Pharmacokinetics and Clinical Implications of Drugs in Human Milk
The Substance Exposed Infant

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Pharmacist with a special interest in the safety of drugs in breastmilk

Objectives of this presentation

- to consider the pharmacokinetics of substances to which babies may be exposed through breastmilk
- to evaluate whether breastfeeding can be continued following exposure to substances
- to discuss how we may support the breastfeeding mother who is using substances during her lactation

Breastfeeding Guidelines for Women with a Substance Use Disorder

- Mothers with substance use disorders (including those receiving medication assisted treatment with methadone or buprenorphine) with no other medical contraindication should be encouraged to breastfeed unless the risks clearly outweigh the medical, psychosocial, and financial benefits of breastfeeding.
- Women using alcohol or drugs should be advised, educated, and supported to cease alcohol or drug use due to risks of harm to infant during parenting and breastfeeding.

Northern New England Perinatal Quality Improvement Network.

www.nnepqin.org/a-toolkit-for-the-perinatal-care-of-women-with-opioid-use-disorders

Trust

- Communication with pregnant women with a history of substance use regarding infant feeding should emphasize solidarity with, and respect for, the woman in order to support continued engagement in her needed care and support for high quality parenting
- Self reporting
- Screening of mother
- Screening of baby

Substances with significant risk to the baby resulting in withdrawal needing support

- Heroin
- Cocaine
- Opioids
- Daily or frequent cannabis use
- Illicit amphetamines, benzodiazepines, Illicit opioids
- Intravenous substance use
- Benzodiazepines in excess or long term
- Daily or heavy alcohol use particularly in pregnancy

Opioids – prescribe more?

A letter to the editor in the *New England Journal of Medicine* in 1980 reported that:

- of 11,882 hospitalized people who were prescribed opioids, only four became addicted. However there was little evidence to back up these claims of non addiction .
- A widely cited 1986 study, involving only 38 people, advocated using opioids to treat chronic pain unrelated to cancer

Oxycontin and increase in use opioids

- Prescriptions for opioids grew though 1980s and 1990s
- Oxycontin and Fentanyl were used more
- Purdu Pharm emphasized the safety, efficacy and low potential for addiction of prescription opioids.
- Chronic pain increases and we develop a tolerance for opioids so higher doses and long term use begins
- Tolerance develops and desperation to fund what becomes a problem

Tracing the US opioid crisis to its roots 2019

www.nature.com/articles/d41586-019-02686-2

Overdose Death Rates Involving Opioids, by Type, United States, 2000-2017

Olfson M, Rossen LM, Wall MM, Houry D, Blanco C. Trends in Intentional and Unintentional Opioid Overdose Deaths in the United States, 2000-2017. *JAMA*. 2019;322(23):2340–2342

