Target Audience: Emergency Medicine Residents, Medical Students

Primary Learning Objectives:

1. Recognize signs and symptoms of clonidine toxicity
2. Describe elimination techniques effective for clonidine toxicity
3. Describe the roles of therapeutic interventions in the patient with clonidine toxicity including the indications, contraindications, and efficacy

Secondary Learning Objectives: detailed technical/behavioral goals, didactic points

1. Describe the pathophysiology of clonidine toxicity
2. Compare clonidine with other overdoses and exposures that cause bradycardia and hypotension, especially with regard to the differences and similarities in presentation, diagnosis, and management
3. Discuss the management priorities for the emergent stabilization of the patient with clonidine toxicity
4. Describe the differences in overdose management in young pediatric patients (compared with older children, adults, and geriatric patients) and in patients prescribed the medication vs. those who are naïve to the medication

Critical actions checklist:

1. Obtain point-of-care serum glucose
2. Obtain an ECG
3. Protect the airway (positioning, continuous observation, endotracheal intubation, etc.)
4. Administer IV crystalloid fluid boluses
5. Provide hemodynamic support (atropine, norepinephrine, etc.)
6. Administer physostigmine (for agitation)
7. Consult Poison Center or toxicologist
8. Admit to the PICU

Environment:

1. Room Set Up – ED critical care area
    a. Manikin Set Up – Mid or high fidelity pediatric simulator, simulated sweat
    b. Props – Standard ED equipment

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CASE SUMMARY

SYNOPSIS OF CASE

This is a case of a 5-year-old otherwise healthy boy who is found somnolent by his parents. Unknown to them at the time, he ingested approximately 10 clonidine tablets. The pills belong to his older brother who takes them for ADHD. He was scooped up by his parents and driven to the emergency department. On arrival he is bradycardic, hypotensive, and somnolent. He will need cardiovascular and airway support, and ultimately, PICU admission.

SYNOPSIS OF HISTORY

Johnny is previously healthy, in his usual state of health, until found by his parents. He was thought to be playing video games in his bedroom (shared with his older brother Tommy). His mother went to check on him and found him excessively somnolent and difficult to wake up. There is no suspicion of trauma. Parents will not know this until later, but he took about 10 clonidine tablets (each 0.1 mg) that his brother uses to treat ADHD. No other medications are missing.

SYNOPSIS OF PHYSICAL

On arrival he is notably somnolent, with decreased respirations (RR 6) and miosis (pupils 2mm). With stimulation he will moan and localize pain. His airway is patent, he has a gag reflex, and there is an absence of pooled secretions in his pharynx. His blood pressure is 70/35, heart rate is 62. Rectal temperature is 36.5. SaO_2 94% on room air. There are no signs of trauma. His skin is warm, dry. Pulses are weak but present. Reflexes are intact.

SCORING GUIDELINES

The case will test the examinee's ability to detect a cardiodepressant toxidrome and to treat it.

Score up the examinee's performance if:

- naloxone is considered as an antidote, though it will not work
- activated charcoal is given once endotracheal intubation is performed
- Social Work consultation is requested

Score down the examinee's performance if:

- the examinee does not interrogate the family for medication access that would explain the presenting signs and symptoms
- early IV access is not obtained
- airway management is delayed (either a NRB mask or intubation will be acceptable initially)
- pharmacologic support does not include norepinephrine
- activated charcoal is given before intubation is a potentially dangerous action
- Toxicology consultation is not considered
- the examinee attempts to admit the child to the ward

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CRITICAL ACTIONS

1. **Obtain point-of-care serum glucose**

   Obtain a point-of-care serum glucose in a patient with altered mental status.
   Cueing Guideline: The nurse can ask if the doctor knows what is causing the patient's altered mental status and if there are any bedside tests that can be done to elucidate the etiology.

2. **Obtain an ECG**

   Obtain an ECG. Correctly interpret findings. The ECG will be helpful in ruling out a widened QRS complex suggesting TCA toxicity and cardioactive steroid (digoxin-like) effects.
   Cueing Guideline: The nurse can ask if the doctor would like an ECG (this prompt can be delivered if the learner requests that the patient be placed on continuous telemetric monitoring).

