MHIF FEATURED STUDY:
Heart EXPAND CAP

DESCRIPTION: a single-arm study evaluating the OCS™ Heart System and extended criteria donor hearts (those that are currently not transplanted or are seldom transplanted in the US)

CRITERIA LIST/ QUALIFICATIONS:

Donor Heart Inclusion
- Expected total cross-clamp time of ≥4 hours; OR expected total cross-clamp time of ≥2 hours PLUS one of the following risk factors:
  - Donor age 45-55 years, inclusive, with no coronary catheterization data
  - Donor age ≥55 years
  - Left ventricular septal or posterior wall thickness of >12 mm, but ≤16 mm
  - Reported down time of ≥20 min, with stable hemodynamics at time of final assessment
  - Left heart ejection fraction (EF) ≥40%, but ≤50% at time of acceptance of offer
  - Donor angiogram with luminal irregularities with no significant CAD (≤50%)  
  - History of carbon monoxide poisoning with good cardiac function at time of donor assessment
  - Social history of alcoholism with good cardiac function at time of donor assessment
  - History of diabetes without significant CAD on angiogram (≤50%)

We are excited to announce the successful use of our first TransMedics Organ Care System (OCS™), aka “Heart in the Box”
Minneapolis Heart Institute Foundation® Cardiovascular Grand Rounds

Title: **Taming the Dragon: Management Options for Opioid Use Disorder In The Compromised Cardiovascular Patient**

Speakers: Katherine G. Katzung, MD  
Chair, Abbott Northwestern Emergency Department  
Director, Addiction & Toxicology, Abbott Northwestern Hospital  
Assistant Medical Director, Mission Detox Center  
Consultant, Minnesota Regional Poison Center

**Date:** September 30, 2019  
**Time:** 7:00 – 8:00 AM  
**Location:** Minneapolis Heart Institute Building, Suite 100, Learning Center

**OBJECTIVES**

At the completion of this activity, the participants should be able to:

1. Summarize the timeline of the opioid epidemic, current state, and neurobiology of addiction.
2. Review the common scenarios of cardiovascular patients admitted to the hospital and how it can impact care and care decision-making -- infectious endocarditis, Takotsubo cardiomyopathy associated with opioid withdrawal.
3. Discuss treatment options for opioid use disorder, including medication assisted treatment (MAT), while optimizing compliance and outcomes for cardiovascular patients.

**ACCREDITATION**

**Physician** - Allina Health is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Allina Health designates this live activity for a maximum of 1.0 **AMA PRA Category 1 Credit(s)™.** Physicians should only claim credit commensurate with the extent of their participation in the activity.

**Nurse** - This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.0 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

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Allina Health, Learning & Development intends to provide balance, independence, objectivity and scientific rigor in all of its sponsored educational activities. All speakers and planning committee members participating in sponsored activities and their spouse/partner are required to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of this conference.

The **ACCME defines a commercial interest** as “any entity” producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests - unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest.
Moderator(s)/Speaker(s)
Dr. Katherine G. Katzung has disclosed that she DOES NOT have any real or apparent conflicts with any commercial interest as it relates to presenting the content in this activity/course.

Planning Committee
Dr. Alex Campbell, Jake Cohen, Jane Fox, Dr. Kevin Harris, Dr. Kasia Hryniewicz, Rebecca Lindberg, Amy McMeans, Dr. Michael Miedema, Dr. JoEllyn Moore, Pamela Morley, Dr. Scott Sharkey, Maia Hendel and Jolene Bell Makowesky have disclosed that they DO NOT have any real or apparent conflicts with any commercial interest as it relates to the planning of this activity/course. Dr. Mario Gössl has disclosed the following relationships – Edwards Life Sciences: Grant/Research Support; Abbott Vascular, Caisson: Consultant; Speaker’s Bureau: Edwards Lifesciences. Dr. David Hurrell has disclosed the following relationship – Boston Scientific: Chair, Clinical Events Committee.

