The Opioid Crisis and Its Effect on Transplantation

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Baylor University Medical Center
Dallas, TX
The Opioid Epidemic

How Bad is it?
Opioid Epidemic
How Bad Is It?

Overwhelming

July 5th 2016  Akron, Ohio

“The day carfentanil the the streets of Akron. On that day, 17 people overdosed and one person died in a span of 9 hours....”

“....In 2016, Summit Count (Akron) had 312 drug deaths — more than triple the 99 cases two years before. There were so many last year, that on three separate occasions the country had to request refrigerated trailers to store the bodies because they’d run out of space in the morgue.”
Opioid Epidemic
How Bad Is It?

Futile

“First responders are finding that, with fentanyl and carfentanil, the overdoses can be so severe that multiple doses of naloxone — the anti overdose medication that goes by the brand name Narcan — are need to pull people out…”

“….E.M.S. crews are hitting them with 12, 13, 14 hits of Narcan with no effect” said Mr. Burke, likening a shot of Narcan to “a squirt gun in a house fire”
“Across the country, someone dies of an opioid overdose every 24 minutes. In Massachusetts, the death toll is five people a day…”

“In the face of this epidemic, Cambridge could become the first city to take a step that until recently might have seemed unthinkable: It might place lockboxes on street corners to give the public easy access to naloxone, a medication that can rapidly revive people who have overdosed”
Opioid Epidemic
How Bad Is It?

Desperate

An overdose simulation organized by a group of doctors, police officers and students testing Narcan dispensers proposed for Cambridge, Mass. Erik Jacobs for The New York Times

Source: NYTimes 5/9/17
Opioid Epidemic
How Bad Is It?

Ingenuity

“One clinic has installed an intercom, and requires people to respond…”

“Another clinic has designed a reverse-motion detector that sets off an alarm if there is no movement in the bathroom once the door is closed.”
Opioid Epidemic
How Bad Is It?

Necessity

“Some clinics and restaurants check on bathroom users by having staff knock on the door after 10 or 15 minutes ….”
Opioid Epidemic
How Bad Is It?

Frustration

“As overdose deaths pile up, a medical examiner quits the morgue”

“It’s almost as if the Visigoths are at the gates, and the gates are starting to crumble. I’m not an alarmist by nature, but this is not overhyped. It has completely overwhelmed us.”

“It makes me feel like may hair is on fire, and I don’t even have hair”
Opioid Epidemic
How Bad Is It?

Frustration

As Overdose Deaths Pile Up, a Medical Examiner Quits the Morgue

Source: NYTimes 10/7/17
The Opioid Epidemic

So What Is It?
## Opioids - A Primer

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| Oral Opioid Analgesics | - Morphine, hydrocodone, hydromorphone, oxycodone  
                         - Vary in potency, duration and onset of action                                          |
| Heroin              | **“Pure” Heroin**  
                         - White powder; can be smoked or snorted  
                         - South America and Southeast Asia origin  
                         - Found in US markets east of Mississippi River                                      |
|                     | **Black Tar Heroin**  
                         - Sticky, must be dissolved, diluted and injected  
                         - Mexican origin  
                         - Found in US markets west of Mississippi River                                      |
| Synthetic Opioids    | **Fentanyl**  
                         - Used for cutting heroin as cheap, very potent                                         |
|                     | **Carfentanil**  
                         - Extremely potent analogue of fentanyl                                                  |
| Opioid Substitute    | **Methadone**  
                         - Partial agonist of opioid receptor. Useful for treating addiction                    |

Source: D Goldberg, 2017
Introduction

The opioid epidemic is a national tragedy that is growing.

It has led to many deaths from overdoses and other drug related diseases, numbers that are growing exponentially.

It has affected populations, communities, and even politics and an end is not in sight. It is causing significant impacts on medical resources.