3. **Protect the airway**

   Protect the airway, especially as the patient's ability to protect the airway worsens as the case moves forward.
   Cueing Guideline: Nurse asks the doctor if he is concerned about this patient's airway given the patient's mental status.

4. **Administer IV crystalloid fluid boluses**

   Administer IV crystalloid fluid boluses (20 mL/kg) until response.
   Cueing Guideline: The nurse can ask if the doctor would like to do anything about the worrisome heart rate or blood pressure.

5. **Provide hemodynamic support**

   Provide hemodynamic support. This support may include atropine, norepinephrine, or attempts at transcutaneous pacing.
   Cueing Guideline: The nurse can ask if the doctor would like to do anything about the worrisome heart rate or blood pressure.

6. **Consider naloxone**

   Consider naloxone.
   Cueing Guideline: The nurse can ask if the doctor if anything can be given for the patient's symptoms (especially if the learner has identified an opioid-like toxidrome)

7. **Consult Toxicology**

   Consult Toxicology (either the Poison Center or a consultant in toxicology)
   Cueing Guideline: RN can ask the doctor if anyone has called the Toxicologist yet. RN may also ask if there is anything more we can do to help improve the patient's condition.

8. Admit to the PICU

Admit to the PICU. Patient will not be stable for any other destination.
Cueing Guideline: RN can ask the doctor if anyone has called the pediatric intensivist to arrange for a definitive disposition decision.

Critical Actions Checklist[1]

Resident Name	
Case Description	

Skills measured **Core competencies: PC** Patient care, **MK** Medical knowledge, **IC** Interpersonal and communication skills **P** Professionalism, **PB** Practice-based learning and improvement **SB** Systems-based practice	Very Unacceptable		Unacceptable		Acceptable		Very Acceptable	
Data Acquisition (D) PC MK I	1	2	3	4	5	6	7	8
Problem Solving (S) PC MK PB	1	2	3	4	5	6	7	8
Patient Management (M) PC MK IC P PB SB	1	2	3	4	5	6	7	8
Resource Utilization (R) PC PB SB	1	2	3	4	5	6	7	8
Health Care Provided (H) PC SB	1	2	3	4	5	6	7	8
Interpersonal Relations (I) IC P	1	2	3	4	5	6	7	8
Comprehension of Pathophysiology (P) MK PB	1	2	3	4	5	6	7	8
Clinical Competence (C) PC MK IC P PB SB	1	2	3	4	5	6	7	8

Critical Actions

Yes	No		Comments:
		Obtain IV access	
		Obtain an ECG	
		Protect the airway	
		Administer IV crystalloid fluid boluses	
		Provide hemodynamic support	
		Consider naloxone	
		Consult Toxicology	
		Admit to the PICU	

Yes	No	
		Dangerous actions

[1] Modified ABEM Oral Certification Examination checklist and scoresheet

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HISTORY

Age: 5

Sex: Male

Name: Johnny B. Good

Method of Transportation: Parent's own vehicle

Person giving information: Mother

Presenting complaint: Somnolence

Onset and Description of Complaint: Mom found him this way. Unclear onset or duration.

Past Medical History: None. Born on time. No hospitalizations or surgeries. Immunizations UTD.

Medications: None.

Habits: Playing video games.

Family Medical History: Brother with ADHD.

Social History: Lives with both parents and older brother (8).

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PLAY OF CASE GUIDELINES

This is a case of an otherwise healthy 5-year-old boy who accidentally ingests a small number of his brother's clonidine tablets. The case will test the examinee's ability to detect a cardiodepressant toxidrome and to treat it.

1. The patient will not be able to provide a history to explain his symptoms and the mother will not initially know what happened. There will not be a history of ingestion when the child is delivered to the emergency department. The examinee will need to find a way to confirm this. If asked, the family will reveal that the patient's sibling is on clonidine, and if asked, a family member will search the bedroom where an empty bottle of clonidine will be found (10 tablets will be missing).

2. There are no co-ingestants in the case, but the examiner will have to find a way to get more details from the family about the home environment. Score down if the examinee does not interrogate the family for medication access that would explain the presenting signs and symptoms.

3. The patient will present with hypoxia caused by somnolence and lethargy. The airway will be initially clear (using a non-rebreather mask will suffice initially), but the respirations will be slow, and the patient will demonstrate evidence of worsening hypoxia (oxygen saturation will worsen) and altered mental status. The patient will ultimately require intubation (if delayed, the vitals will worsen and/or the patient will vomit). Score down if airway management is delayed.

