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Latest Trends in the Heroin Epidemic and the Responsibility of the Pharmacist in Controlling Heroin Abuse

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Abstract
Over the last few years, there has been an exponential increase in morbidity and mortality associated with heroin abuse. The current rise in heroin abuse and overdose is attributed to widespread use and abuse of prescription opioids, which can produce significant euphoric effects in humans. In fact, reports suggest that heroin abusers initially become addicted to prescription opioids but subsequently switch to heroin because it is cheaper and more easily available than prescription opioids. Over the years, the purity of heroin available for illicit use has been on the decline. Smugglers and heroin vendors have started mixing heroin with other clandestinely prepared, potent, analgesic opioids such as fentanyl. Fentanyl is 30 to 50 times more potent than heroin, and the combination can be quite lethal to abusers due to the increased potency and effects on the body’s respiratory centers which may result in death. This review will mainly focus on some of the recent trends in heroin abuse and recent changes in laws with respect to dispensing and possession of naloxone, an effective antidote against heroin overdose. Finally, the role of the pharmacist in countering the current heroin epidemic by recognizing at-risk populations and providing the proper resources to addicts to prevent further heroin/opioid-related overdose fatalities will be discussed.
Figure 1. Number of Annual Submissions Involving Heroin to NFLIS from Various State and Local Forensic Labs.1-11

Figure 2. Number of Annual Submissions Involving Fentanyl to NFLIS from Various State and Local Forensic Labs.1-11
Drug Abuse

Heroin Addiction: An Historical Perspective and Changing Trends

Heroin is chemically derived from the naturally occurring opioid morphine, extracted from the opium poppy plant. Bayer originally introduced heroin to the market in 1898 as a cough suppressant and sedative due to its superior efficacy over the standard morphine or codeine. However, by 1910, it became clear that heroin had the potential to be extremely addictive. Later in 1924, heroin production was banned by the U.S. Heroin Act. However, this also started the dawn of heroin’s black-market manufacturing and abuse. Subsequent to this prohibition, the first major increase in heroin abuse in the United States occurred during the 1960s. This wave of heroin abuse correlated with the return of troops from the Vietnam War, who started heavily abusing heroin in Vietnam. The most recent wave of heroin abuse started around 2000, which was mainly perpetrated by the expansive abuse of opioid painkillers over the previous two decades. A large percentage of current heroin abusers actually start using prescription opioids first and then switch to heroin because it is cheaper and easier to obtain.

There have been a number of new reports that suggest changes in the trends of heroin abuse. Previously, heroin was typically abused by nonwhite populations living in urban areas. Currently, heroin abuse has also spread to suburban and rural areas, predominantly among whites. In addition to the shift in location and race, there is also a shift seen in the mean age of heroin abusers. The median age of heroin abusers has gone up from 16 years of age in the 1960s to 20 years of age in the 1980s and now has increased to 23 years of age. These changing trends suggest a wider, more atypical environment in which heroin is being abused.

Changes in Purity of Heroin

During the wave of heroin abuse through the 1960s and 1980s, heroin was smuggled into the United States from Southeast Asia, Afghanistan and Nigeria. Beginning in the 1990s through today, most of the heroin found in the United States is imported from Mexico and South America. Currently, it is recognized that there are two distinct heroin markets that dominate the United States. The East Coast of the United States normally receives most of its heroin from South American countries, whereas the West Coast heavily imports heroin from Mexico. Interestingly, the DEA has reported a decline in the purity of heroin over the last few years with an increase in price per milligram of heroin. The declining purity in heroin has initiated a dangerous trend among vendors and smugglers of mixing (cutting) heroin with other drugs, such as fentanyl, to enhance its effects. Since fentanyl is a significantly more potent opioid than heroin and morphine, the risk of overdose and subsequent death significantly increases, especially with an uneducated user. These fentanyl derivatives are “cut” or diluted into heroin in an attempt to expand the quantity of the product for sale as well as shorten the time to the “rush” or euphoria. Additionally, due to its high potency, fentanyl acts quickly and requires only a low volume to achieve a high. Together, these characteristics are economically beneficial for the dealers of heroin. Yet the addition of fentanyl to heroin provides a much greater risk of toxicity to the drug abuser for several reasons including contamination of the drug product itself and the unpredictable additive effects of the combination of these two opioids. In fact, knowing how much fentanyl to add to heroin is often guesswork. Additionally, when the user receives the product, they are unlikely to know how much of the drug is needed to attain a high, which increases the chance of an overdose.

