Blow Darts for the Agitated Delirium Patient

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Objectives

- Discuss Agitated Delirium
  - 160 years and we still don't know much
  - 2 years and we're learning?
- Recognize the patient with EXDS
- Discuss treatment options for agitated patients
  - Benzos, Typical & Atypical Antipsychotics
- Review pros/cons of above

Case 1

- 24 y.o. male, drinking heavily at a party
  - Possibly other substances on board
- Becomes a bit too rambunctious, falls, breaks through glass-topped table with his head
- Multiple lacerations to scalp
- Does not want EMS transport; fights vigorously

Case 2

- Mom calls EMS because her 19 y.o. son is acting strangely – thinks people are after him, is concerned his stepfather is trying to kill him.
- Has been talking to his sister, who died 6 months ago
- No psychiatric history
- Is calm and cooperative until you attempt to check his BP, at which point he becomes extremely agitated and is convinced you are trying to kill him, too

Case 3

- Police called for 30 y.o. male on a narrow ledge on the wrong side of a 6’ fence above a highway overpass, threatening to jump.
- 30’ to the road surface.
- No shirt, glistening with sweat…at night, in spring, in Minnesota
- Brandishing a sharpened stick and a broken bottle; has cut himself with the bottle
- Threatens anyone & everyone who gets near

Agitated

"A state of motor restlessness accompanied by mental tension"

- Signs may include
  - pacing, hand wringing, clenched fists, hitting objects
  - Yelling, threatening, pressured speech
- Potential causes include
  - Psychiatric / Dementia
  - Drugs / Medications
  - Infections (especially CNS infections)
  - Trauma / brain injury
  - Thyrotoxicosis
  - All of the above, and a few million other causes

Delirium

"An organic mental syndrome characterized by global cognitive impairment stemming from a medical condition. . .A disturbance of consciousness, with reduced ability to focus, sustain, or shift attention"

- Signs may include:
  - Abrupt onset, waxing & waning severity
  - Disturbances in attention & recent memory; disorientation
  - Easily distractible, can't maintain a conversation
- May present as agitation in 1/3 of elderly patients with delirium
- Unrecognized delirium increases morbidity/mortality

Agitation + Delirium?

- Sort of… but not quite that simple
- Every case is different but “The consistency lies with subjects who are delirious with evidence of psychomotor and physiologic excitation.”
- Not yet a formal medical or psychiatric diagnosis
  - That doesn’t mean it doesn’t exist
- AKA Excited Delirium (EXD)
- Or Excited Delirium Syndrome (EXDS)

Agitated Delirium

- First described in 1849:
- Bell, L. On a form of disease resembling some advanced stages of mania and fever, but so contradistinguished from any ordinary observed or described combination of symptoms so as to render it probable that it may be an overlooked and hitherto unrecorded malady.

American Journal of Insanity 1849, 6:97-127

AMERICAN

JOURNAL OF INSANITY,

FOR OCTOBER, 1849.

ARTICLE I.

On a Form of Disease resembling some advanced stages of mania and fever, but so contradistinguished from any ordinarily observed or described combination of symptoms, as to render it probable that it may be an overlooked and hitherto unrecorded malady: by LUTHER V. BELL, M. D., Physician and Superintendent of the McLean Asylum for the Insane, Somerville, Mass.

*changed the name to “American Journal of Psychiatry” in 1921

Bell's Mania

- 40 cases out of ~1700 patients, 1836-1849
- Sudden onset, tremulous, anxious, flushed
- Pacing, agitated, often had to be restrained
- "struggle with the utmost desperation, irrespective of the number or strength of those who may endeavor to restrain him"
- Emphasized differences between this and other similar diseases – DT's, mania, meningitis, advanced typhoid
- "three quarters terminated fatally;"
  - the other cases resolved with no sequelae
- Autopsy presents "a meagre and scarcely appreciable amount of changes"

Agitated Delirium

- Scattered case reports of Bell's Mania until 1950's
- Fell off the radar screen as psychiatric treatment changed
- Resurfaced in the mid-1980's
  - Wetli, et al. reported on some recreational cocaine users who had died with a very different presentation than the typical cocaine toxicity – "agitated delirium"
  - levels much lower than the usual fatal cocaine OD
  - High levels of cocaine metabolites suggesting a recent binge

Cocaine-associated agitated delirium and sudden death in recreational cocaine users. *J Forensic Sci* 1985 30:873