4. Score down if early IV access is not obtained. IV access is mandatory. If the examinee is sluggish in ordering a line, peripheral attempts will fail and an IO will be needed. If fluids are not instituted early, the patient will become more hypotensive. Fluids alone will not raise the blood pressure or heart rate.

5. Score up for considering naloxone as an antidote, though it will not work.

6. Score down if pharmacologic support does not include norepinephrine. Atropine is reasonable, and it will increase the heart rate by about 10 bpm, but not help BP.

7. It is reasonable to consider head CT, though it will be negative. If head CT is considered, the examinee must secure the airway before allowing the child to leave the department or must accompany the child to the radiology suite.

8. Activated charcoal should not be administered unless the child is intubated first. It is not required for the simulation and will cause aspiration if attempted without a secure airway. OG lavage is not available.

9. Toxicology consultation is indicated and required (the PICU attending will ask the examinee to contact the on-call toxicologist if this has not been down yet).

10. The patient will require PICU admission for continued observation and serial reassessments.

Required Actions within the First Two Minutes

- Point-of-care glucose ordered (patient with altered mental status)
- Peripheral IV access ordered/inserted and fluid boluses started
- ABG/VBG, electrolytes, other diagnostics, and ECG are ordered
- Initial (empiric) supportive interventions for airway, breathing, circulation, and mental status until clonidine toxicity is deduced, recognized, or confirmed by history

Branch Points

- **IF NO POINT-OF-CARE GLUCOSE IS ORDERED WITHIN THE FIRST TWO MINUTES,** patient becomes more confused and obtunded.
- **IF NALOXONE IS ORDERED AND ADMINISTERED WITHIN THE FIRST TWO MINUTES,** no response to this intervention is noted.
- **INITIAL INTERVENTIONS TO IMPROVE HYPOXIA (e.g., NON-REBREATHER MASK) WILL INITIALLY IMPROVE THE HYPOXIA (the oxygen saturation will increase). THE RESPIRATORY RATE, HOWEVER, WILL CONTINUE TO WORSEN. THE PATIENT WILL ULTIMATELY REQUIRE ENDOTRACHEAL INTUBATION.**
- **IF NO ENDOTRACHEAL INTUBATION IS PERFORMED INITIALLY,** the respiratory and heart rates will continue to worsen and the patient will become more hemodynamically unstable **– OR –** the patient will vomit.
- **IF IV ACCESS IS DELAYED,** then access will not be achievable, and the patient will require intraosseous needle insertion.
- **IV FLUID BOLUSES SHOULD BE ADMINISTERED AT THE BEGINNING OF THE CASE. HOWEVER, THE HYPOTENSION WILL NOT BE RESPONSIVE TO IVF BOLUSES.**
- **IF A VASOPRESSOR (e.g., NOREPINEPHRINE) IS GIVEN,** the patient's blood pressure will improve, but **ONLY AFTER IV FLUIDS ARE ADMINISTERED**.
- **TRANSCUTANEOUS PACING WITH CONSISTENT CAPTURE WILL NOT BE POSSIBLE.**

Required Actions over the Next Four Minutes

- Clonidine toxicity should be recognized by this time
- Diagnostics should be returned as ordered
- Hypoxia and bradypnea (respiratory failure) should be treated by this time
- Treatment for the bradycardia and hypotension should be initiated at this time
- Toxicology consultation should be considered at this time