Heroin and Fentanyl: Pharmacologic Mechanisms and Reward Pathway

Two hydroxyl groups of morphine are replaced with less polar acetyl groups in the heroin molecule, which is also known as diacetylmorphine (Figure 3). This makes heroin more lipophilic than morphine, which allows it to cross the blood-brain barrier faster. After passing the blood-brain barrier, plasma esterases de-acetylate heroin to monoacetylmorphine. Monoacetylmorphine is then hydrolyzed to morphine, which produces its agonistic effects on opioid receptors, initiating the sensation of euphoria. Heroin may be administered via nasal inhalation, oral smoke inhalation or intravenous injection. Although intravenous injection has the fastest onset of action, the drug rapidly produces euphoric effects by any administrative technique. When injected intramuscularly, euphoria is attained after a few minutes, compared to the few seconds taken by intravenous injection. If inhaled by smoking or sniffing, euphoria arises after approximately 15 minutes. The initial euphoric high usually lasts 45 seconds to several minutes, but the general feeling of well-being continues three to five hours after administration depending on the level of drug potency or abuser tolerance.
Fentanyl is a synthetic opioid that is frequently used in veterinary and human practice. It is also used in both the inpatient hospital and outpatient settings.\textsuperscript{20,27} Fentanyl has many derivatives which include alfentanil, sufentanil, remifentanil and carfentanil. These derivatives can be administered by injection, transdermal patch or transmucosal lozenge.\textsuperscript{27} Typically, fentanyl or its derivatives are used as anesthetics adjunct to general anesthesia during surgery and analgesics for chronic pain relief or preoperative pain. Additionally, fentanyl is used to treat severe pain often associated with trauma, burns, orthopedic conditions and terminal illness; it also reduces cough and diarrhea.\textsuperscript{15} Fentanyl and other opioids are preferred in the clinical setting because they do not cause loss of consciousness, euphoria or sedation when used for analgesia.\textsuperscript{19,29} The benefits seen in patients that use fentanyl or its derivatives include, but are not limited to, the following: decreased amounts of adverse reactions, higher patient satisfaction, higher quality of life, improved compliance and a decreased need of rescue medications. Adverse drug reactions are usually only experienced when fentanyl is abused.\textsuperscript{28} A review study done by Kornick et al. found that the benefits of using fentanyl as a prescription medication outweigh its potential risks.\textsuperscript{28}

Fentanyl is estimated to be 30 to 50 times more potent than heroin and between 50 to 100 times more potent than morphine.\textsuperscript{19-21} This increased potency of fentanyl makes it lethal even at low doses.\textsuperscript{21} The lethal dose of fentanyl is estimated to be 2 mg in humans.\textsuperscript{27} Due to the low lethal levels of fentanyl, it is very easy for a patient or a drug abuser to overdose on this medication. As it is often mixed with other drugs to produce a more powerful and dangerous street drug, there is an increased incidence of drug overdose with fentanyl use.\textsuperscript{20}

The actions of morphine, heroin, fentanyl and other opioid analgesics are mediated primarily by binding to the mu opioid receptors in the neurons of the brain, spinal cord and gastrointestinal tract.\textsuperscript{23,29} These mu opioid receptors are G proteins coupled to adenyl cyclase. Binding of the opioid to these receptors inhibits the production of adenyl cyclase, blocking calcium ion channels and opening potassium ion channels in the neuron to inhibit neurotransmitter release.\textsuperscript{30} The eudophic effects of opioids, including heroin, are mediated by mesolimbic dopaminergic neurons, which originate from the ventral tegmental area in the midbrain.\textsuperscript{31} The activity of these dopaminergic neurons are regulated by inhibitory gamma-amino-butyric acid (GABA) neurons. When an opioid such as morphine acts on the mu opioid receptor, the result is the inhibition of GABA release at synapses thus decreasing GABA’s inhibitory effect on dopaminergic neurons. Without GABA-mediated inhibition, dopamine release is uninhibited at dopaminergic neuron terminals in areas of the brain associated with brain reward, such as the nucleus accumbens, producing a sensation of euphoria.\textsuperscript{32}

