this report will update this policy. Policy H-100.962, "The Use of Hormones for Anti-Aging: A Review of Efficacy and Safety," based on a previous Council report, states that proponents of anti-aging therapies have the responsibility to prove claims of a positive risk/benefit profile through well-designed, randomized, placebo-controlled clinical trials. The goal of Policy H-460.907, "Encouraging Research Into the Impact of Long-Term Administration of Hormone Replacement Therapy in Transgender Patients," is reflected in the title of the policy. Finally, Policy D-140.957, "Ethical Physician Conduct in the Media," seeks to establish guidelines for physician endorsement and dissemination of medical information in the media.

METHODS

English-language articles were selected from a search of the PubMed database through August 2016 using the search terms "off-label hormone therapy," "bioidentical hormone," and "off-label" with the terms "estrogen," "progesterone," "thyroid hormone," "dehydroepiandrosterone," "testosterone," "growth hormone," and "hCG." Additional articles were identified from a review of the references cited in retrieved publications. Searches of

selected medical specialty society websites were conducted to identify clinical guidelines and position statements. Additionally, Internet searches were conducted for "wellness clinics."

BACKGROUND

Women's Health Initiative

The findings of the Women's Health Initiative (WHI) are an important backdrop to the marketing of off-label hormone therapies. The initial results of the WHI were summarized in CSAPH Report 5-A-09.[5] Briefly, following publication and analysis of the results of the WHI, the U.S. Preventive Services Task Force (USPSTF) recommended against the routine use of combined hormone therapy (estrogen plus progestin) for the prevention of chronic conditions in postmenopausal women and the routine use of estrogen alone for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. Subsequently, the FDA also required estrogen/progestin or estrogen-only products to contain a black box warning on the potential serious adverse events associated with long-term administration.[5] A reanalysis of the WHI data suggests that combined hormone therapy may be appropriate for younger, low-risk women who are seeking short-term relief from menopause symptoms, but the USPSTF continues to recommend against the use of combined hormone therapy for disease prevention or long-term health improvement.[6]

Off-Label Prescribing

When the FDA approves a drug or device and its product labeling, it does so for a specific use or indication. When a physician prescribes a drug for an indication that is not included in the product labeling, or at a dosage outside the recommended range, or uses a different route of administration, or for a patient from a population excluded from the label recommendation (e.g., pediatric), such uses are termed "unlabeled" or "off-label." Off-label prescribing is not illegal because the FDA does not regulate the practice of medicine (21 U.S.C. § 396). Once a drug product has been approved for marketing, physicians may prescribe it for uses or in treatment regimens or patient populations that are not included in the approved product labeling. AMA Policy H-120.988 strongly supports the option of off-label prescribing "when such use is based upon sound scientific evidence or sound medical opinion."

The prevalence and clinical importance of off-label prescribing in routine patient care are substantial. In general, off-label prescribing ranges from 10-20%, but is much higher in certain medical specialties (e.g., oncology) and patient populations (e.g., pediatrics, patients with rare diseases).[7-12] Accordingly, the spectrum of off-label uses is wide. They can be a source of innovation and new practices, represent primary therapy or the standard of care, or they may represent the only available therapy or be a therapy of last resort. Concerns include a lack of substantial evidence supporting safety and efficacy for many off-label uses and the potential for increased costs when newer branded drugs are used in this manner. Recently, the lack of strong scientific evidence to support many common off-label uses, and an increased frequency of adverse events leading to discontinuation of therapy, have led to calls for more scrutiny of such practices.[10,13,14]

In one study of hormone prescribing in primary care clinics, more than 20,000 new prescriptions were issued between 2005 and 2009; 5.2% of them were for off-label uses.[15] Additionally, a recent survey of the activity of compounding pharmacies estimated that 26 to 33 million hormone therapy prescriptions are compounded annually for 2 to 3 million individuals.[4,16] All compounded preparations are by definition not FDA-approved, even if they include FDA-approved drugs. Limited pathways exist for non-FDA-approved drugs to be compounded and supplied to patients.

APPROVED HORMONE THERAPIES

A number of FDA-approved hormone products exist. These include, but are not limited to, steroidal hormones, aromatase inhibitors, gonadotropin releasing hormones (GnRHs), GnRH analogs, GnRH antagonists, selective estrogen receptor modulators (SERMs), antiandrogens, somatostatin analogs, growth hormone (hGH), hGH secretagogues, human chorionic gonadotropin (hCG), and thyroid hormones. There are several labeled uses for these hormone therapies; Table 1 provides class examples of FDA-approved hormones and examples of indicated uses for the class. Table 1 also notes some off-label uses of hormone therapies, most of which lack supporting scientific evidence.

