#FSHP2018

New Uses of Old Medications

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Break Through Branch Out

Disclosure

- I do not have anything to disclose

Break Through #FSHP2018 Branch Out

Objectives

- Describe the use of ketamine as a sedative
- Discuss the role of phenobarbital for alcohol withdrawal
- Evaluate the use of valproic acid for sedation in the critically ill population
- Discuss the use of enteral clonidine in the critically ill population

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Goals for sedation during mechanical ventilation

- Greater interest toward an analgosedation approach for sedation in the ICU
- Analgosedation: emphasis is placed on relieving pain and discomfort prior to instituting sedative–hypnotic agents that do not have analgesic properties
- Traditionally achieved with opioid analgesics that have sedative properties, but the intended focus is on analgesia

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Sedation Options

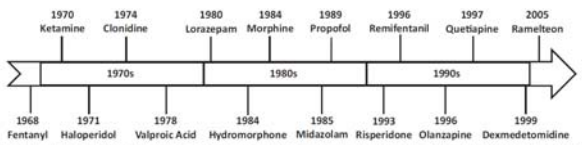

Figure 1. Food and Drug Administration "sedative" approval timeline for selected agents. From 1970–2000, the Food and Drug Administration approved four to five agents per decade that have been used for comfort in adult ICU patients. Most of these agents are used off label, except for midazolam, propofol, remifentanil (continuation as an analgesic into the immediate postoperative period), and dexmedetomidine. Year of injectable formulation approval was used except for clonidine, valproic acid, and second-generation antipsychotics.

Pharmacotherapy. 2017. 37:1309-1321.

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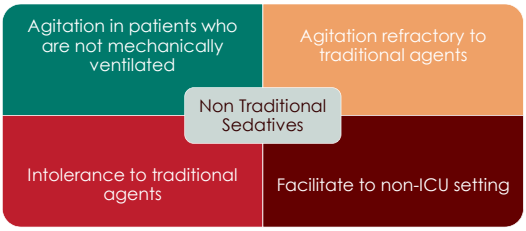
Non Traditional Sedatives



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Ketamine Infusion as a Sedation Adjunct

- Rapidly acting dissociative anesthetic agent with analgesic properties
- **Mechanism of action:**
  - Primarily through noncompetitive antagonism at N-methyl-D-aspartate receptor (NMDA)
  - Minor effects via opioid receptor blockade, gamma-aminobutyric acid (GABA) inhibition, central nervous system anticholinergic pathways

Ketamine Infusion as a Sedation Adjunct

- **Differences compared to other sedatives**
  - Unlike other sedative ketamine does not reduce blood pressure or impair gastrointestinal motility
  - Favorable pulmonary effects
    - Bronchodilation with improved dynamic compliance
    - Preservation of respiratory drive

Ketamine Infusion as a Sedation Adjunct

Positive Differences	Negative Differences
• Minimal effect on respirations • Minimal effect on bowel motility • May increase blood pressure	• Psychomimetic adverse effects • ICP manipulations

SCCM Pain, Agitation and Delirium Guidelines

- **Ketamine**
  - Attenuates the development of acute tolerance to opioids. May cause hallucinations and other psychological disturbances
  - **Dosing Recommendations**
    - **Loading dose:** 0.1–0.5 mg/kg IV
    - **Maintenance dose:** 0.05– 0.4 mg/kg/hour IV
  - No studies have compared clinical outcomes in ICU patients sedated with either ketamine or other sedative agents

Ketamine Infusion as a Sedation Adjunct

Title	Ketamine Infusion for Adjunct Sedation in Mechanically Ventilated Adults
Objective	Description of experience using continuous infusion ketamine for adjunct sedation in adult mechanically ventilated patients
Study Design	Retrospective Review
Outcomes	Dosing and patient population Effectiveness: SAS goals within range 24 hours before/hours
Population	146 patients at a tertiary academic medical center
Results	**Dosing range**: 0.04-2.5 mg/kg/hour IV continuous infusion **Effectiveness**: Alternative sedatives reduced or discontinued without the addition of another agent in 63% patients

Pharmacotherapy. 2018. 38(2):181-188.

Ketamine: Place in Practice

- Adjunct agent when other sedatives have been maximized/failed
  - Extracorporeal membrane oxygenation
  - Status epilepticus
  - Bridge to wean from long term continuous infusion benzodiazepine

Phenobarbital for Alcohol Withdrawal Syndrome (AWS)

Chronic alcohol exposure

- Long term ethanol exposure results in changes to the neurotransmitters
  - Gamma-aninobutyric acid (GABA) receptors
  - Glutamate receptors
    - *N*-methyl-D-aspartate (NMDA) receptor
  - Noradrenergic activity

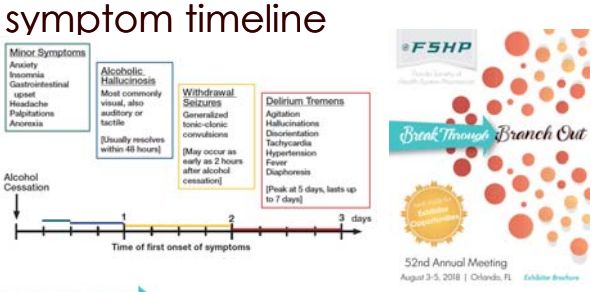
Benzodiazepines (BZD) for alcohol withdrawal

