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The Opioid Overdose Epidemic and Deceased Donor Liver Transplantation

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Philadelphia College of Osteopathic Medicine
Graduate Program in Biomedical Sciences
School of Health Sciences

The Opioid Overdose Epidemic and Deceased Donor Liver Transplantation

A Capstone in Public and Population Health Leadership by Edmund Peacock

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Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science
in Biomedical Sciences, Public and Population Health Leadership Concentration

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ABSTRACT

Objective: To study the effects and trends of the opioid overdose epidemic on deceased donor liver transplantation and examine how some regions more effectively utilize their population of overdose deaths for recovery of livers for transplant.

Background: Increases in the rate of overdose deaths have led to a growing portion of the deceased organ donor population arising from overdose events^{1,2}. Many transplant centers and recipients decline these livers from overdose donors due to concern for disease transmission and the stigma around addiction and drug use³. The risks of using these livers for transplant are continuing to decrease as treatments for diseases such as hepatitis C ensure the safety of the recipient despite the donor's history of drug use, and research has indicated that these organs are comparable in quality and recipient survival to organs recovered from other donors^{1,4,5}.

Research Strategies: Use the Pubmed and Google for gathering academic data and published papers to determine national and regional trends in recovery and transplant of livers from donors who died of overdose. Additional data gathered from Centers for Disease Control—CDC—and the Organ Procurement and Transplant Network—OPTN, as well as the Scientific Registry of Transplant Recipients—SRTR—report.

Expectations: This project seeks to determine usage trends in donated livers from donors who died by the mechanism of anoxic injury secondary to drug overdose or intoxication and compare those data around usage rates regionally to determine what potential strategies may work for maximizing the usage of these livers for transplant to help address the organ transplant shortage.

INTRODUCTION

The United States is currently facing a shortage of organs for transplant, and many people on the transplant waitlist will die prior to being transplanted¹. To address this organ shortage, it is critical that many people become living donors and that a majority of people are registered to be organ donors following their death. In addition, it is crucial that when people pass away in situations where deceased organ donation is possible, that the organizations and hospitals that coordinate and perform organ recovery and transplant recover and transplant as many organs as efficiently as possible. Despite this nationwide coordinated effort, there are still areas in which improvements can be made and more organs can be recovered and transplanted. One of those areas of major recent growth and potential further growth is the use of organs from donors who have died following a drug overdose.

BACKGROUND

Over the last several decades, the United States has witnessed a major increase in the numbers of opioid and intravenous drug overdose deaths⁶. This trend has been helped along by a host of contributing factors including the increased rates of opioid prescription by medical providers, increased marketing of opioids by pharmaceutical companies, increased rates of drug use and depression from economic downturns, and, more recently, the influx of more synthetic opioids into public consumption such as fentanyl^{1,6}. These overdoses have led to an increased number of younger people experiencing anoxic events

stemming from respiratory and cardiac arrests. Under these circumstances, they face a high likelihood of no meaningful neurological recovery or even brain death. This increased likelihood of brain death in otherwise young and healthy people makes them ideal candidates for deceased organ donation. The increasing rates of overdose deaths have led to anoxic events becoming the largest portion of donor death mechanism, passing CVA/stroke and traumatic injury in 2014 (Figure 1)². Because of this fact, many organ procurement organizations (OPOs) and transplant centers have made concerted efforts to utilize these organs for transplant, but many are still being needlessly discarded or not recovered.



Figure 1. Cause of death among deceased liver donors nationally ²

The United States Opioid Epidemic

The United States has seen a marked increase in opioid overdose deaths since the 1990s. According to the CDC, from 1999-2019 nearly 500,000 people died from an overdose related to opioid use⁶. This epidemic has been classified into three different waves. The

first wave occurred with an increase in opioid prescriptions in the 1990s which was a mix of semi-synthetic and natural opioids⁷. The reaction to this growing trend of prescribed opioid overdoses led to a decrease in opioid prescriptions and greater controls on the overprescribing of opioid medications. Unfortunately, many people were already struck with opioid use disorder when this occurred, and this drove the second wave of the opioid epidemic where they began to seek heroin as a replacement for the previously available prescription opioids. This second wave started in 2010 with a marked increase in the number of heroin deaths⁸. As the market for heroin increased, illicit drug manufacturers saw an opportunity to increase profits with the introduction of illicitly manufactured synthetic opioids such as fentanyl. This growth in the availability of synthetic opioids and their increased combination with heroin, counterfeit pills, and cocaine led to the third wave of the opioid epidemic in 2013⁹.

