Clonidine as a Strategy for Discontinuing Long-term Sedation with Dexmedetomidine in Critically Ill Patients

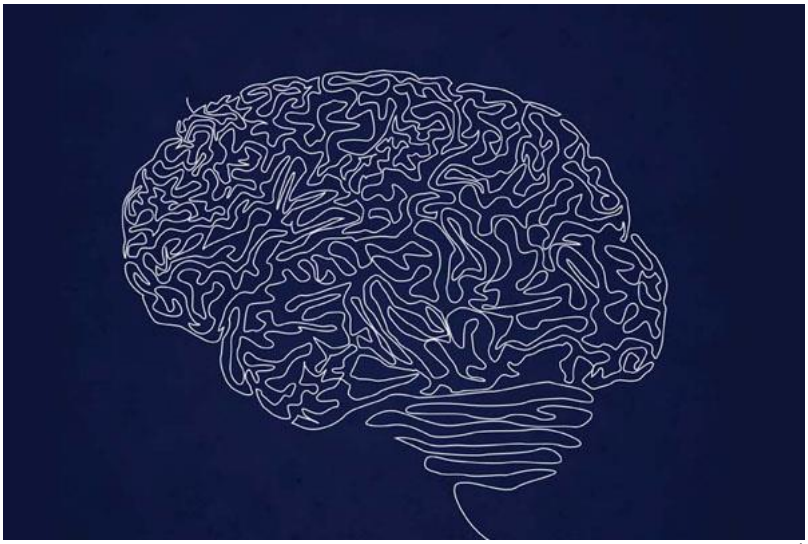

Illustration from *Vanderbilt Medicine Magazine*, Summer 2015[1]

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October 14, 2016

Learning Objectives:

1. Describe the mechanism for dexmedetomidine withdrawal syndrome.
2. Identify an appropriate candidate for transitioning from dexmedetomidine to clonidine.
3. Select an appropriate clonidine regimen for sedation.

I. Incidence and Risk Factors[2]
   a. Agitation and anxiety occur frequently in critically ill patients
      i. ≤52% occurrence seen with and without mechanical ventilation (MV)
   b. Independent risk factors for the development of agitation include
      i. Sepsis or presence of fever
      ii. Alcohol abuse or psychoactive medications prior to admission
      iii. Hypo- or hypernatremia

II. Outcomes Associated with Agitation[2]
   a. Increased intensive care unit (ICU) length of stay (LOS)
   b. Increased rate of nosocomial infections
   c. Need for surgical re-intervention
   d. Device removal (e.g., catheters and mechanical ventilator tubing – "self extubation")
      i. Annual ICU cost associated with device removal >$250,000[3]

III. Sedation Goals[4]
   a. Provide physical and mental comfort and decrease anxiety
   b. Assist with synchrony with mechanical ventilation
   c. Decrease risk of harm to patient and others
   d. Maintain appropriate sedation level for patient-specific goals

IV. Targeting an Appropriate Sedation Level[4]
   a. Light sedation level associated with improved outcomes
      i. ↓ MV duration, overall LOS, and incidence of delirium
      ii. Recommended for most critically ill patients
      iii. Deep sedation when clinically indicated (e.g., status epilepticus, concurrent paralytic, etc.)
   b. Utilization of validated sedation scales to minimize sedative use[4,5]
      i. Sedation-Agitation Scale (SAS)[6]
      ii. Richmond Agitation-Sedation Scale (RASS)[7]
   c. Perform daily spontaneous awakening trials (SAT) to assess level of sedation

V. Selection of Sedative[4]
   a. No preferred sedative agent
   b. Selection based on:
      i. Patient specific indication and goals
      ii. Drug pharmacology
      iii. Associated cost of sedative
   c. Non-benzodiazepine regimens "may be preferred" in MV patients
      i. Benzodiazepine (BZD) based sedation associated with ↑MV duration and risk of delirium

Table A. Comparison of Sedative Agents[4,8]				
	Mechanism	Active Metabolites	$t_{1/2}$	Adverse Effects
Diazepam (Valium®)	$GABA_A$[a] agonist	Yes	20-120 h	Respiratory depression, hypotension
Lorazepam (Ativan®)	$GABA_A$ agonist	No	15-20 min	Respiratory depression, hypotension, propylene glycol-related toxicity
Midazolam (Versed®)	$GABA_A$ agonist	Yes	3-11 h	Respiratory depression, hypotension
Propofol (Diprivan®)	$GABA_A$, glycine, nicotinic, and M1[b] agonist	No	3-12 h → 50 h	Respiratory depression, hypotension, hypertriglyceridemia, propofol-related infusion syndrome
Dexmedetomidine (Precedex®)	α_2 agonist	No	1.8-3.1 h	Bradycardia, hypotension
Ketamine (Ketalar®)	NMDA[c], opioid antagonist; ↑adrenergic tone	Yes	5-17 min → 300 min	Hypertension, tachycardia, CNS excitation, psychotomimetic effects (hallucinations, psychosis)

a. Gamma-aminobutyric acid receptor
b. Muscarinic acetylcholine receptor
c. *N*-methyl-D-aspartate receptor