NON-ENDORSEMENT OF COMMERCIAL PRODUCTS AND/OR SERVICES
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Pfizer, Inc

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If audited by a licensing board or submitting for license renewal or certification renewal, boards will ask you not the entity providing the education for specific information on each activity you are using for credit. You will need to demonstrate that you attended the activity with a copy of your certificate/evidence of attendance, a brochure/flier and/or the conference handout.

Each attendee at an activity is responsible for determining whether an activity meets their requirements for acceptable continuing education and should only claim those credits that he/she actually spent in the activity.

Maintaining these details are the responsibility of the individual.

PLEASE SAVE A COPY OF THIS FLIER AS YOUR CERTIFICATE OF ATTENDANCE.

My signature verifies that I have attended the above stated number of hours of the CME activity.

Signature: ____________________________________________________________________________

Allina Health - Learning & Development - 2925 Chicago Ave - MR 10701 - Minneapolis MN 55407
Taming The Dragon: Management Options For Opioid Use Disorder In The Compromised Cardiovascular Patient

Katherine G. Katzung, MD, FACEP, FASAM
Director, Addiction Medicine & Toxicology Program
Chair, Department of Emergency Medicine
Abbott Northwestern Hospital

OBJECTIVES

• Summarize the timeline of the opioid epidemic, current state, and neurobiology of addiction.
• Review common scenarios of cardiovascular patients admitted to the hospital and how it can impact care and medical decision-making.
  • Case Review – Infectious Endocarditis
• Discuss treatment options for opioid use disorder, including medication-assisted treatment, while optimizing compliance and outcomes for cardiovascular patients.
I have no relevant financial arrangements with commercial interests to disclose.

The Scope of the Problem
3 Waves of the Rise in Opioid Overdose Deaths

Other Synthetic Opioids
- e.g., tramadol and fentanyl, prescribed or illicitly manufactured

Commonly Prescribed Opioids
- Natural & Semi-Synthetic Opioids
- and Methadone

Heroin

**Wave 1:** Rise in Prescription Opioid Overdose Deaths
**Wave 2:** Rise in Heroin Overdose Deaths
**Wave 3:** Rise in Synthetic Opioid Overdose Deaths

**SOURCE:** National Vital Statistics System Mortality File.

Fig. 1 Annual opioid prescribing rates in the USA, 2006-2015: prescribing rates by number of days’ supply; average daily morphine milligram equivalent (MME) per prescription; and average number of days’ supply per prescription [4].

A Little Light Reading…

- DREAMLAND by Sam Quinones
- DOPESICK by Beth Macy

https://www.health.state.mn.us/opioiddashboard#EDData
Neurobiology of Addiction

“Addiction is a brain disease. This is not a moral failing. This is not about bad people who are choosing to continue to use drugs because they lack willpower.”

Michael Botticelli

Director of National Drug Control Policy
Obama Administration
DEPENDENCE

• Frequent & repeated use of opioids leads to structural/physiological changes in the brain.
  • Normal brain function requires the presence of opioids.
• Drug withdrawn → withdrawal syndrome.
• Physical dependence can occur without addiction!

ADDICTION

• A primary, chronic disease of brain reward, motivation, memory, and related circuitry.
• Characterized by compulsive drug seeking & use despite harmful consequences.
• Involves cycles of relapse and remission.
Brain Disease Model of Addiction

Addiction: The Reward Pathway

Opioid (Positive Reinforcement) → Bind Opioid Receptors → Dopamine Release → Feel Good → Compulsive Behavior

Schuckit MA. Treatment of opioid use disorders. NEJM. 2016;375:357-368

**Table 1. Diagnostic Criteria for an Opioid-Use Disorder.**

- Use of an opioid in increased amounts or longer than intended
- Persistent wish or unsuccessful effort to cut down or control opioid use
- Excessive time spent to obtain, use, or recover from opioid use
- Strong desire or urge to use an opioid
- Interference of opioid use with important obligations
- Continued opioid use despite resulting interpersonal problems, social problems (e.g., interference with work), or both
- Elimination or reduction of important activities because of opioid use
- Use of an opioid in physically hazardous situations (e.g., while driving)
- Continued opioid use despite resulting physical problems, psychological problems, or both
- Need for increased doses of an opioid for effects, diminished effect per dose, or both†
- Withdrawal when dose of an opioid is decreased, use of drug to relieve withdrawal, or both†