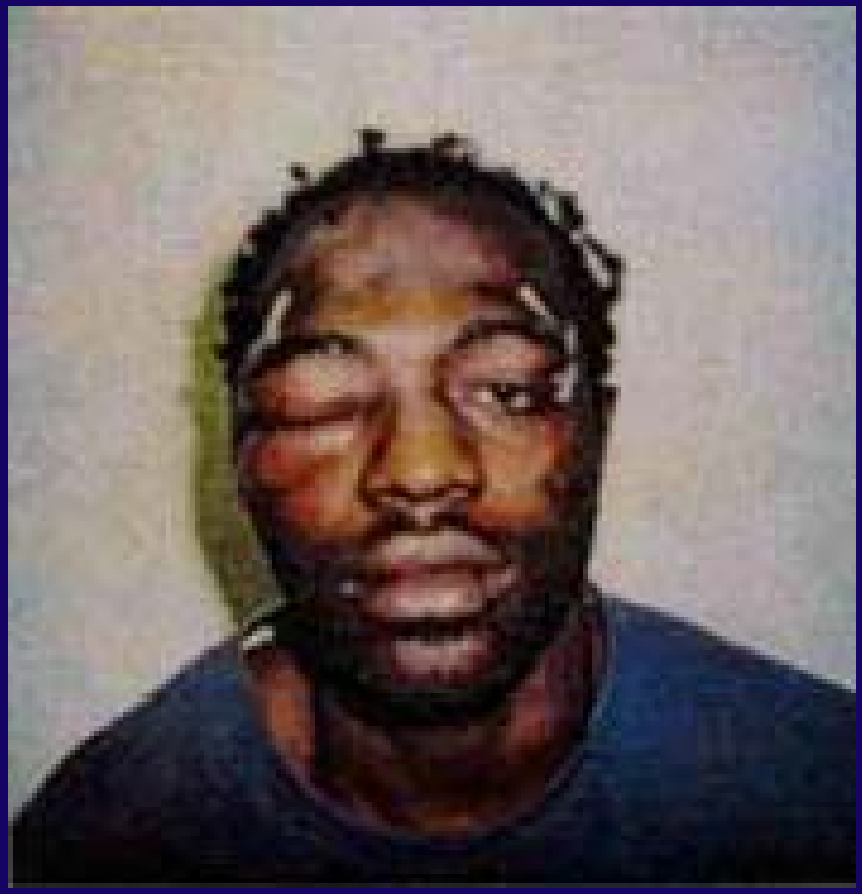
Agitated Delirium

Remained an ill-defined disorder for ~20 years,
mainly discussed in forensic journals

Typical case (in literature from the 1980's):

- Acute drug intoxication (usually cocaine)
- Often had a history of mental illness
- Struggle with law enforcement
- Vigorous control measures (physical, chemical, or electrical)
- Sudden, unexpected death
- No definite cause of death at autopsy

Made as a diagnosis of exclusion… at autopsy



Police Brutality

- Increased interest in police brutality in the 1990's
- Case reports of patients arresting during/after violent struggles with multiple officers
- Often profoundly acidotic
  - pH as low as 6.25
- Hyperthermia, rhabdomyolysis

Police Brutality?

- Drugs often thought to be the culprit BUT
- Some patients died of bradyarrhythmias
- Most had no evidence of V fib / Vtach arrest
- Drug levels often lower than would be expected, and in some cases undetectable
- No clear findings at autopsy…

Hogtied

- One common theme seemed to be violent struggle against restraints,

  +/- officers “sitting” on the restrainee
- Canadian study of 21 unexpected deaths
  - All deaths associated with physical restraint
  - 18/21 with prone position, 8 with chest pressure
  - 3/21 with pressure applied to the neck
  - No clear cause at autopsy
  - Drug levels (when present) consistent with recreational use; some cases had signs of a recent binge

Hogtied

- Some thought that this impaired ventilation, preventing patients from compensating for lactic acidosis
- Several studies showed that, while some measures of pulmonary function are impaired, it doesn't have a measureable effect
  - Healthy volunteers
  - On exercise machines
  - No drugs on board (maybe…)