Mu opioid receptor agonists cause a variety of other physiological reactions including respiratory depression, slowing of gastrointestinal movement causing constipation and bradycardia.\textsuperscript{29} The most life-threatening effects is depression of the respiratory centers, which are located in the medulla of the brain stem. A reduction in glutamate-induced excitation decreases respiratory activity, which leads to a decreased sensitivity to changes in oxygen and carbon dioxide levels.\textsuperscript{29,32} Decreased sensitivity to levels of these gases results in hypoventilation causing hypoxia in tissues and ultimately leading to brain and subsequent organ shutdown and death in an overdose situation. If an overdose is survived, the prolonged lack of oxygen to the brain may cause severe brain damage.

When opioids are combined, the effects may be additive or synergistic.\textsuperscript{33} When morphine is combined with fentanyl, the analgesic effect is increased from that of either drug alone by at least twofold. In one study, morphine combined with fentanyl increased analgesia in mice from 10 percent with only morphine, and 15 percent with only fentanyl, to 30 percent when combined. The increased effects from combining opioids have highly unpredictable effects in vivo due to its illegal production and, therefore, cause severe increases in fatalities due to overdose.\textsuperscript{33}

### Opioid Tolerance, Cross-tolerance and Incomplete Cross-tolerance

Chronic use of opioids leads to tolerance, meaning that an increasingly higher dose is necessary to have the same effects as previous exposures.\textsuperscript{34} With repeated activation of the mu opioid receptors, as in heroin or fentanyl abuse, the mu opioid receptors either undergo desensitization, down-regulation or receptor internalization. Losing opioid receptors due to these three pathways decreases the number of receptors available to cause a response. This phenomenon is called tolerance.\textsuperscript{33} As a consequence, using the same dose of an opioid (e.g., heroin) will no longer produce the same euphoria. Additionally, tolerance can develop through any route of administration of an opioid.

In addition to tolerance, opioid abuse can be complicated by issues of cross-tolerance and incomplete cross-tolerance.\textsuperscript{23} Cross-tolerance is the state of being tolerant to different chemicals or drugs that act on the same receptor. All opioids acting via the mu opioid receptors exhibit cross-tolerance to each other at varying degrees. Incomplete cross-tolerance occurs when tolerance to one drug is developed, but another drug that acts on the same receptor does not develop tolerance and produces normal effects. This second drug that the body is not yet tolerant to can be used at a much smaller dose, which may be useful in minimizing side effects. However, the risk for deadly overdose greatly increases. Due to the unpredictable nature of incomplete cross-tolerance of opioids, the risk of overdose is increased when two different opioids are coadministered that act on the same receptor. For example, consider the coadministration of morphine and methadone which both act on the mu receptor. A person tolerant to morphine would need a significantly higher dose of morphine compared to a drug-naive individual to produce an analgesic effect. In contrast, the person would still be responsive to a normal dose of methadone due to incomplete cross-tolerance. Use of methadone doses equivalent to high
In this particular patient, as heroin and fentanyl both act on the mu opioid receptor, incomplete cross-tolerance is a possible consequence of using the two together and can increase incidences of overdose.

**Mortality Due to Heroin Overdose**

Between 2000 and 2013, the incidences of heroin overdose and death increased across the United States. A recent study of 28 states (AL, AZ, CO, FL, IL, IN, IA, KS, KY, MA, MI, MN, MO, MT, NE, NV, NH, NM, NY, NC, OH, OK, OR, RI, SC, UT, VA, WA) confirmed that the rate of heroin use increased from 2008 to 2012, with the rate doubling between 2010 and 2012. Overall, the data from the 28 states analyzed in this study encompassed 56 percent of the population of the United States and indicated that there is a growing problem with heroin mortality in the country. Importantly, the largest number of deaths from heroin overdose was seen in two different populations: males and whites. Figures 4 through 7 depict various trends in heroin mortality per 100,000 people from 2008 to 2012.