Sedation with Alpha-2 Agonists

I. Dexmedetomidine (Precedex®)[9]
   a. Indicated for short-term sedation of non-intubated patients peri-procedurally (≤24 hours)
   b. Shown to be safe and effective for long-term sedation ≤30 days[10]
   c. Advantages
      i. Provide sedation and sympatholysis
      ii. Analgesic-sparing effects
      iii. No effect on respiratory depression
      iv. Similar pharmacokinetic and pharmacodynamic predictability shown with weight based dosing in pediatric patients[11,12]
   d. Biphasic Adverse Effect Profile[9]
      i. Initial transient hypertension associated with loading dose (LD)
      ii. Bradycardia and hypotension associated with continuous infusion (post LD)
         a. Initial reports in adult ICU sedation patients of bradycardia ~5% and hypotension ~25%

Table B. Rates of Adverse Events with Dexmedetomidine (DEX) in Critically Ill Patients[13–15]

Study	Population[a]	DEX Reported Adverse Events[b], no. (%)
Pandharipande, et al. (2007)	• MICU patients ≥18 years with MV >24h • DEX vs. lorazepam sedation titrated to goal RASS (physician dependent)	• Bradycardia: 9/52 (17%) • Hypotension: 13/52 (25%)
Riker, et al. (2009)	• MICU patients ≥18 years with MV >72h • DEX vs. midazolam sedation titrated to goal RASS (-2 to +1)	• Bradycardia: 103/244 (42.2%) • Hypotension: 137/244 (56.1%)
Jakob, et al. (2012)	• MICU patients ≥18 years with MV • Trial 1 (MIDEX): DEX vs. midazolam sedation titrated to goal RASS (0 to -3) • Trial 2 (PRODEX): DEX vs. propofol sedation titrated to goal RASS (0 to -3)	• Bradycardia (MIDEX, PRODEX): 35/247 (14.2%), 32/246 (13.0%) • Hypotension (MIDEX, PRODEX): 51/247 (20.6%), 32/246 (13.0%)

a. Percent of Medical ICU (MICU) patients by trial: Pandharipande (71%), Riker (85.7%), Jakob (MIDEX 73.1%, PRODEX 54.6%)
b. Definitions of adverse events by trial[c]:
   - Pandharipande: hypotension (SBP <80mmHg); bradycardia (HR <60bpm)
   - Riker: hypotension (SBP <80mmHg, DBP < 50mmHg, or ≥30% baseline decrease); bradycardia (HR <40bpm or ≥30% baseline decrease)
   - Jakob: Relevant changes in vital signs according to established clinical practice
c. SBP (systolic blood pressure), DBP (diastolic blood pressure), HR (heart rate)

II. Dexmedetomidine withdrawal syndrome[16–18]
   a. Characterized by sympathetic over-activity
      i. Tachycardia, hypertension, diaphoresis, agitation
   b. Suggested risk following abrupt discontinuation of drug

Table C. Characterizing Dexmedetomidine Withdrawal Syndrome

Study	Population	DEX Intervention	Clinical Course	Outcome
Case Reports[19–22,16]				
Enomoto, et al. (2006)	10-month male post liver transplant	Dose: 0.4-1.4µg/kg/h Duration: 3 weeks D/c[a]: 48-hour taper	Symptoms: Anxiety, restless, uncomfortable, ↓respiratory status Onset post d/c: 6 hours	• Resolved with DEX administration • 14-day taper
Weber, et al. (2008)	2-year male post cardiac surgery	Dose: 0.3-0.8µg/kg/h with intermittent 0.5µg/kg doses Duration: 6 days D/c: No taper	Symptoms: Emesis, hypertension, tachycardia Onset post d/c: 3 hours	• Resolved with DEX administration • 32-hour taper
Darnell, et al. (2010)	8-week female with respiratory failure	Dose: 1µg/kg LD, followed by 0.5-2µg/kg/h Duration: 3.5 days D/c: 6-hour taper	Symptoms: Agitation, diarrhea, mydriasis, occasional sneezing, tachycardia, ↑muscle tone Onset post d/c: 2 hours	• Resolved with DEX administration • Discontinued 9-hours post readministration with symptom improvement
Miller, et al. (2010)	2-year male post cardiac surgery	Dose: 0.75µg/kg LD, followed by 0.7µg/kg/h Duration: 11 days D/c: No taper	Symptoms: Asymmetric pupils, neurologic changes (blank stare, agitation, ↓verbal communication) Onset post d/c: 5 hours	• Resolved ≤48 hours without intervention
Kukoyi, et al. (2013)	a. 61-year female with severe sepsis	Dose: 1µg/kg LD, followed by 0.7-1.4µg/kg/h Duration: 7 days D/c: 8-hour taper	Symptoms: Agitation, combative, hypertension, tachycardia, ↓respiratory status Onset post d/c: 6 hours	• Resolved ≤12 hours with clonidine (CLON) administration • CLON 0.2mg PO q8h, ↓0.1mg/day x6 days
	b. 46-year female with severe sepsis	Dose: 0.2-1.4µg/kg/h Duration: 6 days D/c: 6-hour taper	Symptoms: Agitation, diaphoresis, mydriasis, tachycardia Onset post d/c: Unspecified	• Resolved ≤24 hours with CLON administration • CLON 0.1mg PO q8h x1 day, 0.1mg BID x1 day, then 0.1mg daily x2 days
Retrospective Case Series[17,23]				
Burbano, et al. (2012)	CCU patients[b] <18 years with DEX use >72 hours	Dose: (by age group) <1yr: Mean 0.76µg/kg/h ≥1yr: Mean 0.7µg/kg/h Duration: >7 days in 23/62 patients (37.1%) D/c: 12-hour taper in 44/62 patients (71.0%)	Symptoms: no. (%) ○ Agitation 17/62 (27.4) ○ Hypertension 22/62 (35.0) ○ Tachycardia 17/62 (17.8)[c] ○ Tachycardia + hypertension 10/62 (16.1) Onset post d/c: 12 hours	• Hospital protocol: Titrate 0.1-0.4µg/kg/h q8-24h, restart DEX with agitation and reinitiate titration ≥6 hours • 20 patients excluded due to CLON use, where: ○ 17/20 withdrawal prevention ○ 3/20 withdrawal treatment

