

# Loperamide Misuse and Recommendation for Yearly Federal Legislative Evaluation of New Law: “Combat Loperamide Epidemic Act (CLEA)”

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## Citation

E L Sullivan, P A Clark, J Chowdhury. *Loperamide Misuse and Recommendation for Yearly Federal Legislative Evaluation of New Law: “Combat Loperamide Epidemic Act (CLEA)”*. The Internet Journal of Public Health. 2017 Volume 5 Number 1.

DOI: [10.5580/IJPH.51199](https://doi.org/10.5580/IJPH.51199)

## Abstract

The United States experienced more deaths from drug overdoses in 2014 than previous recorded years. One-hundred twenty eight Americans died daily from drug overdose. This represents a 200% increase, vs the year 2000, involving opioid pain relievers and heroin. When prescription opioids and heroin are unavailable extreme amounts of antidiarrheal medication is becoming a popular means for opioid users’ mimicking feelings of euphoria and reducing opioid withdrawal symptoms. This new method has the potential for fatal results. The active ingredient which abusers seek is loperamide. The Federal Drug Administration (FDA), from 1976-2015, reported incidences of life-threatening cardiac dysrhythmias linked with ingestion of high dose loperamide. More than half required hospitalization and 10 cases of death resulted. Opioid users misuse this drug, physicians are unaware of its misuse, and opioid users arrive at the Emergency Department with cardiac toxicity of unknown origin. Loperamide is inexpensive, readily available, legal, and undetectable on routine drug tests. We propose yearly federal evaluation of a proposed law entitled: Combat Loperamide Epidemic Act (CLEA) based upon growing number of cases of loperamide misuse. Modeled after the Combat Methamphetamine Epidemic Act of 2005 (CMEA) and incorporated into the Patriot Act signed by President Bush on March 9, 2006. Although current death rates from loperamide misuse are low compared to heroin (8,375 total 2013) and opioid abuse (>28,000 total 2014), from a medical and ethical perspective, it seems clear that the FDA must evaluate future need of new regulations to protect people from this form of drug use. To show seriousness nature of misuse, loperamide will be evaluated ethically using basic ethical principles of respect for persons, beneficence, nonmaleficence and justice.

## INTRODUCTION

Reports from 2014 showed approximately 128 Americans died each day from drug overdose representing a 137% increase overall and a 200% increase in the rate of overdose deaths involving opioid pain relievers and heroin since the year 2000 (1). While overdose rates continue to rise an additional challenge is opioid abusers now turn to extreme amounts of loperamide, an anti-diarrhea medication to mimic opioid euphoria and manage opioid withdrawal effects. Most opioid abusers use loperamide as a “bridge” to ease opioid withdrawal symptoms including muscle pains, vomiting, diarrhea and nausea. Recommended dosage of loperamide is no more than 8 milligrams daily, however some opioid abusers are ingesting as many as one hundred 2 milligram tablets daily (2) to promote the drug’s entrance into the central nervous system. Directions for misuse have been found on multiple websites (3,4) and lack of associated

social stigma adds to its abuse potential. The purpose of this article is threefold. First, this article will put forth a pharmaceutical analysis of loperamide and its effects. Second, a medical analysis on the abuse of loperamide and detection in emergency departments. Third, this article will provide an ethical analysis of the abuse of loperamide and need for yearly federal legislative evaluation.

## PUBLIC HEALTH INFLUENCE

Loperamide is now being referred to as the “The Poor Man’s Methadone” (5). Reports received by the Federal Drug Administration (FDA), from 1976-2015, showed 48 incidences of life-threatening cardiac dysrhythmias linked with ingesting high-doses of loperamide or concomitant use of loperamide with medications which decrease its metabolism thus increasing systemic levels. Unreported cases were not included. Of these 48 incidences, 31 cases