Concerns Regarding Donors from Overdose Deaths

One of the major concerns regarding the transplantation of organs from drug overdose deaths is the transmission of disease³. Intravenous drug overdose death donors are of particular concern due to their heightened exposure to hepatitis B, hepatitis C, and HIV³. Due to this concern, it has historically been harder to place these organs for transplant even when they have negative pre-recovery serologies³. For some recipients, they may see their transplant as the only shot they will have and opt to wait for another organ that has a lower risk of disease transmission. While it is true that there is some increased risk for disease transmission, the overall quality of the organs from overdose donors is on par

with those from traumatic death donors based on recipient survival five years post-transplant^{1,5}. Young traumatic death donors have historically been viewed as the gold standard for organ donation potential¹.

Beyond recipient concerns, transplant centers across the country all have varying levels of risk they will accept for their recipients. Some will be more aggressive and transplant a higher number of transplant candidates with more marginally viable organs while others will be more discerning with what organs they accept and which patients they transplant to ensure a higher percentage of positive outcomes. This risk can range from quality of organ accepted based off of donor past medical history, pre-recovery lab results, as well as visualization and biopsy of the organ, and health status of the recipient. However, many transplant centers are far more risk averse than their peers and will decline organs based off their social history of IV drug use. Regionally, the host OPO which arranged organ recovery may change their recovery practices based on their available resources and the potential for acceptance based off of previous cases. In addition, some local hospitals may be unaware that an overdose patient who has a history of HCV can potentially be an organ donor and will not aggressively notify their regional OPO until the patient's family has decided to withdraw care or care has already been withdrawn.

Examples of Positive Developments in Overdose Death Donation

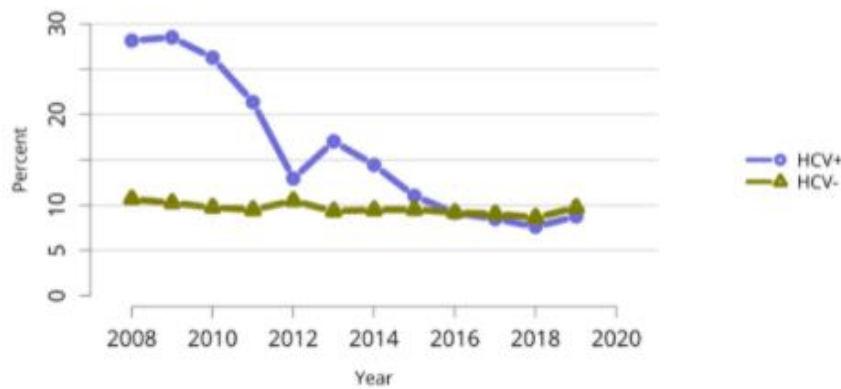
Of the many areas hit by the opioid epidemic, New England was of particular note as an early epicenter, and New England Donor Services (NEDS), the OPO in the area, made a

deliberate effort to maximize their recovery of organs from this growing pool of potential donors. They focused on aggressive pre-recovery serology testing, comprehensive discussion of donor risk with transplant centers, and education of local hospitals on the potential for organ donation even in the setting of positive serologies¹⁰. This included HCV, HBV, and HIV nucleic acid testing or NAT testing for all donors in addition to the previous use of antigen and antibody testing¹⁰. This additional testing allowed NEDS to shrink the window for development of potential unknown donor derived infection from several weeks to several days¹⁰. This allowed for an increased confidence in the safety of transplanting organs even if a donor was a known user of IV opiates. Following these changes, the percentage of donors from the NEDS donor service area (DSA) rose from a low of 10% in 2013 to 27% in 2016, compared to 7% to 13% over that same timespan nationally. Additionally, the development of treatments for HCV and the realization that HCV positive organs are viable for transplant allowed NEDS to quadruple the total number of HCV positive donors over that same timespan¹⁰.

Positive Developments in HCV Positive Donation

Based on the population of IV opiate users, the major disease of concern is Hepatitis C or HCV¹¹. HCV is the leading blood borne illness in the United States and was historically the leading disease etiology behind a person being listed for a liver transplant¹¹. The large percentage of waitlist recipients with preexisting HCV led to a focus in transplant of first utilizing these organs for recipients who were already HCV positive. The discovery and increased use of direct-acting antivirals (DAAs) for HCV changed the patient outlook for

many with the disease and allowed for a cure rate of nearly 90%¹². In addition, the use of these DAA regimens has led to the percentage of patients in the liver transplant waitlist declining from 30.6% down to 12.6% over the previous decade². Following the use of these treatments for HCV patients, transplant researchers began looking into the potential for transplanting HCV positive donors to HCV negative recipients. The percentage of liver transplant candidates developments have led to their being no discernable difference in the rate of discard for livers based on donor HCV status (Figure 2)².