Whalen, et al. (2014)	PCU patients[d] <21 years with DEX use >72 hours	Dose: 0.7µg/kg/h for 90/98 patients (91.8%) Duration: Median 141 hours (range 72-2472) D/c: 63/98 (64.3%) utilized titration schedule	Symptoms[e]: Statistically significant changes from baseline post DEX d/c: ○ ↑SBP at 1h, 4h, 24h (p=0.027, 0.034, 0.028) ○ ↑DBP at 30min, 4h (p=0.005, 0.006) ○ ↑HR at 30min, 2h, 4h, 24h, 48h (p=0.01, 0.006, <0.001, 0.002, 0.03)	• Hospital protocol: ○ DEX ≥5 days: Titrate ↓20% daily ○ DEX <5 days: No taper • CLON initiated in 15/87 patients ○ 10/15 withdrawal treatment
Prospective Studies Describing Hemodynamic Changes[24,25]				
Venn, et al. (2003)	MICU patients ≥18 years with MV and DEX use ≤7 days	Dose: 0.1µg/kg LD, followed by mean 1.0±0.7µg/kg/h Duration: Mean 33 hours (range 13-72) D/c: Not described	Vitals: ○ BP post d/c, mean • 3 to 16 hours: 137/65 to 135/65 mmHg (baseline 125/62 mmHg) ○ HR post d/c, mean • 3 to 16 hours: 93 to 105 bpm (baseline 76 bpm)	• Sustained increases in blood pressure and HR from 3 hours to 16 hours post d/c • No clinically significant rebound phenomenon
Shehabi, et al. (2004)	Patients ≥18 years with MV and DEX use >24 hours	Dose: Mean 0.4µg/kg/h (range 0.2-0.7) Duration: Mean 81 hours (range 40-168) D/c: No taper	Vitals: (change from baseline) ○ SBP 5 hours post d/c • 143mmHg (±24) → 154mmHg (±24) ○ HR 14 hours post d/c • 86 (±17) → 97bpm (±17)	• Maximum increase in SBP: 7% • Maximum increase in HR: 11%

a. Regimen for discontinuing DEX
b. Cardiac ICU patients (90%), where 39/62 (63%) patients were <1-year
c. Of the 17 patients experiencing tachycardia: 1) 90% of episodes occurred within 6 hours after DEX discontinuation, 2) associated with abrupt discontinuation vs. weaned (42 vs. 14%, p=0.045)
d. Pediatric ICU patients (52.9%), where median age 3.8 years (range 0.04-17)
e. SBP (systolic blood pressure), DBP (diastolic blood pressure), HR (heart rate)

III. Clonidine
    a. Centrally-acting alpha-2 agonist with variety of indications[26–28]:
        i. Hypertension treatment
        ii. Attention deficit hyperactivity disorder (ADHD) monotherapy or adjunct therapy
        iii. Cancer-related pain management via epidural infusion
    b. Widely used as sedative in critically ill patients[29]
        i. Adjunct therapy for neonatal abstinence syndrome for opiate exposure in utero[30]
        ii. Enteral clonidine shown to be effective as sedative in MV patients[31–34]
            a. Oral (PO), transdermal, and solution for epidural available in the United States

Table D. Comparison of Dexmedetomidine and Clonidine[9,18]

	Dexmedetomidine (DEX)	Clonidine (CLON)
Alpha binding specificity (α_2:α_1)	1600:1	200:1
Formulation	IV	PO
Peak Effect	15-30 min	3 h
Half-life ($t_{1/2}$)	2-3 h	8-12 h
Sedative Effects	+++	+
Cost	+++	+

Use of Clonidine for Discontinuing Long-term Dexmedetomidine

I. Description of dexmedetomidine withdrawal syndrome
    a. Withdrawal reported in patients of all ages (8 weeks to 61 years)[21,16]
    b. Associated symptoms reported in literature consistent with sympathetic over activity
        i. Most common symptoms include agitation and/or anxiety, tachycardia, and hypertension
        ii. Onset of symptoms reported ≤6 hours
    c. Associated with variety of dexmedetomidine regimens
        i. With and without LD
        ii. Range of continuous infusion rates (0.2 to 2 μg/kg/h)[16,21]
        iii. Range of dexmedetomidine durations (3 days to 3 weeks)[19,21]
        iv. With and without taper for discontinuation
    d. Resolution of symptoms described by various strategies
        i. Dexmedetomidine reinitiation, followed by extended taper (≤14 days)[19]
        ii. Clonidine transition[16,17,23]
            a. Kukoyi, et al. describe two patients with successful resolution of symptoms ≤12-24 hours
            b. Burbano, et al. excluded 20 patients from cohort due to clonidine use
                - 85% initiated on clonidine for withdrawal prevention
            c. Whalen, et al. cohort included 15 patients transitioned to clonidine
                - 67% initiated on clonidine for withdrawal treatment

II. Clinical Questions
    a. Can we characterize dexmedetomidine withdrawal syndrome in order to differentiate patients at high risk from those at low risk?
    b. Is clonidine a safe and effective strategy for prevention of dexmedetomidine withdrawal syndrome?
    c. Which clonidine regimen is most appropriate for prevention of dexmedetomidine withdrawal syndrome?

