Regulatory History and Background

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Topics to be Covered

- Regulatory History of Opioids for Treatment of Opioid Addiction
- Labeling of Neonatal Opioid Withdrawal Syndrome in Extended-Release and Long-Acting (ER/LA) Opioid Analgesics
- NOWS and Labeling of Opioids for Treatment of Opioid Addiction

Methadone

- Full μ-opioid receptor agonist
- Long duration of action due to slow accumulation and elimination
- Avoids highs and lows of shorter acting opioids that can impair daily functioning and prevents the subjective effects of illicit opioids
- Available formulations include tablets, syrup and dispersible tablet intended to be dissolved before dispensing

Methadone Regulatory History

- Marketed since 1947 under 1938 Federal Food, Drug, and Cosmetic Act, which only required demonstration of safety, and prior to 1962 amendment requiring demonstration of efficacy
- Found to be effective in 1970 Drug Efficacy Study Implementation (DESI) notice for
  - Treatment of moderate to severe pain
  - Treatment of acute withdrawal symptoms during detoxification from opioids
- 1972 regulations allowed for maintenance treatment of opioid addiction in opioid treatment programs (OTPs)
- Narcotic Addict Treatment Act of 1974 (NATA) passed to amend Controlled Substances Act
  - Specific opioid medications could be dispensed by OTPs
  - Enforcement-based system overseen by FDA's Office of Compliance

Methadone Regulatory History

- Enforcement-based system replaced by accreditation-based system overseen by Center for Substance Abuse Treatment (CSAT) of Substance Abuse and Mental Health Services Administration (SAMHSA) in 2001
- Pregnant women in the regulations
  - Priority for admissions to OTPs
  - Programs must have policies and procedures that reflect their special needs
  - Services must be provided either by the OTP or by referral to appropriate healthcare providers

Buprenorphine

- Partial μ-opioid receptor agonist
- Partial agonist properties confer limit on euphorigenic and respiratory depressant effects compared to full agonists
- Avoids highs and lows of shorter acting opioids that can impair daily functioning and prevents the subjective effects of illicit opioids
- Formulations indicated for addiction treatment are tablets and films to be applied to oral mucosa
- Formulations with naloxone are intended to confer an additional measure of deterrence against parenteral use
- Naloxone not well-studied in pregnancy and products without naloxone preferred in pregnant women

Buprenorphine Regulatory History

- Drug Addiction Treatment Act of 2000 (DATA) amended Controlled Substances Act to allow for prescribing of a schedule III drug approved for treatment of narcotic addiction, such as buprenorphine, by practitioners in an office-based setting
- Practitioners must certify that they have received adequate training (frequently met by taking a qualifying 8-hour course)
- DATA does not address the treatment of pregnant women or stipulate the content of training with regard to pregnant women

Levomethadyl acetate (LAAM)

- Levomethadyl acetate (LAAM) is a synthetic opioid analgesic structurally related to methadone with properties that allowed for thrice-weekly dosing
- LAAM approved in 1993 for use in OTPs under the same regulatory framework as methadone
- LAAM labeling changed in 2001 to reflect newly identified safety concern with QT interval prolongation and cases of torsade de pointes
  - Agency concluded that drug continued to have favorable risk/benefit profile but as 2nd line therapy
  - ECG monitoring recommended
  - Boxed warning included
  - Many OTPs discontinued offering LAAM
  - Manufacturer discontinued marketing

Neonatal Opioid Withdrawal Syndrome (NOWS)

- Caused by prolonged exposure to opioids during gestation followed by abrupt cessation of opioid exposure at birth
- Characterized by CNS irritability, autonomic over-reactivity, and gastrointestinal dysfunction
- If severe enough and untreated, outcomes can be very serious, such as seizures and death
- Also sometimes referred to as Neonatal Abstinence Syndrome (NAS) though this term could include multiple different substances

Stakeholder Concern about Rising Incidence of Neonatal Opioid Withdrawal

- May 2013 letter submitted to FDA by National Association of Attorneys General noting increased incidence of "neonatal abstinence syndrome" (neonatal opioid withdrawal) due to prescription opioid exposure during pregnancy
- Requested "black box warning" on prescription opioid analgesics