UNAPPROVED HORMONE THERAPIES

Beyond the pattern of FDA-approved medications being used off-label without support of scientific evidence, many hormones being prescribed for both medical and non-medical indications are not FDA-approved products. These include dietary supplements and compounded products.

Dietary Supplements

Dietary supplements are regulated by the Dietary Supplement Health and Education Act of 1994 (DSHEA).[17] Under DSHEA, dietary supplements are not regulated as drugs. Manufacturers, not the FDA, are responsible for evaluating the safety and labeling of products before marketing to ensure that they meet all legal requirements. Thyroid hormone and dehydroepiandrosterone (DHEA) are two common hormones found in commercially available dietary supplements. Recent studies have revealed that one in three older adults are using five or more prescription medications and approximately half regularly use over-the-counter dietary supplements and medications.[18] In addition to concerns with dietary supplement quality and contamination,[19] there is a high risk of adverse events associated with the use of multiple medications and dietary supplements. Half of all potential major drug-drug interactions identified in outpatients involved over-the-counter products.[18]

Compounded Hormone Therapies (Bioidentical Hormones)

Bioidentical hormones are semi-synthetic hormones that are chemically synthetized from a natural starting material, most commonly a plant sterol sourced from soybeans or the Mexican yam.[20] Bioidentical hormones are structurally identical to hormones produced in the body. Some are commercially available products approved by the FDA (e.g., micronized estradiol), and many are compounded preparations that are not FDA-approved. Compounded bioidentical hormones have become popular because of direct-to-consumer marketing by compounding pharmacies, commercial wellness clinics, and some individuals outside of the medical community along with media depiction as safer, natural, and more effective alternatives to prescription hormone therapies. Although compounded bioidentical hormones are not FDA-approved, they do require a prescription. The term bioidentical hormones does not include over-the-counter herbal preparations or plant-based products with estrogenic activity.

The term “bioidentical hormone” does not have a standardized definition, which adds to the confusion regarding the identity, use, and safety of the products. Depending on the context in which it is used, the term can imply natural (not synthetic), compounded, plant derived, or structurally identical to human hormones.[21] The term “bioidentical hormone therapy” has been recognized by the FDA and The Endocrine Society as a marketing term and not a description based on scientific evidence.[20,22-24] Therefore “compounded hormone therapy” (CHT) will be used to describe these preparations throughout this report. Furthermore, CHT often not only refers to compounded hormone preparations, but may be inclusive of the initial diagnostic testing and monitoring that is repeated over time on a patient.

Regulation. CHTs are prepared in compounding pharmacies and are regulated under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Section 503A applies to traditional compounding pharmacies and §503B applies to compounding outsourcing facilities which produce bulk amounts of products (e.g., for hospitals or in the event of drug shortages). The vast majority of the products that are the focus of this report are compounded in traditional compounding pharmacies and are therefore regulated under §503A. Compounded drugs are not subject to the same rigorous evaluation and approval process as prescription drugs that are FDA-approved. Section 503A describes that compounded drug products are exempt from three sections of the FD&C Act including those concerning current good manufacturing practice (cGMP); the labeling of drugs with adequate directions for use, standardized labels, or product inserts (including any black box warnings); and the approval of the drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs).[25] Additionally, the statute puts restrictions on the compounding of products that are essentially copies of drugs that are commercially available.[26] Previously, §503A also included restrictions on advertising or promotion of the compounding of drugs or drug classes or the solicitation of prescriptions for compounded drugs, but these provisions were deemed unconstitutional by the U.S. Supreme Court in 2002.[27] Traditional compounding pharmacies are not required to register with the FDA, investigate or report adverse events, or report sales under §503A. Currently, individual state boards of pharmacy maintain oversight of traditional compounding pharmacies under §503A while the FDA maintains a risk-based enforcement approach with respect to violations of the FD&C Act.

Evidence Base. Little scientific evidence exists to support specific claims of efficacy of CHT preparations. A literature review produced no adequate randomized placebo-controlled trials. Authors of a literature review of randomized controlled trials of CHT progesterone cream for the relief of menopause-related vasomotor symptoms found three studies.[28] None of the trials applied FDA methodology for evaluating symptom relief and the search authors determined in their review that the data presented do not support the use of CHT progesterone cream for the relief of menopause-related vasomotor symptoms.