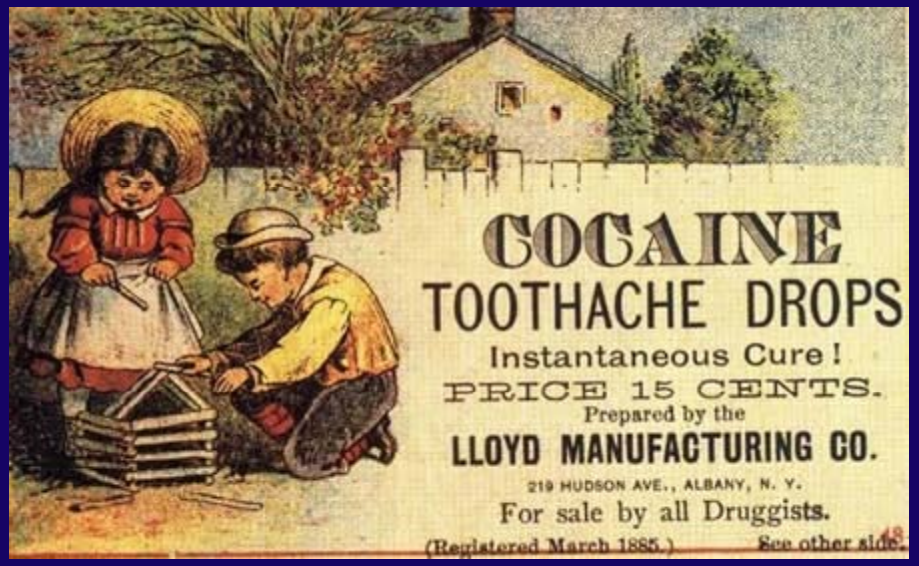
Typical Study Participant

Pick Me Up

- While restraints probably don't cause an acidosis, struggling against them might compound an already existing derangement caused by stimulants like
  - LSD
  - PCP
  - Amphetamines
  - And especially

Cocaine – a brief aside

- Brought back to Europe from South America in the 1500's
- Not chemically isolated until 1855
- Improved purification process published in 1860
  - As a PhD dissertation!
- 1st local anesthetic



Cocawine

- In 1863, Mariani, a chemist who had read accounts of cocaine use by native Peruvians, had the brilliant idea to dissolve coca leaves in wine
  - Earned an award from Pope Leo XIII
- By 1885 Parke-Davis sold cocaine in various forms, including a cocaine mixture that could be injected directly into the user's veins
  - They even included a needle
- Not a controlled substance in the US until 1970!

To the Pole!

"Forced March" brand pills

"Containing the combined active principles of Kola Nut and Coca Leaves"

"Allays hunger and prolongs the power of endurance"

The March of Progress

- Astute clinicians realized that not everyone with what looked like agitated delirium died
- Study published in 2001 suggested a mortality rate of 8.3% (18/214) for patients with EXDS
- Meanwhile, other studies were showing:
  - Most, but not all cases were drug-related;
    - Cocaine was by far the most common
  - Some patients had psychiatric illness
    - Some relation with stopping treatment
  - A very few had systemic illnesses

EXDS Task Force

Assembled in 2008 to decide

1. if the entity commonly referred to as “excited delirium” exists, and
2. if so, whether it could be better defined, identified, and treated.

- Did not include Chuck Norris

EXDS – Current "Definition" (2009)

- 6 of 10 criteria
- "Subjects are incoherent and combative, and the struggle is more severe than anyone anticipates"
- "exhibit intense struggling even when a struggle is futile and self mutilation is a result"

FEATURE	FREQUENCY % (95% CI)
Pain Tolerance	100 (83-100)
Tachypnea	100 (83-100)
Sweating	95 (75-100)
Agitation	95 (75-100)
Tactile Hyperthermia	95 (75-100)
Police Noncompliance	90 (68-99)
Lack of Tiring	90 (68-90)
Unusual Strength	90 (68-90
Inappropriately Clothed	70 (45-88)
Mirror/Glass Attraction	10

Epidemiology

- Incidence – unknown
  - Canadian police looked at over 1M interactions –
    - 24 cases out of 698 use-of-force
    - 2-5% of use-of-force cohort
- Incidence of death among patients suspected to have EXDS – unknown
  - 18 fatalities in 214 cases in one report
  - Maybe around 8-10%?

Dopamine

- Currently, researchers think dopamine is the key
  - Movement regulation
  - Hypothalamic function
  - Behavioral reinforcement
  - Higher cognitive function
- Dopamine processing becomes abnormal in cocaine abusers
  - And is even more abnormal in those who die from EXDS

Dopamine

- Cocaine prevents reuptake of dopamine in the synapse; excess dopamine leads to hyperactivity and hyperthermia
- Over time, dopamine receptors are downregulated due to chronic overstimulation
- Chronic cocaine users have increased α-synuclein
  - Adaptive - helps increase reuptake of dopamine
- EXDS victims have decreased levels in some parts of the brain, and only slight increase in others

Dopamine Transporters

- Help clear the excess dopamine from the synapse
- Both the amount & functionality of dopamine transporters are increased in chronic cocaine users. . . But not in EXDS victims
- Some schizophrenic patients have similar abnormalities in dopamine processing
- Antipsychotics block dopamine receptors

Serotonin

- Cocaine also inhibits serotonin reuptake
- Serotonin may help regulate dopamine transmission
- Chronic cocaine users also have increased serotonin transporter amount & function
- Again, EXDS victims lack these protective changes
- EXDS is possibly on a spectrum with NMS

