Learning Objectives:
By the end of this presentation, the participant should be able to
1. Explain mechanisms of drug shortages
2. Discuss the FDA’s role and authority in drug shortages
3. Anticipate the impact drug shortages can have on patient care
4. Examine potential safety issues resulting from drug shortages
5. Propose strategies and recommendations for management of drug shortages
INTRODUCTION

I. Drug Shortage Background
   A. Statistics and Survey
      1. 2011 ASHP Survey\(^1\)
         a. Impact of recent drug shortages
            i. Nearly half of institutions of $\geq 400$ beds experienced $\geq 30$ drug shortages during 2010
         b. Resource utilization to manage shortages
            i. Estimated annual labor cost of $\$216$ MILLION for all health systems nationwide
         c. Adequacy of currently available information resources
            i. 70% of respondents felt information available to manage drug shortages was less than good (rated 1-3 on a 5 point Liker scale)

   B. Trend in Drug Shortages

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>120</td>
</tr>
<tr>
<td>2002</td>
<td>88</td>
</tr>
<tr>
<td>2003</td>
<td>73</td>
</tr>
<tr>
<td>2004</td>
<td>58</td>
</tr>
<tr>
<td>2005</td>
<td>74</td>
</tr>
<tr>
<td>2006</td>
<td>70</td>
</tr>
<tr>
<td>2007</td>
<td>129</td>
</tr>
<tr>
<td>2008</td>
<td>149</td>
</tr>
<tr>
<td>2009</td>
<td>166</td>
</tr>
<tr>
<td>2010</td>
<td>210</td>
</tr>
<tr>
<td>2011</td>
<td>267</td>
</tr>
</tbody>
</table>


C. FDA Authority\(^2\)
   1. What the FDA can do
      a. Expedite review of facilities and/or drug approvals
      b. Allow the importation and use of foreign drugs
   2. What the FDA cannot do
      a. Force manufacturers to produce a specific product
      b. Forces manufacturers to notify the FDA of a potential or current shortage
         i. EXCEPTION: Single source or medically necessary product
            ▪ Medically necessary drug product: a drug product that is used to treat or prevent a serious disease or medical condition for which there is no other adequately available drug product that is judged by medical staff to be an appropriate substitute.
II. Contributing factors
   A. Supplier\(^2\)
      1. Raw and bulk material availability
         a. Disruption of supply
         b. Natural vs. synthetic
         c. Sole and primary source shortages or disruptions
            i. Affects multiple manufacturers
         d. Importation of resources
            i. 80% of sources are outside the U.S.
            ii. Impacted by political conflicts, climate, disease, natural disasters, etc.
   B. Regulatory Issues\(^2,3\)
      1. Impact on manufacturers and suppliers
         a. Noncompliance with current good manufacturing processes (cGMPs)
            i. Outdated equipment or processes
            ii. Complex manufacturing processes
               ▪ i.e. monoclonal antibodies, large molecule drugs, biosimilars, vaccines, etc.
            iii. Decreased resources for maintenance of equipment and facilities
               ▪ Companies shifting investment to new drug development
               ▪ Mergers and personnel losses
         b. This may result in delays due to:
            i. Recalls
               ▪ Typically minor lapse affecting only certain lots
            ii. FDA sanctions
            iii. Increased product testing
         c. Limited FDA resources
            ▪ Site inspections
   C. Manufacturer\(^2-4\)
      1. Sole and primary manufacturers
         a. More vulnerable due to less redundancy in market
      2. Change in product formulation or manufacturer
         a. FDA approval
         b. Site inspections
         c. Lag time before adequate production of new formulation
            i. Transition from chlorofluorocarbon propelled albuterol MDIs to hydrofluoralkanes in 2006
      3. Manufacturer’s product decision and economics
         a. Profitability
            i. Availability of generic/competitor products
               ▪ “Me too” drugs (statins, beta blockers, proton pump inhibitors, ACE inhibitors)
            ii. Market size
               ▪ “Orphan drug policy”
            iii. Patent life
            iv. Drug-approval status
         v. Regulatory compliance requirements
            ▪ Cost of production in-line with cGMPs
         vi. Anticipated clinical demand
            ▪ Chronic vs. acute disease
         vii. Manufacturer rationing
            ▪ Scaling down for less profitable drugs
         b. Notification of production decisions
i. “Manufacturers are not required to notify FDA of a drug discontinuations unless the product is a sole-source or medically necessary product”
   - For medically necessary products, the FDA can encourage other manufacturers to produce the drug or request the manufacturer to not suspend production until an alternate source is available

4. Industry consolidation/manufacturer mergers
   a. As the number of manufacturers of a given product decreases, so the resiliency of the supply chain
   b. Mergers and consolidation may result in the following:
      - Narrowing the focus of a product line
      - Moving manufacturing facilities, creating a temporary lapse in production and delayed availability
      - Merging of two manufacturers with similar product lines, often resulting in single-source products
         1. Example: vaccinations, many are single source products

D. Wholesaler/Distributors
   1. Restricted drug product distribution and allocation
      a. Market approval requirements
      b. Restrictions on available quantities
         i. Suppliers and end users must comply with manufacturer agreements
      c. Order direct from manufacturer/specialty distributor

E. Non-traditional Distributors (Gray-market or Alternative Distributors)²⁷:
   1. Gray market
      a. Purchasing drugs from end users (infusion companies, home care companies, hospitals) and selling to other end users
      b. “Price-gouging”
         i. In Fall 2011, Congressman Elijah E. Cummings from Maryland, along with Senator John D. Rockefeller IV, Chairman of the Senate Committee on Commerce, Science, and Transportation, and Senator Tom Harkin, Chairman of the Senate Committee on Health, Education, Labor, and Pensions joined forces to investigate gray market companies and their activities. Their investigation revealed the following:

<table>
<thead>
<tr>
<th>Drug Distributor</th>
<th>Example of Price-Gouging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Medical Supply</td>
<td>Selling paclitaxel for $500 per vial; typical contract price is approximately $65 per vial.</td>
</tr>
<tr>
<td>Allied Medical Supplies Inc.</td>
<td>Selling cytarabine, another chemotherapy agent used in leukemia patients, for $990 per vial while the typical contract price is approximately $12 per vial</td>
</tr>
<tr>
<td>Premier Health Services Inc.</td>
<td>Selling leucovorin for $270 per vial; typical contract price is approximately $5 per vial</td>
</tr>
<tr>
<td>PRN Pharmaceuticals</td>
<td>Selling fluorouracil for $350 per vial; typical contract price is approximately $15 per vial</td>
</tr>
<tr>
<td>Reliance Wholesale Inc.</td>
<td>Selling magnesium sulfate for over $400 for 25 vials; typical contract price is approximately $9 per 25 vials</td>
</tr>
</tbody>
</table>

2. Stockpiling and price escalation on products in short supply
   i. Stockpiling creates an artificial shortage, exceeding the capabilities of manufacturers

3. Inability to ascertain product pedigree and source reliability
   i. Source may be outside of the U.S.
ii. Manufacturing, storage, and shipping process may be unknown and potentially compromised

4. Compounding pharmacies
   i. May not meet the same standards as a traditional, FDA regulated manufacturer’s product

F. End users (Pharmacy, Hospital, Patient)\textsuperscript{2,4-6}
   1. Inventory practices
      a. “Just-in-time” inventory management
         - Common practice of most manufacturers, distribution centers, and health systems
         - Reduces the cost of on hand inventory in an effort to optimize cash flow
         - A shortage at any point of the supply chain ultimately affects the end user, and potentially patients
      b. Poor ordering practices
      c. Stockpiling in anticipation of price increases
      d. Hoarding due to rumors of impending shortages
         i. Hoarding and stockpiling create an artificial shortage, exceeding the capabilities of manufacturers
      e. Delivery delays
      f. Hospital location
      g. Ability to borrow
   2. Unexpected increases in demand and shift in clinical practice
      a. New indication for existing product
      b. Disease outbreak
         i. Centers for Disease Control and Prevention (CDC) 2006 Recommendation
            - All Children ages 6 to 59 months should receive the influenza vaccination
      c. Updated guidelines or recommendations
            - Hydromorphone and morphine stock recommendations
               1. Recommendation to stock hydromorphone and morphine in different strengths (i.e. 1 mL prefilled syringes of hydromorphone 1 mg/1 mL; 2 mL prefilled syringes of morphine 2 mg/mL)
               2. As a result of the above recommendation, 1 mg/mL (1 mL) ampules became unavailable, resulting in a switch to the 1 mg/mL (1 mL) Carpuject prefilled syringe. Consequently, the prefilled syringe and ampule were in short supply. This forced many hospitals to return to the 2mg/mL concentration, creating greater potential for errors.
               3. Impact on patient safety: IV hydromorphone was prescribed at dose intended for morphine and administered to patients, resulting in two patient deaths.
      d. Shifts in drug use
         i. Increased utilization of alternative agents due to a drug shortage, creating a potential for an additional drug shortage

G. Natural disasters\textsuperscript{2}
   1. Facility damages
   2. Compromised product
   3. Problem may be exacerbated by an increased need for the product, secondary to the natural disaster
Drug Shortages by Primary Reason for Disruption in Production and Supply 2010 - 2011

- API (Active pharmaceutical ingredient) shortage 43%
- Business decision: discontinuation 15%
- Delays in manufacturing or shipping 10%
- Demand increase 8%
- Improper labeling 5%
- Loss of manufacturing site 9%
- Non-API component shortage 4%
- Other/Unknown 4%
- Problems at manufacturing facility 2%

Adapted from: Food and Drug Administration. A Review of FDA’s Approach to medical Product Shortages. October 31, 2011; 1-44
BACKGROUND: IMPACT ON PATIENT CARE

III. Impact of Drug Shortages on Patient Care

A. Patient safety
   1. Adverse effects of therapeutic alternatives
   2. Compromise or delay in medical treatment of procedures
   3. Failure to treat and progression of disease
   4. Medication errors
   5. Investigational studies halted

B. 2010 ISMP national survey
   1. 64% of respondents believed the shortage posed a risk of adverse patients outcomes
   2. 35% reported their facility had experienced a near miss during the past year due to drug shortages
   3. 1 in 4 reported actual errors
   4. 1 in 5 reported adverse patients outcomes during the past year

SEDATION

IV. Drug Shortages Impact on Sedation

A. Drug shortages in the ICU
   1. Drug shortages threaten the safety and quality of care for critically ill patients
   2. Notable critical care shortages over past few years
      a. Propofol, thiopental, succinylcholine, vecuronium, nicardipine, 23.4% sodium chloride, fosphenytoin, epinephrine, norepinephrine, ephedrine, neostigmine, amikacin, intravenous trimethoprim/sulfamethoxazole, and foscarnet
   3. Prolonged mechanical ventilation is required in 3-6% of adults admitted to an intensive care unit (ICU)