Possibly most of all, the field of transplantation has been markedly affected by the opioid epidemic and it is leading to dramatic changes in practice.
The relationship between the opioid crisis and transplantation is complex and multifaceted and I will examine it in four parts:

1) The Opioid Epidemic and the Impact on Organ Donation

2) The Opioid Epidemic and HCV+ Donors

3) Opioids and the Pretransplant Patient

4) Opioids and Posttransplant Patient Management
Opioid Epidemic and the Impact on Organ Donation
Opioid Epidemic
Overview

- Drug Overdose ➔ Most common cause of death for people < 50 yrs
  ➔ More deaths than MVA and firearms combined

- Demographics ➔ Impacts primary poor, rural, white males
  ➔ Appalachian, Northeast, Southwest
Opioids and Organ Donation
Organ Donors

Number of Organ Donors By Year

- **Total Organ Donors**

Source: UNOS
Opioids and Organ Donation

Organ Donors

Number of Organ Donors By Year

- Total Organ Donors

3% variation over an 8 year period

Source: UNOS
Opioids and Organ Donation
Organ Donors

Number of Organ Donors By Year

Source: UNOS

21% increase over 3 yrs
Opioid Epidemic
Impact on Mortality
Opioid Epidemic
Common Causes of Death in US

Source: CDC and Bloomberg
Opioid Epidemic
Drug Overdose Deaths 1980 - 2016

Year

Deaths

0  10,000  20,000  30,000  40,000  50,000  60,000  70,000

Opioid Epidemic
Drug Overdose Deaths 1980 - 2016

Year

Deaths

Opioid Epidemic
Drug Overdose Deaths 1980 - 2016

Essentially Flat Curve 1980-1995
Opioid Epidemic
Drug Overdose Deaths 1980 - 2016
Opioid Epidemic
Drug Overdose Deaths 1980 - 2016

Peak Firearm Deaths (1993)
Opioid Epidemic
Drug Overdose Deaths 1980 - 2016

Peak HIV Deaths (1995)
Peak Firearm Deaths (1993)
Opioid Epidemic
Drug Overdose Deaths 1980 - 2016

Year

Deaths
0 10,000 20,000 30,000 40,000 50,000 60,000 70,000

Drug Overdose Deaths (2016) 65,000 persons
Peak MVA Deaths (1972)
Peak HIV Deaths (1995)
Peak Firearm Deaths (1993)
Opioid Epidemic
Overdose Deaths by Drug in 2016

Opioids represent 75% of drug overdose deaths

Number of Deaths

- Heroin: 25%
- Opioids: 44% (25,000 deaths)
- Methadone: 6%
- Amphetamines: 11%
- Cocaine: 13%
Opioid Epidemic
Overdose Deaths by Drug in 2016

Opioids represent 75% of drug overdose deaths.
What is Causing These Overdose Deaths?
What is Causing These Overdose Deaths?

Potency of synthetic opioids
Opioid Epidemic
Relative Strength of Opioid Analgesics

Fentanyl is 100x more potent than morphine
Opioid Epidemic
Relative Strength of Opioid Analgesics

Fentanyl
Opioid Epidemic
Relative Strength of Opioid Analgesics

Fentanyl
Opioid Epidemic
Relative Strength of Opioid Analgesics

Fentanyl
Opioid Epidemic
Relative Strength of Opioid Analgesics

Fentanyl
Opioid Epidemic
Relative Strength of Opioid Analgesics

Carfentanil is 10,000x - 100,000x more potent than morphine
Opioid Epidemic
Relative Strength of Opioid Analgesics

- Lethal Dose of Heroin
- Lethal Dose of Fentanyl
- Lethal Dose of Carfentanil

Less Potent

More Potent
The Opioid Epidemic

Who is Most Impacted?
<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>All External Causes</th>
<th>Poisonings</th>
</tr>
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<tbody>
<tr>
<td>White Non-Hispanics</td>
<td>33.9</td>
<td>32.8</td>
<td>22.2</td>
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<tr>
<td>Black Non-Hispanics</td>
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White vs Hispanic  > 4 x higher  ≤ High School vs ≥ College  > 8 x higher

Source: Case et al. PNAS. 2015
### Opioid Epidemic

#### Mortality Rate by Ethnicity

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White vs Hispanic  > 4 x higher  ≤ High School vs ≥ College  > 8 x higher

Source: Case et al. PNAS, 2015
Opioid Epidemic
Mortality Rate by Ethnicity

% Change in Mortality

Non-Hispanic Whites

+11%

Hispanics

-14%

Non-Hispanic Blacks

-23%

Year


Source: NY Times

↑mortality rate of non-Hispanic whites age 25-54 yrs over
Drug overdoses are expected to remain the leading cause of death for Americans <50 yr.