Literature Evaluation

Table E. Terry K, et al. Evaluating the transition from dexmedetomidine to clonidine for agitation management in the intensive care unit. *SAGE Open Med*. 2015; 3: 2050312115621767[35]

Objective	• Evaluate DEX discontinuation within 8 hours of enteral CLON administration
Methods	
Study Design	• Single center, retrospective cohort from 02/2014 to 02/2015
Inclusion	• Initiated on DEX and received ≥1 dose of CLON for the purpose of sedation
Exclusion	• Initiated on non-enteral form of CLON • CLON given for indication besides sedation
Intervention	• CLON 0.1mg PO/enteral q 6-8 hours ○ Dose titrated for sedation goal via RASS unless hemodynamic changes prohibit further titration

Outcomes	Primary
	• Rate of DEX discontinuation ≤8 hours of CLON initiation
	• Rate of DEX re-initiation ≤24 hours ("CLON failure")
	Secondary
	• Efficacy
	  ○ Confusion Assessment Method for the ICU (CAM-ICU)[a] and RASS[b] scores
	  ○ Rates of rescue sedation
	• Safety
	  ○ Occurrence of MAP <65 or >90mmHg, HR <50 or >110bpm, SBP <90mmHg, or arrhythmia

Statistics	• 70% discontinuation rate within 8 hours defined as successful *a priori* • Non-normally distributed compared via Mann-Whitney U test • Categorical data compared via chi-square • Statistical significance defined at ≤0.05 • Sample size calculations not performed (cohort = all meeting inclusion)
Results	
Baseline	• 42 patients screened for eligibility ○ 16 excluded (15/16 initiated CLON for indication other than sedation)

Variable	N = 26
Age, mean (SD) years	54.4 (16.9)
Male, n (%)	17 (63.0)
APACHE II, median (IQR)	18 (14-22)
Mechanical ventilation, n (%)	4 (14.8)
ICU indication - cardiac surgery, n (%)	21 (80.7)
CABG[c], n (%)	7 (26.9)
ICU LOS, median (IQR)	8 (4-10.5)
Hospital LOS, median (IQR)	12.5 (7-28)

Outcomes

Primary Outcome, n (%)	N=26
DEX d/c ≤8h of CLON	17 (65.4)[d]
DEX re-initiation ≤24h	0 (0)

Secondary Outcomes			
	DC* (n=17)	nDC** (n=9)	p-value
RASS, median (IQR)	0 (0-2)	0 (-2-2)	---
CAM-ICU positive, n (%)	3 (17.6)	4 (44.4)	---
DEX duration prior to CLON (h), median (IQR)	24 (14.5-39)	13 (4-32)	0.14
DEX rate at CLON start, µg/kg/h (IQR)	0 (0-2.5)	0.7 (0.45-0.7)	**0.01**
DEX rate ≤0.4µg/kg/h, n (%)	15 (88.2)	2 (22.2)	**0.01**

	CLON exposure ≤8h, mg, median (IQR)	0.1 (0.1-0.2)	0.1 (0.1-0.15)	1.0
	Total CLON exposure, mg/ICU day, median (IQR)	0.35 (0.2-0.5)	0.5 (0.4-1.0)	**0.04**
	CLON duration, d, median (IQR)	2 (1-4.5)	3 (2-5)	0.55
	Rescue sedation, n (%) Opioid monotherapy	16 (94) 11 (65)	9 (100) 3 (33)	---
	Safety, n (%)			
	Hypotension	6 (35.5)	4 (44.4)	---
	Unintentional CLON use ICU discharge Hospital discharge	 14/26 (54) 6/26 (23)		 --- ---
	*DC: Patients who discontinued dexmedetomidine ≤8h of clonidine administration **nDC: Patients who did not discontinue dexmedetomidine ≤8h of clonidine administration			

Critique	• Limited by retrospective nature of study
	• Successful transition from DEX to CLON based on an assumed discontinuation rate
	  o 8 hour goal based on pharmacokinetics of clonidine
	• Predominantly cardiac ICU patients in which ~30% admitted for CABG surgery
	  o Sedation goal varies by population (i.e., surgical vs. medical patients)
	  o Optimal sedation strategy varies by indication, where opiates might be preferred for post-surgery sedation
	  ▪ Opiate rescue sedation associated with patients more likely to transition successfully
	• Lacking matched comparator group
	• No standardized intervention protocol
	  o Variations in CLON initiation (DEX rate, timing of initiation)
	  o Lack of protocol resulted in high rates of unintentional CLON use beyond indicated period
	  o Optimal CLON wean not observed
	• Missing baseline sedation regimen besides DEX use
	• nDC group characteristics:
	  o Significantly higher DEX rates at CLON initiation
	  o Lower duration of DEX at CLON initiation
	  o CAM-ICU positive patients
	• Similar rates of hypotension between groups
	  o Lacking baseline rates of hypotension
	• Difficult to generalize due to small cohort			

a. Confusion Assessment Method for the ICU (CAM-ICU) algorithm found in Appendix A
b. Richmond Agitation-Sedation Scale (RASS) algorithm found in Appendix B
c. Coronary artery bypass grafting
d. 13/26 (50%) patients discontinued DEX ≤4h (median 1 hour, IQR 0.5-4.5)

Table F. Lardieri AB, et al. Effects of clonidine on withdrawal from long-term dexmedetomidine in the pediatric patient. *J Pediatr Pharmacol Ther*. 2015; 20(1): 45-53[36]