**DSM-V Criteria**

**Triad:**
- Loss of Control
- Physiologic Changes
- Consequences

**Severity:**
- 2-3 = Mild
- 4-5 = Moderate
- 6+ = Severe
None or low risk  At risk  Mild  Moderate  Severe

Increasing amounts, higher-risk substances or situations  Craving, loss of control, consequences

tolerance and withdrawal can appear anywhere

Case Review
Admission 10/13/18 – 11/9/18

• 21yo F w/hx of heroin IVDU, admitted for severe sepsis, respiratory failure, and presumed infectious endocarditis.

• CV Surgery – No surgical intervention; 6 weeks antibiotics & repeat ECHO.

---

**Culture**

RESULT: **MSSA**

*Staphylococcus aureus*

Methicillin susceptible by mecA gene PCR
Positive Blood Culture tested by PCR for the 24 most common blood pathogens and 3 antibiotic resistance genes.

---

**TEE 10/17/18**

**Procedure:** TEE w/ Bubbles, Color Doppler and Limited Spectral Doppler.

**Indication for study:** Endocarditis
**Cardiac Rhythm:** Sinus tachycardia. Study quality: Fair.

**Final Impressions:**

1. Normal left ventricular size, normal global systolic function with an estimated EF of 65 - 70%.
3. Moderately sized vegetation on the tricuspid valve. 1.7 cm x 0.8 cm pedunculated mass on the atrial side of the septal leaflet. Second fixed mass on the ventricular side of the anterior leaflet.
4. Atrial septum is intact.
5. Negative bubble study.
6. No evidence of thrombus present in the left atrial appendage.
Admission 10/13/18 – 11/9/18

- Septic Emboli
- Hepatitis C
- Failed Extubation → Tracheostomy
- Stress Cardiomyopathy
  - 11/1/18 – EF 28%
  - 11/7/18 – EF 60-65%
- Discharged to Bethesda.
  - IV Cefazolin

Hospitalizations for drug abuse-related infective endocarditis increased from 2002 to 2016

Alongside the opioid epidemic, the percentage of U.S. hospitalizations for infective endocarditis that were associated with drug abuse nearly doubled from 2002 (8.0%) to 2016 (16.3%).

Geographic Trends, Patient Characteristics, and Outcomes of Infective Endocarditis Associated With Drug Abuse in the United States From 2002 to 2016

Amer N. Kadri, Bryan Winer, Adrian V. Hernandez, Georges Nakhoul, Johnny Chahine, Brian Griffin, Gosta Pettersson, Richard Grimm, Jose Navia, Steven Gordon, Samir R. Kapadia, and Serge C. Harb

Incidence Rates: Non-DA IE vs. DA IE

Prevalence Ratio of DA in Patients with IE

MHIF CV Grand Rounds- Sep. 30, 2019

Surgery for IE carries the greatest risk of any valve surgery, and outcomes differ widely among centers and surgeons. AATS agrees with the European Society of Cardiology recommendation that specialized endocarditis teams should manage patients with IE at referral centers with access to cardiac surgery input early in its evaluation.3-5

Drug abuse is associated with increased risk of relapse and recurrent, difficult-to-cure IE. Rehabilitation, seamless transition of care, and mobilization of social support are essential for any chance of success.

Admission 2/7/19 – 3/14/19

- Left Bethesda AMA after 2 weeks & lost to follow-up.
- Ongoing heroin IVDU.
- Readmitted with MRSA bacteremia, septic emboli, respiratory failure....
- Ethics, Psychiatry, Pain teams involved.
Tricuspid Valve Replacement 2/20/19

- TVR with 33-mm St. Jude Epic Bioprosthetic Valve
- 2/22 – Tracheostomy
  - Large ruptured mycotic pulmonary artery aneurysm → successfully coiled.
- 3/12 – TVR Thrombus → Anticoagulation

  - Completed antibiotics & Rule 25 Assessment
  - 4-6 week wait for inpatient treatment