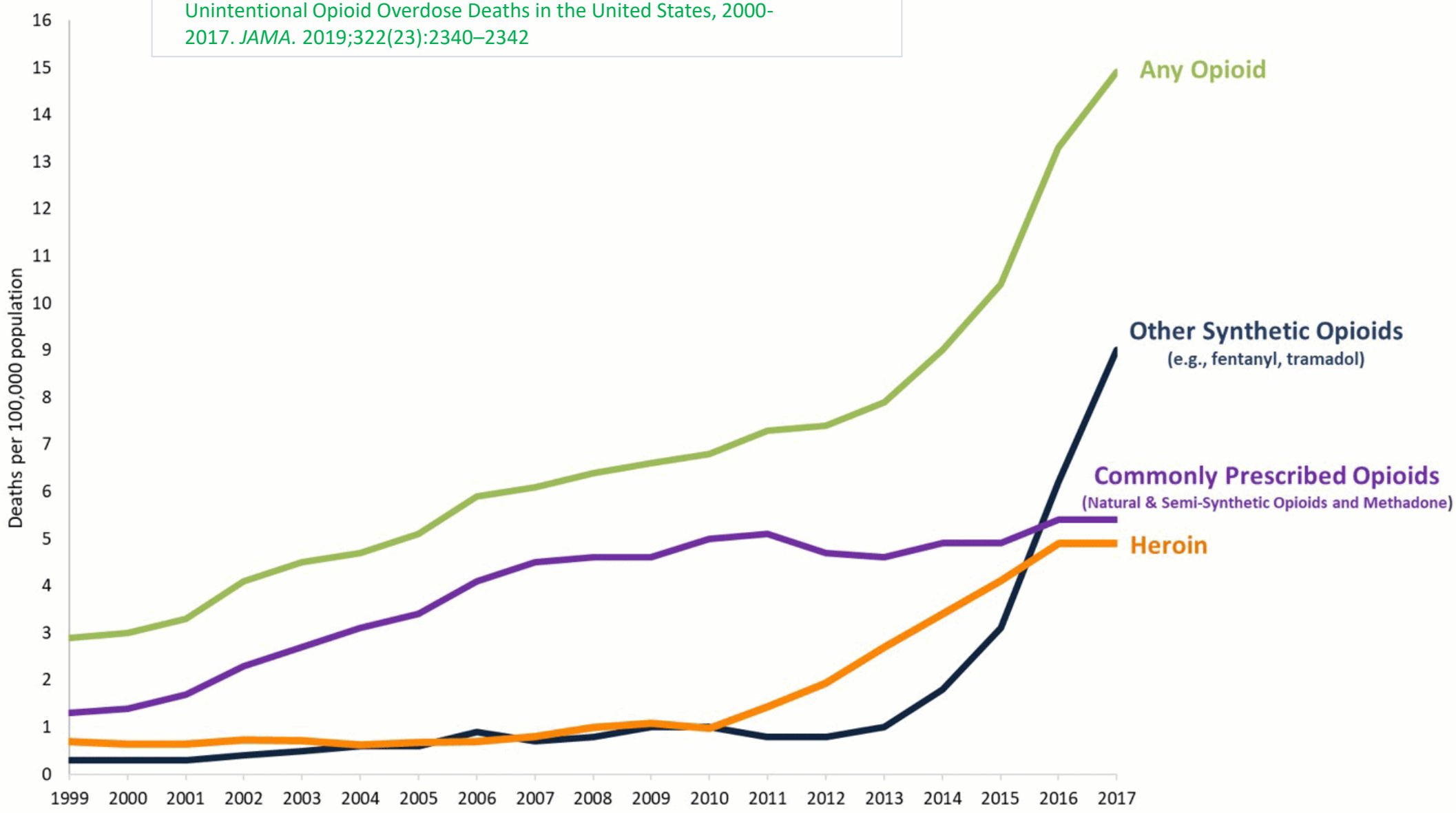
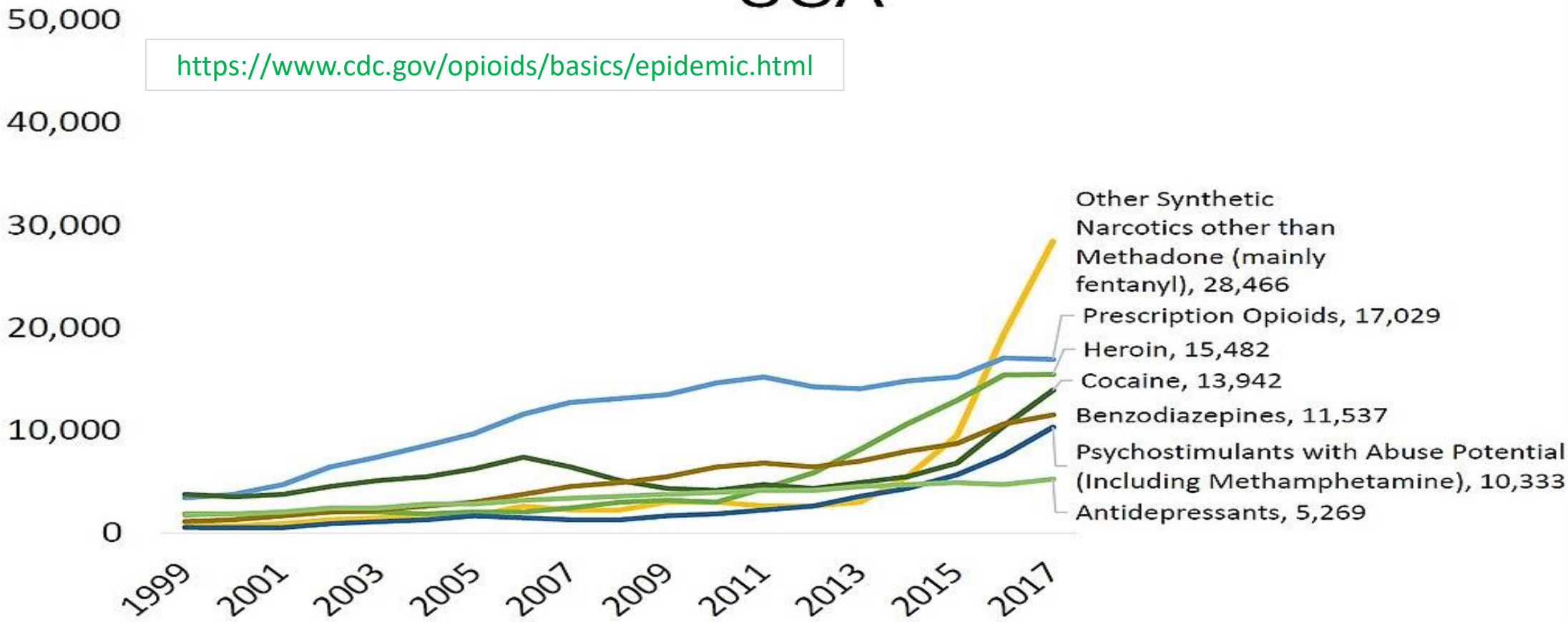