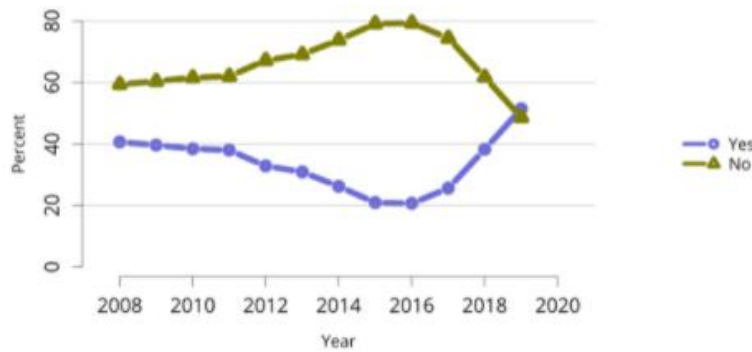


OPTN/SRTR 2019 Annual Data Report

Figure 2. National rate of organ discard for livers from donors by HCV status²

Additionally, the growth in the use of DAAs and their effectiveness has grown the percentage of adult recipients willing to accept a liver from an HCV positive donor. It is now nearly a fifty-fifty split of recipients willing to accept HCV positive livers and those who are not with more recipients being open to receiving an HCV positive liver (Figure 3)². But there is still much room for improvement in education and awareness so that

recipient will be more willing to accept these livers knowing that they can be treated with DAAs.



OPTN/SRTR 2019 Annual Data Report

Figure 3. The percentage of adult liver waitlist recipients willing to accept HCV positive livers²

Missed Opportunities

Despite these major gains in the areas of donation after drug overdose and HCV positive organ donation, there are some studies which indicate that there are potential organ donors being missed. A 2018 study analyzed nationally available data from OPTN and the CDC to demonstrate that while the percentage of donors from overdose rose nationally from 1.1% to 12.7% between 2000 and 2016, only 1.62% of all overdose deaths ended in organ donation¹³. This was despite 28.2% of overdose deaths occurring within healthcare facilities¹³ where it would appear that resuscitation, family discussions, and organ donation work up could be completed. So it would appear that there is much more potential for organ recovery from these cases moving forward. This study also indicated that there are regional differences in how effective organ recoveries are from

overdose donors. The region with the highest percentage of overdose deaths that led to donation was region 8 in the Midwestern US at 2.36% of overdose deaths which was more than double the rate in region 4 covering Texas and Oklahoma (Figure 4)¹³. This was despite the fact that region 8 had among the lowest overdose mortality rates (Figure 5)¹³, which would indicate that they had more effective resources and strategies to lead to donation from overdoses as well as more aggressive local transplant centers who pursued transplants from donors who died from an overdose.

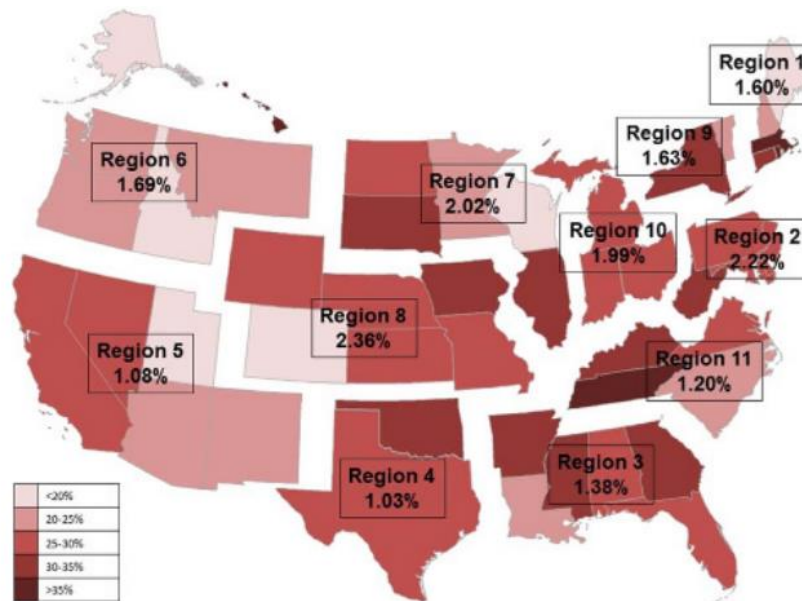


Figure 4. Percentage of all drug overdose deaths that become organ donors by donation region¹³