- On oxycodone up to discharge; not prescribed at discharge.
  - “was due to drug use/abuse history and that she would need PCP to provide narcotics.”
• Admitted for sepsis and recurrent endocarditis.
• Ongoing heroin & methamphetamine IVDU.
• Recurrent vegetation on tricuspid valve.
• CV Surgery:
  • “No surgical intervention recommended given reoperative nature and use of her "one shot" surgical approach, in addition to the high rate of recidivism and active drug use.”
• Left AMA
When Is Enough Enough? The Dilemma of Valve Replacement in a Recidivist Intravenous Drug User

Sarah C. Hull, MD, MBE, and Farid Jadbabaie, MD
Yale School of Medicine, Section of Cardiovascular Medicine, Yale-New Haven Hospital, New Haven; and Yale School of Medicine, Section of Cardiovascular Medicine, West Haven VA Medical Center, West Haven, Connecticut

Should patients who use illicit drugs be offered a second heart-valve replacement?

Based on the principle of equal treatment and expected survival, we claim that this group of patients should receive the same treatment as other patients in whom a corresponding treatment effect is expected.

Suboptimal Addiction Interventions for Patients Hospitalized with Injection Drug Use-Associated Infective Endocarditis

Elana S. Rosenthal, MD, PhD,1,2 Adolfo W. Karchmer, MD, PhD,2,3 Jesse Theisen-Toupop, MD,1,2 Roger Araujo Castillo, MD, MPH,1,2
Chris F. Rowley, MD, MPH1,2
1Division of Infectious Diseases, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Mass; 2Harvard Medical School, Boston, Mass; 3Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Mass.


Table 2  Addictions Interventions for Patients Admitted with Current or Previous Admission for Endocarditis Associated with Injection Drug Use

<table>
<thead>
<tr>
<th>Drug Use</th>
<th>Sentinel Admission (n = 102)</th>
<th>Readmission (n = 131)</th>
<th>IDU Readmission (n = 42)</th>
<th>Admission with Surgery (n = 48)</th>
<th>All Admissions (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient consults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social work</td>
<td>82/95 (86.3)</td>
<td>66/123 (53.7)</td>
<td>16/39 (41.0)</td>
<td>42/45 (93.3)</td>
<td>148/219 (67.6)</td>
</tr>
<tr>
<td>Addiction clinical nurse</td>
<td>22/93 (23.7)</td>
<td>9/122 (7.4)</td>
<td>4/39 (10.3)</td>
<td>14/45 (31.1)</td>
<td>31/215 (14.4)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>23/96 (24.0)</td>
<td>12/123 (9.8)</td>
<td>4/40 (10.0)</td>
<td>8/45 (17.8)</td>
<td>35/219 (16.0)</td>
</tr>
<tr>
<td>Discharge planning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge summary</td>
<td>57/102 (55.9)</td>
<td>30/131 (30.5)</td>
<td>23/42 (54.8)</td>
<td>11/48 (22.9)</td>
<td>97/233 (41.6)</td>
</tr>
<tr>
<td>Plan for MAT</td>
<td>8/102 (7.8)</td>
<td>18/131 (13.7)</td>
<td>5/42 (11.9)</td>
<td>3/48 (6.3)</td>
<td>26/233 (11.2)</td>
</tr>
<tr>
<td>Narxoxone prescription</td>
<td>0/102 (0)</td>
<td>0/131 (0)</td>
<td>0/42 (0)</td>
<td>0/48 (0)</td>
<td>0/233 (0)</td>
</tr>
</tbody>
</table>
Abbott Northwestern 7/21/19 – Present

- Admitted with septic shock, requiring Levophed, acute renal failure.
- MSSA with Prosthetic Valve Endocarditis

**Final Impressions:**
*Limited Echocardiogram performed*
1. Tricuspid valve is replaced with 33mm St Jude Epic tissue prosthesis. Very large, highly mobile and friable appearing echodensities are seen involving the prosthetic tricuspid leaflets, prolapsing fully into the RA during diastole, producing severe tricuspid stenosis (mean gradient 22 mmHg at HR 103 bpm), and moderate regurgitation.
2. Normal LV size, mildly increased wall thickness, normal global systolic function with an estimated EF of 55 - 60%.
3. Severely enlarged right atrium.
4. Right ventricular cavity size is normal, global systolic RV function is borderline.
5. The inferior vena cava is dilated, respiratory size variation less than 50%, consistent with elevated right atrial pressure.