B. Sedation
   1. Patients in ICU frequently require invasive monitoring and support that may lead to anxiety, agitation, and pain
      a. Multiple causes in critically ill patients
         i. Underlying medical conditions
         ii. Acute medical or surgical illness
         iii. Invasive medical and nursing interventions
         iv. Mechanical ventilation
         v. Medications
         vi. Hospital acquired illness
         vii. Environmental stressors
   2. Goal
      a. Patient that is arousable and comfortably sedated
         i. Monitoring
            ▪ Provide a semi-quantitative score to standardize treatment endpoints and help avoid under/oversedation (See Appendix A for monitoring scales)
            1. Ramsay Sedation Scale
            2. Richmond Agitation-Sedation Scale (RASS)
3. Complications of oversedation\textsuperscript{10,11}
   a. Prolonged mechanical ventilation
   b. Increase length of stay
   c. Increased risk of complications
   d. Increased diagnostic testing
   e. Inability to evaluate for delirium
   f. Hemodynamic effects (hypotension/bradycardia)

4. Complications of undersedation\textsuperscript{10,11}
   a. Patient recall
   b. Agitation/anxiety
   c. Device removal
   d. Ventilator dysynchrony
   e. Tubes/line displacement
   f. Hemodynamic effects (hypertension/tachycardia)
   g. Pain/discomfort

5. Ideal sedative\textsuperscript{10,11}
   a. Rapid onset, titratable, short elimination half-life
   b. Minimal hemodynamic effects
   c. Lack of respiratory depression
   d. Anxiolytic
   e. Analgesia
   f. Ability to arouse and assess

6. Commonly used sedatives\textsuperscript{10,11}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
Drug (mechanism) & Elimination & Onset/Duration \\
\hline
Lorazepam (benzodiazepine/GABA-nergic) & Glucuronidation; half-life 10 hours & 5-20 minutes/ 6-8 hours; up to 24-72 hours in elderly/cirrhosis \\
\hline
Midazolam (benzodiazepine/GABA-nergic) & CYP3A4; half-life 3 hours & 5-10 minutes/ 1-4 hours (longer in renal dysfunction/obesity) \\
\hline
Propofol (non-benzodiazepine/GABA-nergic) & Conjugation; half-life 6 hours & 30 – 50 seconds/ 3 – 10 minutes (dose dependent) \\
\hline
Dexmedetomidine (alpha-2 adrenergic agonist) & CYP2A6 and glucuronidation; half-life 2 hours & Immediate/ approximately 6 minutes (longer in liver failure) \\
\hline
\end{tabular}
\caption{Commonly used sedatives}
\end{table}

7. Use of sedatives\textsuperscript{12}
   a. Propofol is the most commonly used sedative among mechanically ventilated patients in the U.S.

\begin{center}
\includegraphics[width=\textwidth]{chart.png}
\end{center}

b. Propofol is commonly used in short, medium and long-term sedation over other commonly used sedatives in mechanically ventilated patients in the U.S.


8. Propofol shortage\textsuperscript{13}
   a. October 2009
      i. Two of the three U.S. manufacturers of propofol re-called their products
         - Hospira pharmaceuticals
            1. Found particulate matter in one or more batches
            2. May 2010
               a. Had not yet returned to market
               b. Expanded its recall to all products in customer’s inventories
         - Teva pharmaceuticals
            1. Microbial contamination
            2. Summer 2010
               a. Announced they will not return to market
      ii. Propofol became a single source product in the U.S. market

9. Advantages and disadvantages of alternative sedatives\textsuperscript{10,11}

<table>
<thead>
<tr>
<th>Sedative</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>Inexpensive</td>
<td>Propylene glycol toxicity at high doses (anion gap metabolic acidosis), longer half-life, prolonged sedation with continuous infusion</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Shorter acting in preserved organ function; fast onset</td>
<td>Drug interactions, active metabolite accumulates in renal impairment, prolonged sedation in renal impairment and obesity</td>
</tr>
<tr>
<td>Propofol</td>
<td>Short acting; fast onset; ↓ duration of mechanical ventilation; cost</td>
<td>↓ blood pressure, ↑ triglycerides, pancreatitis, propofol infusion syndrome, proinflammatory</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Very short duration; some analgesic properties; ↓ duration of mechanical ventilation</td>
<td>↓ blood pressure, ↓ heart rate, cost</td>
</tr>
</tbody>
</table>
10. What to expect with increased use of benzodiazepines
   a. Clinical evidence

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial design</strong></td>
<td>Randomized, multi-center, open-label trial</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To compare duration of mechanical ventilation for patients randomized to receive lorazepam by intermittent bolus administration vs. continuous infusions of propofol using protocols that include scheduled daily interruption of sedation.</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>N = 172 patients admitted to the MICU of the University of North Carolina Hospitals and the University of Chicago Hospitals between October 2001 and March 2004</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Inclusion criteria** | • Age ≥ 18, anticipated requirement for mechanical ventilation for > 48 hrs based on assessments of respiratory strength and gas exchange during the first 24 hrs, and at least one of the following
  o Requirement of six or more doses of lorazepam
  o Requirement of a total of 10 mg of lorazepam within 24 hours
  o Judged by the primary ICU team to require continuous sedation due to agitation or ventilatory asynchrony
  • If patients did not meet these criteria within the first 4 days of intubation they were no longer eligible |
| **Exclusion criteria** | • Known hypersensitivity to lorazepam or propofol
  • Benzodiazepine dependence
  • High risk of alcohol withdrawal
  • Known history of pancreatitis or clinical evidence of pancreatitis
  • Pregnancy or breastfeeding
  • Resuscitation from cardiac arrest without recovery of mental status
  • Head trauma or acute neurologic injury with Glasgow Coma Scale score < 8
  • Transfer from an outside institution where sedatives had already been administered for > 24 hrs
  • Death was expected within 24 hrs |
| **Interventions** | • After randomization, if patients developed clinical evidence of discomfort, they were assessed and treated as determined by the primary ICU team
  • Patients that continued to show signs of anxiety and/or agitation despite assessment and treatment of pain were initiated on the study sedative regimen they were assigned
  • Due to differences in onset of sedation between the two regimens, it was not possible to blind caregivers and therefore was conducted as an open-label study
  • Patients randomized to lorazepam received doses ranging from 2 – 4 mg every 4 hours (~0.044 mg/kg)
  • Patients randomized to propofol received 1% propofol infusion at 5 mcg/kg/min with the infusion rate increased every 10 minutes as needed with a maximum dose of 80 mcg/kg/min, and had serum triglycerides monitored on enrollment and every 4 days thereafter
  • A Ramsay score of 2 – 3 (corresponding to the patient being cooperative, oriented and tranquil or able to respond to commands) was targeted in both groups
  • Ramsay score of 4 (brisk response to light glabellar tap or loud auditory stimulus) was targeted in cases of clinically significant ventilator asynchrony
  • In both groups patient arousal was assessed every 2 hours and rates of sedatives adjusted as necessary for targeted Ramsay score
  • At the discretion of the primary physician patients were allowed to receive haloperidol intermittently for acute hyperactive delirium
  • Patients received ≥ 2 mg of morphine sulfate or an equivalent opiate every 4 hours with the ability to increase by 2 mg increments and continuous morphine infusions were allowed when high dose of sedatives were required
  • For patients requiring greater sedation despite receiving a maximum dose of propofol or lorazepam were considered a treatment failure and switched to an alternative sedation regimen
  • In the propofol group patients were considered treatment failures if serum triglycerides increased to > 500 mg/dL, and were switched to lorazepam
  • Sedation was withheld daily to allow patients to wake up and follow simple commands (tracking with eyes, squeezing fingers, moving tongue, etc.) and resumed when patients showed signs of |

*Clinical Implications of Drug Shortages*
agitation or discomfort
- On resumption of sedation, doses were decreased by half if the time to achieve awakening was > 6 hours
- Once requiring only occasional small doses of sedatives their regimens were stopped and then maintained on lorazepam 1 or 2 mg in PRN intervals of ≥ 8 hours

Endpoints
- Primary outcome was the median number of ventilatory days
  - Measured from the time of intubation to the initial time a patient became free from mechanical ventilation for at least 72 consecutive hours
- Secondary outcomes included
  - 28-day ventilator-free survival
  - ICU length of stay
  - Hospital length of stay
  - Hospital mortality

Statistical analyses
- Based on pilot survey data, performed a simulation study to determine the sample size of 130 patients to show a 2-day difference in median ventilator days with a power of 0.9 and an α = 0.05
- Data were analyzed using an intent-to-treat analysis
- Ventilator days and length of stay were compared using the Wilcoxon rank-sum test
- Continuous variables were compared using the Student’s t-test for unequal variances
- Categorical outcomes were compared using the chi-square test of Fisher’s exact test
- All statistical analysis were two-sided

RESULTS

Baseline characteristics
- 64 patients were randomized to the intermittent lorazepam group and 68 patients were randomized to the propofol group
- 62% of patients in each group were mechanically ventilated with pneumonia, acute respiratory distress syndrome, or septic shock
- Patients were similar in age, gender, and illness severity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lorazepam</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>51.0 ± 16.8</td>
<td>54.0 ± 7.7</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>34 (53)</td>
<td>34 (50)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>34 (54)</td>
<td>35 (52)</td>
</tr>
<tr>
<td>African-American</td>
<td>25 (40)</td>
<td>32 (47)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (6)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia and/or ARDS</td>
<td>27 (42)</td>
<td>30 (43)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>13 (20)</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Other shock</td>
<td>3 (5)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Hemothysis/alveolar hemorrhage</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Sickle cell chest syndrome</td>
<td>3 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>4 (6)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>1 (2)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>4 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>4 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>3 (5)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>APACHE II, mean ± SD</td>
<td>22.9 ± 7.7</td>
<td>20.7 ± 7.3</td>
</tr>
<tr>
<td>GCS, ICU admission, mean ± SD</td>
<td>13.1 ± 3.0</td>
<td>12.4 ± 3.8</td>
</tr>
<tr>
<td>Chronic liver disease, n (%)</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Renal failure, n (%)</td>
<td>13 (20)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>University of North Carolina, n (%)</td>
<td>41 (64)</td>
<td>39 (57)</td>
</tr>
<tr>
<td>University of Chicago, n (%)</td>
<td>23 (36)</td>
<td>29 (43)</td>
</tr>
<tr>
<td>Sedatives prior to randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam, mg, mean ± SD</td>
<td>26.9 ± 21.1</td>
<td>31.0 ± 23.2</td>
</tr>
<tr>
<td>n = 38</td>
<td></td>
<td>n = 36</td>
</tr>
<tr>
<td>Propofol, mg, mean ± SD</td>
<td>3501 ± 2751</td>
<td>3405 ± 5470</td>
</tr>
<tr>
<td>n = 34</td>
<td></td>
<td>n = 40</td>
</tr>
<tr>
<td>Morphine, mg, mean ± SD</td>
<td>52.2 ± 48.7</td>
<td>61.4 ± 98.4</td>
</tr>
<tr>
<td>n = 52</td>
<td></td>
<td>n = 57</td>
</tr>
</tbody>
</table>
Primary and Secondary Endpoints