Figure 2. **National Drug Overdose Deaths** Number Among All Ages, 1999-2017

USA

https://www.cdc.gov/opioids/basics/epidemic.html



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Benzodiazepines

- Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67%, from 8.1 million to 13.5 million.
- Overdose deaths involving benzodiazepines increased more than 7 times between 1999 and 2015.
- The risk of overdose death goes up nearly fourfold when benzodiazepine are used with opioids yet rates of co-prescribing benzodiazepines and opioids nearly doubled between 2001 and 2013.
- *BMJ* in 2017 found that 17% of individuals who used prescription opioids in 2013 also used benzodiazepines, up from 9% in 2001
- Xanax and Valium used for anxiety and insomnia – may be sourced on the internet for misuse

Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis *BMJ* 2017;356:j760

Mothers using substances in pregnancy

- Less likely to engage with prenatal care
- Risk of pre term birth increases
- Possibility of foetal abnormalities
- Risk of seizures
- Little opportunity for antenatal screening
- Baby may be born with unexpected NAS

Neonatal abstinence syndrome (NAS)

Symptoms in baby:

- Irritable
- Difficult to feed
- Vomiting and diarrhoea
- High pitched cry
- Hyper reflexes

Was this expected from antenatal discussions with mother?

Women are more likely to have chronic pain, be prescribed prescription pain relievers, be given higher doses, and use them for longer time periods than men. Women may become dependent on prescription pain relievers more quickly than men

Understanding of pharmacokinetics

- How do we evaluate the risk of the drug passing through breastmilk?
- How do we manage breastfeeding?
- How do we support the mother

Risk of drug passing to baby via breastmilk

vs risk of not breastfeeding

Codeine

- A pro drug metabolised to morphine by cytochrome P450 2D6 (CYP2D6) enzyme
- Genetics influences how much gets into the bloodstream
- In some it is ineffective as an analgesic, because they don't have the gene, others it works effectively and no side effects
- However, a third group has multiple copies of the gene and can transform 20% of the codeine into morphine (instead of 7 -10%) leading to a potentially toxic level in breastmilk
- Symptoms of CNS depression in baby include: failure to feed, sedation, limpness and failure to gain weight
- mothers usually experience drowsiness and constipation too