Objective	• Compare withdrawal symptoms in patients receiving CLON to those not receiving CLON while being weaned from long-term DEX
Methods	
Study Design	• Single center, retrospective cohort from 01/2009 to 12/2012
Inclusion	• PICU patients ≥2 weeks and ≤18 years on MV for acute pulmonary disease • Receiving DEX ≥5 days and initiated on CLON enteral or topical patch
Exclusion	• Cyanotic heart disease • Primary pulmonary hypertension • Neuromuscular respiratory failure • Ventilator-dependent on PICU admission • Patient-controlled analgesia (PCA), epidural, or sedation ≥24 hours prior to admission

Intervention	• CLON initiation and dosing based on physician preference
	  ○ Transdermal CLON placed ≥48 hours prior to DEX discontinuation
	• DEX titration: ↓0.2-0.5 µg/kg/h q12h
	  ○ Goal rate of 0.2-0.5 µg/kg/h for discontinuation

Outcomes	<u>Primary</u> • Withdrawal symptoms ≤24 hours post DEX titration (WAT-1)[a] <u>Secondary</u> • Safety ○ Incidence of rebound hypertension or tachycardia[b]
Statistics	• Descriptive statistics to characterize population • Wilcoxon signed rank test to compare primary and secondary outcomes • Statistical significance defined at <0.05
Results	
Baseline	

Variable	CLON (n=12)	None (n=8)	p-value
Age, yr (IQR)	1.5 (0.67-3.3)	1.0 (0.85-1.3)	0.62
Male, n (%)	6 (50)	5 (62.5)	0.67
Weight, kg (IQR)	12.3 (8.0-19.0)	9.8 (8.5-12.3)	0.52
Admission - respiratory failure, n (%)	5 (41.7)	4 (50)	1.00
ICU LOS, days, median (IQR)	16.6 (13.2-26.9)	12.9 (9.8-20.3)	0.18
Hospital LOS, days, median (IQR)	29.1 (22.0-35.9)	19.9 (16.0-28.7)	0.27
MV duration, days, median (IQR)	12.3 (10.5-20.3)	7.5 (6.5-14.4)	0.12

Outcomes

- Characteristics of CLON:
  - Starting dose with CLON transdermal patch 100 µg/24h: 11/12 patients (91.7%)
    - Mean dose: 9 µg/kg/day (range 2.9-18.2)
  - CLON patch applied an average 5.6 days prior to DEX discontinuation

Primary Outcome	CLON (n=11)	None (n=6)	p-value
Elevated WAT-1[c], mean (range)	0.8 (0-6)	3.2 (0-8)	0.49
Elevated WAT-1, no (%)	4/11 (36.4)	4/6 (66.7)	---

Secondary Outcomes	CLON (n=12)	None (n=8)	p-value
DEX duration, h (IQR)	241.8 (185-406.3)	134 (117-144)	**0.003**
DEX total dose, µg/kg, median (IQR)	232.7 (158.3-336.1)	126.1 (102.1-157.5)	**0.031**
DEX dose, mean µg/kg/h, range	1.0 (0.53-1.81)	1.0 (0.42-1.73)	0.91
Concurrent opioid d/c, n (%)	5 (41.7)	3 (37.5)	1.00
Rebound systolic HTN, n (%)	2 (16.7)	0 (0)	0.50
Rebound diastolic HTN[b], n (%)	4 (33.3)	1 (12.5)	0.60
Rebound tachycardia[b], n (%)	3 (25)	4 (50)	0.36
Postwean HR, bpm, mean (range)	112.0 (88.5-151.5)	138.4 (117-168.3)	**0.003**
Change from post- to prewean HR, bpm, mean (range)	3.6 (-39.6-47.5)	29.9 (5.5-74.7)	**0.042**

Critique	• Limited by retrospective nature of study
	• Predominantly medical ICU patients where ~46% admitted for respiratory failure
	• WAT-1 score validated in opiate and BZD withdrawal in pediatric patients
	  ○ 40% patients in cohort with concurrent opioid discontinuation
	• Included matched comparator group
	  ○ 19 patients with 20 treatment course (one patient with 15-day separation between courses)
	  ○ Missing WAT-1 scores for 3 patients (CLON: 1 patient vs. None: 2 patients)
	  ○ WAT-1 score only described in None group[c]
	• No standardized intervention protocol
	  ○ DEX initiated after preferred sedation regimen failure (opioids or BZD)
	  ▪ Missing reason for initial sedative failure
	  ○ Variations in CLON initiation (DEX rate, timing of initiation)
	  ○ CLON dose based on treatment of neonatal abstinence syndrome (NAS)
	  ▪ Appropriate initiation of transdermal patch, however dosing modifications based on taping transdermal patches to inhibit drug absorption
	  ▪ Actual doses used (1.5 μg/kg q4h) higher than studied in NAS (1μg/kg q4h)[d]
	  ▪ Optimal CLON wean not observed
	• Missing baseline sedation regimens besides DEX use beyond concurrent opioid discontinuation
	• CLON group characteristics:
	  ○ Longer DEX duration, higher DEX total dose
	• No difference found between withdrawal symptoms or safety outcomes
	  ○ Higher rates of rebound hypertension with CLON intervention
	  ▪ No reports of hypotension or bradycardia with CLON intervention
	• Difficult to generalize due to small cohort

a. Withdrawal Assessment Tool-1 (WAT-1) found in Appendix C. WAT-1 scores recorded by bedside nurse every 4-6 hours.
b. Rebound hypertension (HTN) and tachycardia defined as ↑ ≥20% from baseline during post-wean time period
c. WAT-1 scores within the None group most commonly: tremor (15), uncoordinated repetitive movements (15), and time to gain calm (13)
d. Agthe, et al. (2009) randomized 80 infants with in utero opiate exposure (89% methadone, 69% heroin) to receive diluted tincture of opium (DTO) +/- clonidine for treatment of neonatal withdrawal syndrome (NWS)[30]
  ○ CLON regimen 1 μg/kg every 4 hours fixed dose schedule