- Median ventilator days were significantly lower in the propofol group compared to the intermittent lorazepam group (5.8 vs. 8.4, p = 0.04)
- This was consistent with hospital survivors (4.4 vs 9.0, p = 0.006) but was not found in non-survivors (7.2 vs 7.5, p = 0.66)
- Due to a greater number of patients with renal failure being randomized to the lorazepam group, a secondary analysis of ventilator days excluding patients with renal failure was conducted which did not substantially change the difference in ventilator days for all patients (5.8 propofol vs 8.5 lorazepam, p = 0.07) or hospital survivors (4.9 propofol vs 9.1 lorazepam, p = 0.01)
- Hospital length of stay (LOS) was not significantly different overall (8.3 days propofol vs. 10.4 days lorazepam, p = 0.20)
- In hospital survivors, ICU LOS was shorter in the propofol group (8.6 vs 12.7, p = 0.05)
- Hospital LOS and mortality were not significantly different

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam</th>
<th>Propofol</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>64</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Ventilator days for all patients, median</td>
<td>8.4 (4.6, 14.7)</td>
<td>5.8 (3.5, 10.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ventilator days for survivors, median</td>
<td>9.0 (5.3, 16.8) n = 40</td>
<td>4.4 (3.0, 8.7) n = 43</td>
<td>0.006</td>
</tr>
<tr>
<td>Ventilator days for non-survivors, median</td>
<td>7.5 (4.0, 11.4) n = 24</td>
<td>7.2 (4.2, 13.2) n = 25</td>
<td>0.66</td>
</tr>
<tr>
<td>28-day ventilator-free survival, median</td>
<td>10.2 (0, 20) n = 40</td>
<td>18.5 (0, 24) n = 43</td>
<td>0.06</td>
</tr>
<tr>
<td>ICU LOS for all patients, median</td>
<td>10.4 (6.7, 16.8) n = 40</td>
<td>8.3 (5.2, 15.2) n = 43</td>
<td>0.20</td>
</tr>
<tr>
<td>ICU LOS for survivors, median</td>
<td>12.7 (7.8, 19.1) n = 40</td>
<td>8.6 (5.0, 14.7) n = 43</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU LOS for non-survivors, median</td>
<td>9.5 (5.3, 12.0) n = 24</td>
<td>9.3 (6.0, 18.1) n = 25</td>
<td>0.68</td>
</tr>
<tr>
<td>Hospital LOS for all patients, median</td>
<td>20 (12, 30) n = 40</td>
<td>18 (12, 29) n = 43</td>
<td>0.55</td>
</tr>
<tr>
<td>Hospital LOS for survivors, median</td>
<td>22.5 (14, 33) n = 40</td>
<td>19 (10, 32) n = 43</td>
<td>0.16</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>24 (38) n = 40</td>
<td>25 (37) n = 43</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Approaches to weaning and patient responses

- Percent of days on SBT was performed when a screen was passed, mean ± SD | 90 ± 26 | 89 ± 24 | 0.85 |
- Patients for whom an SBT or extubation was withheld because of oversedation, n (%) | 9 (14) | 5 (7) | 0.21 |
- Reintubations, n (%) | 9 (16) | 7 (12) | 0.59 |
- Self-extubations, n (%) | 1 (2) | 3 (5) | 0.62 |
- Tracheostomies, n (%) | 12 (19) | 12 (18) | 0.90 |

AUTHORS’ CONCLUSIONS

For medical ICU patients requiring > 48 hours of mechanical ventilation and intravenous sedation, use of propofol infusions with daily sedative interruption results in significantly fewer ventilator days compared with intermittent bolus dosing of lorazepam. The shorter duration of mechanical intervention is associated with fewer ICU days for survivors. Contrary to published guidelines, this study supports the use of propofol for patients who require significant amounts of sedation for prolonged periods of mechanical ventilation, as long as daily interruption of the propofol infusion is part of the sedation strategy.

APPLICATION

With propofol in shortage there may be an increase in the use of benzodiazepine use such as lorazepam. This may increase the time patients are mechanically ventilated, therefore increasing the potential for complications as well as cost. To circumvent these potential problems practitioners will need to monitor patients more closely and apply appropriate strategies to reduce length of mechanical ventilation.
11. Additional trials comparing propofol with benzodiazepines
   a. Validation of prolonged mechanical ventilation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Drugs</th>
<th>Time to Extubation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carasco G, et al. Chest. 1993&lt;sup&gt;16&lt;/sup&gt;</td>
<td>MICU/SICU (n = 88)</td>
<td>Propofol v. Midazolam</td>
<td>Medium: Propofol 0.4 ± 0.1 h Midazolam 13.5 ± 4 h</td>
<td>Medium: P &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Long: Propofol 0.8 ± 0.3 h Midazolam 36.6 ± 6.8 h</td>
<td>Long: P &lt; 0.05</td>
</tr>
<tr>
<td>Hall RL, et al. Chest. 2001&lt;sup&gt;17&lt;/sup&gt;</td>
<td>MICU/SIVU (n = 99)</td>
<td>Propofol v. Midazolam</td>
<td>Propofol: 8.4 h Midazolam: 46.8 h</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Barrientes-Vega R, et al. Crit Care Med. 1997&lt;sup&gt;18&lt;/sup&gt;</td>
<td>MICU/SICU (n = 108)</td>
<td>Propofol v. Midazolam</td>
<td>Propofol: 4 ± 3.9 h Midazolam: 48.9 ± 47.2 h</td>
<td>P = 0.0001</td>
</tr>
</tbody>
</table>

12. Comparing two therapeutic alternatives
   a. Clinical evidence

---


**Trial design**
- Prospective, double-blind, multi-center, randomized trial

**Objectives**
- To compare the efficacy and safety of prolonged sedation with dexmedetomidine vs midazolam for mechanically ventilated patients

**Enrollment**
- Between March 2005 and August 2007, N = 375 medical/surgical ICUs were enrolled throughout 68 centers in 5 countries

**METHODS**

**Inclusion criteria**
- ≥ 18 years of age
- Intubated and mechanically ventilated for less than 96 hours prior to start of study drug
- Anticipated ventilation and sedation of at least 3 days

**Exclusion criteria**
- Trauma or burns as admitting diagnosis
- Dialysis
- Pregnancy or lactation
- Neuromuscular blockade other than for intubation
- Epidural or spinal analgesia
- General anesthesia 24 hours prior to or planned after the start of study drug infusion
- Serious central nervous system pathology (acute stroke, uncontrolled seizures, severe dementia)
- Acute hepatitis or severe liver disease (Child-Pugh class C)
- Unstable angina or acute myocardial infarction
- Left ventricular ejection fraction < 30 %
- Heart rate < 50 bpm (beats per minute)
- Second or third degree heart block
- Systolic blood pressure < 90 mmHg despite continuous infusion of 2 vasopressors before the start of study drug infusions

**Interventions**
- Patients were randomized 2:1 to receive dexmedetomidine starting at 0.8 mcg/kg/hr or 0.06 mg/kg/hr for midazolam and could be adjusted to a RASS sedation range from -2 to +1
- Optional blinded loading doses (1 mcg/kg of dexmedetomidine or 0.05 mg/kg of midazolam) could be administered at the investigator’s discretion
- If patients in either group were not adequately sedated by study drug titration they could receive open-label bolus dose of 0.01 to 0.05 mg/kg of midazolam at 10 – 15 min intervals until adequate sedation was achieved
- Fentanyl bolus doses of 0.5 -1 mcg/kg as needed every 15 minutes
- A daily arousal assessments was performed where patients within the RASS range of -2 to +1 were considered away when they could perform 3 out of 4 tasks (open eyes to voice command.
track investigators with eyes, and stick out tongue
• If patients were oversedated to RASS score of -3 to -5, study drug was interrupted until the patient achieved a RASS score between -2 and 0

Endpoints
• Primary efficacy endpoint was the percentage of time within the targeted sedation range (RASS score -2 to +1)
• Secondary efficacy endpoints included:
  o Prevalence and duration of delirium
  o Use of fentanyl and open-label midazolam
  o Nursing shift assessments (using a scale from 0 to 10 with 10 indicating patient was communicating, cooperating, or tolerating)
  o Duration of mechanical ventilation
  o ICU length of stay
• Safety endpoints
  o Vital signs
  o Hyperglycemia (at least 1 serum glucose value > 150 mg/dL)
  o Infections
  o 30 day mortality

Statistical analyses
• Based on previous pilot studies, estimated the time within the targeted sedation range for dexmedetomidine was 85% and midazolam 77%, enrollment of 250 dexmedetomidine patients and 125 midazolam patients would have a power of 96% at an α of 0.05 to detect a 7.4% difference in the primary efficacy endpoint
• Primary efficacy and safety analyses were conducted on all randomized patients who received any study drug
• Mann-Whitney test was used to compare time within targeted RASS range differences in both treatment groups, comparisons for delerium-free days, duration of study drug, and dose of rescue medications
• Treatment differences in nursing assessment scores were assessed with the Wilcoxon test
• Delirium and use of rescue medications were compared using the Fisher’s exact test
• Time to extubation and length of ICU stay were calculated and assessed using Kaplan-Meier survival analysis and log-rank test with a Bonferroni adjustment
• Statistical tests were 2 sided with p ≤ 0.05 considered statistically significant

RESULTS
Baseline characteristics
• 375 patients were randomized and 366 patients received study drug, comprising the primary analysis study population (n = 244 in dexmedetomidine group and n = 122 in midazolam group)
• Most patients (294 of 366) were treated in the U.S.
• Patients were well matched between both groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dexmedetomidine (n = 244)</th>
<th>Midazolam (n = 122)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.5 (14.8)</td>
<td>62.9 (16.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Men</td>
<td>125 (51.2)</td>
<td>57 (46.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Weight, mean (SD) kg</td>
<td>88.1 (33.9)</td>
<td>87.8 (31.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)</td>
<td>19.1 (7.0)</td>
<td>18.3 (6.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Medical ICU patients</td>
<td>212 (86.9)</td>
<td>103 (84.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Surgical ICU patients</td>
<td>32 (13.1)</td>
<td>18 (14.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>182 (74.6)</td>
<td>94 (77.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Shock</td>
<td>78 (32)</td>
<td>45 (36.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>156 (63.9)</td>
<td>76 (62.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childs-Pugh A</td>
<td>124 (51.0)</td>
<td>54 (44.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Childs-Pugh B</td>
<td>115 (47.3)</td>
<td>67 (54.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatinine, median (IQR), mg/dL</td>
<td>1.0 (0.7 – 1.4)</td>
<td>1.1 (0.8 – 1.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Pre-study drug sedative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>195 (79.9)</td>
<td>100 (82.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Propofol</td>
<td>125 (51.2)</td>
<td>56 (45.9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>1 (0.4)</td>
<td>2 (1.6)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Time from ICU admission to start of study drug, median (IQR), h

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine (n = 244)</th>
<th>Midazolam (n = 122)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.6 (22.2 – 64.9)</td>
<td>39.3 (24.5 – 72.8)</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