required hospitalization resulting in 10 deaths. Greater than 24 incidences were seen after 2010 (6). According to the American College of Emergency Physicians (ACEP), a 10-fold increase of loperamide abuse was shown in web-based reports from 2010-2011. Within these reports 70% of users misused loperamide to self-treat opioid withdrawal and 25% reported misuse of loperamide for its euphoric properties (7). Nationwide, calls to poison control centers increased by more than double from 2010-2014 (87 calls 2010 vs 190 calls in 2014) reporting intentional abuse or misuse with loperamide (8). During 2011-2015, a seven-fold increase in calls were received by the Upstate New York Poison Center related to loperamide abuse or misuse. These calls reported a 71% increase related to intentional loperamide consumption from 2011 through 2014 (7). In addition, two specific cases of death outlined by William Eggleston in the Annals of Emergency Medicine state after loperamide misuse medical support failed including cardiopulmonary resuscitation (CPR), naloxone, and standard advanced cardiac life support (ACLS) (9). In June 2016 the FDA sent a Safety Announcement with warnings against high doses of loperamide (6) and in November 2016 a black box warning was added to brand loperamide to include “Cases of Torsades de Pointes, cardiac arrest, and death have been reported with the use of a higher than recommended dosages” (10).

Although the reported misuse of loperamide is much lower (quantitative reports not found) compared to heroin (586,000 disorder related users reported in 2014) (11) vs opioids (1.9 million disorder related users reported in 2014) (11) and the death rates of loperamide misuse (10 reported 1976-2014) (6) vs heroin (8,375 reported in 2013) (12) vs opioids (>28,000 including prescription opioid pain relievers reported in 2014) (13), trends in loperamide misuse continue to grow with an expected increase in upcoming years of associated deaths.

Loperamide is easy to obtain, affordable, and believed to be safe without potential for abuse. Drug levels are not visible within routine drug tests. Local stores sell loperamide, 2 milligram tablets, in bottles of 400 tablets for \$7.59, less than 2 cents per tablet. Recommended daily dose of loperamide, 4 tablets per day (8 milligrams/day) would cost an individual less than 8 cents per day. Those abusing loperamide spend approximately \$2.00 per day when achieving an abusive dose of one hundred 2 milligram tablets per day (5). This is in comparison to the average cost

of 0.1 gram (single dose) of heroin street sold for \$15-\$20 with doses up to \$150-\$200 per day for high abusers; brand-name OxyContin street sold for \$50 to \$80/pill; generic oxycodone street sold for \$12 to \$40/pill; and pharmacy sales of prescribed opioids for approximately \$6/pill (14,15).

## **LOPERAMIDE APPROVAL/PHARMACOKINETICS/PHARMACODYNAMICS:**

Loperamide, was created in 1969, FDA approved in 1976 (16) and most commonly used for: gastroenteritis, traveler’s diarrhea, chemotherapy induced diarrhea, inflammatory bowel disease, irritable bowel syndrome, and short bowel syndrome. It was found to be safe and effective at a maximum dose of 8 mg in a 24 hour period (17). Effects shown at opioid receptor sites, placed loperamide in Schedule V classification (1977), of the Controlled Substance Act, by the Drug Enforcement Administration (DEA) (2). The abuse potential of loperamide was thought to be limited given poor bioavailability and lack of penetration through the blood brain barrier. Additional studies found loperamide to have low physical dependence and supported safety (18). At recommended doses the drug poses no significant side-effects and presents no serious threat of abuse. In 1988, the Schedule V classification was removed and over the counter purchase made available within the United States.

Loperamide inhibits intestinal peristalsis via  $\mu$ -opioid receptor agonism, calcium channel blockade, calmodulin inhibition, and reduced paracellular permeability. Extensively metabolized in the liver and excreted through the feces and urine, loperamide slows down peristalsis by acting on the  $\mu$ -opioid receptors in the myenteric plexus of the large intestine binding to opiate receptor sites possessing opiate agonist activity both in vivo and in vitro (19). The  $\mu$ -opioid receptor is a key regulator of gastrointestinal motility and secretion acting as a mediator for opiate-induced bowel dysfunction (20). It is the primary binding site for loperamide efficacy. Penetrating the blood brain barrier, at higher doses, individuals can experience heightened euphoric feelings found with commonly abused opiates. This creates the potential for abuse along with the ability to decrease of opioid related withdrawal symptoms. Grapefruit juice (P450 inhibition), energy drinks, pepper, and quinine (P-gp inhibition) combined with loperamide and the aforementioned drugs can prolong euphoric effects and reduce withdrawal effects of opioids via reduced loperamide

metabolism (2).