Synthetic opioids, (primarily fentanyl and its analogues) continue to push the mortality rate higher.

Source: Case et al. PNAS, 2015
Opioid Epidemic
Overdose Death by Opioid Type

Opioid Epidemic

Age Distribution of Overdose Deaths

- 2012 -2015 shows significant upswing of 25 -44 year olds

Source: CDC
The Opioid Epidemic
What is the Cause?
Opioid Epidemic
Causes

What is Causing the Opioid Epidemic?

- Narcotics are commonly prescribed by physicians
  - Intended to be used “appropriately”
  - Compton W et al NEJM (2016) described 10.3 million using Rx opioids non medically/not prescribed.

- National Health and Nutrition Examination Survey
  1999-2006: % adults using Rx opioid last 30d  5.0% → 6.9%
  1999-2012: % adults using Rx opioid  >>morphine 17.0% → 37.0%
  1999-2010: Rx opioid sold ↑4x over 11 yrs

Source: D Goldberg, 2017 “Impact of the Opioid Epidemic on Organ Donation”
Opioid Epidemic
Causes

Why is Heroin Commonly Abused?

- △ in M.D. prescribing habits have led to under-Rx after initial over-Rx opioids

- Cost: Heroin vs oral opioids
  Oxycodone: $30 for 30mg oxycodone tab
  $20 for 2x10mg/325mg Percocent tab
  Heroin: $5-10 for bag of heroin (1-5 bags per day)

- Onset of Action: Rapid
  IV: Peak onset 20 s Duration: 4 hrs
  Smoking: Peak onset 10 min Duration: 5 hrs
  Snorting: Peak onset 30 min Duration: 3-5 hrs

Source: D Goldberg, 2017 “Impact of the Opioid Epidemic on Organ Donation”
Opioid Epidemic
Reasons for the Opioid Epidemic

- Use of Pain Scale
- Patient Satisfaction Metrics
- Entitlement
- Millennials
- Drug Promotion by Pharma Companies
- Initial MD Over-Rx
- Subsequent MD Under-Rx
The Opioid Epidemic

Where is This Occurring?
The opioid epidemic does not appear to be affecting all of the US equally.

The most frequent geographic location is related to the demographics of the opiate abuser.

Location are places where rural, white populations predominate.
Opioid Epidemic
Geographic Impact

Age-Adjusted Rates of Overdose Deaths Per State

Predomiance of deaths in the Appalachian region, Southwest and industrial heartland

Source: CDC
Opioid Epidemic
Geographic Impact

Age-Adjusted Rate of Drug Overdose Deaths by State
- 2010
- 2015

Predominance of Overdose Deaths Occur in the:
- Appalachian States
- Northeast States
- Southwest States
- Industrial Heartland
Opioid Epidemic
Geographic Impact

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Opioid Epidemic
Geographic Impact

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- 2015

Predominance of Overdose Deaths Occur in the:
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States:
- West Virginia
- New Hampshire
- Kentucky
- Ohio
- Rhode Island
- Pennsylvania
- Massachusetts
- New Mexico
- Utah
- Tennessee
- Connecticut
- Delaware
- Maine
- Maryland
- Michigan
- Nevada
- Indiana
- Arizona
- Louisiana
- Oklahoma
- District of Columbia
- Missouri
- Vermont
- Wyoming
- New Jersey
Opioid Epidemic
Geographic Impact

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Opioid Epidemic
Geographic Impact

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- Northeast States
- Southwest States
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The Opioid Epidemic

Does this Geographical Specificity Impact Organ Donation?
The Opioid Epidemic

Does this Geographical Specificity Impact Organ Donation?