Delirium at enrollment, (CAM-ICU-positive)

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine (n = 244)</th>
<th>Midazolam (n = 122)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>138 (60.3)</td>
<td>70 (59.3)</td>
<td>0.82</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; IQR, interquartile range

aAPACHE II scores recorded using worst values over previous 24 hours from time of study enrollment (mean, 40 hours following ICU admission).
bKnown or suspected infection with 2 or more systematic inflammatory response syndrome criteria and at least 1 new organ system dysfunction.
cPatients with blood pressure maintained via infusions of dopamine, dobutamine, norepinephrine, epinephrine or vasopressin prior to start of study drug.
dCalculated from patients treated with study drug and delirium assessments at baseline (229 with dexmedetomidine, 118 with midazolam).

efficacy outcomes

- No difference in the primary efficacy outcome, percentage of time within the target RASS range (77.3% for dexmedetomidine-treated patients vs 75.1% for midazolam-treated patients; 95% CI, -3.2% -7.5%; P = 0.18)
- Similar percentage of patients successfully completed all daily arousal assessments and had study drug interrupted to achieve the target sedation range
- Prevalence of delirium was 54% in the dexmedetomidine-treated patients vs 76.6% in the midazolam-treated patients (95% CI, 14% -33%; P < 0.001)
- More patients treated with dexmedetomidine had study drug stopped because of extubation (59% vs 45%; P = 0.01) with a Kaplan-Meier estimated median time to extubation being 1.9 days shorter than midazolam treated patients (3.7 days vs 5.6 days; P= 0.01)
- Median length of ICU stay was similar between both groups

Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexmedetomidine (n = 244)</th>
<th>Midazolam (n = 122)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in target sedation range (RASS score -2 to +1), mean, %</td>
<td>77.3</td>
<td>75.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Patients completing all daily arousal assessments</td>
<td>225 (92)</td>
<td>103 (84.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Patients requiring study drug interruption to maintain RASS score -2 to +1</td>
<td>222 (91)</td>
<td>112 (91.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>Duration of study drug treatment, median (IQR), d</td>
<td>3.5 (2.0 – 5.2)</td>
<td>4.1 (2.8 – 6.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to extubation, median (95% CI), d</td>
<td>3.7 (3.1 – 4.0)</td>
<td>5.6 (4.6 – 5.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>ICU length of stay, median (95% CI), d</td>
<td>5.9 (5.7 – 7.0)</td>
<td>7.6 (6.7 – 8.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence, %</td>
<td>132 (54)</td>
<td>93 (76.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean delirium-free days</td>
<td>2.5</td>
<td>1.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Open-label midazolam use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. treated</td>
<td>153 (63)</td>
<td>60 (49)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dose, median (IQR), mg/kg</td>
<td>0.09 (0.03 – 0.23)</td>
<td>0.11 (0.03 – 0.28)</td>
<td>0.65</td>
</tr>
<tr>
<td>Fentanyl use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. treated</td>
<td>180 (73.6)</td>
<td>97 (79.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Dose, median (IQR), mcg/kg</td>
<td>6.4 (1.8 – 26.3)</td>
<td>9.6 (2.9 – 28.6)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

The mean difference in percentage of time within target sedation range between the dexmedetomidine and midazolam treatment groups was calculated using Mann-Whitney test.
Calculated using Kaplan-Meier survival analysis, with differences between treatment groups assessed by the log-rank test. Log-rank P values were adjusted for multiple comparisons using the Bonferroni method.
Number of days alive without delirium during study drug treatment.
Calculated as the total dose during study treatment divided by body mass.
A. Time to extubation was calculated from the start of study drug to the time of extubation after which no reintubation occurred. Patients not extubated were censored at time of study drug discontinuation. B. Length of ICU stay was calculated from start of study drug to time of order for ICU transfer. Patients without discharge were censored at the time of study drug discontinuation.

Safety outcomes

- All-cause 30-day mortality from ICU admission was not different between treatment groups (22.5% for dexmedetomidine-treated patients vs 25.4% for midazolam-treated patients; *P* = 0.60)
- A similar percentage of patients stopped study drug infusions due to adverse events (16.4% for dexmedetomidine vs 13.1% for midazolam; *P* = 0.44)
- Significantly more bradycardia (HR < 40 bpm) in dexmedetomidine vs midazolam (42.2% vs 18.9%; *P* < 0.001)
- A trend towards more bradycardia intervention (titration or interruption of study drug) was also seen in the dexmedetomidine group (4.9% vs. 0.8%; *P* = 0.07)

### Safety Outcomes:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexmedetomidine (n = 244) n (%)</th>
<th>Midazolam (n = 122) n (%)</th>
<th><em>P</em>-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>103 (42.2)</td>
<td>23 (18.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bradycardia with intervention</td>
<td>12 (4.9)</td>
<td>1 (0.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>62 (25.4)</td>
<td>54 (44.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tachycardia with intervention</td>
<td>25 (9.8)</td>
<td>12 (9.8)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Hypotension</td>
<td>137 (56.1)</td>
<td>68 (55.7)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Hypotension with intervention</td>
<td>69 (28.3)</td>
<td>33 (27)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>106 (43.4)</td>
<td>54 (44.3)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypertension with intervention</td>
<td>46 (18.9)</td>
<td>36 (29.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Metabolic (hyperglycemia)</td>
<td>138 (56.6)</td>
<td>52 (42.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Infections</td>
<td>25 (10.2)</td>
<td>24 (19.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>30-d mortality*</td>
<td>55 (22.5)</td>
<td>31 (25.4)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*See “Outcome Measures and Safety End Points” for definitions and details of variables

*Indicates mortality rate for 30 days after ICU admission

---

**AUTHORS’ CONCLUSIONS**

“This investigation showed no difference in the time patients spent within the sedation target range with dexmedetomidine or midazolam. Despite this similarity in sedation levels, dexmedetomidine shortened time to removal from mechanical ventilation and reduced the prevalence of delirium.”

**APPLICATION**

With propofol in shortage, two competing options may be the use of other sedatives such as midazolam and dexmedetomidine. In this trial dexmedetomidine was associated with a decrease in days of mechanical ventilation and delirium while maintaining appropriate target sedation when compared to midazolam and therefore may be a better option in certain populations. However the cost of dexmedetomidine and potential adverse hemodynamic effects may offset some the advantages with the use of dexmedetomidine.

---

Clinical Implications of Drug Shortages 16
13. Expected impact of propofol shortage

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before shortage (n = 153)</th>
<th>After shortage (n = 128)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients administered each continuous sedation infusion ≥ 24 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>9</td>
<td>27</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>7</td>
<td>14</td>
<td>0.04</td>
</tr>
<tr>
<td>Midazolam</td>
<td>36</td>
<td>73</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Propofol</td>
<td>94</td>
<td>15</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Duration of all continuous sedation infusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days</td>
<td>6 (3 – 12)</td>
<td>5 (3 – 9)</td>
<td>0.02</td>
</tr>
<tr>
<td>As a percent of time on mechanical ventilation</td>
<td>94 (68 – 111)</td>
<td>59 (35 – 82)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Duration, days, of each sedation infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>1.3 (0.5 – 2.5)</td>
<td>2.8 (1.5 – 4.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>3.0 (1.5 – 4.0)</td>
<td>4.5 (2.5 – 7.5)</td>
<td>0.347</td>
</tr>
<tr>
<td>Midazolam</td>
<td>4.0 (2.5 – 9.0)</td>
<td>4.0 (2.5 – 8.0)</td>
<td>0.446</td>
</tr>
<tr>
<td>Propofol</td>
<td>4.5 (3.0 – 8.0)</td>
<td>4.0 (2.0 – 9.5)</td>
<td>0.763</td>
</tr>
<tr>
<td>Midazolam equivalents of sedation infusion administered, mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average (for all patients in each group)</td>
<td>1117 (575 – 2200)</td>
<td>450 (200 – 1247)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Average (for only those patients administered drug)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>68 (14 – 109)</td>
<td>81 (41 – 216)</td>
<td>0.278</td>
</tr>
</tbody>
</table>


METHODS

**Inclusion criteria**
- Mechanically ventilated ≥ 48 hours
- Successfully extubated
- Discharged from the ICU
- Received ≥ 24 hours of continuously infused lorazepam, midazolam, propofol, and/or dexmedetomidine during the period of intubation
- Patients who received a tracheostomy were only included if they did not require mechanical ventilation at the time of ICU discharge

**Exclusion criteria**
- Patients who died while mechanically ventilated or underwent terminal wean from mechanical ventilation
- Patients who were not identified from the institutional pharmacy database

**Interventions**
- None
Patients frequently received more than one continuously infused sedative over the course of their intensive care unit stay; reported as median (interquartile range of 25th to 75th percentile) unless otherwise noted; neuromuscular blocker information was missing for four patients in the after group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Shortage (n = 153)</th>
<th>After Shortage (n = 128)</th>
<th>P-value Between Before and After Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62.1 ± 15.9</td>
<td>57.0 ± 16.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Male, %</td>
<td>64.4</td>
<td>63.3</td>
<td>0.72</td>
</tr>
<tr>
<td>Medical service,%</td>
<td>78.4</td>
<td>64.0</td>
<td>0.008</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19 ± 5.7</td>
<td>20.1 ± 6.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

### Results

Baseline characteristics

- The after group had a longer median duration of mechanical ventilation than the before group (9.6 vs 6.7 days; p = 0.02).
- Fewer after patients received ≥ 24 hours of continuous propofol infusion (94% vs 15%; p < 0.0001) and more received ≥ 24 hours of continuous infusion lorazepam, midazolam, or dexmedetomidine (p = 0.04, < 0.001, < 0.001 respectively).
- After group had a shorter duration of continuously infused sedation, received fewer total midazolam equivalents of sedation, and was administered sedation at a lower average infusion rate, and was more likely to receive continuous neuromuscular blocker therapy.
- The after group was younger (57 ± 16.7 vs 62.1 ± 15.9; p = 0.01), were less likely to be admitted to a medical service (p = 0.008), had a slightly higher admission APACHE II score (20.1 ± 6.3 vs 19 ± 5.7; p = 0.1), was more likely to be admitted with acute alcohol withdrawal (9.6% vs 4.6%; p = 0.09), and more likely to receive pressure-controlled ventilation (9.3% vs 4.6%; p = 0.07).
- Other clinical and demographic factors were similar between the two groups.