Two observational studies were found evaluating menopausal symptom relief for 3-6 months in patients receiving CHT preparations from a wellness clinic which offer low-level evidence that CHT improves menopausal symptoms. The first study involved 296 women receiving various CHT treatments, doses, and routes of administration and showed a statistically significant improvement in emotional symptoms such as irritability and anxiety.[29] The second study involved 200 women receiving estrogen, progesterone, testosterone, or some combination of the three hormones either via topical or sublingual administration. The results of this study showed that topical CHT was not as effective as sublingual CHT at reducing vasomotor, mood, and quality-of-life symptoms.[30]

CHT preparations can be inconsistent in dose and purity. After reports of quality control problems associated with CHT, the FDA conducted two surveys to evaluate compounded drugs. In 2001, the FDA evaluated 29 compounded drugs from 12 different compounding pharmacies and reported that while none of the samples failed identity testing, 10 (34%) of the samples failed standard quality testing, including potency testing.[31] In another survey in 2006, the FDA collected 198 samples from compounding pharmacies; 73 were finished compounded drug products; 33% of these products did not conform to information on the label.[32] Other reports of both subpotent products and products containing excessive amounts of active ingredient(s) exist.[22] One preliminary pharmacokinetic study in which plasma estradiol levels achieved with CHT doses commonly thought to be bioequivalent to FDA-approved products were compared to the FDA-approved estradiol patch. The plasma levels achieved with all doses of the CHTs were significantly lower than with the estradiol patch.[33]

The Endocrine Society, The American Association of Clinical Endocrinologists, American Congress of Obstetricians and Gynecologists, American Society for Reproductive Medicine, The North American Menopause Society, and The Women's Health Practice and Research Network of the American College of Clinical Pharmacy have issued position statements outlining their concerns regarding CHT, specifically mentioning patient safety because of the lack of evidence-based research regarding clinical effectiveness and inherent risks associated with hormone compounding.[1,23,34-37] Policy D-120.969, "FDA Oversight of Bioidentical Hormone (BH) Preparations," urges the FDA to take several actions regarding bioidentical hormones.

CHT Marketing and Conflicts of Interest. There have been some ethical and conflict of interest issues associated with commercial wellness clinics and compounding pharmacies that prescribe and dispense CHT. Some compounding pharmacies that sell CHT also market the products to the public by providing listings of their offerings and offer referrals to providers who can prescribe the CHT. Some proprietors of commercial wellness clinics have published peer-reviewed journal articles that have been viewed as misleading[38] and questionable rhetorical approaches may be used to appeal to those lacking scientific literacy, for example, failing to distinguish between "cutting edge medicine" and "untested or unproven therapies."[39]

CHT proponents often use the WHI trial results as part of a marketing approach to promote CHT as safer than traditional hormone therapies, emphasizing that CHT is different from the hormones used in the WHI study, and either implying or directly claiming that CHT is safer than FDA-approved preparations, despite a lack of evidence to substantiate this claim.[39,40] In addition, the FDA requires that patient package inserts and class labeling black box warnings reflective of the findings of the WHI be included with all FDA-approved estrogen and progesterone products. Because CHTs are not FDA-approved products, they are exempt from FDA labeling and warning requirements, and patient package inserts and the black box warnings are not included.[22] The lack of warnings may lead some patients to conclude CHTs are safer.[1]

Additional claims often employed as marketing tactics by CHT prescribers and compounders also cannot be substantiated.[21,41] For example, the claim that CHT has improved delivery compared to FDA-approved hormone therapies has not been evaluated in clinical trials.[21] Some clinicians also advocate for saliva testing as a way to provide customized therapy for patients, an approach that lacks scientific validity (see below).[35]

Patient Perspective. Surveys indicate that approximately one in three individuals who use hormone therapy rely on CHT and believe it is "natural."[16] Using terms such as "bioidentical" and "natural," health care providers are able to market and prescribe CHT as distinctly different treatments from traditional hormone replacement therapies and as alternatives to prescription drugs. CHT appeals to consumers who seek more holistic healthcare approaches and tend to reject synthetic, manufactured pharmaceutical drugs.[42] Surveys indicate that patients who seek CHT do so because of a lack of satisfaction with their primary care physicians. Wellness practitioners are perceived as better listeners, and as validating their symptoms and willing to find solutions.[42] There is abundant promotion from celebrities who have published popular books and magazine articles discussing hormone therapies.[39,43-46]

Among patients receiving hormone replacement therapies, only 14% of respondents knew that CHT was not FDA-approved.[47] Additionally, those patients view the fact that compounding of CHT is not under FDA purview as part of the appeal. Furthermore, they view the customization as less dangerous even though opponents view this as one of the biggest risks of CHT.[42] Even when it is pointed out that a lack of safety data and product information does not mean CHT is safe, patients continue to believe CHTs are safer than FDA-approved hormone therapies.[48]

Hormone Customization. A major appeal of CHT is that the treatment is marketed as customized to each individual patient, compared to mass-produced FDA-approved pharmaceuticals. Most compounding pharmacies have the capability to prepare hormone therapies for various routes of administration including oral, sublingual, percutaneous, implant, injectable, or suppository. The pharmacokinetic properties are unknown for the majority of these compounded hormone preparations.