Yes
Opioid Epidemic
Impact on Transplant per Region
Opioid Epidemic
Impact on Transplant per Region

Northeast
Opioid Epidemic
Impact on Transplant per Region

Northeast
Appalachians
Opioid Epidemic
Impact on Transplant per Region

Northeast
Appalachians
Industrial Heartland
Opioid Epidemic Impact on Transplant per Region

- Northeast
- Appalachians
- Industrial Heartland
- Southwest
Opioid Epidemic
Impact on Liver Transplants per Region
Opioid Epidemic
Impact on Liver Transplants per Region

Percent Change in Liver Transplants

Year

Region 1
Region 11
Region 4
Region 3
Region 5 / 10
Region 2
Region 8
Region 6
Region 7
Region 9
Northeast
Opioid Epidemic
Impact on Liver Transplants per Region
Opioid Epidemic
Impact on Liver Transplants per Region

Percent Change in Liver Transplants

Year

Region 1
Region 11
Region 4
Region 3
Region 5
Region 2
Region 8
Region 6
Region 7
Region 9

Industrial Heartland
Opioid Epidemic
Impact on Liver Transplants per Region

Percent Change in Liver Transplants

Year


Region 1
Region 11
Region 4
Region 3
Region 5 / 10
Region 9
Region 2
Region 8
Region 6
Region 7
Southwest
Arizona +202%
California +8%
Opioid Epidemic
Impact on Liver Transplants per Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Year</th>
<th>Percent Change in Liver Transplants</th>
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</thead>
<tbody>
<tr>
<td>Region 1</td>
<td>2017</td>
<td>+8%</td>
</tr>
<tr>
<td>Region 2</td>
<td>2017</td>
<td>+202%</td>
</tr>
<tr>
<td>Region 3</td>
<td>2017</td>
<td>+10%</td>
</tr>
<tr>
<td>Region 4</td>
<td>2017</td>
<td>+20%</td>
</tr>
<tr>
<td>Region 5</td>
<td>2017</td>
<td>+5%</td>
</tr>
<tr>
<td>Region 6</td>
<td>2017</td>
<td>+2%</td>
</tr>
<tr>
<td>Region 7</td>
<td>2017</td>
<td>+1%</td>
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</table>

- Region 1: Northeast
- Region 2: Industrial Heartland
- Region 3: Appalachian
- Region 4: Southwest
- Region 5: California +8%
- Region 6: Arizona +202%
Opioid Epidemic
Impact on Liver Transplants per Region

- Organ allocation has been one of the most contentious issues in liver transplantation for the last 5 years.

- Discrepancy
  
  Region A
  - Population ↗
  - Organ Donation ↓

  VS

  Region B
  - Population ↓
  - Organ Donation ↗

- Political pressure for redistricting  ➔  Change organ allocation rules
Organ allocation has been one of the most contentious issues in liver transplantation for the last 5 years.

- Discrepancy
  - Region A: Population ↓, Organ Donation ↓
  - Region B: Population ↑, Organ Donation ↑

- Political pressure for redistricting → Change organ allocation rules
The UNOS regions and OPOs with organ donation now roughly correspond to those areas where the opioid epidemic predominates.

Fixed decisions regarding organ allocation are being considered in which calculations are being made from the variable opioid epidemic.

Aggressive strategies that might reduce the opioid epidemic, would also quickly alter the organ donation calculation.

Subsequent re-redistricting would not be as rapid.
Opioid Epidemic and Transplant
First Summary

- Opioids have quickly become the leading cause of death in < 50 yr
- The opioid epidemic predominantly impacts rural young white males in:
  1) Northeast US
  2) Appalachians
  3) Industrial Heartland
  4) Southwest US
- The opioid epidemic has dramatically increased the number of organ donors
- The increase in US donor organs is not homogenous and is clustered in the UNOS Regions where the epidemic predominates
- Decisions on future redistricting and organ allocation need to consider the variable impact of opioid epidemic
Opioids and Organ Donation

HCV+ Donors
Opioids and Organ Donation
HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

- Recent abrupt rise in incidence of acute HCV

- Acute HCV incidence has \( \uparrow 3x \) over last few years.