Branch Points

- **IF NO POINT-OF-CARE GLUCOSE IS ORDERED WITHIN THE FIRST TWO MINUTES,** patient becomes more confused and obtunded.
- **IF NALOXONE IS ORDERED AND ADMINISTERED WITHIN THE FIRST TWO MINUTES,** no response to this intervention is noted.
- **INITIAL INTERVENTIONS TO IMPROVE HYPOXIA (e.g., NON-REBREATHER MASK) WILL INITIALLY IMPROVE THE HYPOXIA (the oxygen saturation will increase). THE RESPIRATORY RATE, HOWEVER, WILL CONTINUE TO WORSEN. THE PATIENT WILL ULTIMATELY REQUIRE ENDOTRACHEAL INTUBATION.**
- **IF NO ENDOTRACHEAL INTUBATION IS PERFORMED INITIALLY,** the respiratory and heart rates will continue to worsen and the patient will become more hemodynamically unstable **– OR –** the patient will vomit.
- **IV FLUID BOLUSES SHOULD BE ADMINISTERED AT THE BEGINNING OF THE CASE. HOWEVER, THE HYPOTENSION WILL NOT BE RESPONSIVE TO IVF BOLUSES.**
- **IF A VASOPRESSOR (e.g., NOREPINEPHRINE) IS GIVEN,** the patient's blood pressure will improve, but **ONLY AFTER IV FLUIDS ARE ADMINISTERED**.
- **TRANSCUTANEOUS PACING WITH CONSISTENT CAPTURE WILL NOT BE POSSIBLE.**
- **NURSE MAY PROMPT FOR THE PICU CONSULTATION** if not already requested.

Required Actions over the Remainder of the Case

- Clonidine toxicity should be recognized by this time
- Diagnostics should be returned as ordered
- Hypoxia and bradypnea (respiratory failure) should be treated by this time
- Treatment for the bradycardia and hypotension should be initiated at this time
- Toxicology consultation should be considered at this time
- PICU consultation for definitive disposition and placement

For Examiner Only

PHYSICAL EXAM

Vital Signs: BP: 70/35 mmHg P: 42/minute R: 6/minute T: 36.5C (100.2F) POx: 94% (room air)

General Appearance: Somnolent, minimally responsive.

HEENT: Pupils are 2-mm, sluggish. Gag reflex present. No pooling of oral secretions. Atraumatic. Supple neck.

Lungs: Clear.

CV: Bradycardic. Weak peripheral pulses.

Abdomen: Soft, no tender, non-distended. Bowel sounds are present.

Extremities: Atraumatic. No edema.

Back: Unremarkable.

Neurological: Somnolent. Moans with painful stimuli. Localizes pain. Eyes open with voice commands. Normal reflexes. Normal tone. No focal deficits. No clonus or myoclonus.

Skin: Dry.

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STIMULUS INVENTORY

#1	Complete blood count
#2	Basic metabolic panel
#3	Urinalysis
#4	Liver function tests
#5	Arterial blood gas
#6	Creatinine phosphokinase
#7	Toxicology
#8	Coagulation studies
#9	Point-of-care serum glucose
#10	ECG
#11	Lactate

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LAB DATA & IMAGING RESULTS

Stimulus #1	
Complete Blood Count (CBC)	
WBC	12,000/mm^3
Hemoglobin	12.5 g/dL
Hematocrit	36%
Platelets	115,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2	
Basic Metabolic Profile (BMP)	
Sodium	135mEq/L
Potassium	4.0mEq/L
Chloride	104 mEq/L
Bicarbonate	22 mEq/L
Glucose	80 mg/dL
BUN	25 mg/dL
Creatinine	1.1 mg/dL

Stimulus #3	
Urinalysis	
Color	Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Negative
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0-2/hpf
RBC	0-2/hpf

Stimulus #4	
Liver Function Tests	
AST	35 U/L
ALT	38 U/L
Alk Phos	60 U/L
T. Bilirubin	0.8 mg/dL
Albumin	4 mg/dL
Protein	7 mg/dL

Stimulus #5	
Arterial Blood Gas	
pH	7.34
pCO_2	36 mm Hg
pO_2	90 mm Hg
HCO_3	22 mEq/L
SaO_2	97% (FiO_2=0.21)

Stimulus #6	
Creatine phosphokinase	
CPK	80 U/L

Stimulus #7	
Toxicology	
Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	Undetectable
Urine drug screen	
Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative

Stimulus #8	
Coagulation Studies	
INR	1.0
PTT	32 seconds

Stimulus #9
Point-of-care serum glucose
80 mg/dL

Stimulus #10	
ECG	Sinus bradycardia

Stimulus #11	
Lactate	1.5 mmol/L

Stimulus #1

Complete Blood Count (CBC)

WBC	12,000/mm^3
Hemoglobin	12.5 g/dL
Hematocrit	36%
Platelets	115,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2

Basic Metabolic Profile (BMP)

Sodium	135mEq/L
Potassium	4.0mEq/L
Chloride	108 mEq/L
Bicarbonate	22 mEq/L
Glucose	80 mg/dL
BUN	25 mg/dL
Creatinine	1.1 mg/dL