Table 2: Comparison of unadjusted factors that could affect duration of mechanical ventilation between the two groups and their relationship to days of mechanical ventilation.
Worse PaO$_2$/FiO$_2$ ratio in first 24 hrs after ICU admission  

|         | 250 (175 – 352) | 240 (180 – 354) | 0.56 | - |

Primary reason for ICU admission

| Respiratory (non-acute respiratory distress syndrome) | 25 | 22 | 0.79 | - |

Sepsis/Acute respiratory distress syndrome

| Cardiac | 20 | 15 | 0.33 | - |
| Neurologic | 17 | 19 | 0.63 | - |
| Toxic/metabolic | 6 | 5 | 0.86 | - |
| Gastrointestinal | 5 | 9 | 0.41 | - |
| Trauma | 4 | 6 | 0.68 | - |
| Other | 1 | 7 | - | - |

Active alcohol withdrawal, %

| Admission SCr, mg/dL | 1.11 (0.8 – 1.99) | 1.09 (0.7 – 1.77) | 0.35 | - |

Pressure controlled ventilation the most frequent ventilator mode, %

| Use of pressure controlled ventilation ≥ 24 hrs, % | 20 | 18.4 | 0.6 | - |

*Reported as either mean ± SD or median (interquartile range of 25$^{th}$ to 75$^{th}$ percentile; *APACHE II score was missing in one patient in the after group; worse PaO$_2$/FiO$_2$ ratio and SCr missing in three patients in the after group.

Endpoints

- The unadjusted geometric mean of duration of mechanical ventilation was 20% longer in the after group compared to the before group (p = 0.05)
- However when adjusted for covariates that affected duration of mechanical ventilation (admission to medical service, APACHE II score, and use of pressure controlled ventilation as most frequent ventilator mode), the duration of mechanical ventilation was only 7% longer in the after group (p = 0.35)

Table 3: Estimated difference in days of mechanical ventilation between the after and before groups: Unadjusted and multivariable adjusted linear regression models of log$_{10}$ days (n = 277 subjects)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Model (R$^2$ = 0.012)</th>
<th>Adjusted Model (R$^2$ = 0.103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter estimate</td>
<td>SE</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.89</td>
<td>0.03</td>
</tr>
<tr>
<td>Before vs After$^a$</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Medical service</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Clinical Implications of Drug Shortages 19
Clinical Implications of Drug Shortages

Pressure-controlled ventilation the most frequent mode of mechanical ventilation

<table>
<thead>
<tr>
<th></th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>0.19</th>
<th>0.08</th>
<th>0.02</th>
</tr>
</thead>
</table>

*The total sample size in the study was 281. Two subjects were excluded from these regression models because high-frequency oscillating ventilation. Two others were excluded because they were missing the mode of ventilation or the APACHE II score; *coefficients show the estimated difference in the log_{10} days of mechanical ventilation between the before and after periods. Positive values indicate the average duration of mechanical ventilation is higher in the after compared to the before groups.*

**AUTHORS' CONCLUSIONS**

“In conclusion, our study showed that a national shortage of propofol did not have a notable effect on the duration of mechanical ventilation among non-cardiac ICU patients at our academic institution. However, in an era of ever-increasing ICU drug shortages, future research is required to determine those factors that affect the supply of intravenous medications that are routinely used in the ICU, evaluate the impact of proposed legislation focused on alleviating this issue, and measure impact of any ICU medication shortage on patient outcome.”

**APPLICATION**

Due to the propofol shortage it has been necessary to utilize therapeutic alternatives. In prospective clinical trials, propofol has been shown to decrease the duration of mechanical ventilation when compared to benzodiazepines. However, this may not translate as readily to clinical practice outside of a controlled environment. Therefore it is important to keep in mind other strategies to help limit the duration of mechanical ventilation to prevent complications.

14. Expectations of alternative agents
   a. Prolonged and/or oversedation
      i. Benzodiazepine accumulation
         • Prolonged intubation
            1. Ventilator associated pneumonia
         • DVT/PE
         • Unable to screen for delirium
         • Post-traumatic stress disorder
   b. Delirium
      i. More common with benzodiazepines
      ii. Associated with
         • Higher mortality
         • Prolonged mechanical ventilation
         • Increased length of stay
         • Poor recovery to baseline functional status
   c. Infection
      i. Benzodiazepines
         • Limit neutrophil chemotaxis, phagocytosis, and reactive oxygen species
   d. Cardiovascular effects
      i. Hypotension
         • Common to all sedative opioids
      ii. Bradycardia
      iii. Tachycardia
      • Withdrawal of prolonged sedation
   e. Adverse drug reactions (ADRs)
      i. ISMP Med Safety Alert, ADRs of propofol during shortage
         • Unintended intraoperative awareness occurred when a patient was given too little propofol based on weight in an attempt to conserve supplies
         • Misprogrammed dexmedetomidine concentration in a smart pump; the drug was not in the library because it had never been used before the propofol shortage; the patient received a 20-fold overdose for 5 hours
Physician unfamiliar with dexmedetomidine dosed the drug in mcg/kg/minute instead of mcg/kg/hour
Infused midazolam at usual propofol rate; entire bag infused within a few hours, leading to oversedation
A paralyzed, ventilated patient received no sedation because propofol was not available and an alternative drug was never prescribed
Inadequate sedation with benzodiazepines led to agitation and self-extubation; one patient bit through her tongue

15. Suggestions to Overcome Disadvantages of Alternative Sedatives

a. Protocolized sedation\textsuperscript{10,11}
   i. May entail:
      - Using medications with shorter half-lives
      - Titrating sedation to pre-specified end-points of sedation scales
      - Mandating temporary cessation of sedative infusion
      - Utilizing intermittent sedatives instead of continuous
   ii. Benefits:
      - Reduce ADRs
      - Decreased unnecessary diagnostic testing
      - Reduce duration of mechanical ventilation
      - Shorten length of stay

b. PRN vs continuous benzodiazepines\textsuperscript{10,11}
   i. Benefits:
      - Decreased accumulation
      - Lower doses

c. Daily interruption of sedation\textsuperscript{10,11,22}
   i. Sedatives and analgesics are interrupted until patients are awake and able to follow commands, then re-sedated as appropriate
   ii. Benefits:
      - Reduced duration of mechanical ventilation
      - Shorter ICU length of stay
      - Fewer diagnostic studies for altered mental status (i.e. CT scan)
      - Lower daily doses of sedatives
      - Less post-traumatic stress disorder

d. Analgesia based sedation\textsuperscript{23}
   i. Sedation vs. no sedation
   ii. Receiving appropriate analgesia without the use of sedatives
   iii. Benefits:
      - Reduced duration of mechanical ventilation
      - Shorter ICU length of stay

e. Education of practitioners/nurses/pharmacists
   i. Therapeutic alternatives
      - Pros and cons
      - Changes in protocols and order sets
      - Concentration differences (programming pumps)
   ii. Monitoring
   iii. Potential ADRs
      - Differences in dosing
      - Programming pumps
      - Concentration differences
V. Drug Shortages Impact on Oncology

A. Epidemiology of cancer in the United States

1. Estimated that nearly 1.6 million people would be diagnosed with cancer in 2011
2. Males have a 21% risk of developing cancer before age 50
   a. Most common males: prostate cancer
3. Females have a 15% chance of developing cancer before age 70
   a. Most common in females: breast cancer

B. Oncology drug shortages

1. As of late 2011, nearly 80% of drug shortages were sterile injectable drugs
   a. Oncology drugs have been the most severely impacted class of medications, with 30% of the sterile injectable shortages in shortage being a chemotherapy agent

C. Causes of oncology drugs: multi-factorial

1. Cytarabine
   a. Bedford: equipment maintenance, manufacturing delays, concentrate on other products
   b. Hospira: crystallization of select lots
   c. APP: crystallization or precipitation of select vials
2. Leucovorin
   a. Bedford: manufacturing delays
   b. Teva: manufacturing delays
   c. APP: increased demand
3. Bleomycin
   a. Bedford: product discontinuation
   b. Hospira: increased demand
   c. Teva: manufacturing delays
   d. APP: increased demand
D. Patients affected by oncology drug shortages

1. Drug shortages may affect over half a million patients annually.
2. Estimates of patients treated annually with oncology drugs in shortage.

![Graph showing the number of patients affected by drug shortages](image)


E. Broad impact of an oncology drug shortage

1. One drug shortage impacts numerous disease states.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Methotrexate</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Bladder cancer</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Breast cancer</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td></td>
<td>Endometrial Cancer</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td></td>
<td>Hepatoblastoma</td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td></td>
<td>Acute lymphocytic leukemia</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td></td>
<td>Small cell lung cancer</td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td></td>
<td>Hodgkin lymphoma</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin's lymphoma</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>Squamous cell</td>
</tr>
<tr>
<td></td>
<td>Neuroblastoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
<td></td>
</tr>
</tbody>
</table>

F. Clinical implications of drug shortages in oncology:

1. Ethical dilemmas
   a. Rationing resources
   b. Treating based on prognosis
      i. Which patient do you treat?
         1. Early disease or advanced disease
         2. Pediatric or adult patient
         3. Research or non research patient
   2. Delay in treatment
      a. May be unavoidable due to lack of medication

Clinical Implications of Drug Shortages
i. Progression of untreated disease
ii. Worsened prognosis
   ▪ Advanced colorectal cancer:
     1. 14% decrease in overall survival with each 4 week delay in chemotherapy
   ▪ Breast cancer:
     1. 3-month delay in treatment may contribute to increased tumor size, advanced disease state, and poorer long-term prognosis

3. Increased Toxicities
   a. Colon cancer
      i. Colon cancer in the U.S. in 2011:
         ▪ Estimated 101,000 new cases
         ▪ Estimated 49,000 deaths
         ▪ Approximately 80 – 90% of patients will develop metastatic disease
         ▪ Treatment may include a combination of surgery, chemotherapy, and radiation
   ii. Treatment
      ▪ National Comprehensive Cancer Network (NCCN) Guidelines
         1. Common chemotherapy regimens
            a. FOLFOX:
               i. Oxaliplatin + 5-fluorouracil (5-FU) + leucovorin
            b. XELOX:
               i. Oxaliplatin + capecitabine (oral prodrug of 5-FU)
      iii. A potential approach to the shortage of leucovorin/5-FU:
         ▪ Capecitabine based regimen compared to a 5-FU/leucovorin based regimen:

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial design</strong></td>
<td>Randomized, two arm, open-label phase III, noninferiority study</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>Evaluative whether capecitabine plus oxaliplatin (XELOX) is noninferior to fluorouracil, folinic acid, and oxaliplatin (FOLFOX-6) as first line therapy for metastatic</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>N = 2,034</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>≥ 18 years</td>
</tr>
<tr>
<td></td>
<td>Pathologically confirmed colorectal cancer</td>
</tr>
<tr>
<td></td>
<td>Unresectable metastatic disease</td>
</tr>
<tr>
<td></td>
<td>Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1</td>
</tr>
<tr>
<td></td>
<td>No prior systemic treatment</td>
</tr>
<tr>
<td></td>
<td>Adequate hematologic/clotting, hepatic, and renal function</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Clinically significant cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Current and/or recent full dose anticoagulant or thrombolytic therapy</td>
</tr>
<tr>
<td></td>
<td>CNS metastases</td>
</tr>
<tr>
<td></td>
<td>Serious non healing wound or bone fracture</td>
</tr>
<tr>
<td></td>
<td>Bleeding diathesis or coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Proteinuria ≥ 500 mg/24hrs</td>
</tr>
<tr>
<td></td>
<td>Pregnancy or breast feeding</td>
</tr>
</tbody>
</table>
### Interventions