## **CLINICAL HARM OF HIGH DOSE LOPERAMIDE**

Respiratory and central nervous system depression were reported after supra-therapeutic doses in adults (21), and symptoms involving the central nervous system were seen in children ingesting high doses of loperamide (22). Opiate like adverse effects have been reversed via use of naloxone in multiple cases and loperamide is considered naloxone responsive (21). Opiate withdrawal symptoms were seen when continued high doses of loperamide were discontinued. Such symptoms required methadone supportive treatment. Loperamide has been shown to inhibit sodium and calcium channels in the heart resulting in prolongation of the QRS complex and QT/QTc interval (23). This abnormality can lead to fatal ventricular dysrhythmias such as Torsades de Pointes. Drugs including cimetidine, gemfibrozil, quinidine, ritonavir, clarithromycin, and erythromycin reduce loperamide metabolism resulting in greater concentrations of loperamide and increased side effects (24).

## **IDENTIFYING LOPERAMIDE MISUSE**

Loperamide benefit is seen within the literature in a number of studies. Loperamide has been used in the successful treatment of diarrhea safely and effectively (17). With its proven benefit, identification of misuse can be difficult. The physician-patient relationship holds great importance regarding opioid pain reliever prescribing, opioid pain reliever use, heroin use, and identifying abuse of loperamide. Westermeyer and Gihyun (2015) speak of a required clinical model of symmetry between physician and patients for treatment of substance use disorder (SUD). Symmetry includes identifying physician-patient expectations, developing mutually productive interactive approaches to meet expectations, identifying unproductive approaches, and together shaping events to benefit patient recovery (25). Physicians and ancillary health care providers need to be aware of this new form of abuse. An efficient physician-patient relationship is necessary regarding loperamide misuse, given the dangerous cardiac manifestations caused by the drug.

Unless the FDA is aware of its potential for more deaths, nothing will be done to address misuse of loperamide in regards to legislation and regulations. If federal regulations potentially minimize the number of patients overdosing on loperamide, then not only would medical resources be saved but many lives as well. People have the right to access

medications that are beneficial to them. However, if a medication can be abused and limitations can be placed on it protecting individuals, then ethically limitations must be established.

## **ETHICAL ANALYSIS**

Opioid addictions increase daily and health care professionals must face this sweeping epidemic immediately and realistically. It has become clear opioid abusers are seeking numerous alternatives to address withdrawal symptoms and find alternatives with euphoric properties. Loperamide meets both requirements. Loperamide is inexpensive, readily available, legal and lacks social stigma associated with use. Physicians are unaware of its overuse and as a result, opioid abusers are arriving at Emergency Departments with cardiac toxicity of unknown origin. To show seriousness nature of misuse, loperamide will be evaluated ethically using basic ethical principles of respect for persons, beneficence, nonmaleficence and justice.

Respect for persons incorporates two ethical convictions: first, individuals should be treated as autonomous agents; and second, persons with diminished autonomy are entitled to protection. The principle of respect for persons divides two separate moral requirements: requirement to acknowledge autonomy and requirement to protect those with diminished autonomy (26). The patient-physician relationship is a covenant based on mutual respect and trust. A fiduciary relationship based on honesty. Ethicist Edmund Pellegrino argues the patient-physician relationship is composed of three elements: the patient who is ill and seeking assistance with a need, the physician who will take responsibility for assisting with the needs, and the act of medicine (27). In this relationship the patient is vulnerable needing assistance of the physician to help make correct medical decisions. “The decision-making process initiates the relationship between the two and will result in a chosen form of treatment” (27). Physicians must be sensitive to the patient’s vulnerability and respect patient autonomy unless it violates the conscience of the physician. The next phase is medical intervention. The physician employs his or her skills to help restore the patient to health or alleviate as much suffering as possible. The patient and physician are in a relationship that hopefully results in a particular medical treatment. Ethicists Pellegrino and Thomasma argue among obligations that arise from the patient-physician relationship is technical competence: the act of the medical professional is inauthentic and a lie unless it fulfills the expectation of