Stimulus #3

Urinalysis

Color	Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Negative
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0-2/hpf
RBC	0-2/hpf

Stimulus #4

Liver Function Tests

AST	35 U/L
ALT	38 U/L
Alk Phos	60 U/L
T. Bilirubin	0.8 mg/dL
Albumin	4 mg/dL
Protein	7 mg/dL

Stimulus #5

Arterial Blood Gas

pH	7.34
pCO_2	36 mm Hg
pO_2	90 mm Hg
HCO_3	22 mEq/L
SaO_2	97% (FiO_2=0.21)

Stimulus #6

Creatine phosphokinase

CPK	80 U/L

Stimulus #7

Toxicology

Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	Undetectable

Urine drug screen

Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative

Stimulus #8

Coagulation Studies

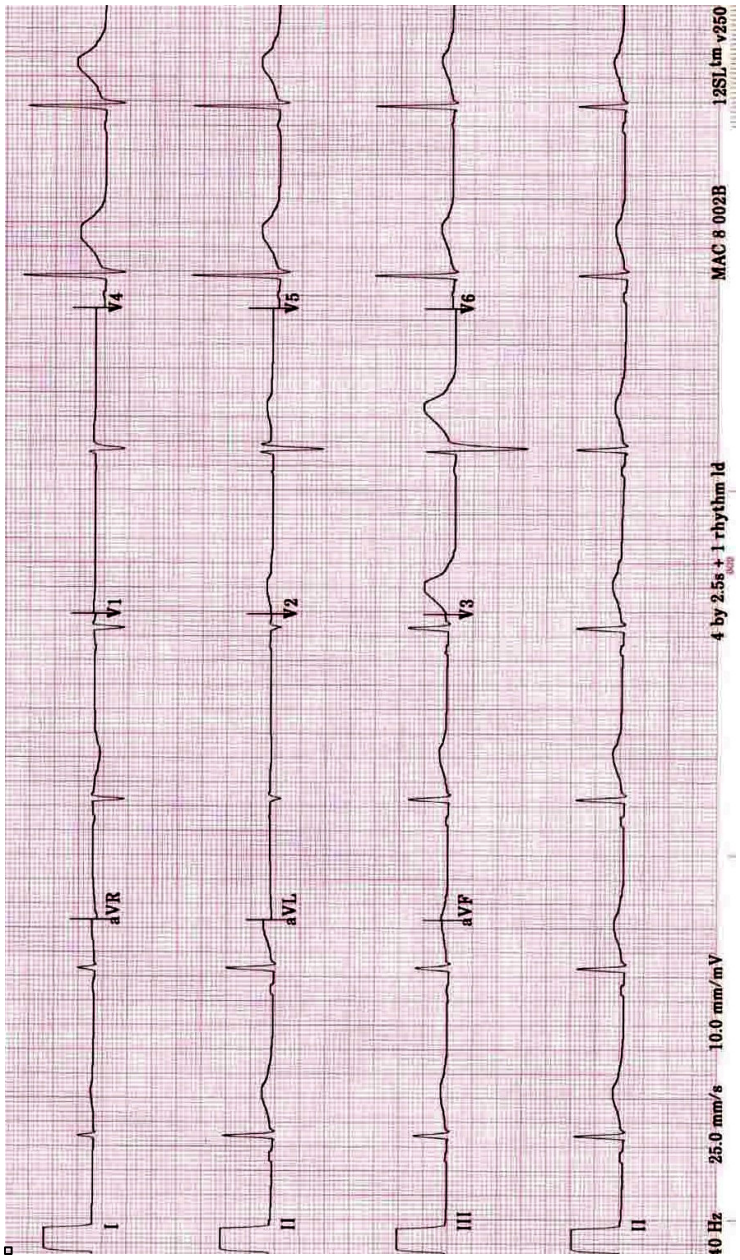
INR	1.0
PTT	32 seconds

Stimulus #9

Serum glucose

80 mg/dL

Stimulus #10


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
40 Hz
25.0 mm/s
10.0 mm/mV
4 by 2.5s + 1 rhythm ld
MAC 8 002B
12SL tm v250

Consult Discussion: Clonidine

Background: Clonidine is a centrally acting antihypertensive commonly used in the treatment of hypertension and ADHD. It reduces blood pressure by decreasing sympathetic outflow from the CNS. Clonidine is often utilized as a sedative in the setting of ADHD and to alleviate opiate and nicotine withdrawal syndromes. It is available in both oral and transdermal forms. The transdermal form allows slow, continuous release of drug over 1 week; however, this formulation contains significantly more drug (approximately 2.5 mg in a 0.1mg/day formulation). Approximately 50% of the drug may remain in the patch after therapeutic use. Numerous cases of toxicity have occurred from dermal, mouthing, or ingesting the product.