Pharmacokinetics of codeine

- Plasma protein binding 7%
- Half life 2.9 hours
- Milk plasma ration1.3-2.5
- Oral bio availability complete
- Relative infant dose 0.6% - 8.1%
- All gone from the body in 15 hours
- BUT if a mum uses very high doses regularly there can be a significant level of morphine in milk

Can mum breastfeed? A real example

- Just asking for some advice for a lady who is about 28 weeks pregnant.
- She is taking codeine 30-60mg (maximum of 8 daily)

  oramorph 5-10mls 4-6hrly

  fentanyl patches (75mcg/hr).
- Would all these opiates in combination be compatible with breastfeeding?
- In her medical notes she is described as in chronic pain and receives prescriptions issued weekly

- Does doctor recognise she is addicted?
- Has he/she found it easier to keep prescribing rather than challenge and support withdrawal?
- Or has patient refused to discuss/seek help?

Pharmacokinetics of oxycodone

- Plasma protein binding 45%
- Half life 2 – 4 hours
- Milk plasma ration 3.4
- Oral bio availability 60-87%
- Relative infant dose 1.01% - 4.55%
- The rates of infant CNS depression (n=533)
  - oxycodone group - 20.1%;
  - codeine group - 16.7%;
  - acetaminophen group - 0.5%.

Lam J, Kelly L, Ciszkowski C et al. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. J Pediatr. 2012;160:33-37.

Pharmacokinetics of hydromorphone (dilaudid)

- Plasma protein binding 8-19%
- Half life 2.6 hours orally
- Milk plasma ration 2.56
- Oral bio availability 60%
- Relative infant dose 0.67%
- Can lead to respiratory difficulty but less passes through milk than other opioids

Colorado Hospitals Use New Approach To Treat Opioid-Exposed Newborns

https://cpcqc.org/qii/chosen/

By STEPHANIE DANIEL • 17 HOURS AGO

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Managing outcomes for babies exposed to opioids prenatally www.chosencollaborative.org/

- 25 hospitals in Colorado, Wyoming and Montana
- At start (2017)70% babies treated with medication and average hospital stay for baby was 2 weeks
- After study <10% treated with medication and most discharged within 6 days
- Between 2011 and 2016 reported cases of NAS (neonatal abstinence syndrome) increased 120% but study found incidence of exposure even higher (possibly due to coding errors in maternal/infant health records?)
- Parental engagement reported

- Behavioural techniques to soothe babies to withdrawal
- Guidelines for safe breastfeeding and discharge plans
- Demonstrated cost savings
- Supported by qualitative interviews with families and staff

Incidence of substance exposure

- The 2013 National Survey on Drug Use and Health reported that in USA, 5.4% of all pregnant women were current illicit drug users. https://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf
- This included 14.6% of women between 15 and 17 years of age and 8.6% between 18 and 25 years of age, all pregnant.
- Rates of neonatal abstinence syndrome have increased from 1999 to 2013

2,419 among 1,610,733 births (1.5 per 1,000 births)

To 8,270 among 1,385,371 (6.0 per 1,000 births)

https://www.cdc.gov/mmwr/volumes/65/wr/mm6531a2.htm

Pharmacokinetics of Cocaine

Babies exposed to cocaine through breast milk may experience extreme irritability, tremulousness, vomiting, and diarrhoea.