technical competence (28). This means that patients can expect their physicians to offer the same standard of diagnostic and therapeutic services to all patients. The final phase of the relationship is outcome. The effect of the caring activity is assessed according to the physical well-being of the patient. Reciprocity of the relationship completes the patient-physician relationship and upholds respect and dignity of the patient. Health care professionals, especially physicians, must not only be aware of misuse of loperamide but they must begin to advocate for legislation and regulations to protect opioid abusers who are vulnerable patients due to addiction. Opioid abusers lack autonomy because the addiction is an impediment to his/her reason. These individuals are not thinking clearly, are abusing their bodies, and their addiction has potential to lead to serious injury and even death. Failure to care for the patient holistically clearly violates the ethical principle of respect for persons. If hospitals and health care professionals are committed to treating every person with dignity and respect, then the barriers to addiction and treatment must be lifted to ensure this commitment, and emphasis must be placed on patient dignity and respect. Recognizing the impact of loperamide abuse and advocating for new regulations will help to achieve this goal.

Beneficence involves the obligation to prevent and remove harms and to promote the good of the person by minimizing possible harms and maximizing possible benefits. Beneficence includes nonmaleficence, which prohibits the infliction of harm, injury, or death upon others. In medical ethics this principle has been closely associated with the maxim *Primum non nocere*: Above all do no harm. A number of initiatives can be instituted in Emergency Departments. First, physicians must become more aware of the potential for misuse of loperamide. Second, new drug screens must be initiated that detect overdoses of loperamide. Third, any misuse or abuse of loperamide must be immediately reported to the FDA’s Medwatch on-line registry. Fourth, loperamide in the past was a prescription drug and a controlled substance in the same class as cocaine and methadone. Just as the FDA regulated the sale of pseudoephedrine, ephedrine and phenylpropanolamine under the Combat Methamphetamine Epidemic Act of 2005, physicians must advocate that the FDA and the Drug Enforcement Administration (DEA) evaluate the same for loperamide. Abuse of loperamide requires yearly review for new legislation and regulations. If further regulations are found necessary, sale of any medication containing

loperamide must be limited to behind the counter purchase and limits placed on the number of tablets of loperamide that can be purchased in a 30-day period. This will promote the good of the person, minimizing potential harms and maximizing potential benefits. There is no doubt that there will be push-back from the pharmaceutical industry, however, profit can never stand in the way of patient safety. These actions would satisfy the tests of both beneficence and nonmaleficence.

Finally, the principle of justice recognizes each person should be treated fairly, equitably, and given his or her due. Justice pertains to distributive justice, which concerns fair and equitable allocation of resources, benefits and burdens, according to a just standard. Inequality concerning access to medical care is a well-documented fact. To allow individuals addicted to opioids, to have easy access to a drug like loperamide that is an alternative to opioids is an egregious violation of the principle of justice. Justice dictates people should be treated in a similar manner if at all possible. If there are medications that are good for patients like loperamide, but these medications are being abused as an alternative to opioids, then failure to protect vulnerable patients violates the basic tenet of justice, that is, to treat all people fairly and equitably. Instead to be sold over-the-counter, federal regulations can be placed on loperamide so that those addicted to opioids would not have easy access to this drug. This has been quite effective with pseudoephedrine, which is found in both prescription and over-the-counter products used to relieve nasal and sinus congestion, because it can also be used to produce methamphetamines. FDA regulations limit the monthly amount purchased, requires individuals to present photo identification to purchase such medications and requires retailers to keep personal information about these customers for at least 2 years after purchase of these medicines. These same regulations can be placed on loperamide. This will protect drug abusers, who can be looked upon as vulnerable people, from obtaining loperamide easily. Limiting access to loperamide could also be cost effective. If federal regulations potentially minimize the number of patients overdosing on loperamide, not only would medical resources be saved but many lives as well. This meets the condition of justice but more specifically, the conditions of distributive justice in regards to fair and equitable allocation of medical resources. People have the right to have access to medications that are beneficial to them. However, if a medication can be abused and limitations can be placed that

protects all individuals, then ethically these limitations must be established. Implementing FDA regulations on loperamide, similar to those placed on pseudoephedrine, can save medical resources and save lives. Failure to regularly assess the need for implementation of these regulations is ethically irresponsible and morally objectionable.