Table G. Gagnon DJ, et al. Transition from dexmedetomidine to enteral clonidine for ICU sedation: an observational pilot study. *Pharmacotherapy*. 2015; 35(3): 251-259[37]

Objective	• To identify patients for DEX transition to CLON safely and effectively
Methods	
Study Design	• Prospective, observational pilot study from 01/2014 to 03/2014

Inclusion	• ≥18 years receiving DEX infusion for 12-24 hours with favorable response
	  ○ SAS 3-4[a]
	  ○ Hemodynamically stable (MAP ≥65mmHg + SBP ≥90mmHg + HR ≥50bpm)

Exclusion	• Vasopressor support • AV conduction defects ≥ 1° block • Cardiac ICU or cardiothoracic surgery ICU patients

Intervention	• CLON initiation at 0.2-0.5mg q6h, where:
	  ○ 0.2mg initiated if DEX <0.7 µg/kg/h, <100kg, or older patients
	  ○ ≥0.3mg initiated if DEX ≥0.7 µg/kg/h, ≥100kg, or younger patients
	  ○ Adjusted by ↑↓ clonidine 0.1mg to maintain goal sedation (SAS 3-4)
	• DEX titration: ↓25% of baseline ≤6 hours of each clonidine dose if no agitation occurs
	• CLON titration: ↑dosing interval (q8h → q12h → daily → discontinue) every 24 to 48 hours

Outcomes	<u>Efficacy</u> • DEX and CLON use over 5 transition phases[b]:  • SAS, CAM-ICU[c], CPOT or NRS[c] scores • Concurrent BZD and opioid use[c] (rescue sedation) <u>Safety</u> • Incidence of HR <50bpm, MAP <65mmHg or SBP <90mmHg • Incidence of new 2° or 3° AV node block • Presence of clonidine withdrawal syndrome[e] (CWS)
Statistics	• Continuous variables compared via Wilcoxon signed rank test • Categorical and binary variables compared via Chi-square • Statistical significance defined at <0.05
Results	
Baseline	

Variable	N=20
Age, median yrs (IQR)	62 (54-73)
Male, no. (%)	13 (65)
Alcohol abuse, no. (%)	6 (30)
APACHE III, median score (IQR)	62 (54-80)
MV, no. (%)	13 (65)
Critical care admissions, no. (%)	15 (75)
Admission - respiratory, no. (%)	12 (60)
DEX indication - agitation, no. (%)	12 (60)

Outcomes

Outcomes of Transition Phases

	DEX maintenance (n=20)	Transition (n=20)	CLON maintenance (n=20)	CLON taper day 1 (n=17)	CLON taper final day (n=17)	Post CLON (n=8)
Phase duration, h (range)	28 (19-36)	23 (2-53)	72 (38-118)	---	57 (55-93)	48 (48-48)
DEX infusion rate, µg/kg/h	1.0 (0.7-1.2)	0.9 (0.7-1.0)	---	---	---	---

CLON total daily dose	---	1.1 (0.9-1.1)	1.2 (0.9-1.2)	0.8 (0.6-0.9)	0.3 (0.3-0.4)	---
Efficacy events, no. (%)						
Pain	10 (50)	6 (30)	9 (45)	---	13 (76)	7 (88)
Agitation	10 (50)	13 (65)	5 (25)	---	2 (12)	2 (25)
Delirium	10 (50)	11 (55)	8 (40)	---	5 (29)	3 (38)
Fentanyl[d], µg (range)	891 (471-1286)	1250 (486-2434)	387 (171-839)	---	561 (286-969)	300 (163-618)
Safety events, no (%)						
HR ≤50bpm	0 (0)	0 (0)	1 (5)	---	1 (6)	0 (0)
MAP <65 or SBP <90	8 (40)	7 (35)	4 (20)	---	2 (12)	2 (25)
AV node block	0 (0)	0 (0)	0 (0)	---	0 (0)	0 (0)

Total cohort outcomes	(N=20)
Successful transition <24h, no. (%)	10 (50)
Successful transition <48h, no. (%)	15 (75)
Rate of clonidine taper, days, median (range)	2.4 (1.4-7)
CWS, no. (%)	1 (5.0)[f]