- **XELOX**
  - Oxaliplatin 130 mg/m² on day 1
  - Capecitabine 1,000 mg/m² twice daily x 2 weeks
  - 3 week cycles

- **FOLFOX-4**
  - Leucovorin 200 mg/m², days 1 & 2
  - Fluorouracil 400 mg/m² IV bolus and 600 mg/m² IV over 22 hrs, days 1 & 2
  - Oxaliplatin 85 mg/m², day 1
  - 2 week cycles

- Treatment was continued until disease progression (PD) or for 48 weeks (up to 16 cycles of XELOX or 24 cycles of FOLFOX-4)

### Endpoints

- **Primary end points:**
  - Progression-free survival (PFS)

- **Secondary end points:**
  - Overall survival (OS)
  - Overall response rate (ORR)
  - Duration of response
  - Time to treatment failure

### Statistical analyses

- The intent-to-treat (ITT) population included all randomized patients
- Eligible patient population (EPP) was the ITT minus patients who did not receive one dose of study drug or who had major protocol inclusion/exclusion violations
- 1,200 PFS events in the EPP population would provide 90% power with an α level of 0.25
- The EPP was used for the primary analysis of noninferiority
- A noninferiority test for PFS was conducted using a two-sided significance level of 2.5% and a noninferiority margin of 1.23 (noninferiority was concluded if the upper limit of 97.5% CI of HR was ≤ 1.23)
- PFS was stratified based on demographic and baseline characteristics using a Cox model
- A noninferiority test for ORR was conducted using a two-sided significance level of 2.5% and a noninferiority margin of 0.66 (noninferiority was concluded if the lower limit of 97.5% CI for the odds ratio was > 0.66)
- Treatment failure was analyzed using Cox models and presented as Kaplan-Meier estimates with a hazard ratio of 97.5%
- OS was assessed with logistic regression using a 97.5% CI
- Duration of response was presented as Kaplan-Meier estimates with 97.5% CIs.

### RESULTS

#### Patient Populations:

- ITT population = 2,034
- EPP population = 1,904
- Safety population = 1,304

#### Treatment and follow-up:

- The median dose intensities (ratio of dose received: dose planned) were ≥ 0.89 among all treatment arms
- The median follow-up period for PFS and OS were 17.7 months and 29.7 months, respectively

#### Baseline characteristics and demographics:

- Well balanced among treatment arms
- Median age was approximately 61 years old
- The majority of all patients had a primary tumor site in the colon with two sites of metastatic disease
- Approximately three-quarters of patients had not received prior adjuvant therapy

#### Primary Endpoint of PFS:

- XELOX 8.0 months vs FOLFOX-4 8.5 months (HR 1.05; 97.5% CI, 0.94 – 1.18)

#### Secondary end points:

- Overall survival (OS):
  - XELOX 19.8 months vs FOLFOX-4 19.6 months (HR 1.00 97.5% CI, 0.88 – 1.13)
- Overall response rate (ORR):
  - Investigator assessed 48% with FOLFOX-4 versus 47% with XELOX (HR 0.94; 97.5% CI 0.77 – 1.15)
Clinical Implications of Drug Shortages

### Independent review committee

- 37% with FOLFOX-4 versus 37% with XELOX (HR 1.00; 97.5% CI 0.81 – 1.23)

#### Duration of response:
- XELOX 7.6 months vs FOLFOX-4 7.5 months (HR 1.00; 97.5% CI, 0.85 – 1.18)

#### Time to treatment failure:
- XELOX 6.3 months vs FOLFOX-4 5.9 months (HR 1.08; 97.5% CI, 0.97 – 1.20)

### Safety Analysis

- FOLFOX-4 was associated with increased rates of grade 3/4 neutropenia/granulocytopenia (44% vs 7%), febrile neutropenia (4.8% vs 0.9%) while XELOX was associated with more grade 3/4 diarrhea (20% vs 11%) and hand-foot-syndrome (6% vs 1%)

- Adverse reaction grading:
  - Grade 1: Mild adverse event
  - Grade 2: Moderate adverse event
  - Grade 3: Severe adverse event
  - Grade 4: Life-Threatening adverse event
  - Grade 5: Death due to adverse event

- The most common reasons for treatment discontinuation were diarrhea and neurosensory toxicity

### Authors’ Conclusions

The authors concluded that XELOX (capecitabine based regimen) is noninferior to FOLFOX-4 (5-FU/leucovorin based regimen) as a first line treatment option for patients with metastatic colorectal cancer and may be considered as an appropriate treatment regimen for patients. The authors further specified that while the progression free survival appears to be similar for the treatment regimens, the toxicity profiles differ, with neutropenia occurring more frequently in FOLFOX-4 treated patients and diarrhea being more common with XELOX.

### Application

Variations of both XELOX and FOLFOX regimens are recommended by the NCCN guidelines for the treatment of metastatic colorectal cancer, with other clinical trials comparing capecitabine based regimens to 5-FU/leucovorin based regimens with similar survival and toxicity results (Rothenberg et al, Ducreux et al)\(^\text{36,37}\). While using a capecitabine containing regimen rather than a 5-FU/leucovorin regimen will not have a negative impact in terms of treatment outcomes, patients will likely experience increased toxicities in the form of grade 3 or 4 diarrhea and hand-foot-syndrome.

#### 4. Decreased Efficacy

  a. Hodgkin lymphoma (HL)\(^\text{24,35}\)
    i. Hodgkin lymphoma in the United States in 2011
      - Estimated 8,830 new cases and 1,300 deaths annually
      - Most patients are diagnosed between the ages of 15 and 30
      - Curable in at least 80% of patients
    ii. Hodgkin lymphoma classification
      - Lymphocyte-predominant HL: 5% of U.S. cases
      - Classical HL: 95% of U.S. Cases
        a. Nodular Sclerosis
        b. Mixed cellularity
        c. Lymphocyte depleted
        d. Lymphocytic rich
  b. Treatment
    i. NCCN HL treatment guidelines\(^\text{35}\)
      - Classical HL recommended treatment regimens
        1. ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine
          a. Standard of care option
        2. Stanford V: cyclophosphamide, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone
          a. Standard of care option
Clinical Implications of Drug Shortages

3. MOPP: mechlorethamine, vincristine, procarbazine, prednisone
4. BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

- A potential approach to the shortage of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD regimen):
  - MOPP compared to ABVD

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial design</strong></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
</tr>
</tbody>
</table>
| **Inclusion criteria** | • No prior treatment  
  • Stage IIIB, IIIA, IIIB disease |
| **Exclusion criteria** | • Prior chemotherapy or radiation treatment  
  • Stage I or stage IV disease |
| **Interventions** | • MOPP (N=114)  
  **MOPP cycles 1 - 3**  
  Absence of Tumor Progression  
  Radiation therapy  
  **MOPP cycles 4 - 6**  
  • ABVD (N=118)  
  **ABVD cycles 1 - 3**  
  Absence of Tumor Progression  
  Radiation therapy  
  **ABVD cycles 4 - 6** |
| **Evaluation of treatment response occurred at end of cycle six** |  
  • Complete remission (CR) = absence of all signs and symptoms of disease for a minimum of 1 month  
  • CR patients were followed every 3 months for 2 years and every 6 months thereafter  
  • Resistance to 1st line treatment was defined as failure to attain CR at the end of treatment OR relapse in the first 12 months following a CR at the end of treatment |
| **Endpoints** | 7-year results:  
  • Overall survival (OS)  
  • Freedom from progression (FFP)  
  • Relapse-free survival (RFS) |
| **Statistical analyses** | • Differences in the incidence of CR were determined using a Chi squared test  
  • Probabilities of FFP and RFS were reported as Kaplan Meier curves  
  • Survival analyses were conducted using a log rank test  
  • Differences in cardiac and pulmonary function tests were described in terms of the mean (±1SD) and Student's unpaired t test |
| **RESULTS** |  
  • Median age in both groups was 31 years  
  • More than half of patients in each treatment group were classified as having bulky disease (involvement of one or more lymphoid regions):  
    • 51.8% in the MOPP groups  
    • 57.6% in the ABVD group  
  • Presenting with symptoms (A = no systemic symptoms; B = temperature > 38°C, drenching night sweats, weight loss > 10% of body weight in previous 6 months)
Clinical Implications of Drug Shortages

- A symptoms in MOPP and ABVD: 26.6% and 28%, respectively
- B symptoms in MOPP and ABVD: 73.7% and 72%, respectively
- Median follow-up period was 7 years (84 months)
- Median doses administered in cycles 1 – 3 for both groups was > 80%
- Patients received subtotal nodal radiation or total nodal radiation therapy, depending on age/reproductive status and degree of myelosuppression:
  - Subtotal nodal radiation in MOPP and ABVD: 60.9% and 66.1%, respectively
  - Total nodal radiation in MOPP and ABVD: 39.1% and 33.9%, respectively
- Postirradiation chemotherapy modifications in cycles 4 – 6 (could not be completed, dose was administered at 50%, or delay in treatment due to prolonged bone marrow suppression):
  - MOPP: 59.8%
  - ABVD: 20.2%

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Complete Remission (CR)</th>
<th></th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MOPP (N = 114)</td>
<td>ABVD (N = 118)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>92 (80.7)</td>
<td>109 (92.4)</td>
<td></td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>Bulky Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45 (81.8)</td>
<td>49 (98)</td>
<td></td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Yes</td>
<td>47 (79.7)</td>
<td>60 (88.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>29 (96.7)</td>
<td>32 (97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>63 (75)</td>
<td>77 (90.6)</td>
<td></td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>Overall Survival (OS) at 7 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Deaths</td>
<td>34</td>
<td>22</td>
<td></td>
<td>---</td>
</tr>
<tr>
<td>Deaths due to progressive lymphoma</td>
<td>29 (25.4)</td>
<td>12 (10.2)</td>
<td></td>
<td>---</td>
</tr>
<tr>
<td>All cause total survival</td>
<td>67.9%</td>
<td>77.4%</td>
<td></td>
<td>---</td>
</tr>
<tr>
<td>Survival of patients dying from Hodgkin lymphoma</td>
<td>70.8%</td>
<td>88%</td>
<td></td>
<td>---</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Freedom from progression (FFP) and relapse-free survival (RFS) at 7 years</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>62.8%</td>
<td>80.8%</td>
<td>p &lt; 0.002</td>
</tr>
<tr>
<td>RFS</td>
<td>77.2%</td>
<td>87.7%</td>
<td>p = 0.06</td>
</tr>
</tbody>
</table>