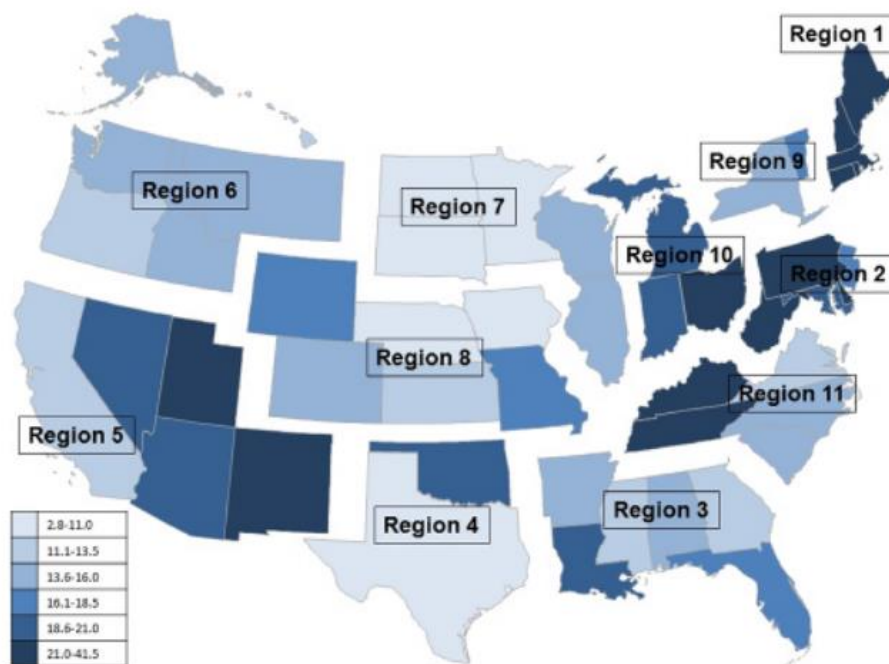


Figure 5. Age adjusted mortality rates from drug overdose by donation region ¹³

RESEARCH STRATEGIES

To complete this project, the PubMed database and Google Scholar were utilized to track down relevant studies completed on the transplantation of organs from overdose donors completed over the last decade. This was done in order to get a sense of how the changing landscape of donation over that time was effected by the continued overdose epidemic. While going through these articles, it became clear that a major asset for this project would be the databases supplied by the Centers for Disease Control (The CDC), the Organ Procurement and Transplantation Network (OPTN), and the Scientific Registry

for Transplant Recipients (SRTR). These three databases had up to date information on the rates of overdose deaths, the rates of organ recovery from overdose death donors, and the various rates of transplant from overdose death donors and HCV positive donors. Additionally, the SRTR tracked and reported the openness of recipients on the transplant waitlist to receiving organs from overdose death donors and HCV positive donors.

DISCUSSION

The issues surrounding the overdose epidemic and organ donation are wrought with ethical dilemmas and concerns. In any instance where the possibility for deceased donor organ donation exists, there is undoubtedly always an underlying tragedy. In many cases, these tragedies can lead to some good for others and additional peace for the family and loved ones of overdose victims if they are able to donate their organs to a person in need. Unfortunately, for many on the transplant waitlist, it would appear that there is still some missed opportunity for the maximizing of donated organs from the population of overdose deaths. As discussed above, in 2018 upwards of 28.3% of overdose deaths occurred in healthcare settings, while only 1.62% actually went forward with organ donation¹³. Understandably, the rest of the nearly 75% of overdose deaths that occur outside of healthcare settings would be difficult to move forward with due to having no infrastructure in the field for organ recovery. Some ideas have been put forth towards addressing this issue, which included a short run pilot program in New York City referred to as the Rapid Organ Recovery Ambulance Service¹⁴. This is a special ambulance service that would be sent out to maximize the potential for organ recovery from deaths that occur in the field and allow for more time to receive consent from family members to move forward with donation. This would be done by hooking up the recently deceased to a reperfusion machine in order to ensure that their organs are being perfused after they are declared dead. This program was abandoned due to ethical concerns regarding the use of these measures on someone who is declared dead, and if reperfusion of deceased organs constitutes a reversal of death by cardiac criteria since no one can be declared