**Reversal of Heroin Intoxication/Overdose with Naloxone**

Symptoms of heroin intoxication are grouped into what is known as the "opioid triad." The triad of symptoms includes pinpoint pupils, unconsciousness and respiratory de-
pression (Figure 8), which is defined as less than 12 breaths per minute. Naloxone (Narcan®), an opioid-receptor antagonists, has the highest affinity for the mu opioid receptor. It acts as an effective antidote to opioid overdoses, thus reversing the effects of opioid drugs such as fentanyl and heroin. Naloxone has many forms of administration including intranasal inhalation, intramuscular (IM) injection, intravenous (IV) injection undiluted by IV push, IV continuous injection diluted in 5 percent dextrose in water (DSW) or normal saline (NS) 4 to 8 mcg/mL, or subcutaneously (SC) into the thigh. Intranasal administration of naloxone has several advantages including low risk of exposure to blood because there is no needle, fast administration, rapid onset of action, requires little training for administrator and is extremely effective.

Figure 8. The Opioid Triad of Intoxication (Opioid Overdose Symptoms).

Naloxone begins to have effects on the body in two to five minutes depending on the route of administration and has a 30 to 90 minute duration of action. Administrators of the drug should remain with the patient for the 30 to 90 minute period in the event that readministration is required. According to the algorithms for Advanced Cardiac Life Support (ACLS) protocols, the initial dose ranges from 0.4 to 2 mg/mL and is given every two to three minutes until the desired outcome is reached to treat opioid overdoses. Up to 10 mg is given as a total dose because the mechanism of action is short-lived, and repeated doses may be required depending on the opioid drug being antagonized. Doses should be repeated given until breathing has increased from none to minimal breathing. There is no tolerance build-up or abuse potential for naloxone.

Side effects of naloxone when reversing opioid use include nausea, vomiting, sweating and tachycardia. As naloxone does not have any drug-drug interactions and is safe for pregnant women, it is fairly safe to give when an opioid overdose is suspected but not confirmed. If there is no opiate agonist present in the body, naloxone will have no effect on the body, thus no harm would occur if a patient was misdiagnosed with an opioid overdose and given naloxone. When an opioid overdose is suspected, emergency medical services should be contacted immediately after a witness administers naloxone (or in concurrence if there is another witness available to do so) to have the best chance for the patient survival.

Candidates to be considered for naloxone treatment include patients with a history of opioid overdose, a suspected history of nonmedical opioid use, receiving high-dose opioid prescriptions, receiving the first prescription for an opioid substance, receiving buprenorphine treatment for addiction, on opioid prescriptions with respiratory illnesses, with limited access to emergency medical services or by patient request. Additionally, as health care professionals, pharmacists and prescribers are considered to be part of the at-risk community for abuse because of easy access to prescription drugs, especially opioids. It is estimated that 10 to 15 percent of health care professionals are addicted to drugs or alcohol.

As of 2014, over 150,000 people in the United States are trained and have received naloxone kits. Those involved with the training have already reported having a positive impact on over 26,000 overdoses nationwide. The kits come in two formulations: intranasal and intramuscular. The intranasal kit includes two naloxone 2 mg/2 ml prefilled syringes and two atomizers, while the intramuscular kit includes two naloxone 0.4 mg/ml vials and two intramuscular syringes. Both of the kits contain step-by-step instructions for responding to an opioid overdose and directions for naloxone administration. The kits are to be stored at room temperature and protected from light; kits cannot be stored in places that are susceptible to seasonal temperature changes, such as a vehicle, in order to maintain effectiveness. Each kit has a shelf life between 12 and 18 months, and syringes should not be filled until the drug is needed. Each intramuscular kit costs roughly $44 and intranasal kits cost around $40, which is fairly inexpensive compared to other means of medical treatment that would be involved if naloxone was not received in an overdose situation. It is estimated that annual medical costs resulting from opioid overdose reach $72 billion. Although these kits are available to first medical response teams, depending on state laws, bystanders, family/friends of drug abusers, and pharmacies are also permitted to possess naloxone kits and distribute them. The laws regarding who is allowed to possess naloxone across the country, and which states have legislation providing immunity to individuals seeking treatment or providing treatment, is shown in Figure 9.