- Plasma protein binding 91%
- Half life 5 mins -1 hour
- Milk plasma ration ?
- Oral bio availability 35%
- Relative infant dose ?

https://breastfeeding-and-medication.co.uk/fact-sheet/breastfeeding-and-cocaine

Studies on cocaine

- 11 mothers admitted to using in pregnancy, highest levels in milk of one who admitted to last using 5 days before birth
- Cocaine on the nipples? Three hours following breastfeeding, she discovered the infant choking, blue and gasping for air. The infant had flexed limbs and his eyes "rolled back“. Needed CPR
- Difficult to study because of lack of data on use and purity

I used cocaine 72 hours ago, I was told it only was in milk briefly so fed 2 hours later and continued to do so. Now I’m worried

Pharmacokinetics of Cannabis

- Plasma protein binding 95-99%
- Half life 25-57 hours
- Milk plasma ration 8
- Oral bio availability 4-12%
- Relative infant dose ?
- Crosses the blood brain barrier
- Sits in fat tissues
- Do we know the result from chronic use?

https://breastfeeding-and-medication.co.uk/thoughts/breastfeeding-and-cannabis

Pharmacokinetics of Methadone

- Plasma protein binding 89%
- Half life 13-55 hours
- Milk plasma ration 0.68
- Oral bio availability 50%
- Relative infant dose 1.9% - 6.5%

- infant of mother died at 3 1/2 months of SIDS, it was not due to methadone, as none was present in the infant's plasma and the infant was significantly supplemented with formula.
- Abrupt cessation of breastfeeding has precipitated neonatal abstinence syndrome later

Pharmacokinetics of Buphrenorphine

- Plasma protein binding 96%
- Half life sub ling 37 hours
- Milk plasma ration 1.7
- Oral bio availability sub ling 29%
- Relative infant dose 0.09% - 2.52%
- No evidence of adverse effects in breastfed baby though studies limited

Pharmacokinetics of Heroin

- Plasma protein binding 35%
- Half life 2-6 minutes
- Milk plasma ration 2.45
- Oral bio availability <35%
- Relative infant dose ?
- A prodrug that is rapidly converted to 6-monoacetylmorphine and then to morphine. With oral use, rapid and complete first-pass metabolism occurs in the liver; morphine levels peak about 30 minutes after the oral dose. When smoked or snorted the onset of heroin can be within seconds and peak in minutes. When injected the onset of heroin is within seconds; this route completely avoids first pass metabolism.
- Tolerance develops in mother?
- Ability to care for baby?
- Adulterants are common and varied?

Ecstasy (Gamma Hydroxybutyric Acid)

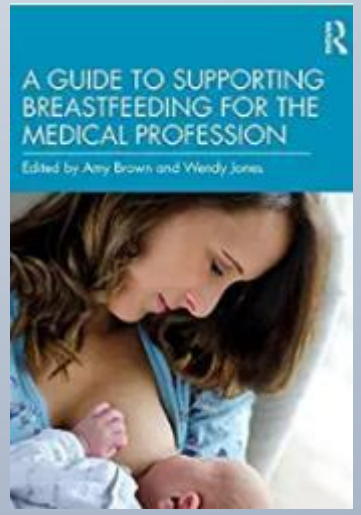
- Plasma protein binding ?
- Half life 20-60 minutes
- Milk plasma ration ?
- Oral bio availability good
- Relative infant dose ?
- Milk levels “probably” be low to undetectable after 12 hours
- Discard milk for 24 hours particularly if more than one dose

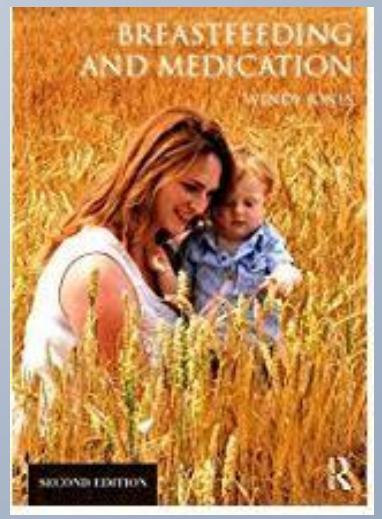
Pumping

- To maintain supply?
- Does mum have a breast pump?
- Does she have clear instructions on how often to pump?
- What if baby is being cared for but mum wants to provide breastmilk or breastfeed when in contact with the baby
- Does carer know what to look out for at times when baby is receiving breastmilk e.g softer stools? What is normal and what is of concern and needs medical attention