brain dead in the field with current standards and technology. This would constitute violate the “dead donor rule” which is the basis for deceased organ donation. It states that life critical organs can only be removed for donation after a donor is declared dead via circulatory cessation or a brain death diagnosis¹⁴. It also would require emergency responders to fulfill two rolls as both the resuscitator if there is a chance at saving a person’s life, or as the first line of the organ recovery process. This could create a question for the family about if all potential avenues for saving their loved one’s life were taken, which is already a misconception that the organ donation process is trying to combat regularly.

So if the nearly 75% of overdose deaths outside of a healthcare setting are likely out of the realm of recovery, the main area of maximizing the potential for donated organs lies in maximizing those overdose fatalities that occur within a hospital or clinic. This could be achieved through a variety of ways including further education for staff to recognize when to refer a potential donor to their local OPO for the first stages of work up, or by having an automated referral system to cut down on the required time to make a referral. This would lessen the burden on the hospital staff making the referral, and increase the time available to the OPO to effectively mobilize and utilize their resources in order to maximize the potential for organ donation from overdoses. Additionally, increasing the use of reperfusion machines for organs in marginal donation settings such as donation after cardiac death (DCD) or donors with acute organ injury related to their anoxic event. Reperfusion machines already commonly used with kidney recovery in order to assess their function post recovery and maximize the time that they are viable for transplant. If

the technology reaches a sufficient point, it could open the door for increased recovery of organs from DCD donors or even open the door for recovery from field overdose deaths that the Rapid Organ Recovery Ambulance Service was designed to address.

Further advances could be made by changing the national organ donor registry from an opt-in to an opt-out system. This would change the playing field by making it on the individual citizen to state that they do not wish to be an organ donor rather than making them state that they want to be an organ donor¹⁵. On the surface, this would immediately grow the pool of registered organ donors nationally and make some dent in the organ shortage that the country faces, but it would not address the shortage entirely or even make a huge impact. A 2019 study sought to estimate the effects that a change to an opt-out system would have in the United States and found that it did note an improvement in the number of organs transplanted, particularly for livers and kidneys¹⁵. The study concluded that for livers with an ideal allocation to the recipients who could maximize the number of years' post-transplant that an opt-out system added 2,109-2,125 total life years gained with a 5% increase in donation up to a 10,541 life years gained with 25% increased donation nationally¹⁵. However, there are a host of ethical questions regarding the shift to an opt-out system rather than remaining with our current opt-in system. And further, the infrastructure needed to maximize these available donors would need to be built out nationally. In fact, Spain, who instituted an opt-out donor registry in 1979 has stated that they found a greater effect on their donation numbers following the placement of dedicated donation coordinators within each hospital within the country¹⁶. So perhaps, the US would be better off increasing the functional donation infrastructure both within

OPOs and within hospitals in order to maximize the current pool of donors that we have access to rather than creating an opt-out donor system that has potential ethical concerns and could face public backlash.

RECOMMENDATIONS FOR FUTURE STUDIES

As discussed above, further study in the use of reperfusion machines for maintaining and assessing organ viability after recovery could go a long way towards maximizing donation from overdose donors. Additionally, further investigation into the ethical concerns around and the feasibility of programs such as the Rapid Organ Recovery Ambulance could open doors for recovery of organs from those who died in the field, as is often the case with overdoses.

As far as evaluating the current missed opportunity, a further systematic review of all overdose deaths could be in order. By breaking them down by age, if they are declared dead upon arrival to the hospital, if they are resuscitated, if they are ventilated, and if they have a neurological work up prior to death could help to parse out how many of the overdose deaths that occur in healthcare settings actually do have viability for organ recovery given our current organ recovery system and technology. In addition to the above breakdowns, seeing if there are certain hospitals where additional resources could be spent to educate on the potential for donation from these overdose deaths could lead to more effective work between that hospital and their OPO.

Lastly, further studies could be made into recipient mindset as they go through the organ transplant process. Following up on why they are concerned about accepting increased risk donors could help to come up with strategies to continue to grow the percentage of

recipients willing to accept donated organs from overdose deaths. Furthermore, it could help transplant centers become more aggressive with accepting these donated organs and even pursue organs from HCV positive donors for their recipients regardless of their recipient's HCV status.

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