What To Do?

- Commitment – Chemical Dependency Treatment
- Ethics Consultation
- Pain Medicine Consultation
- Psychiatry Consultation → Competency
- Addiction Medicine Consultation → Medication Assisted Treatment
- Surgery?
Medication-Assisted Treatment

Methadone vs. Suboxone

Milestones In Treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>Methadone is approved by the FDA for detoxification</td>
</tr>
<tr>
<td>1973</td>
<td>Methadone is approved by the FDA for maintenance</td>
</tr>
<tr>
<td>1974</td>
<td>Opioid Treatment Programs (OTP’s) able to dispense Methadone for maintenance treatment</td>
</tr>
<tr>
<td>1984</td>
<td>Oral Naltrexone is approved by the FDA</td>
</tr>
<tr>
<td>2000</td>
<td>Drug Addiction Treatment Act of 2000 (DATA 2000) allowed qualified physicians to offer Office Based Opioid Treatment (OBOT)</td>
</tr>
<tr>
<td>2002</td>
<td>Buprenorphine is approved by the FDA</td>
</tr>
<tr>
<td>2010</td>
<td>Extended-release injectable naltrexone is approved by the FDA</td>
</tr>
<tr>
<td>2016</td>
<td>Comprehensive Addiction and Recovery Act (CARA) - Allows Nurse Practitioners and Physician Assistants to become eligible to prescribe buprenorphine for treatment of opioid use disorder</td>
</tr>
</tbody>
</table>
Addiction consultation services – Linking hospitalized patients to outpatient addiction treatment

Paul Trowbridge a,b,c, Zoe M. Weinstein a, Todd Kerensky a, Payel Roy a, Danny Regan a, Jeffrey H. Samet a,c, Alexander Y. Walley a

- 2015 Analysis of Boston Medical Center Addiction Consult Service implementation and linkage to care outcomes.

![Substance Use Disorder (n=337)]

Number of Encounters

<table>
<thead>
<tr>
<th>Substance Use Disorder</th>
<th>Number of Encounters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>147</td>
</tr>
<tr>
<td>Alcohol</td>
<td>117</td>
</tr>
<tr>
<td>Cocaine</td>
<td>75</td>
</tr>
<tr>
<td>Sedatives</td>
<td>51</td>
</tr>
<tr>
<td>Marijuana</td>
<td>90</td>
</tr>
<tr>
<td>Methadone</td>
<td>29</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>8</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>1</td>
</tr>
<tr>
<td>Naltrexone - Any OUD</td>
<td>0</td>
</tr>
<tr>
<td>Naltrexone - Only OUD</td>
<td>0</td>
</tr>
</tbody>
</table>

![Medication]

Number of Encounters

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of Encounters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>70</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>40</td>
</tr>
<tr>
<td>Naltrexone - OUD</td>
<td>5</td>
</tr>
<tr>
<td>Naltrexone - Methadone</td>
<td>7</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>33</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>12</td>
</tr>
<tr>
<td>Topiramate</td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 2. Medications recommendations for substance use disorders.

Linkage & Retention

![Follow-Up Rates by Medication]

Follow-Up Rates by Medication

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Methadone (n=70)</th>
<th>Buprenorphine (n=33)</th>
<th>Naltrexone - Any OUD (n=4)</th>
<th>Naltrexone - Only OUD (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Follow-up</td>
<td>76% 49% 33%</td>
<td>0% 39% 27%</td>
<td>27%</td>
<td>13% 29%</td>
</tr>
<tr>
<td>30 Days</td>
<td>54% 39% 27%</td>
<td>0% 27% 0%</td>
<td>0% 0%</td>
<td>0% 0%</td>
</tr>
<tr>
<td>90 Days</td>
<td>39% 27% 13%</td>
<td>0% 0% 0%</td>
<td>0% 0%</td>
<td>0% 0%</td>
</tr>
<tr>
<td>180 Days</td>
<td>29% 18%</td>
<td>0%</td>
<td>0% 0%</td>
<td>0% 0%</td>
</tr>
</tbody>
</table>

Fig. 3. Follow-up rates by medication.
Meta-analysis, flexible-dose buprenorphine and methadone had similar results for reducing illicit opioid use.