To achieve "individualized" hormone therapy for each patient, many CHT clinicians recommend saliva (and occasionally blood, serum, or urine) hormone testing. The implication is that the results of the saliva hormone test will aid in the determination of the type, dosage, and route of administration of hormone therapy prescribed for the patient.[34] However, actual hormone customization is very difficult to achieve because of hormone pharmacokinetics and physiologic variation. There is no evidence that hormonal concentrations in saliva are biologically meaningful, can be used to customize hormone therapies, or predict therapeutic effect.[37] Furthermore, saliva hormone assays do not have independent quality control programs, lack an accepted reference range[36] and the FDA has stated that no scientific evidence supports the use of saliva testing to titrate hormone dosages or monitor hormone levels.[35]

Commonly Prescribed CHTs. Two of the most commonly prescribed CHTs in the United States are bi-est (two estrogens) and tri-est (three estrogens).[21] Bi-est is a formulation of 20% 17β-estradiol and 80% estriol and tri-est is a formulation of 10% estrone, 10% 17β-estradiol, and 80% estriol (see Table 2). These percentages are calculated on a milligram-per-milligram basis and not estrogenic potency or concentration. Because these formulations are not FDA-approved, the actual milligram amounts can vary depending on the specific prescription that is written for each patient. No placebo-controlled clinical trials evaluating the safety or effectiveness of bi-est or tri-est preparations have been conducted. Also of note is that there is no form of estriol that is an FDA-approved product; however, estriol can be legally compounded because a USP monograph on estriol exists.

The Wiley Protocol is a commonly prescribed, patented[49] CHT that uses high amounts of estradiol and progesterone in a "cyclical and rhythmic pattern" as opposed to "static dosing" to mimic the hormone levels of a 20 year-old female. Since the development of the first protocol, additional protocols have been developed utilizing testosterone (for women), testosterone and DHEA (for men), thyroid hormones, and cortisol (see Table 2).[50] One study examined the standardization of Wiley Protocol CHT preparation concentrations from a selection of the compounding pharmacies approved to distribute the product. Despite the use of standardized instructions and compounding materials distributed with the Wiley Protocol products, not all pharmacies passed quality control measures for the CHTs tested.[51] This study did not evaluate the clinical effectiveness of the Wiley Protocol but made the claim that clinical studies are currently underway evaluating its effectiveness in pre- and post-menopausal women and in patients with cancer, osteoporosis, and multiple sclerosis. No evidence of such trials could be located in PubMed, clinicaltrials.gov, or the Cochrane Register of Controlled Clinical Trials.[51]

TX-001HR is solubilized 17β-estradiol and natural progesterone combined in a single gelatin capsule for the treatment of vasomotor symptoms in postmenopausal women.[52] It is currently being evaluated in a phase 3 placebo-controlled clinical trial (REPLENISH) for the treatment of menopause-related moderate to severe vasomotor symptoms. If it is approved, TX-001HR would become the first FDA-approved hormone therapy that combines 17β-estradiol and natural progesterone in a single treatment similar to CHT.[52]

SPECIFIC CONDITIONS

Below are some disorders and conditions for which CHT and off-label therapies are commonly prescribed.

Aging

Hormone therapy for anti-aging was reviewed in CSAPH Report 5-A-09.[5] The decline of endogenous hormones is common with aging and the off-label use of hormone therapies to reverse the effects of aging is wide-spread. Large scale, randomized, placebo-controlled studies are still lacking to support the use of any hormone therapies for anti-aging purposes. Studies evaluating their long-term effects and risks when used off-label are also lacking.[53]

Female Sexual Dysfunction, Low Libido, and Sexual Desire

The most common sexual dysfunction in women is known as female sexual interest/arousal disorder (FSAD) in *DSM-5* (previously hypoactive sexual desire disorder (HSDD) in *DSM-IV-TR*).[54] Treatment options include non-pharmacologic approaches such as education, counseling, and psychotherapy. There is currently one FDA-approved product, flibanserin, for FSAD.[55] It is a non-hormone, mixed function serotonin agonist/antagonist. In addition to flibanserin, several hormone therapies have been used off-label to treat FSAD. Randomized controlled trials using testosterone for sexual dysfunction in women had mixed results and efficacy is unclear. Testosterone may benefit secondary outcomes such as well-being and vitality, but these are difficult to distinguish from the combined effects of testosterone and estrogen.[36] The American Congress of Obstetricians and Gynecologists reaffirmed their Practice Bulletin in 2015 summarizing clinical management guidelines for female sexual dysfunction. These guidelines support the use of transdermal testosterone as an effective short-term treatment of FSAD ($\leq$ 6 mos), with little evidence to support longer use.[56] Other possible off-label hormone therapies for this condition include conjugated estrogens, the SERM ospemifene, and DHEA, but evidence to support their use is limited or inconsistent.[1,57,58] CHT has become an option because the limited number of FDA-approved products containing testosterone does not meet the needs of all women and the ability to customize a hormone therapy is readily available.[1] However, the inconsistencies in CHT dose and purity remain a concern.