Critique

- Only prospective study evaluating DEX transition to CLON to date
  - Recruited 20 patients within 3-month period
- Medical, surgical , and neurologic ICU patients where 60% initiated DEX for agitation
- Lacking matched comparator group
- Well-described protocol for DEX transition to CLON
  - CLON dose of 0.2-0.3mg based on initial review of 0.1mg suggesting ↓efficacy
  - Degree of variation in protocol with provider specific practice
- Included evaluation of baseline sedation regimen and changes in regimens during transition phases
- 5/20 patients (25%) unable to successfully transition <48 hours
  - 3/5 unable to transition with history of alcohol abuse
- Lower rates of hypotension with CLON monotherapy therapy
  - No change in rates of bradycardia
  - Clonidine withdrawal syndrome described in one patient
- Difficult to generalize due to small cohort

a. Sedation Agitation Scale (SAS) found in Appendix D. SAS scores recorded by bedside nurse every 4 hours.
b. Transition phases as follows: 1. Dexmedetomidine maintenance (calendar day preceding first dose of clonidine and continued until clonidine initiation), 2. Transition phase (clonidine initiation until dexmedetomidine permanently discontinued), 3. Clonidine maintenance (dexmedetomidine discontinued and until clonidine taper begins), 4. Clonidine taper phase (clonidine doses reduced with goal of discontinuation), 5. Post-clonidine phase (two calendar days following final dose of clonidine)
c. Confusion Assessment Method for use in the ICU (CAM-ICU), Critical Care Pain Observational Tool (CPOT), and Numerical Rating Scale (NRS) found in Appendices A, E, and F, respectively. CPOT and NRS scores recorded by bedside nurse every 4 hours, while CAM-ICU scores were recorded every 12 hours.
d. Equivalents of medications used for rescue sedation included:
   - Fentanyl equivalents (100µg IV fentanyl = 1.5mg IV hydromorphone = 10mg IV morphine = 20mg PO oxycodone = 10mg IV methadone)
   - Lorazepam equivalents (1mg IV lorazepam = 3mg IV midazolam = 0.25 mg PO clonazepam = 5mg IV diazepam = 0.5 PO alprazolam = 10mg PO chlordiazepoxide)
e. Clonidine withdrawal syndrome defined as presence of BP >180/120 or P 120, subjective headache (sustained), nervousness, insomnia, palpitations, anxiety, restlessness, tremor, emotional instability, flushing or vomiting.
f. CWS described in one patient with concomitant methadone and clonazepam withdrawal

Summary of Trials

Table H. Comparison of Primary Literature[35–37]			
	Terry, et al. (2015)	Lardieri, et al. (2015)	Gagnon, et al. (2015)
Population	• Adult cardiac surgery patients ○ MV ~15% ○ ICU LOS 4-10 days	• Pediatric MICU patients ○ MV ~46% ○ ICU LOS 10-27 days	• Adult mixed ICU patients (excluding cardiac) ○ MV~65% ○ ICU LOS 5-16.5 days
Concomitant Sedation	• Baseline sedation not described • Opiate rescue sedation more common with DC group	• Opiate d/c ~40% pts • BZD d/c ~30% pts	• Opiate, BZD, and propofol requirements well-described
DEX Intervention	• DEX dose: Requirements lower (≤0.4μg/kg/h) in DC group ○ Median transition time 1 hour • DEX duration: 4-39 hours	• DEX dose: 1.0 μg/kg/h (mean) • DEX duration: 241 hours (median) • DEX d/c: ↓0.2-0.5 μg/kg/h q12h	• DEX dose: 1.0 μg/kg/h (mean) • DEX duration: 28 hours (median) • DEX d/c: ↓25% of baseline dose ≤6° of each CLON dose
CLON Intervention	• CLON dose: 0.1mg PO/enteral q 6-8 hours	• CLON dose: 100 μg/24h transdermal (1.5 μg/kg q 4 hours)	• CLON dose: 0.2-0.5mg enteral q 6 hours
Adverse Events	• Hypotension (35-45%) • High rate of unintentional CLON use post study period	• No difference in BP or HR in patients receiving CLON	• Lower rates hypotension with CLON therapy • No difference in HR between groups • Clonidine withdrawal syndrome observed in 1 patient

Associated Cost Benefit

Gagnon, et al. - Drug Acquisition Costs[a37]	
	3-month observation period, dollars
Dexmedetomidine, median cost per patient (range)	$1948 (744-2,816)
Clonidine, median cost per patient (range)	$20 (9-27)
Cost avoidance per patient[b]	$819-2,338
Cost avoidance total cohort[b]	$15,359-52,138

a. Drug acquisition estimated based on average wholesale price (AWP) per Micromedex drug database (accessed 06/2014).
b. Cost avoidance based on drug costs alone. Did not assess length of stay, operational or equipment costs.

Ongoing Studies

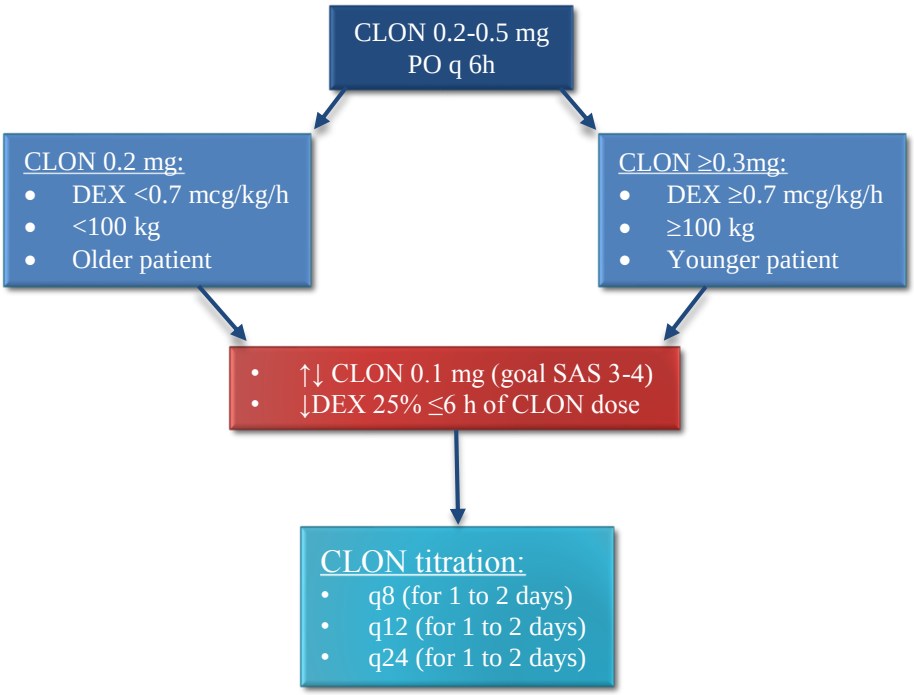
I. Tobias, et al. Use of clonidine to Prevent Withdrawal Following Prolonged Dexmedetomidine Infusions[38]
   a. Retrospective Cohort of patients who received dexmedetomidine infusion >3-5 days and oral clonidine transition
      i. Estimated enrollment: 200 patients (seniors, adults, pediatrics)
      ii. Primary outcome: Evidence of withdrawal (via Withdrawal Assessment Tool version 1 [WAT-1])
      iii. Estimated study completion: March 2017