- Timing of \( \uparrow \) HCV incidence parallels the opioid epidemic

- The \( \uparrow \) acute HCV matches the demographics and geography of the opioid epidemic
Opioids and Organ Donation
HCV+ Donors

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Opioids and Organ Donation
HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

↑ Opioids/Heroin ➔ ↑ Overdose Deaths ➔ ↑ Organ Donors
Opioids and Organ Donation
HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

↑ Opioids/Heroin → ↑ Overdose Deaths → ↑ Organ Donors

+ 

↑ Opioids/Heroin → ↑ HCV Transmission → ↑ Acute HCV+
Opioids and Organ Donation
HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

↑ Opioids/Heroin → ↑ Overdose Deaths → ↑ Organ Donors

+ 

↑ Opioids/Heroin → ↑ HCV Transmission → ↑ Acute HCV+

= 

↑ HCV+ Organ Donors
Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV+ Organ Donors

- Total Donors
- HCV+ Donors
Opioids and Organ Donation

HCV+ Donors

Median Deceased Donor Age By HCV Status

- Median age of HCV+ donor: 47 yr in 2012 → 35 yr in 2016 (↓ 12 yr over 5 yr)
Opioids and Organ Donation
Utilizing HCV+ Donors

- We have been transplanting HCV+ donor liver allografts into HCV+ recipients for almost 20 years with acceptable outcomes.

Hepatitis C Positive Grafts may be used in Orthotopic Liver Transplantation: A Matched Analysis

Sammy Saab\textsuperscript{a, b, *}, Rafik M. Ghobrial\textsuperscript{b}, Ayman B. Ibrahim\textsuperscript{c}, Gregg Kunder\textsuperscript{b}, Francisco Durazo\textsuperscript{a, b}, Steven Han\textsuperscript{a, b}, Douglas G. Farmer\textsuperscript{b}, Hasan Yersiz\textsuperscript{b}, Leonard I. Goldstein\textsuperscript{b} and Ronald W. Busuttil\textsuperscript{b}

Orthotopic liver transplantation (OLT) is a definitive treatment for decompensated liver disease. Whereas the 1-year survival for patients with decompensated cirrhosis is less than 60%, orthotopic liver transplantation achieves overall 5-year survival rates of greater than 60–70% (2–5). Currently, the leading indication for liver transplantation is

- Many centers are very comfortable using HCV+ donor livers.
Opioids and Organ Donation
Utilizing HCV+ Donors

- Many HCV+ kidney donor allografts have gone untransplanted however.

- 2/3 of kidneys from HCV+ donors are discarded

Source: D Goldberg, 2017
Opioids and Organ Donation
HCV+ Donors

Change in Incidence of HCV — Impact of HCV - DAA Therapy

- The landscape of HCV has changed dramatically over the last few years
- Key has been the HCV Direct Acting Antiviral Agents (HCV - DAA)
  HCV - DAA → SVR in 98 - 99% pts
    - Across multiple genotypes
    - Previous unresponsive to Rx
- Mild side effect profile has made staying on Rx easy
- Last decade saw a impressive ↓ in HCV infection
- Nearly all listed transplant patients have had their HCV treated
Opioids and Organ Donation
HCV+ Donors

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

Table 2. Response during and after Treatment.

<table>
<thead>
<tr>
<th>Response</th>
<th>Sofosbuvir-Velpatasvir (N = 624)</th>
</tr>
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<tbody>
<tr>
<td>HCV RNA &lt;15 IU/mL</td>
<td></td>
</tr>
<tr>
<td>During treatment period — no. (%)</td>
<td></td>
</tr>
<tr>
<td>At wk 2</td>
<td>355 (57)</td>
</tr>
<tr>
<td>At wk 4</td>
<td>564 (90)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 wk after treatment period — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Any genotype</td>
<td>615/624 (99)</td>
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<tr>
<td>1a</td>
<td>205/210 (98)</td>
</tr>
<tr>
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<td>117/118 (99)</td>
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<td>5</td>
<td>34/35 (97)</td>
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<tr>
<td>6</td>
<td>41/41 (100)</td>
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<td>Virologic failure — no. (%)</td>
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<tr>
<td>During treatment</td>
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<td>After treatment</td>
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</table>

12 week therapy
1 tablet daily
Cure Rate = 99.7%
622/624 pts
Opioids and Organ Donation
HCV+ Donors

Change in Incidence of HCV — Impact of HCV - DAA Therapy

↑ Rx HCV - DAA  ➔  ↓ HCV+ Chronic ESLD
pts listed for OLTx
Opioids and Organ Donation
Utilizing HCV+ Donors

- Because of the opioid epidemic, there are significantly more HCV+ donors:
  - 335 HCV+ donors (2012)
  - 682 HCV+ donors (2016)
  - 2x more HCV+ donor allografts over last 4 yrs

- HCV+ allografts are youngest of the last 20 years, and are younger than HCV- allografts. The age means improved allograft quality.