Perimenopause/Menopause

Currently, numerous FDA-approved hormone replacement therapies are available to treat menopausal symptoms and to prevent osteoporosis including estrogen-only therapies, progestin-only therapies, combination estrogen/progestin therapies, and combination estrogen/SERM therapy.[59] These formulations vary in dosage, route of administration, and source (i.e., some are considered bioidentical, others are synthetic, and some are derived from animals). Non-oral estrogen formulations may be associated with reduced risk of venous thromboembolism and stroke.[36] Women who still have a uterus and are taking estrogen therapy for the relief of menopausal symptoms are advised to also take progestin therapy; evidence shows that progestins inhibit estrogen-induced endometrial stimulation and reduce the risk of endometrial hyperplasia and cancer.[60] Topical progesterone is not adequate for endometrial protection, and there are case reports of endometrial cancer associated with its use.[61-64]

Many women have turned to CHTs as a treatment for menopausal symptoms despite the limited data to support improved safety or efficacy with these therapies.[1] In one comparative pharmacokinetic study, plasma estradiol levels achieved with CHTs (commonly thought to be bioequivalent to FDA-approved products) were significantly lower than with the estradiol patch. Even higher doses of the compounded product resulted in lower levels of estradiol than the patch. Also of note were the variable patterns of estrogen absorption observed with some of the compounded formulations.[33] There is no evidence to support the use of CHTs with unpredictable pharmacokinetics in place of several FDA-approved and tested choices for hormone replacement therapy.

Male Hypogonadism and Infertility

Although the term hypogonadism commonly refers to low testosterone levels, by definition, it describes impaired spermatogenesis and low hormonal production. Testosterone supplementation in hypogonadic men further decreases sperm production and many of these patients seek alternative treatments for increasing testosterone in order to maintain (or restore) spermatogenesis and fertility. The goal in these patients is typically to inhibit the negative feedback on the hypothalamic-pituitary axis, promote endogenous testosterone production, and increase the production of the gonadotropins LH and FSH. The hormone therapies used for male hypogonadism and fertility

include hCG injections, hCG and human menopausal gonadotropin (hMG) injections, the SERM clomiphene citrate, hCG injections with testosterone, or aromatase inhibitors such as anastrozole. All of these therapies are off-label except for the hCG injections.[65,66] Evidence is lacking to support the routine use of aromatase inhibitors for this condition.[65,67,68]

Gender Re-affirming

Several hormone therapies are used in transition therapy for transgender individuals. All of the treatments for gender re-affirming therapy are off-label. No randomized clinical trials have been conducted to determine the optimal dosages and treatment paradigms for gender re-affirming hormone therapies, but specific treatment guidelines have been recommended.[69-71]

The treatment goal for transgender men (female to male patients) is to induce virilization, including the cessation of menses and the development of male-pattern hair growth and physique.[69] Hormone therapies recommended in The Endocrine Society's Clinical Practice Guideline include testosterone cypionate, enanthante, and undecanoate injections, transdermal testosterone gels, and testosterone patches.[70] Other therapies being used include implantable testosterone pellets, medroxyprogesterone or lynestrenol (for cessation of menses), and finasteride (for treatment of male pattern baldness that may occur with testosterone treatments).[69,72]

The treatment goals for transgender females (male to female patients) are to induce breast formation, obtain a more female distribution of fat, and reduce male-pattern hair growth. To accomplish these goals, endogenous action of androgens must be stopped.[69] Hormone therapies recommended in The Endocrine Society's Clinical Practice Guideline include estradiol valerate or cypionate injections, transdermal estradiol patches, oral estradiol tablets, the antiandrogens spironolactone and cyproterone acetate (which is not an approved drug in the U.S.), and GnRH agonists (such as goserelin). Other therapies, not considered first-line, that are used include the antiandrogens flutamide, nilutamide, or bicaluatmide, and 5α-reductase inhibitors finasteride, and dulasteride.[69,72] Some clinics that provide services for transgender individuals recommend CHT preparations made by compounding pharmacies such as topical testosterone and estradiol creams for cost saving purposes, since many of the necessary drug therapies are not covered by insurance.[72] There is no evidence that custom CHTs are safer or more effective than FDA-approved therapies.