Prescription Opioid Labeling in 2013

- Opioids with indication for treatment of pain had precautionary language for NOWS in the pregnancy and/or specific populations sections in labeling

FDA Evaluation of New Safety Information

- As part of an evaluation of the medical literature relevant to opioid analgesics, FDA determined that there was new safety information that documented increases in the incidence of Neonatal Abstinence Syndrome (NAS), including NOWS, and justified safety labeling changes for the Extended-Release and Long-Acting Opioid Analgesic products

FDA action on ER/LA opioid analgesic labeling

- Boxed warning appropriate to warn prescribers and patients of risk of NOWS because
  - risk is potentially life-threatening if unrecognized or untreated
  - can be prevented or reduced in frequency or severity with careful monitoring and clinical management
- Safety labeling change notification letter sent September 2013
  - Boxed warning
  - Statement in Warnings and Precautions
  - Brief statement in Pregnancy section referring to other warnings

Current NOWS Labeling in ER/LA Opioid Analgesics (approved 4/16/14)

- Boxed Warning:

  Prolonged use of TRADENAME during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Current NOWS Labeling in ER/LA Opioid Analgesics (approved 4/16/14)

- Warnings and Precautions 5.3 Neonatal Opioid Withdrawal Syndrome

  Prolonged use of TRADENAME during pregnancy can result in withdrawal signs in the neonate. **Neonatal opioid withdrawal syndrome**, unlike opioid withdrawal syndrome in adults, **may be life-threatening if not recognized and treated**, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and **ensure that appropriate treatment will be available**.

  Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

- 8.1 Pregnancy

  Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly

Incidence of NOWS (NAS) in Setting of Opioid Maintenance Therapy During Pregnancy

- Among studies with an objective scoring system (such as the Finnegan Neonatal Abstinence Score), the incidence of medically treated NAS ranged from 45% to 97% of neonates born to methadone-maintained mothers
- In a randomized controlled trial of methadone and buprenorphine in the comprehensive care of 175 pregnant women, the incidence of treatment for NAS in the offspring of mothers remaining in the study through delivery was about 50%

NOWS statements in Labeling for Opioids Indicated for Treatment of Opioid Addiction

- Currently, NOWS precautionary statements are in the Warnings and Precautions, Pregnancy, and/or Drug Abuse and Dependence sections
- FDA is currently considering changes to product labeling or use of other risk communication tools
- Goal is to communicate risk in a manner that is useful to prescribers and patients and consistent with FDA regulations and guidance on product labeling

Stakeholder Concern about Potential Negative Impact of Labeling Changes

- June 2013 letter from American Society of Addiction Medicine, September 2013 letter from American College of Obstetrics and Gynecology, October 2013 Citizen Petitions from National Advocates for Pregnant Women
  - Could reduce number of opioid-addicted pregnant women who are recommended to or maintained on opioid agonist treatment
  - Discontinuation of treatment likely to result in relapse to nonmedical use of opioids, which will increase risk to pregnant women and their babies
  - Labeling could be used to justify "punitive and counterproductive child welfare interventions"
  - Could lead pregnant women with opioid addiction not to seek addiction treatment or prenatal care

Summary

- Agonist maintenance treatment for opioid addiction with methadone and buprenorphine has a unique regulatory framework
- Communications about risk in past may have unintentionally led to less treatment options for patients (i.e. LAAM)
- NOWS may occur in neonates with prolonged exposure to opioids during gestation and may be life-threatening if not recognized and treated
- FDA is considering new risk communications concerning NOWS that address opioid products indicated for treatment of opioid addiction
- Stakeholders have raised concern about the potential adverse consequences for pregnant patients with opioid addiction of new risk communications concerning NOWS

Evidence of Increasing Frequency of NAS and NOWS

- Agency for Healthcare Research and Quality Database 2000-2009
  - Rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001)
  - Concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001])

FDA review of NOWS

- Factors that influenced incidence, severity, onset, and duration of NOWS
  - Type of opioid
  - Pharmacokinetics of opioid
  - Dose of opioid
  - Presence of polysubstance abuse
  - Neonatal characteristics