Summary and Conclusion

I. Unanswered questions
   a. Predicting dexmedetomidine withdrawal syndrome (DWS)
      i. Associated dose and duration unclear to predict DWS in patients
         a. Risk stratifying patients based on these parameters may be beneficial
   b. Patients who may not benefit from transition from DEX to CLON
      i. High risk of transition failure
         a. Delirium[35]
         b. History of alcohol or substance abuse[37]
      ii. High risk of adverse events
         a. Hypotension and bradycardia
            - Cardiac ICU or cardiac surgery patients[35]
         b. Clonidine withdrawal syndrome
            - Described in one patient with concurrent treatment of substance abuse[36]
         c. Unintentional CLON use beyond indicated period[35]

II. Conclusions
   a. Transitioning patients from DEX to CLON advantages:
      i. CLON decreases sedation requirements
         a. Opioid sparing effect[37]
      ii. Decreased ICU LOS
      iii. Decreased patient and hospital costs
   b. Populations with increased transition rate without associated adverse effects
      i. Medical, surgical, or neurology ICU patients without vasopressor requirements
      ii. Agitation as indication for sedation
      iii. Patients tolerating DEX sedation without hemodynamic compromise
      iv. Patients without history of alcohol or substance abuse

III. Recommendation
   a. Recommended CLON strategy[37]



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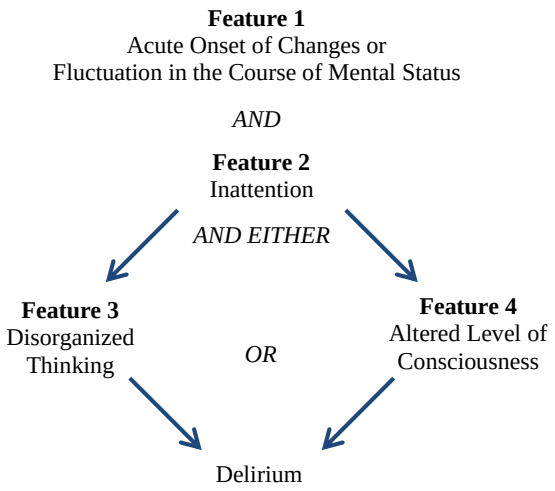
Appendices

Appendix A. Confusion Assessment Method for the ICU (CAM-ICU)[39]



Appendix B. Richmond Agitation-Sedation Scale (RASS)[7]

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (>10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Appendix C. Withdrawal Assessment Tool-Version 1 (WAT-1)[40,41]

Information from patient record, previous 12 hours	
Any loose /watery stools	No = 0 Yes = 1
Any vomiting/wretching/gagging	No = 0 Yes = 1
Temperature > 37.8°C	No = 0 Yes = 1
2 minute pre-stimulus observation	
State	SBS[1] ≤ 0 or asleep/awake/calm = 0 SBS[1] ≥ +1 or awake/distressed = 1
Tremor	None/mild = 0 Moderate/severe = 1
Any sweating	No = 0 Yes = 1
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1
Yawning or sneezing	None or 1 = 0 ≥2 = 1
1 minute stimulus observation	
Startle to touch	None/mild = 0 Moderate/severe = 1
Muscle tone	Normal = 0 Increased = 1
Post-stimulus recovery	
Time to gain calm state (SBS[1] ≤ 0)	< 2min = 0 2 - 5min = 1 > 5 min = 2
Total Score (0-12)	

Appendix D. Sedation-Agitation Scale (SAS)[6]

Score	Term	Description
7	Dangerous agitation	Pulling at ET tube, removing catheters, climbing over bed rail, striking staff, thrashing side-to-side
6	Very agitated	Does not calm, despite frequent verbal reminding of limits; required physical restraints, biting ET tune
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Appendix E. Critical-Care Pain Observation Tool (CPOT)[42]

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Frowning, brow lowering, orbit tightening	Tense	1
	All of the above plus eyelid tightening	Grimacing	2
Body movements	Does not move at all	Absence of movements	0
	Slow, cautious movements, rubbing pain site	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, trying to climb out of bed	Restlessness	2
Muscle tension	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing by tolerating	1
	Asynchrony	Fighting ventilator	2
OR	OR	OR	
	Talking in normal tone or no sound	Talking in normal tone or no sound	0
Vocalization	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0-8

Appendix F. Numerical Rating Scale (NRS)[41]

Extremely Sedated — Extremely Agitated