- Because of Rx HCV - DAA, there are significantly fewer HCV+ ESLD pts.

- It has become harder to find a recipient for HCV+ livers, so otherwise suitable organs have been discarded.
Opportunities

1) Use of organs that were previously discarded

2) \( \downarrow \) waiting time for recipient

3) \( \downarrow \) wait list mortality

4) No \( \triangle \) posttransplant survival — Often young donors

5) Opportunity for some recipients who might not get a donor
Pitfalls

1) Infecting patient with potentially lethal virus

2) HCV - DAA Rx is expensive (Who is the payor?)

3) HCV - DAA Rx not indicated for treating acute HCV

4) HCV - DAA Rx are paid for after willfully infecting patient.
### Opioids and Organ Donation

#### HCV+ Donors into HCV - Liver Recipients

<table>
<thead>
<tr>
<th>HCV+ Deceased Donor Liver Transplants by Recipient HCV Status at Time of OLTx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transplant Year</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>1995</td>
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<td>1997</td>
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</tbody>
</table>

**Source:** Stewart, unpublished analysis 2017
Opioids and Organ Donation
HCV+ Donors into HCV - Liver Recipients

HCV+ Deceased Donor Liver Transplants by Recipient HCV Status at Time of OLTx

Source: Stewart, unpublished analysis 2017
Opioids and Organ Donation

HCV+ Donors into HCV - Kidney Recipients

HCV+ Deceased Donor Kidney Transplants by Recipient HCV Status at Time of OLTx

Source: Stewart, unpublished analysis 2017
Opioids and Organ Donation
HCV+ Donors into HCV - Kidney Recipients

HCV+ Deceased Donor Kidney Transplants by Recipient HCV Status at Time of OLTx

Source: Stewart, unpublished analysis 2017
Opioids and Organ Donation
HCV+ Donors into HCV - Heart Recipients

HCV+ Deceased Donor Heart Transplants by Recipient HCV Status at Time of OLTx

Source: Stewart, unpublished analysis 2017
Opioids and Organ Donation
HCV+ Donors into HCV - Heart Recipients

HCV+ Deceased Donor Heart Transplants by Recipient HCV Status at Time of OLTx

<table>
<thead>
<tr>
<th>Year</th>
<th>HCV Donor +/ Recipient +</th>
<th>HCV Donor +/ Recipient -</th>
</tr>
</thead>
<tbody>
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<tr>
<td>2015</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: Stewart, unpublished analysis 2017
THINKER Trial — Kidney Transplant Trial

- Transplanting
- Hepatitis C Kidneys
- Into
- Negative
- Kidney
- Recipients

- Pilot trial for transplanting HCV+ donors into HCV - recipients
  - 10 HCV - kidney recipients consented
  - Mean waiting time 58 d
  - Kidney from HCV+ donor
  - Recipient viremic by POD 3
  - Rx with elbasvir-grazoprevir* for 12 wks
  - 100% cured of HCV

*Can be used at any level of renal function, no cardiotoxicity
USHER Trial — Heart Transplant Trial

- Pilot trial for transplanting HCV+ donors into HCV - recipients
  - 10 HCV - heart recipients transplanted
  - Heart from HCV+ donor
  - Rx with elbasvir-grazoprevir* for 12 wks
  - 100% cured of HCV

*Can be used at any level of renal function, no cardiotoxicity, no amiodarone interaction
Opioids and Organ Donation
HCV+ Donors into HCV - Recipients

Logistics for Any Transplants Using HCV+ Donor / HCV - Recipient

1) 100% assurance every single pt can be treated after transplant

2) Pts have to be educated early about the potential benefits and risks

3) Issues with treating patients early posttransplant
   - Not all become viremic
   - ↑immune = ?↓drug efficacy
   - ↑contraindications/drug interactions
   - Transplant complications ↓Rx success
   - Drugs not stocked in hospital pharmacy

4) Cost of therapy — Impact on transplant contract
   - $ 100,000 for Rx course
   - ?Treat with the first 90 d
HCV+ Donors into HCV - Recipients

Logistics for Any Transplants Using HCV+ Donor / HCV - Recipient

Liver / Kidney Transplant

Baylor Dallas is one of few centers in the US approved for Gilead trial of 30 HCV+ donors/HCV- recipient liver and kidney transplants.