## **PROPOSED SOLUTION**

We propose yearly federal legislative evaluation of a new law entitled: Combat Loperamide Epidemic Act (CLEA) based upon the growing number of cases of loperamide misuse. This modeled after the Combat Methamphetamine Epidemic Act of 2005 (CMEA) and incorporated into the Patriot Act signed by President Bush on March 9, 2006, would ban over-the-counter sales of any drug containing loperamide. The law would enact the following:

1. Customers would not have direct access to the product before the sale is made.
2. Limited amounts that can be purchased in a single day and in a month.
3. Individuals would be required to present photo identification to purchase such medications.
4. Written or electronic “logbooks” would be maintained listing sales identifying the product by name, quantity sold, names and addresses of purchasers, and dates and times of sales.
5. Retailers would be required to keep personal information about these customers for at least two years after the purchase of these medicines.

Implementation of CLEA would seek to deter loperamide misuse through implementation of restrictive purchasing efforts, initiation of identification requirement for purchase, and continued documentation of purchase. However, consideration of any new regulatory implementation must include evaluation of the challenges faced by the CMEA. The enactment of CMEA showed an initial decrease in methamphetamine use in the United States (29) but those who produce methamphetamines continue to identify diversion with increase in methamphetamine labs seen over recent years. Nationwide methamphetamine lab incidents (seizures of labs, dumpsites, chemicals and glassware) were 24,155 in 2004. With enactment of CMEA an initial decrease was seen (2005: 17,866 incidents) but then rose again in 2008 (8,933 incidents) peaking in 2010 (15,314 incidents) (30). Reports of “smurfers” has surfaced in which individuals from large criminal groups are responsible for purchasing restricted pseudoephedrine (PDE) from multiple pharmacies in a day (29). A study presented in 2014 showed no decrease in methamphetamine deaths (Oregon vs Washington) with CMEA however, a significant difference

in call volume was identified (31). We would anticipate the same trends to occur with CLEA. Studies have also shown CMEA to have increased costs related to inconvenience for legitimate PDE users (32) and a 2007 review stated replacement of PDE with other over the counter nasal decongestants such as phenylephrine (PE) was not a 1:1 replacement based upon differences in metabolism and efficacy studies (33). The author’s stated “Restricting the sale of PDE in order to control the illicit production of methamphetamine will deprive the public of a safe and effective nasal decongestant and force the pharmaceutical industry to replace PDE with PE, which may be an ineffective decongestant. Restrictions on sales of PDE to the public may not reduce the problems associated with methamphetamine abuse.” (33). These same concerns would need to be addressed for CLEA. Loss of access to loperamide, cost relation to other antidiarrheals, increased cost impact (loperamide and other agents) and clinical equivalence to comparative alternatives would all need to be assessed. The proposed CLEA, would seek to continue the purchase of loperamide for its FDA labeled use. If misuse is of concern, both diphenoxylate and bismuth subsalicylate can be considered as alternatives for their antidiarrheal properties.

Although current reported data may not warrant enactment of CLEA, medically and ethically some action has to be taken to protect, and even save the lives of opioid abusers. We propose yearly federal legislative evaluation of loperamide misuse and need for CLEA implementation. To support this yearly review, comprehensive reporting to FDA’s MedWatch program is needed by clinicians, emergency departments, and poison control centers regarding loperamide associated adverse events. From both a medical and ethical viewpoint, it seems clear that the FDA must evaluate future requirement of new regulations to protect people from this method of drug use.

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