Methadone had a slight (but statistically significant) edge for retention in treatment—despite the fact that most studies found no difference.

Buprenorphine has a statistically significant positive impact compared with placebo on:
  - Retention in treatment
  - Illicit opioid use

Methadone
- Full Agonist
- QTc Prolongation
- Drug-Drug Interactions

Buprenorphine
- Partial Agonist
- No QTc Effect
- Few Drug-Drug Interactions
Buprenorphine:
- Partial Agonist – µ Opioid Receptor
  - Binds with high affinity & dissociates slowly.
  - Blocks other opioids from binding.
  - ↓ respiratory depression
- Weak Antagonist – k Opioid Receptor

Buprenorphine Receptor Occupancy

Occu​pied opiate receptors/dose

Percentage of occupied receptors

Dose of buprenorphine (mgs.)
But this hurts!

What happens after surgery?

MICRO-DOSING PROTOCOLS

Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment

Transdermal buprenorphine, opioid rotation to sublingual buprenorphine, and the avoidance of precipitated withdrawal: a review of the literature and demonstration in three chronic pain patients treated with butrans.

Kornfeld H', Beitz H.

Transitioning Hospitalized Patients with Opioid Use Disorder from Methadone to Buprenorphine without a Period of Opioid Abstinence Using a Microdosing Protocol

Dale Terasaki*†, Christopher Smith, and Susan L. Calcatera

1Addiction Medicine Fellowship, University of Colorado Hospital, CEDAR, Aurora, Colorado; 2Department of Medicine, Hospital Medicine, University of Colorado Hospital, Aurora, Colorado

*Corresponding author.
WHAT IS MICRO-DOSING?

• Gradual induction of buprenorphine overlapping with full opioid agonist use.
• Goal = Patient does not develop precipitated withdrawal.
• Repetitive administration of very small buprenorphine doses with sufficient dosing intervals (e.g. 12 hours) should not precipitate opioid withdrawal.
• Because of the long receptor binding time, buprenorphine will accumulate at the receptor.
• Over time, an increasing amount of a full μ-agonist will be replaced by buprenorphine at the opioid receptor.
Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series

Sukhpreet Klaire, MD, CCFP,1 Rebecca Zivanovic, Bsc, MD,2,3 Skye Pamela Barbic, PhD, OT,4,5 Raman Sandhu, MD,6 Nickie Mathew, MD, FRCP,4,6 Pouya Azar, MD, FRCP5,6

The American Journal on Addictions, XX: 1–4, 2018

TABLE 1. Titration schedule for Case 1

<table>
<thead>
<tr>
<th>Buprenorphine/Naloxone*</th>
<th>Hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td><strong>Total Daily Dose</strong></td>
</tr>
<tr>
<td>Day 0</td>
<td>N/A</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.25g SL q4h</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.5 mg SL q4h</td>
</tr>
<tr>
<td>Day 3</td>
<td>1 mg SL q4h</td>
</tr>
<tr>
<td>Day 4</td>
<td>2 mg SL q4h</td>
</tr>
<tr>
<td>Day 5</td>
<td>16 mg SL daily</td>
</tr>
</tbody>
</table>

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.
"If addiction is seen as a moral failing, it will be condemned. If seen as a deficit in knowledge, it will be educated. If the addiction is viewed as an acceptable aberration, it will be tolerated. If the addiction is considered illegal, it will be prosecuted. **If viewed as an illness, it will be treated.**"

CARLO C. DICLEMENTE
QUESTIONS?

Contact Information:

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katherine.katzung@allina.com