Heart Transplant

Baylor Dallas is the pivotal center for HCV+ donor / HCV - recipient heart transplant trial.
Opioid Epidemic and Transplant
Second Summary

- Number of HCV+ donors has doubled in the last 5 yrs
  
- Mean donor age of HCV+ donors has \( \downarrow \) by 12 yrs
  - HCV+ donors are often good quality, young donors

- Great variation in between liver, kidney, heart re: utilization of HCV+ donor

- Efficacy of Rx HCV - DAA in curing HCV means fewer recipients for these HCV+ donors

- Trials underway to use HCV+ donors in HCV - recipients and Rx after with HCV - DAA to eliminate HCV \[ \rightarrow \] Expand donor pool

Directly linked to opioid epidemic
Does the Opioid Epidemic Impact the Transplant Center and Potential Recipients?
Does the Opioid Epidemic Impact the Transplant Center and Potential Recipients?

Yes
Opioids and the Pretransplant Patient
Candidate Listing Practices
Opioids and the Pretransplant Patient Candidate Listing Practices


- Survey of 61 of 114 Liver Transplant Centers regarding pre-OLT opioid use
- There is no national consensus regarding listing patients on opioid Rx

**Transplant Listing Policy**

- **Absolute Contraindication** → 1.6% Opioid Use
  1.6% Methadone Use

- **Relative Contraindication** → 64% Opioid Use
  37% Methadone Use

- Study showed great variability among centers as to practice of listing patients taking opioids
The majority of transplant centers utilize unreliable screening methods
- Self reporting
- Medical records review

Large reliance on toxicology tests however these have limitations
- Timing between exposure and test
- Cross-reactivity of the opiate metabolites and urinary test target

Most accurate method for opiate screening is the State Prescription Drug Monitoring Program (Operational in 49/50 states)
- Underutilized by transplant programs
Opioids and the Pretransplant Patient

Pain Management
Opioids and the Pretransplant Patient
Pain Management

Pain Management in the Pretransplant Patient

- Opioid use can impact potential transplant recipients
- Many pretransplant recipients suffer from chronic pain
  - Renal → HD causes bone degeneration and pain
  - Liver → Liver inflammation from hepatitis causes RUQ pain
    Splenomegaly from portal HTN causes LUQ pain
  - All → Immobility leads to chronic back pain
- Rogal et al 2015: 77% of OLT candidates reported pain as symptom
Pain Management in the Pretransplant Patient

- Many pretransplant patients suffer from chronic pain → Limited options
  - Renal → NSAIDs are avoided in renal disease
  - Liver → Acetaminophen is avoided in liver disease
  
  Altered liver metabolism interferes with metabolism of many pain medications

- Lack of standard pain management choices and ↑ sources of pain leads to ↑ prescribing of narcotics

- Patient have Rx opioid analgesia, often before transplant team involved
Pain Management in the Pretransplant Patient

• Wait-list use of opiates varies with the transplant organ population

  Renal  ➔ 43.1% of transplant recipients received opiates on wait-list

  Liver ➔ 9.3% of transplant recipients received opiates on wait-list

    3% took the highest level of opiate (Level 3 or Level 4)

    65% of these continued at this level posttransplant

• Wait-list use of opiates should be minimized if possible to impact outcomes

Opioids and the Pretransplant Patient
Pain Management
Opioids and the Pretransplant Patient
Outcomes and Survival
Opioids and the Pretransplant Patient Survival Outcomes - Liver

Compared with no use of opiates pre-OLT of ME >10/d was associated with graft failure at 5 years post-OLT.
Opioids and the Pretransplant Patient Survival Outcomes - Liver

Liver Transplant

A. Death After LT, According to Opioid Use on the Waiting List

- Compared with no use of opiates pre-OLT of ME >10/d was associated with mortality at 5 years post-OLT

HB Randall et al. Liver Transplantation 2017
Rx opioid use in the first year after transplant had a strong, graded association of 2-fold increased risk of death and graft loss. Compared with no use, highest level of opiate use (>70 ME/d) predicted:

- 2x risk of death
- 35% risk of death-censored graft failure
- 68% risk of all-cause graft failure

Patients on pre-transplant opiates were likely to persist posttransplant.

