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A plausible causal relationship between the increased use of fentanyl as an obstetric analgesic and the current opioid epidemic in the US

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ABSTRACT

Drug poisoning deaths have more than doubled in the United States since 2000 with fentanyl and fentanyl analogues primarily responsible for the jump in opioid deaths. Robust data indicate a convincing correlation between the exposure of the fetus to other labor medications (morphine, pethidine hydrochloride, barbiturates, phenobarbitone, meperidine, and secobarbital) and the later addiction of young adults to the same category of drug. We present the hypothesis that this effect is also true of the opioid, fentanyl: there is a causal relationship between the increased popularity of fentanyl as a labor anesthetic in the United States since the 1980's and the current epidemic of fentanyl abuse.

Introduction/background

More than 2.5 million Americans are estimated to be addicted to opioids in the form of either prescription drugs or heroin [1]. This is an urgent public health matter. Although the opioid drug epidemic originally focused on the misuse of prescription drugs, the overdose deaths from these have leveled off and the landscape has changed. According to the Centers for Disease Control and Prevention (CDC), the United States' epidemic is worsening, with deaths increasing by 28% between 2015 and 2016. Heroin and non-pharmaceutical fentanyl overdoses are driving these changes, not prescription drugs [2]; prescribing rates of fentanyl have not increased while fentanyl fatalities in the past years have increased by 79% [3]. A high proportion of these fentanyl deaths are a result of illicitly-manufactured fentanyl (IMF) or other synthetic opioid analogues of fentanyl. Recent reports have also revealed an increase in adolescent drug users dying [4].

In the past, the chance of knowing the name of the overdose drug beyond "opioid" was rare, as toxicology testing usually did not differentiate between illicit or synthetic opioid deaths and "prescription" opioids. However, when additional analysis has been done, as it has recently in several states, fentanyl is found to be involved in more than half (56.3%) of all overdose fatalities [5]. The CDC has recently expanded and improved surveillance in 32 states in order to more accurately identify and report the specific drugs involved in deaths [3]. As a result, the January-February 2017 unintentional overdose fatalities in Ohio that were analyzed by a toxicology laboratory showed that 90% of all decedents tested positive for fentanyl with only 5.7% testing positive for heroin. Of those that died from fentanyl, 32% did not test positive for fentanyl's major metabolite, norfentanyl, suggesting that death was very rapid [6].

Fentanyl is 50 times more potent than heroin and 100 times more potent than morphine. Although pharmaceutical fentanyl and IMF are structurally similar, fentanyl analogues vary in potency. For example, the analogue carfentanyl is 100 times more potent than fentanyl and its intended use is not for humans, but large animals. Fentanyl sales are considerably more lucrative than heroin sales. A kilogram of heroin can be purchased for around $6000 and then sold for in the wholesale market for around $80,000. A kilogram of fentanyl can be purchased for less than $5000 and sold for a profit of $1.6 million [7].

Fentanyl was first synthesized in Belgium in 1960. The Janssen research team was focused on finding a fat soluble analgesic that would work faster and have fewer side effects than the then popular morphine and meperidine. Lipid soluble fentanyl was fast acting, working in only 1–2 min after intravenous administration. Effects typical of opioids occurred with fentanyl such as sedation, nausea, vomiting, respiratory depression etc., but not the increase in plasma histamines with resulting pruritus. By 1968 the drug, which was already popular among anesthesiologists in Europe, was approved by the FDA. At first, U.S. availability for fentanyl was limited to distribution only in combination with droperidol at a ration of 1:50 droperidol and later, when available alone, the FDA limited distribution to small amounts (50 μg) due to concerns that fentanyl was too potent and could also lead to abuse problems [8]. Fentanyl was placed under international control in 1964 [9] and appeared on the illicit drug market beginning in the 1970's when it first began to be known for accidental overdoses [10].

Fentanyl became more and more popular in the United States, at first for cardiac and then other surgeries in the late 1970's, with a reported ten fold increase in sales just in the year 1981. In the 1980's the

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Table 1
Studies examining the connection between obstetric pain medications and drug abuse or addiction in offspring.

Citation	Birth years and location studied	Obstetric factors investigated	Drug of abuse	Subjects	Findings	Main outcome	Comment
Jacobson et al. (Obstetric pain medication and eventual adult amphetamine addiction in offspring)	1945–1966 in Stockholm, Sweden	Nitrous oxide administered to mothers in labor	Amphetamine	73 addicts and 109 non-addicted siblings	The risk for amphetamine drug addiction in offspring was found to increase with duration of intermittent administration of pure nitrous oxide	The risk was 5.6 times higher for addicts versus non-addicted unexposed siblings if nitrous oxide had been given for greater than 4.5 h ($p = .005$)	Results were thought to be explained as an effect of imprinting on the fetus
Jacobson et al. Opiate addiction in adult offspring through possible imprinting after obstetric treatment	1945–1966 in Stockholm, Sweden	Administration of opioids, barbiturates, nitrous oxide in labor	Opioids	200 opiate addicts and 262 unexposed siblings	In subjects who had become addicts, their mothers had more likely received opioids or barbiturates or both during labor than unexposed siblings	When outcomes were matched with their own unexposed siblings, the estimated relative risk was 4.7 ($p = .02$)	The results are compatible with imprinting of obstetric medications used in labor on the fetus
Nyberg et al. Obstetric medication versus residential area as perinatal risk factors for subsequent adult drug addiction in offspring	1945–1966 in Stockholm, Sweden	Area of residence compared to hospital of record for birth	Amphetamines and opiates	200 amphetamine addicts and 200 opiate addicts	Neither hospital nor residential area was able to explain opiate addiction. For amphetamine addicts, hospital of birth was found to be a risk factor	Geographical area of subsequent addicts cannot fully explain a high birth rate of future addicts	A “contagious” transmission method of drug addiction by hospital or residential area was not supported by this study
Nyberg et al. Socio-economic versus obstetric risk factors for drug addiction in offspring	1945–1966 in Stockholm, Sweden	Drugs given to mother in labor within 10 h of birth, socio-economic conditions, education of mother, marital status of mother, birth order, birth weight, duration of labor, operative delivery	Amphetamines and opiates	200 amphetamine addicts and 200 opiate addicts compared to their siblings, plus 7100 controls from the general population for socio-economic and birth at a given hospital	After controlling for socio-economic condition factors, the administration of nitrous oxide was a risk factor for amphetamine addiction in offspring	The number of administrations of either opiates, barbiturates, nitrous oxide for more than an hour or any combination thereof, is a risk factor for opiate addiction	The results are in agreements with the concept of imprinting. The unconscious memory of the drugged state at birth may make an individual more disposed to become addicted if exposed as an adult
Nyberg et al. Perinatal medicine as a potential risk factor for adult drug abuse in a North American cohort	1959–1966 in the United States	Opiates and barbiturates given to mother within 10 h of birth meperidine Phenobarbital secobarbital	Cocaine Hallucinogens Narcotics Other “hard” drugs	69 subjects who met the DSMIII criteria for diagnoses of drug abuse or dependence compared to 33 non-abusing siblings	The results replicated the Swedish findings	Unadjusted Odds Ratio of 4.7 for becoming drug dependent in adulthood after perinatal drug exposure of multiple drug doses	In utero exposure of high dose medication during labor may be an important and preventable risk for later substance abuse in humans