Adverse effects are a concern with the use of any hormone therapy. However, serious short-term complications appear to be uncommon, or at least have yet to be reported in literature, for transition therapy; long-term effects have not been characterized. Policy H-460.907 encourages research into the long-term administration of hormone replacement therapy in transgender patients.

SPECIFIC HORMONE THERAPIES

Some FDA-approved drugs and individual CHTs are used as stand-alone therapies for several medical (and non-medical) conditions, and are prescribed by clinicians in various settings.

Testosterone

Testosterone is FDA-approved only for men who have low testosterone levels (≤ 300 ng/dL) in conjunction with an associated medical condition such as cancer chemotherapy or a genetic or endocrine disorder.[73] Replacement therapy for idiopathic low levels or low testosterone due to aging are off-label uses for the drug.[74] A significant proportion of men receiving testosterone therapies lack adequate testosterone serum measurements prior to receiving prescriptions.[74,75] The most common diagnoses for testosterone therapy include hypogonadism, fatigue, erectile dysfunction, and psychosexual dysfunction.[76] The FDA warns about a potential link between exogenous testosterone and the risk of heart attacks and strokes[77] and is requiring manufacturers of testosterone products to conduct a clinical trial to determine the effects of testosterone replacement therapy on cardiovascular outcomes.[74,78] The American Association of Clinical Endocrinologists and the American College of Endocrinology conclude in a position statement, that there is no convincing evidence of an increase or decrease in cardiovascular risk related to testosterone therapy and randomized controlled trials are needed.[79] If physicians choose to prescribe testosterone off-label, they should be well-informed about any potential risks, especially the cardiovascular outcomes.[75]

Androgen deficiency syndrome in women is a controversial concept. For women, testosterone has been used for the treatment of diminished libido, decreased well-being, dysphoric mood, and unexplained fatigue. However, there are no FDA-approved testosterone therapies for women.[36] Patients are increasingly utilizing compounding pharmacies for these therapies, at times in combination with estrogen and progestin. The use of CHT can result in excessive doses and adverse effects.[75]

Dehydroepiandrosterone, Dehydroepiandrosterone Sulphate, and Androstenedione

DHEA and dehydroepiandrosterone sulphate (DHEAS), the sulphate ester of DHEA, are converted to androstenedione and then to estrone or testosterone and further to estradiol or estriol. Studies have associated low DHEA and DHEAS with a myriad of conditions affecting both sexes including depression and reduced cognition, as well as decreased bone mineral density, arthritis, systemic lupus erythematosus and decreased libido and sexual dysfunction in women, and congestive heart failure and increased mortality in men. High levels have been associated with postmenopausal breast cancer and decreased sense of well-being in women.[36,58] Currently, DHEA and DHEAS are not FDA-approved; no pharmaceutical grade DHEA or DHEAS is available in the U.S.; and there are no indications for their use. Nonpharmaceutical grade DHEA and DHEAS are available in over-the-counter dietary supplement products and from compounding pharmacies, but DHEA and DHEAS content can vary significantly.[36,42] Evidence that DHEA or DHEAS is beneficial for any condition is lacking.

Androstenedione was previously available over-the-counter as a prohormone in dietary supplements. The Anabolic Steroid Control Act of 2004 amended the Controlled Substances Act, classified androstenedione as a Schedule III controlled substance, and it was removed from the market.[80]

Human Chorionic Gonadotropin (hCG)

Human chorionic gonadotropin (hCG) is a hormone produced by the human placenta. Injectable hCG is an FDA-approved prescription hormone therapy for treating some forms of female infertility and male hypogonadism. First described in 1954, the "hCG diet" has reemerged as a fad where injectable and/or oral forms of hCG have been prescribed by physicians or distributed by commercial wellness clinics, and a modified version of the diet has been promoted on television.[81,82] Homeopathic hCG-containing products also are sold via the Internet and over-the-counter for weight loss.[83]

Patients on this diet are typically restricted to approximately 500 calories per day and receive hCG doses of approximately 200 international units daily. The hCG diet has been repeatedly refuted in studies and meta-analyses. Experts agree that it is inappropriate and that any weight loss is due to the severe caloric restriction.[2,84-86]

FDA-approved hCG preparations are injections while many of the purported hCG products being sold on the Internet are oral and nasal formulations. There is no evidence to support absorption of hCG via oral or nasal routes of administration. The FDA has received reports of serious adverse events associated with hCG use for weight loss, and there have been recent reports of adverse events and risks associated with the hCG diet in the literature.[2,85] The FDA requires the following warning statement on approved hCG products:

> HCG has not been demonstrated to be effective adjunctive therapy in the treatment of obesity. There is no substantial evidence that it increases weight loss beyond that resulting from caloric restriction, that it causes a more attractive or 'normal' distribution of fat, or that it decreases the hunger and discomfort associated with calorie-restricted diets.

hCG is also used as a doping agent by athletes to stimulate endogenous production of testosterone or to prevent testicular atrophy during prolonged administration of other anabolic substances. It also stimulates the endogenous production of epitestosterone which means that the ratio of testosterone to epitestosterone (T/E ratio), a common parameter in antidoping testing, stays within a normal range and increases the chances of evading detection.[87] There have been, however, analytical tests developed to directly detect doping with hCG.[88]

Human Growth Hormone (hGH)

Human growth hormone (hGH) is an FDA-approved hormone therapy available since the late 1980s for short stature caused by specific diseases or syndromes. In 2003, it was approved despite controversy for the treatment of

idiopathic short stature in children. The American Association of Clinical Endocrinologists and the Pediatric Endocrine Society, in position statements[89,90] concluded that information on the safety and effectiveness of hGH for idiopathic short stature was limited and its use should be individualized and carefully monitored.

hGH also is commonly used off-label for its purported anti-aging effects and ability to increase performance, endurance, lean muscle mass, and exercise capacity. Although studies have evaluated hGH for performance enhancement, none of them have produced evidence to support use by athletes for this purpose.[91] There also is insufficient evidence to support the use of hGH as an anti-aging medicine.[53]

Thyroid Hormone

Thyroid hormone has been used for weight loss and depression in euthyroid individuals despite a lack of evidence for these indications.[92,93] In some cases, thyroid hormone has been found in commercial dietary supplements in doses equal to or greater than those used as replacement therapy in patients with hypothyroidism.[94] These products can cause serious adverse events, including thyrotoxicosis.

FDA-approved formulations of the endogenous thyroid hormones, levothyroxine (LT4) and liothyronine (LT3), are highly effective and safe therapies for the treatment of hypothyroidism. LT4 monotherapy is the recommended first-line hormone therapy. LT4 and LT3 can be administered in a combination therapy with a LT4/LT3 ratio of approximately 14:1 to mimic the ratio secreted by the thyroid gland.[36,95]

"Natural" desiccated, non-synthetic thyroid products of porcine or bovine origin also are available. Compounding pharmacies can use any of the available thyroid medications to create preparations containing various ratios or concentrations according to the prescription request.

CONCLUSIONS

Off-label use of hormone therapies that is not supported by scientific evidence and the use of unapproved hormone therapies (Figure 1, bold) have been the focus of this report. Patients receiving off-label therapies not backed by scientific evidence are more likely to experience adverse drug events.[13,15] Patients are relying on media information to educate themselves about their medical conditions–whether accurate or not.[96] Marketing veiled as educational material and promotion by celebrities has made CHT appear as panacea for many ailments.

Policy H-120.988 supports the clinical decision-making authority of a physician to use an FDA-approved product off-label when such use is based upon sound scientific evidence or sound medical opinion; however, to date the use of compounded hormone therapies is not supported by such evidence. Additionally, traditional compounding is recognized as a legal and important therapeutic when an FDA-approved drug product is not available or does not meet the clinical needs of individual patients. However, in the case of many of the uses for compounded hormones, comparable FDA-approved therapies are available. Further concern is prompted by the fact that compounding pharmacies are exempt from including specific and important safety information on labeled instructions. That lack of information may put patients at risk.

RECOMMENDATIONS

The Council on Science and Public Health recommends the following recommendations be adopted in lieu of Resolution 512-A-15 and the remainder of the report be filed:

1. That Policy D-120.969 be amended by addition and deletion to read as follows:

   D-120.969 ~~FDA Oversight of Bioidentical~~ Compounded Hormone ~~(BH)~~ Therapy Preparations
   Our AMA ~~will~~: (1) recognizes the term "bioidentical hormone" as a marketing term not grounded in science; use of the term "compounded hormone therapy" is preferred; (~~1~~2) will urge that renewed attention be devoted to the ~~of the Food and Drug Administration (FDA) to conduct surveys for~~ purity and potency ~~dosage accuracy~~ of ~~all~~ compounded hormone therapy ~~"bioidentical hormone"~~ formulations; (~~2~~3) will urge continued attention to the ~~FDA to require mandatory~~ reporting ~~by drug manufacturers, including compounding pharmacies,~~ of adverse events related to the use of compounded hormone therapies ~~"bioidentical hormones"~~; ~~(3) urge the FDA to create a registry of adverse events related to the use of compounded "bioidentical hormone" preparations~~;