Dispensing Laws for Naloxone
As of July 22, 2015, section 4729.44 of the Ohio Revised Code and rule 4729-5-39 of the Ohio Administrative Code authorizes a pharmacist or pharmacy intern, under the direct supervision of a pharmacist, to dispense naloxone without a prescription to the following in accordance with a physician-approved protocol: (1) An individual who there is reason to believe is experiencing or at risk of experiencing an opioid-related overdose; (2) A family member, friend, or other person in a position to assist an individual who there is reason to believe is at risk of experiencing an opioid-related overdose; or (3) A peace officer as defined in section 2921.51 of the Revised Code.

These new amendments come with little to no negative effects and are extremely inexpensive. Even while inexpensive, the amendments also save health care dollars in the treatment aspect. It has been estimated that annually overdose fatalities cost about 21.5 million.
Drug Abuse Latest Trends in the Heroin Epidemic and the Responsibility of the Pharmacist in Controlling Heroin Abuse

Figure 9. The Naloxone Dispensing Laws According to State Practice.\textsuperscript{43,46}
States in blue are those with naloxone access and drug overdose Good Samaritan laws. States in green are those with naloxone access laws only. States in yellow are those without either law.

In the past, prescribers have been concerned about “third party prescribing” liability; third party prescribing means the prescription is written for a patient who has not been evaluated by a prescribing order (a standing order). Additionally, witnesses to overdose situations may not want to call for medical assistance in fear of legal punishment. Those witnesses, who do realize the need for naloxone distribution and have the antidote on hand, may choose not to distribute it because of liability concern myths (i.e., witness thinks he/she will be prosecuted for administering incorrectly). Initial evidence from the state of Washington, which amended its law in 2010, is positive with 88 percent of surveyed drug users indicating that they would be more likely to summon emergency personnel during an overdose as a result of the legal change.\textsuperscript{43} Because of these major concerns and fears, the new dispensing laws have aimed to displace those fears and establish grounds for saving the lives of the victims.

The new dispensing laws focus on two goals:

1. The first goal is “Good Samaritan” dispensing, which encourages witnesses of an overdose incident to come forward and get help for the victim without fear of being arrested for illicit drug possession. According to the National Conference of State Legislatures, the so-called “Good Samaritan” laws regarding drug overdoses fall into two primary categories.\textsuperscript{43} The first encourages calling 911 to seek medical assistance for yourself or someone experiencing an overdose by providing criminal immunity for both the person in need and the person who sought help. “New Mexico became the first state to amend its laws to encourage Good Samaritans to summon aid in the event of an overdose. As of June 22, 2016, thirty-five other states and the District of Columbia” follow the Good Samaritan law.\textsuperscript{43,46}

2. The second goal provides varying levels of criminal or civil immunity for those involved with the prescription, possession or emergency administration of the naloxone to reverse the effects of an overdose.\textsuperscript{46} After the clarification of legal immunity for those reporting an overdose, several states began to make moves to incorporate new laws to protect those reporting the overdose. Additionally, prescribers would not be held liable for writing naloxone prescriptions for patients they did not personally evaluate.\textsuperscript{43} This goal strives to provide wider use and prescribing of naloxone. It will allow prescribers to confidently prescribe naloxone without fear of legal repercussion. Depending on the state the pharmacist and patient is living in, the laws for administration will vary. For example, in Ohio, House Bill 170 (passed on March 11, 2014) removed civil liability for prescribers, allowed for third party prescriptions, removed civil liability for lay administration, removed criminal liability for prescribers and lay administration and allowed lay administration to practice unauthorized practice of medi-
Ohio offers an educational program called Project DAWN, which is a community-based education program that distributes naloxone for opioid overdose cases. Participants in the program are given intranasal naloxone when appropriate and receive educational training on the signs and symptoms of an overdose and how to administer naloxone.

Role of the Pharmacist

The pharmacist’s role in protecting patients from an opioid overdose is imperative. Pharmacists are involved in the prevention of overdoses by researching patient history for the use of analgesics, especially opioids, using the Ohio Automated Rx Reporting System (OARRS), or state equivalent reporting system accordingly, and evaluating the patient’s potential for opioid abuse. By identifying patients and health care professionals at risk for overdoses, pharmacists can potentially prevent overdoses before they occur. Additionally, they can identify certain groups of patients with an increased risk of addiction to opioids, such as those with major depressive disorder, bipolar disorder, anxiety disorders, etc.