### Safety

- Delayed treatment induced toxicities
  - Gonadal toxicity was analyzed after completion of combined therapy in 38 male patients (13 in MOPP group, 25 in ABVD group), all who were younger than 40 years of age and only received subtotal nodal irradiation:
    - Azoospermic in MOPP and ABVD: 100% and 36%, respectively
  - Prolonged amenorrhea (no menses for > 6 months) was evaluated in 44 females patients (20 in MOPP group, 24 in ABVD group), all who were younger than 40 years of age and only received subtotal nodal irradiation:
    - MOPP: Of 10 patients greater than the age 30 years of age, 5 were observed to have prolonged amenorrhea
    - None of the patients younger than 30 years of age in the MOPP or any of the 25 patients treated with ABVD showed evidence of prolonged amenorrhea
- Secondary neoplasms within the 7 years: MOPP: 2 patients developed acute non-lymphoblastic leukemia. Both
patients were males, older than 45 years of age, who received total nodal irradiation.
  o ABVD: 4 solid tumors were documented (one soft-tissue sarcoma, one colon cancer, and 2 lung cancer diagnoses, both in heavy smokers)

### Cardiac and Pulmonary Toxicity

- Cardiac and pulmonary function was evaluated in 50 patients, all who were in continuous CR for more than 5 years (24 in MOPP group, 26 in ABVD group)
- Left ventricular ejection fraction was 66.4\% ± 1.7 in MOPP patients versus 65.7\% ± 2.0 in ABVD patients
- Pulmonary fibrosis, identified by chest x-ray, was identified in 3 of 24 MOPP patients (12.5\%) and 12 of 26 ABVD patients (46.2\%)
- ABVD average cumulative dose
  o Bleomycin 107.3 mg/m²
  o Doxorubicin 244.8 mg/m²

### Authors’ Conclusions

Patient treated with ABVD “fared significantly better” in terms of overall survival, complete remission, free-from progression, and remission free survival. Additionally, only patients treated with MOPP showed evidence of irreversible gonadal dysfunction as well as secondary acute leukemia. “ABVD followed by wide-field radiotherapy is confirmed to represent a valid therapeutic alternative to MOPP plus radiotherapy, apparently devoid of sterility and leukomogenesis, and as given in the present study, not associated with cardiotoxicity.”

### Application

While this study is significantly older than what is generally thought of as being acceptable and clinically applicable, it is the landmark trial defining ABVD as the standard of care in Hodgkin lymphoma patients. Currently, ABVD may not be a therapeutic option for patients due to drug shortages. If the previous standard of care (MOPP) was available for treatment, a healthcare provider would expect increased toxicities as well as decreased outcomes.

5. **Eliminating a cure**
   a. Acute myeloid leukemia (AML)\(^{24,37}\)
      i. AML in the United States in 2011
         - Estimated 12,000 new cases and 9,000 deaths
      ii. Complete remission seen in 50 – 70\% of patients with recommended treatment
      iii. Treatment phases:
         - Induction
         - Consolidation
         - Salvage
      iv. NCCN AML treatment guidelines:\(^{37}\)
         - Cytarabine based chemotherapy regimen

#### Treatment Induction

- Cytarabine + anthracyline
  - Category 1 Recommendation

#### Consolidation

- High dose cytarabine + stem cell transplant
  - Category 2B Recommendation
  - Clinical trial

#### Salvage Chemotherapy

- Cladribine + cytarabine ± mitoxantrone or Idarubicin
- High dose cytarabine + anthracyline (if not received previously in treatment)
- Fludarabine + cytarabine ± idarubicin
- Mitoxantrone + etoposide + cytarabine (MEC)
6. Patient safety
   a. Increased risks of adverse drug events
      i. Examples:8
         ▪ 1 gm vial cytarabine reconstituted as a 500 mg vial
            1. Patient received twice the intended concentration
         ▪ Oral etoposide use in place of IV etoposide (IV to PO ratio – 1:2)
            1. Patient received 50% of indicated dose due to error
         ▪ Prediluted methotrexate unavailable
            1. Alternative vial reconstituted incorrectly, resulted in a lower dose administered to the patient
   b. The gray market in oncology
      i. The FDA warning to healthcare providers38:
         ▪ “unscrupulous individuals to introduce non-FDA approved products into the drug supply, which could result in serious harm to patients”
         ▪ Examples:
            1. Filgrastim (Neupogen)
            2. Rituximab (Rituxan)
            3. Trastuzumab (Herceptin)

7. Increased costs39
   a. Paclitaxel, example #1
      i. Paclitaxel average wholesale price (AWP): $0.89/mg
         ▪ Price per dose for a body surface area of 2 m²: paclitaxel 175 mg/m² x 2 = 350 mg x $0.89/mg = $311.50
      ii. Alternative drug: docetaxel average wholesale price (AWP): $23.46/mg
         ▪ Price per dose for a body surface area of 2 m²: docetaxel 75 mg/m² x 2 = 150 mg x $23.46/mg = $3519
      iii. Alternative drug: paclitaxel, protein bound average wholesale price (AWP): $11.20
         ▪ Price per dose for a body surface area of 2 m²: paclitaxel 260 mg/m² x 2 = 520 mg x $11.20/mg = $5824
   b. Leucovorin, example #2
      i. Leucovorin average wholesale price (AWP): $0.04/mg
         ▪ Price per dose for a body surface area of 2 m²: leucovorin 400 mg/m² x 2 = 800 mg x $0.04/mg = $32
      ii. Alternative drug: levoleucovorin average wholesale price (AWP): $3.21
         ▪ Price per dose for a body surface area of 2 m²: levoleucovorin 200 mg/m² x 2 = 400 mg x $3.21/mg = $1284
   c. Doxorubicin, example #3
      i. Doxorubicin average wholesale price (AWP): $1.00/mg
         ▪ Price per dose for a body surface area of 2 m²: doxorubicin 60 mg/m² x 2 = 120 mg x $1.00 = $120
      ii. Alternative drug: epirubicin average wholesale price (AWP): $6.40/mg
         ▪ Price per dose for a body surface area of 2 m²: epirubicin 75 mg/m² x 2 = 150 mg x $6.40 = $960

8. Impact on clinical research
   a. Potential impacts
      i. Protocol violations
      ii. Protocol amendments
      iii. Enrollment numbers
      iv. Standard of care integrity
   b. Coalition of Cancer Cooperative Groups40
      i. National nonprofit organization promoting and facilitating participation in cancer clinical trials
ii. Comprised of members from 10 National Cancer Institute (NCI) – sponsored Cooperative Groups (i.e. Eastern Cooperative Oncology Group, Southwestern Oncology Group)

iii. As of Fall 2011, there were approximately 400 active studies across the Cooperative Groups

  - Half of all studies had at least one drug on the shortage list

c. National Institutes of Health: clinicaltrials.gov\textsuperscript{41,42}

i. National registry for clinical trials

  - Continual protocol amendments due to drug shortages

ii. Examples of number of clinical trials affected

<table>
<thead>
<tr>
<th>Drug in Shortage</th>
<th>Approximate # of Clinical Trials Currently Open in the U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>271</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>126</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>196</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>83</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>267</td>
</tr>
<tr>
<td>Vincristine</td>
<td>193</td>
</tr>
</tbody>
</table>

d. Possible protocol changes

i. NCCN guidelines for management of leucovorin shortage in colon cancer\textsuperscript{31}

  - Use levo-leucovorin:
    1. $200 \text{ mg/m}^2 \text{ levo-leucovorin} = 300 \text{ mg/m}^2 \text{ leucovorin}$

  - Omit from regimen

  - Use lower doses for all patients

  1. Based on clinical data, lower doses are likely to be as effective as higher doses (Appendix B)
VI. Current Recommendations and Approaches

A. National approach:

1. President Obama\textsuperscript{46}
   a. Executive Order 13588 - Reducing Prescription Drug Shortages
      i. On October 31, 2011, President Obama signed an executive order granting the FDA the authority to take actions that will mitigate and prevent current and future drug shortages of lifesaving medications through the following:
   b. Broader Reporting of Manufacturing Discontinuances
      i. The FDA shall use all appropriate administrative tools and authority to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life supporting, life-sustaining, or that prevent debilitating disease.
   c. Expedited Regulatory Review
      i. The FDA may take the steps necessary to expand or expedite its process of regulatory reviews of new drug suppliers, manufacturing sites, and manufacturing changes. The FDA may enact this authority whenever it determines these steps would help avoid or mitigate existing or potential drug shortages. Additionally, in allocating and prioritizing resources and responsibilities, the FDA will take into consideration the severity of the shortage and the medications role and importance on public health.
   d. Review of Certain Behaviors by Market Participants
      i. The FDA will work and communicate with the Department of Justice regarding any findings of shortages that have lead to stockpiling or excessive pricing of the affected drug. The Department of Justice will determine whether these activities have violated the applicable law, and if found, will work in coordination with state and federal regulatory agencies to enforce the law as necessary.
      ii. As appropriate, and in coordination with State and Federal regulatory agencies, enforce whatever actions, if any, it finds necessary.

2. FDA\textsuperscript{25,47}
   a. Actions To Prevent Drug Shortages
      i. Expediting review of new manufacturing sites, new suppliers, and specification changes
      ii. Exercising regulatory flexibility and discretion
      iii. Encouraging other manufacturers to assist or take on production in effort to alleviate the shortage burden and prevent single source manufacturing
   b. Actions in Response to Drug Shortages
      i. Encouraging increased production from other manufacturers
      ii. Working with manufacturers to ensure cGMP compliance and improve production integrity
      iii. Expediting review of regulatory submissions
      iv. Exercising regulatory discretion in approval of controlled importation of foreign products not currently FDA approved
   c. Based on Executive Order 13588, the FDA issued an interim rule, effective January 18, 2012, to expand requirement of a six-month advance notice to the FDA of drug discontinuation to include interruptions in manufacturing. Prior to this, companies only required notification of the FDA six months in advance for discontinuations of sole source, medically necessary drugs.