Risk Assessment: Consider 3 factors: 1)Drug, 2)Dose, and 3)Patient (comorbidities)

1)Drug: About 10% of cases have moderate medical outcome (not life-threatening; some form of treatment is required; e.g., acid-base disturbance, hypotension rapidly responsive to treatment). About 2% are major (life-threatening, or significant disability expected; e.g., repeated seizures, respiratory compromise requiring intubation, ventricular dysrhythmias). Death is uncommon with supportive care, and a good outcome is expected with thorough supportive care.

2)Dose: There is a poor correlation between the clonidine dose ingested and observed clinical effects. Significant CNS depression may occur with doses > 20 mcg/kg, but large doses are sometimes tolerated with minor effects. Onset of clinical symptoms is rapid—usually within 2 hours, and always within 6 hours.

3)Patient comorbidities: Ingestion of 1-2 tablets of clonidine in children is potentially lethal without supportive care: >10 mcg/kg→bradycardia & hypotension; >20 mcg/kg→respiratory depression or apnea.

Mechanism of Action/Toxicity: Clonidine decreases central sympathetic outflow by stimulating alpha-2 adrenergic presynaptic (inhibitory) receptors in the brain. This enhances the activity of inhibitory neurons in the nucleus tractus solitarius in the medulla, resulting in decreased norepinephrine release. It also stimulates alpha-1 adrenergic receptors in the periphery resulting in transient hypertension and vasoconstriction.

Pharmacokinetics: The onset of symptoms is usually rapid (30-90 minutes) with peak effects at 6-12 hours post ingestion. Clonidine is 20-40% protein bound and has a volume of distribution 3.2-5.6 L/kg. The majority of clonidine is eliminated by the kidneys unchanged.

Toxic Dose: As little as one tablet of 0.1mg can produce toxic effects in children; however, 10mg shared by children was without effect in 34-month old twins. Adults have survived ingestion of up to 100mg.

Clinical Presentation: Patients present with sympathetic nervous system depression. Clinical findings include pupillary constriction, lethargy, coma, apnea, bradycardia, hypotension and hypothermia. Paradoxic hypertension may also occur, but is usually transient. Seizures, hypotonia and hyporeflexia have also been described.

Treatment: Patients usually recover with supportive care. All patients with CNS depression should be evaluated for hypoxia and hypoglycemia. Intubate immediately if the patient is not protecting his or her airway. Hypotensive patients should be fluid resuscitated with volume expansion. Use vasopressors when patients do not respond to IVF or in patients with a clinical presentation consistent with CHF, cardiomyopathy or pulmonary edema. Bradycardia is typically mild and usually does not require aggressive therapy. If the bradycardia is severe and patients are symptomatic, atropine may be utilized. Naloxone has been reported to reverse symptoms of clonidine ingestion, but this has not been confirmed and mechanistically does not make sense. The use of alpha antagonists such as tolazoline and yohimbine is controversial and not recommended.

Laboratory/Studies: Serum drug levels are not routinely available.

Decontamination/Elimination: Activated charcoal can be administered if the patient is able to comfortably ingest it; however, it should be administered with caution secondary to the risk of abrupt obtundation and risk of aspiration. There is no evidence that enhanced removal procedures such as hemodialysis are effective.

Expected Course: Associated CNS depression should resolve over 12-36 hours; however, prolonged obtundation has been recorded.

Withdrawal: Abrupt cessation of central antihypertensive agents may result and is characterized by excessive sympathetic activity. Symptoms include, but are not limited to agitation, insomnia, tremor, palpitations and hypertension.

References:
Goldfrank's 10th Edition, 2015
Olson's 6th Edition, 2012
Daly 1st Edition, 2007