- Currently the mainstay of treatment
- Work on the GABA pathway
  - Pathophysiology of complicated alcohol withdrawal involves dysfunction of multiple neurotransmitters
  - Particularly receptors involved in glutamate activity
  - Benzodiazepines do not directly affect those pathways
- Some patients with severe AWS may not respond to high doses of BZD as they develop tolerance to GABA receptor desensitization

Benzodiazepines (BZD) failure for alcohol withdrawal

- Note well defined in the literature
- Benzodiazepine refractory withdrawal symptoms may be described as uncontrolled agitation despite the need for > 40mg lorazepam in the first 3-4 hour
- Patients are more likely to require continuous infusion BZD
  - May result in longer duration of mechanical ventilation and ICU stay

Alcohol withdrawal symptom timeline



Benefits of phenobarbital for AWS

Benefits of phenobarbital for AWS

- Mechanism of action in not completely understood
- Efficacy may be to facilitate GABA inhibitory neurotransmission
- Decreases glutamate activity

Phenobarbital for alcohol withdrawal

Title	Barbiturates for the treatment of alcohol withdrawal syndrome: A systematic review of clinical trials
Study Design	7 studies evaluating the use of barbituates versus BZD included
Summary	• Little high quality evidence • None of the studies demonstrated inferiority of barbituates to BZD • Overall safety profiles of barbituates was comparable to BZD
Trends	• Barbituates tend to confer a greater benefit to patients with severe forms of alcohol withdrawal • Phenobarbital may be an option in AWS that has failed BZD • Barbituates seem to be well tolerated in most patients

J Crit Care. 2016. 32: 101-107.

Patient selection for Phenobarbital

- Persistent CIWA score >15
- Failing benzodiazepine treatment
  - Objective withdrawal signs despite adequate treatment based on CIWA score
- History of refractory treatment to benzodiazepines

Phenobarbital Dosing

- IM Loading Dose ~10-12 mg/kg

Total Dose divided on Day 1
Dose 1: 40% of total dose administered IM x 1
Dose 2: 30% of total dose administered IM x 1 3 hours after dose 1
Dose 2: 30% of total dose administered IM x 1 3 hours after dose 2

Phenobarbital Dosing

- Dose reduction for patients that are at risk for sedation or respiratory compromise
- Phenobarbital loading dose 6-8mg/kg IM

Risk of Sedation	Respiratory Compromise
> 65 years old	Pneomonia
Hepatic dysfunction	Rib fractures
Recent administration of medications that decrease respiratory drive	Chest tube(s)
Head injury	Pulmonary contusion

Phenobarbital Dosing

- PO Maintenance Dose
  - Fixed dose regimens vary in literature
- Breakthrough dosing
  - As needed for substantial withdrawal symptoms
    - HR >120 bpm
    - SBP >150 mmHg
    - Marked agitation

Phenobarbital: Clinical Pearls

- IM is the preferred administration route for loading doses
  - IV administration is associated with increased respiratory depression
  - IV may be administered if needed at a lower dose
- Enteral administration leads to relatively rapid and near complete absorption
- Serum level monitoring is recommended

Phenobarbital

- **Drug-drug interactions**
  - Strong inducer of CYP3A and CYP2C enzyme system
    - Midazolam and fentanyl
    - Warfarin and phenytoin
    - Valproic acid

Phenobarbital

- **Adverse drug effects**
  - Very well tolerated
  - Low incidence
  - Should not be administered to patients at risk for respiratory depression

Valproic Acid for Sedation in Critically Ill Patients

Valproic acid

- Antiepileptic and mood stabilizer
- **Mechanism of action:**
  - Not well understood
  - Blocks voltage-dependent sodium and calcium channels
  - Increases GABA synthesis
  - Potentiates GABA activity at postsynaptic receptors
  - Attenuates the activity of glutamate upon NMDA

Valproic acid

- **Pharmacokinetics/pharmacodynamics:**
  - Small volume of distribution
  - Rapidly enters the central nervous system
  - Undergoes extensive hepatic metabolism
  - Highly protein bound to albumin
  - Half-life ~15 hours

Valproic acid

- **Proposed advantages for ICU sedation**
  - Allows patients to interact with their caregivers
  - Can be administered outside the ICU
  - IV and enteric formulations
  - Low drug cost acquisition
  - Has NOT been associated with respiratory depression, hemodynamic derangements or delirium

Valproic Acid for Sedation in Critically Ill Patients

Title	Valproate for agitation in critically ill patients: A retrospective study
Objective	Evaluate critically ill adults that received valproate for agitaion
Study Design	Retrospective cohort study
Protocol	Dosing led by prescriber, patients received IV and PO dosing
Population	53 adult ICU patients with unspecified agitation
Primary Outcome	Significant reduction in agitation, delirium, opioids and dexmedetomidine on day 3 of therapy Average maintenance dose: 1500mg/day

J Crit Care. 2017. 37:119-125.