Reference sources

- Hale Medications and Mothers Milk – a book and online access www.halesmeds.com/ from which data was taken
- LactMed https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- Jones Breastfeeding and Medication
- Brown and Jones A guide to breastfeeding for the medical professional (Dec 2019)





Let’s change the conversation

- Provide mothers (and their partners) with evidence based information
- Let’s use shared decision making and trust
- Let’s promote and support breastfeeding wherever possible
- Let’s support mum so that she can continue to breastfeed as normal even if that means a hard journey to change her social life

Summary

- We can use pharmacokinetics to assess safety of a medication even if it is a non prescribed drug or used in a higher than normal dose
- We can access specialist reference sources
- We can support mums with expressing if it is necessary and develop a care plan for breastfeeding to reduce withdrawal in the baby
- We can spread the word to our medical colleagues
- We can support mothers who have exposed their baby to substances to change one small step at a time

Be Kind

Value their breastfeeding if that is what they wish

Support them

You don’t have to have the answers but don’t undervalue the importance that you listened to them

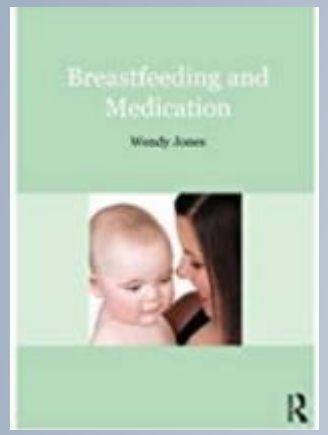
Develop their trust and therefore honesty

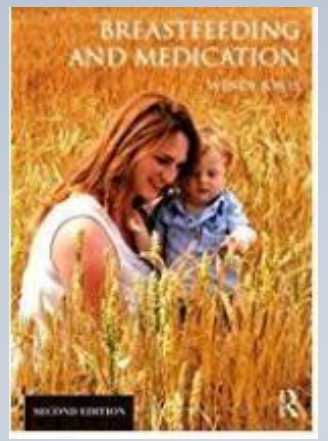
You are working together for the best outcome for baby

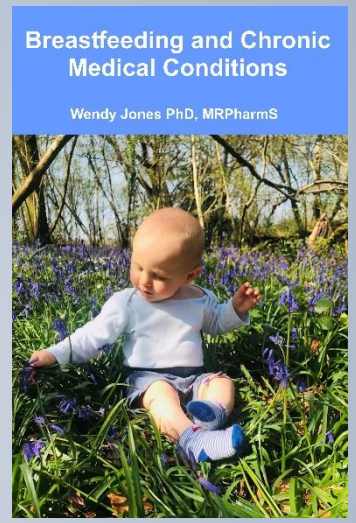
For the mother change may be hard.

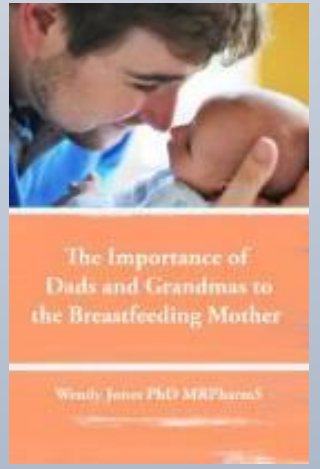
There but for the grace of God go I

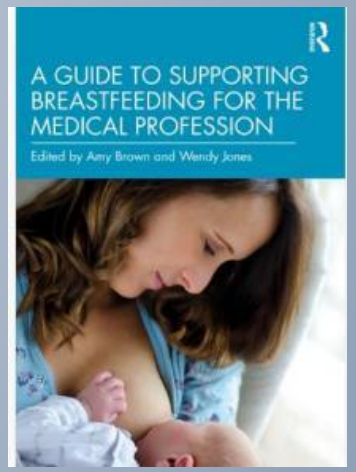
My published books











Healthcare professionals need training on breastfeeding, the safety of drugs in breastmilk and sensitivity to the needs of mothers around infant feeding. If a mum is using a substance she isn't a bad mum, she just got into the wrong place

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www.facebook.com/breastfeedingandmedication