To help prevent overdoses and addiction, pharmacists should counsel patients on the use of opioids and the potential for addiction at the start of a new prescription and with every refill on the medication. If the patient is having a family member or friend pick up the prescription for them, the pharmacist should counsel the individual picking up the medication, and provide hard copy medication guides to give to the patient to explain the main concerns and counseling points. It is also the responsibility of the pharmacist to be informed on the most recent state laws for distributing naloxone in their location of practice. This information can be found online at the Network for Public Health. Pharmacists should know the symptoms for abuse and overdose and know how to administer naloxone in an emergency situation. The main focus of the pharmacist should be to provide information regarding post-overdose treatment as well as guidance in recovering from an addiction. In the state of Ohio, pharmacists can refer patients to Project DAWN locations in order to receive community-based encouragement, education and training on how to cope with and avoid overdoses.

Conclusion

Overdoses as a result of heroin and other opioid medications kill thousands of patients annually. The dangerous trend of mixing clandestinely-prepared fentanyl derivatives with heroin has further increased the incidence of heroin overdose. These deaths can be prevented with lifesaving medication naloxone along with the timely summoning of emergency responders. Amended dispensing laws for naloxone allow pharmacists to distribute naloxone with less liability concerns in emergency situations. Pharmacists have a responsibility to be informed on the latest dispensing laws of naloxone in their state of practice in the event of an emergency overdose situation. Additionally, being knowledgeable about the signs and symptoms of heroin overdose and identifying at-risk patient populations will allow lifesaving interventions to be made available in a timely manner to prevent fatal heroin overdoses.
Drug Abuse

Latest Trends in the Heroin Epidemic and the Responsibility of the Pharmacist in Controlling Heroin Abuse


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Assessment Questions

1. Which of the following corresponds to the concept of incomplete cross-tolerance?
   A. Higher dose of same drug is necessary to achieve same high.
   B. Physical reaction is the same for two different drugs that act on the same receptor.
   C. Tolerance to one drug is developed, but another drug that acts on the same receptor produces normal effects.
   D. Drugs acting on different receptors produce the same effect.

2. Due to the high potency of fentanyl, it requires a low volume to achieve a high. This is not economically beneficial to the dealers of heroin.
   A. True
   B. False

3. Addition of fentanyl to heroin enhances heroin's effect of respiratory depression.
   A. True
   B. False

4. No matter the route of heroin administration, euphoria is achieved quickly. The initial euphoric high lasts ______, but the general feeling of well-being lasts ______.
   A. 45 seconds to several minutes, 3 to 5 hours
   B. 30 minutes to 1 hour, 8 to 12 hours
   C. 1 to 2 hours, 18 to 24 hours
   D. 15 seconds, 8 to 12 hours

5. Naloxone begins to have effects on the body in _____ minutes depending on the route of administration, and _____ minute duration of action.
   A. 10-15; 45-60
   B. 2-5; 30-90
   C. 1-2; 60-90
   D. 2-5; 60-90

6. Which of the following is not a symptom of the Opioid Triad of Intoxication?
   A. Respiratory depression
   B. Unconsciousness
   C. Pinpoint pupils
   D. Tachycardia

7. According to new law amendments, some states provide varying levels of criminal or civil immunity for those involved with the prescription, possession, or emergency administration of naloxone and/or criminal immunity for both the victim and the witness when seeking help by reporting an overdose.
   A. True
   B. False

8. According to the algorithms for Advanced Cardiac Life Support (ACLS) protocols, the initial dose of naloxone ranges from _____ and is given every _____ until the desired outcome is reached to treat opiate overdoses.
   A. 0.4-2 mg/mL; 2-3 minutes
   B. 2-10 mg/mL; 2-3 minutes
   C. 0.4-2 mg/mL; 10-12 minutes
   D. 2-10 mg/mL; 10-12 minutes

9. What is the name of the educational program in Ohio that offers a community-based education and naloxone distribution center for overdose cases?
   A. Good Samaritan Outreach
   B. OARRS
   C. Project DAWN
   D. DSM 5

10. In 2012 the _____ United States had the highest number of heroin overdoses, and in 2012 the _____ United States had the lowest number of heroin overdoses.
    A. midwestern; southern
    B. northeastern; western
    C. northeastern; southern
    D. southern; midwestern

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