Valproic Acid

- **Practical considerations**
  - Most patients studied had both agitation and delirium
  - Impact on agitation most likely resulted from its GABA activity
  - Valproate does not provide analgesia
  - Adverse effects
    - Hepatoxicity
    - Pancreatitis
    - Thrombocytopenia
    - Hyperammonemia

Valproic Acid

- **Starting dose**
  - Varied doses studied
  - Usual dose 1g BID
- **Treatment duration**
  - Treatment goals
  - Concomitant medications
- **Dosing considerations**
  - Enteral formulations may be used
  - Dosing conversion from IV to PO is 1:1

Valproic Acid

- **Monitoring serum levels**
  - Benefits of evaluating valproate serum concentrations
  - Goal levels not established
  - Titrate doses based on response
  - Monitor for toxicity
- **Drug-drug interactions**
  - Carbapenems

Enteral Clonidine for Sedation in Critically Ill Patients

Goals for sedation during mechanical ventilation

- Benzodiazepines may increase the risk of ICU delirium
- The incidence of delirium is less in patients that receive dexmedetomidine for light sedation compared to benzodiazepines
  - Dexmedetomidine is not widely available due to cost
  - Dose limiting adverse effects

Goals for sedation during mechanical ventilation

- Enteral clonidine may be an alternative to dexmedetomidine as an adjunct for sedation in critically ill patients
  - Evidence supporting the use of enteral clonidine in critically ill patients is limited
  - The 2013 PAD guidelines make no recommendation on the use of enteral clonidine

Clonidine: Place in Therapy

- **Mechanism of action**
  - a-2 adrenoreceptor agonist
  - Reduces sympathetic outflow from the central nervous system

Clonidine: Place in Therapy

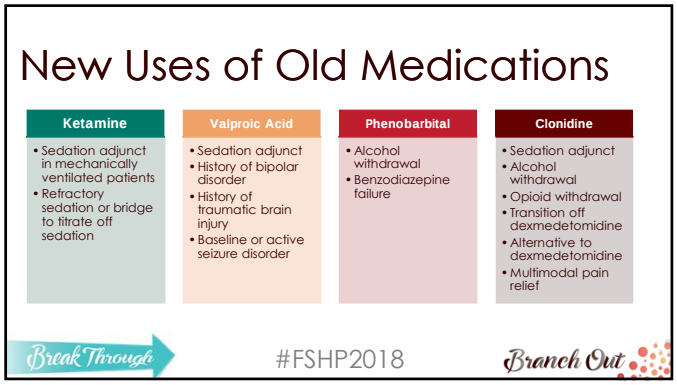
- **Practical considerations**
  - Avoid in patients with hemodynamic stability
    - Need for vasoactive support
    - Bradycardia
  - Clonidine withdrawal or discontinuation syndrome may be a complication
    - Rebound symptoms

Clonidine: Place in Therapy

- **Dosing considerations**
  - Clonidine PO 0.1mg-0.3mg Q6-Q8H
  - Lower starting doses may be appropriate for select patients
    - < 100kg
    - > 70 years of age
    - Patients sedated at doses less than 0.7 mcg/kg/hr dexmedetomidine

Clonidine: Place in Therapy

- Sedation adjunct
- Alcohol withdrawal
- Opioid withdrawal
- Transition off dexmedetomidine
- Alternative to dexmedetomidine
- Multimodal pain relief


New Uses of Old Medications
Ketamine
• Sedation adjunct in mechanically ventilated patients
• Refractory sedation or bridge to titrate off sedation
Valproic Acid
• Sedation adjunct
• History of bipolar disorder
• History of traumatic brain injury
• Baseline or active seizure disorder
Phenobarbital
• Alcohol withdrawal
• Benzodiazepine failure
Clonidine
• Sedation adjunct
• Alcohol withdrawal
• Opioid withdrawal
• Transition off dexmedetomidine
• Alternative to dexmedetomidine
• Multimodal pain relief
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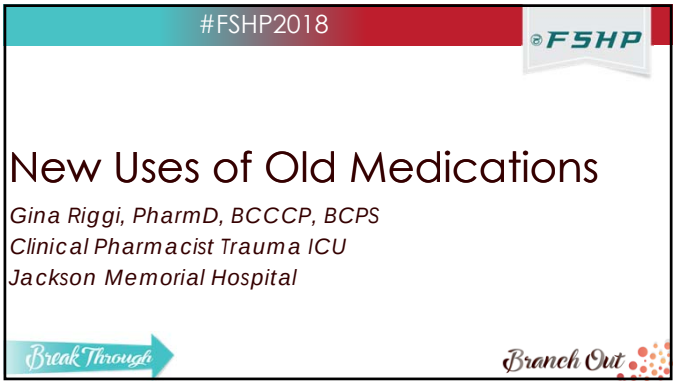
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