(4) recommends that physicians and other prescribers fully inform patients of the potential side effects and risks of the use of compounded hormone replacement therapy; and (5) will request that when drug ingredients with black box warnings are used in compounded products, patients should be informed about the ~~FDA require the inclusion of uniform patient information, such as~~ warnings and precautions associated with the use of such drug ingredients~~, in packaging of compounded "bioidentical hormone" products; and (5) urge the FDA to prohibit the use of the term "bioidentical hormones" unless the preparation has been approved by the FDA.~~

2. Our AMA supports that patients be informed that compounded products are not FDA-approved.

2. That our AMA urge the United States Pharmacopeia to re-examine the validity of the current estriol monograph.

3. That our AMA establish a position that the use of human chorionic gonadotropin (HCG) for weight lost is inappropriate.

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Table 1. Examples of FDA approved hormones.

Class	Class Examples	Examples of Indicated Uses (for Class)	Examples of Off-Label Use (for Class)
Steroidal Hormones	Estradiol Progesterone Testosterone	HRT Breast, endometrial, prostate cancer Male hypogonadism	Gender re-affirming therapy[a] FSAD Low Testosterone, ED, fatigue[a]
Aromatase Inhibitors	Letrozole Anastrozole	Breast cancer treatment; endocrine disorders	Sports doping[a]
GnRH Analogs	Leuprolide Goserelin	Prostate cancer	Gender re-affirming therapy[a]
SERMs	Raloxifene Fulvestrant	Chemoprevention of breast cancer; metastatic breast cancer	FSAD[a] Male hypogonadism
Antiandrogens	Flutamide Bicalutamide	Prostate cancer	Gender re-affirming therapy[a]
Somatostatin Analogues	Octreotide	Acromegaly, gigantism, thyrotropinoma, carcinoid syndrome, VIPomas	Sports doping[a]
Growth Hormone	hGH	hGH deficiency; cachexia from AIDS; SHOX deficiency; Turner syndrome; chronic renal failure; Prader-Willi syndrome; children of short stature because of intrauterine growth retardation; idiopathic short stature	Antiaging[a]; sports doping[a]
hGH secretagogues	Tesamorelin	HIV-associated lipodystrophy	Sports doping[a]; anti-aging[a]
GnRHs	LH FSH	Infertility therapy; reversal of anovulation	Sports doping[a]
GnRH antagonists	Ganirelix Abarelix	Infertility therapy; prostate cancer	
Human Chorionic Gonadotropin	hCG	Infertility therapy	Weight loss[a]
Thyroid Hormone	Levothyroxine Liothyronine	Hypothyroidism	Weight loss[a]; Sports doping[a]

HRT = hormone replacement therapy; ED = Erectile dysfunctin; FSAD = female sexual interest/arousal disorder; GnRH = gonadotropin releasing hormone; SERMs = selective estrogen receptor modulator; VIPomas = vasoactive intestinal peptide-secreting tumors; hGH = human growth hormone; SHOX = Short stature homeobox gene; LH = lutenizing hormone; FSH = Follicle stimulating hormone; HCG = Human chorionic gonadotropin

[a]Lacks scientific evidence

Table 2. Common Compounded Hormone Preparations[a]

Compounded Formulation	Ingredients	Dose	Route of Administration
Bi-est	20% estradiol 80% estriol[c]	1.25-2.5 mg/d[b]	Oral, transdermal, sublingual, or vaginal
Tri-est	10% estradiol 10% estrone 80% estriol[c]	1.25-2.5 mg/d[b]	Oral, transdermal, sublingual, or vaginal
Estriol	Estriol[c]	2.0-8.0 mg/d[b]	Oral, transdermal, sublingual, or vaginal
Progesterone	Progesterone	100-200 mg/d[b]	Oral, transdermal, sublingual, vaginal, or injectable
Wiley Protocol Original™[49]	Estradiol and Progesterone	Multi-phasic rhythmic dosing (amounts vary throughout a 28 day cycle)[49]	Topical
Wiley Protocol for Men™	DHEA and Testosterone	Multi-phasic rhythmic dosing	Topical
Wiley Protocol Thyroid™		Multi-phasic rhythmic dosing	Topical
Wiley Protocol Testosterone™ for Women	Testosterone	Multi-phasic rhythmic dosing	Topical
Wiley Protocol Sparc™ Therapy	Cortisol	Multi-phasic rhythmic dosing	Topical

[a]Data was compiled from several Internet sources and Files et al.[21]
[b]mg amounts can vary depending on the compounding pharmacy
[c]Not an FDA approved drug