KL Lentine et al AJT 2018
Opioids and the Pretransplant Patient Readmission Rates

Kidney LD Donors

• Presurgical use of opioid analgesics is increasingly recognized as a predictor of post-operative complication and resource utilization

• Living donor kidney donors are the closest approximation of a general surgery patient in transplantation

• Lentine et al  AJT 2017

  Donors with the highest levels of pre-donation opiate use were more than 2x as likely to be readmitted to hospital

  6.8% vs 2.6%    OR: 2.49 (CI 1.74 - 3.58)
Study showed great variability among centers as to practice of listing patients taking opioids

Most accurate method for opiate screening is the State Prescription Drug Monitoring Program

Many pretransplant recipients suffer from chronic pain → Limited options

Wait-list Rx of opiates predicts posttransplant opiate use

High pretransplant opiate use significantly ↓ graft survival and ↑ mortality in both liver and kidney transplant patients

High pre-donation opiate use in LD kidney donor → ↑ readmission rates
Opioids and the Posttransplant Patient

Patient Management
Opioids and the Posttransplant Patient
Pain Management

Pain Management in the Posttransplant Patient

- Post-transplant pain can be significant and options are limited
  - Steroid-sparing IS protocols are compounding pain issues
  - NSAIDs are avoided because of concomitant CNI dosing
- Pretransplant opiate use, particularly if long-term can make it difficult to avoid opiates in the posttransplant setting
Opioids and the Posttransplant Patient Pain Management

### Decision to Use Opiates

**Con Rx Opiates post-OLT**

- Significant Side effects (↓ bowel motility, oversedation)
- ↑ risk of graft failure and mortality with high level use
- ↑ risk of hospital readmission with high level use
- ↑ risk of addiction and overdose

**Pro Rx Opiates post-OLT**

- Major traumatic abdominal surgery (Large incision, heavy retraction)
- Limited options to Rx pain
- Steroid sparing IS protocols lose the antinflammatory effects of steroids
- Patient satisfaction scores heavily dependent on pain control
Opioids and the Posttransplant Patient Pain Management

Baylor Dallas Pain Management Strategy for Transplant

- **Intra-operative**
  1) Subcostal TAP block w/ long acting Exparel or bupivacaine

- **Immediate Post-op**
  1) Aggressive early mobilization out of bed POD #1
  2) Minimize all IV opiates → Tylenol#3 PO PRN
  3) Currently trialing low dose ketamine

- **Subsequent Post-op**
  1) Acetaminophen 650 mg PO q4h
  2) Gabapentin 300 mg PO BID
  3) Tramadol 50 mg PO q4h
  4) Tylenol#3 PO PRN *(Replace acetaminophen/tramadol)*
     (* If inadequate analgesia on 1-3)*
Opioid Epidemic and Transplant
Fourth Summary

- Pain management can be difficult because of limited options
- Pretransplant opiate use, particularly if high can hinder opiate avoidance in the posttransplant period
- Use all potential strategies including intra-op TAP blocks and post-op gabapentin
- Move to mobilize the patient very early, POD #1 if possible
- Transition from IV opiates to PO very early w/ goal of codeine as opiate
- Outpatient use gabapentin and tramadol to avoid codeine
Summary
Summary

- The opioid epidemic and organ transplantation have a complex and multifaceted connection. It impacts organ supply, quality, allocation and pre-and post- transplant management and outcomes.

- It is a national health tragedy that needs urgent attention and aggressive intervention by the medical community.

- The opioid epidemic has had a profound impact on organ supply and organ allocation.

- It has necessitated new paradigms for transplantation and donation, and further understanding of circumstance may yield further benefits.