3. Pending Legislation\textsuperscript{48-49}
   a. Be informed of and play an active role in political initiatives effecting drug shortages
      i. Senate bill S.296 “The Preserving Access to Life-Saving Medications Act”
ii. House of Representatives bill H.R.2245 “Preserving Access to Life-Saving Medications Act”

b. Summary of House and Senate Bills
i. Amendment to the Federal Food, Drug, and Cosmetic Act
   ▪ Increased FDA notification requirements for discontinuations or disruptions in production of all medications
   ▪ Establishes penalties for violations of notification requirements
   ▪ Improves distribution of information regarding discontinuations or disruptions for healthcare providers through the FDA’s website
   ▪ Improves collaboration between manufacturers and the FDA to improve continuity of supply

B. Manufacturer approach
1. Financial incentives
   a. Increase reimbursement
   b. Federal subsidizing
   c. Tax credits
   d. Longer exclusivity
2. Working with FDA
   a. Timely reporting of shortages
   b. Develop prevention strategies

C. Professional approach
1. Future research
   a. Clinical trials
      i. Comparing alternative therapeutic strategies
      ii. Identifying compelling indications
   b. Case reports/series
      i. Gain knowledge from other health-systems/practices
   c. Guidelines
      i. Incorporate second and third line therapeutic alternatives consistently
      ii. Approach to rationing resources
         ▪ Identify patient populations in most need or where therapeutic alternatives are not available

D. Local Institution Approach
1. ASHP recommendations
   a. ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health-Systems
2. Adapted recommendations
   a. Preparation phase
      i. Develop a drug shortage task force
         ▪ Composed of representatives from
            1. Physicians
               a. Delegated representatives
            2. Pharmacy
               a. Directors/Clinical coordinators
               b. Clinical/staff pharmacists
               c. Medication safety
               d. Purchasing
            3. Nursing
               a. Chief nursing officer
                  i. Other delegated representatives
         ▪ Preemptive responsibilities
            1. Develop drug shortage policy
            2. Guidelines for non-traditional suppliers
            3. Identify appropriate personnel for handling drug shortages
4. Plan and budget for resource and personnel allocation during shortage

b. Assessment phase

i. Phase 1 (collecting information for drug shortage task force)

   ▪ Pharmacy
      1. Purchaser
         a. Determine duration and specifics of shortage
         b. Attempt to ensure adequate supply without stockpiling
         c. Determine supply of therapeutic alternatives
      2. Directors/Clinical coordinators (delegate as appropriate)
         a. Conduct inventory assessment
         b. Estimate time to impact on health-system
         c. Determine inventory of therapeutic alternatives
         d. Establish a relationship with other-health-systems
         e. Allocation of resources and personnel
      3. Clinical/staff pharmacists
         a. Review clinically significant trials that established the standard(s) of care
         b. Identify potential therapeutic alternatives from comparators used in these trials
         c. Determine expected impact on patient care
            i. Adverse reactions
            ii. Therapeutic outcomes
         d. Estimate changes in the distribution and preparation of drugs in shortage or alternatives
         e. Determine necessary information system updates

   ii. Phase 2 (Assembly of task force)

      ▪ Drug shortage task force
         1. Determine plan for patient care
            a. Therapeutic differences
            b. Prescribing processes
            c. Distribution processes
            d. Budgetary considerations
            e. Risk assessment
         2. Dissemination
            a. Drug shortage action plan
               i. Products affected
               ii. Reason for shortage
               iii. Expected resolution time (if available)
               iv. Inventory on hand
               v. Recommended management
               vi. Alternative therapeutics
               vii. Date action plan effective/next communication
            b. Physicians
               i. Prescribing changes
               ii. Therapeutic alternatives
            c. Pharmacy
               i. Impact of drug shortages
               ii. Therapeutic alternatives
               iii. Changes in processes
            d. Nursing
               i. Changes in nursing processes/protocols
               ii. Educate on potential new ADRs
               iii. Explain differences in expectations to patients

Clinical Implications of Drug Shortages 34
c. Contingency phase
   i. Risk management and liability
      - Education of patients and family members when a drug product shortage will delay or compromise care, especially if they have been receiving the drug product
      - Potential litigation from patients who felt they may have received inadequate care or suffered from adverse events as a result of delays, prioritization, alternative therapies, or nontraditional drug products
      - Risk management and legal representatives should be in communication when all other options fail to provide adequate treatment secondary to drug shortages
   ii. Prioritization
      - Particularly necessary with long-term shortages
      - National organizations (CDC, medical organizations, etc.) may provide guidance on rationing resources
        1. For example influenza vaccine shortage of 2004-05
      - Using drug use evaluations on prescribing data and utilization trends to develop local prioritization criteria
        1. Developed by a multidisciplinary team
    d. Resolution phase
       i. Drug shortage resolved
       ii. Communication of resolution to staff
          - Physicians
          - Pharmacy
          - Nursing
       iii. Reflection
          - What was learned through the process and changes for future shortages
          - Documentation of how drug shortage handled
            1. Therefore already have an outlined plan to implement in the event of a future shortage

VII. Conclusion
   A. The increasing number of drug shortages have created a potential crisis for patients in need of adequate health care
   B. Nationally the federal government and the FDA are working to alleviate and prevent drug shortages, however the number continues to grow
   C. As pharmacists we need to preemptively develop strategies to ensure optimal patient care is provided with the resources available
References:

10. Sessler CN and Varney K. Patient-focused sedation and analgesia in the ICU. Chest 2008;133:552-565
43. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folic acid, or both, as adjuvant chemotherapy for colorectal cancer: randomized trial. Lancet 200;355:1588 – 1596.

Clinical Implications of Drug Shortages
### Appendix A\textsuperscript{10,11}

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Awake</td>
<td>Patient anxious and agitated or restless or both</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Patient cooperative, oriented and tranquil</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Patient responds to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Asleep</td>
<td>A brisk response to a light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>A sluggish response to a light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>No response to a light glabellar tap or loud auditory stimulus</td>
</tr>
</tbody>
</table>

**Richmond Agitation Sedation Scale (RASS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious but movements not aggressive vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Not fully alert, but has sustained awakening (eye-opening/eye contact) to <em>voice</em> (&gt;10 seconds)</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Briefly awakens with eye contact to <em>voice</em> (&lt;10 seconds)</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Movement or eye opening to <em>voice</em> (but no eye contact)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>No response to voice, but movement or eye opening to <em>physical</em> stimulation</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice or <em>physical</em> stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Un-arousable</td>
<td>No response to <em>voice or physical</em> stimulation</td>
</tr>
<tr>
<td>Study</td>
<td>Patient Population</td>
<td>Intervention</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
| A prospective, randomized double blind trial conducted by the QUASAR Collaborative Group (2000) | - Colorectal cancer  
- Adjuvant therapy following complete resection  
- Absence of metastases  
- N = 4927 | 1. High dose folinic acid* + 5-FU  
(high dose = 175 mg IV)  
2. Low dose folinic acid* + 5-FU  
(low dose = 25 mg IV)  
- All patients received 30 IV doses of 5-FU dosed at 370 mg/m².  
- Treatments were given at the same fixed doses for 6 months  
- Treatment course: either six 5-days courses with 4-week intervals or once weekly for 30 weeks  
*Folinic acid = leucovorin | 3-year survival:  
- High dose: 70.1%  
- Low dose: 70%  
- OR 1.04 (95% CI 0.94 – 1.15, p = 0.43)  
Recurrence rate:  
- High dose: 36%  
- Low dose: 35.8%  
- OR 1.00 (95% CI 0.91 – 1.09, p = 0.94)  
- When stratified for site of cancer, stage, gender, age, and chemotherapy schedule, the results did not differ significantly |
| Prospective, randomized trial by Jager and colleagues (1996) | - Metastatic colorectal cancer  
- Unresectable disease  
- No chemotherapy or radiation in the previous 8 weeks  
- N = 291 | 1. High dose LV + 5-FU  
(high dose = 500mg/m² IV)  
2. Low dose LV + 5-FU  
(low dose = 20mg/m² IV)  
- 5-FU was administered as a 500 mg/m² weekly bolus  
- LV was administered as a 2-hour infusion one hour prior to 5-FU  
- Patients were treated until tumor progression | Complete or partial response:  
- High dose: 21.6%  
- Low dose: 17.5%  
(Confidence interval not reported)  
Median duration of response:  
- High dose: 24.8 weeks (95% CI: 20 – 30)  
- Low dose: 23.1 weeks (95% CI: 17 – 27.1)  
Median survival time:  
- High dose: 55.1 weeks (95% CI: 41.2 – 72.4)  
- Low dose: 54.1 weeks (95% CI: 46.4 – 65.5) |
| Prospective, randomized controlled trial by O'Connell and colleagues 1989 | - Metastatic colorectal cancer  
- Unresectable disease  
- No chemotherapy, radiation, or surgery in the previous 8 weeks  
- N = 208 | 1. 5-FU alone  
- 500 mg/m² IV daily for 5 days, cycles repeated every 5 weeks  
2. High dose LV + 5-FU  
- 5-FU 370 mg/m² IV following LV dose daily for 5 days, cycles repeated every 4 weeks, 8 weeks, and every 5 weeks thereafter  
(High dose = 200mg/m²)  
3. Low dose LV + 5-FU  
- 5-FU 370 mg/m² IV following LV dose daily for 5 days, cycles repeated every 4 weeks, 8 weeks, and every 5 weeks thereafter  
(low dose = 20 mg/m²) | Survival  
- 74% of all patients had died at the time of analysis (median follow-up was 11 months)  
- Both LV arms had significantly better survival outcomes (Kaplan-Meier Curve; p ≤ 0.03)  
Tumor Response Rates:  
- 5-FU alone: 10%  
- High dose: 26% (p = 0.04)  
- Low dose: 43% (p = 0.001)  
(Both p-values are relative to 5-FU monotherapy) |
Appendix C

Drug Shortage Communication and Action Plan: IV Ondansetron (Zofran)

Products affected:
- Ondansetron injectable (all presentations, 2-mL and 20-mL 2mg/mL vials and 32 mg/50 mL premixed bags)

Reason for shortage:
- Multiple manufacturers have discontinued or temporarily discontinued their ondansetron injection.
- Remaining manufacturers cannot keep up with demand and have their products on back order.

Expected resolution time:
- Anticipated release date of late February 2012. Pfizer estimates a release date of late March.
- APP and GlaxoSmithKline are releasing 20 mL vials intermittently.
- Baxter has the 32 mg/50 mL premixed bags available.

Inventory on hand:
- CRITICAL LOW – IMMEDIATE ACTION REQUIRED
- Network supply of the 2-mL vials is estimated to be three (3) days based on past utilization.
- There is limited availability of alternative therapies due to critical shortages. Below is an approximation of SFH inventory on hand and national availability:
  - Metoclopramide 10 mg/2 mL injection: >2 week supply; not available
  - Prochlorperazine 10 mg/2 mL injection: <1 week supply; reserve for CINV; not available
  - Promethazine 25 mg/mL injection: >1 week supply limited quantities available
  - Trimethobenzamide 200 mg injection: none on hand; not available
  - Ondansetron oral disintegrating tab (ODT) 4 mg: >1 week supply; on allocation by manufacturer
  - Ondansetron ODT 8 mg: >1 week supply; available

Recommended management:
- Reserve IV formulation for anesthesiology (high-risk PONV) and hematology/oncology, but ondansetron oral disintegrating tablet (ODT) should be considered whenever clinically appropriate.
- Pharmacy will draw up doses for CINV management using the 20 mL multi-dose vials.
- For all other ondansetron injection orders, ondansetron ODT and/or alternative antiemetic therapy should be considered whenever clinically appropriate.
- If ondansetron injection is warranted, doses ordered more frequently than q12-24 hrs will not be accepted. Pharmacy will automatically optimize the frequency to every 12 hours. The prescriber should consider adding other antiemetic therapy to the regimen.

Other available alternatives (limited quantities):

1. Promethazine (Phenergan)
   - 6.25 – 12.5 mg IV every 4-6 hr
   - 12.5 – 25 mg PO/PR every 4-6 hr

2. Prochlorperazine (Compazine):
   - 5 – 10 mg PO 3 or 4 times per day
   - 25 mg PR twice daily

3. Ondansetron ODT (Zofran ODT)
   - 4 – 8 mg PO every 12-24 hr

Date action plan effective: January 30, 2012
Next communication: February 7, 2012