When to Think EXDS

Features in History	# Articles
Male gender	16
Mean age ~30's	16
Sudden onset	4
History of Mental Illness	8
History of Psychostimulant abuse	11
Features evident at scene	**# Articles**
Call for disturbance/psychomotor agitation/excitation	18
Violent/combative/belligerent/assault call	11
Not responding to authorities/verbal commands	1
Psychosis/delusional/paranoid/fearful	13
Yelling/shouting/guttural sounds	7
Disrobing/inappropriate clothing	5
Violence toward/destruction of inanimate objects	7
Walking/running in traffic	3
Subject Obese	5

Features evident on contact	# Articles
Significant resistance to physical restraint	11
Superhuman strength	8
Impervious to pain	3
Continued struggle despite restraint	7
Profuse sweating/clammy skin	3
Features with clinical assessment	**# Articles**
Tachypnea	1
Tachycardia	7
Hyperthermia	12
Hypertension	3
Acidosis	3
Rhabdomyolysis	5

When to Think EXDS

- Particularly likely if
  - Constant or near constant physical activity
  - High pain tolerance
  - Superhuman strength
  - Sweating
  - Tachypnea
  - Tactile hyperthermia
  - Fails to respond to police presence

What Else?

The differential diagnosis for other processes that may look similar to EXDS is long.

A few items of note:

- Hypoglycemia, Heat Stroke
  - Not usually acidotic
- NMS / Serotonin Syndrome
  - Not usually combative
- CNS infection

Other Potential Causes

- Acute psychosis, alcohol withdrawl, alcohol intoxication, traumatic brain injury, atypical seizure (frontal lobe), stimulant intoxication, anticholinergics, other drugs, encephalopathy (hepatic, HIV, infectious), hyponatremia, hyperthyroid, porphyria, hypoxia, hypercarbia…
- Most of these require more extensive medical evaluation & lab testing to diagnose

What to Do

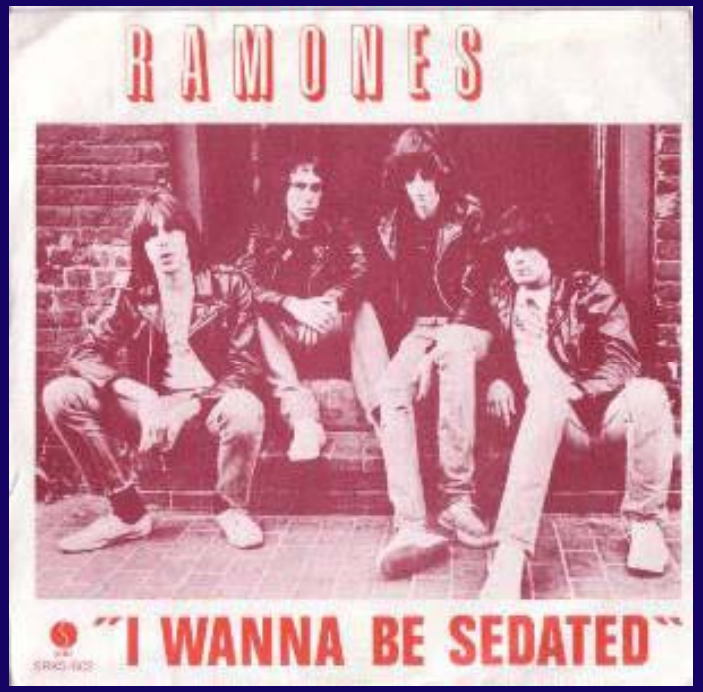
- General Approach to the Agitated Patient
  - Only a small percent of agitated patients will have EXDS
  - Only a small percent of those are at risk for sudden death… we think…
- Make the patient as comfortable as possible
- Develop a therapeutic alliance
- Keep your cool

- De-escalation
  - Requires a (somewhat) rational patient
  - May require “excusing” some folks from the scene
  - Keep your cool
  - Does not work in EXDS
- Avoid struggle & restraints if possible
  - “Yeah, right” – it is possible, sometimes
  - Do what you must to keep yourself, other scene members and the patient safe

- “Physical struggle is a much greater contributor to catecholamine surge and metabolic acidosis than other causes of exertion or noxious stimuli”
- Do what you can to minimize the amount of time the patient spends struggling
  - Keep the patient as comfortable as possible
  - Keep in mind that restraints can be a source of agitation
  - Do what you can to minimize other sources of agitation
- If you must restrain the patient, avoid the prone position if possible
  - Kneeling or standing is preferred

"Most authorities, including this task force, posit the beneficial use of aggressive chemical sedation as first line intervention"

- Be prepared to sedate &/or resuscitate BEFORE attempting to control the patient



Drugs for the Agitated Patient

Agitation is thought to be due to increased dopamine and decreased GABA; role of serotonin much less clear

- Benzodiazepines (facilitate GABA)
- Typical Antipyschotics (decrease dopamine)
- Combinations of the Above
- Atypical Antipsychotics
  - (block serotonin and dopamine)
- Other agents?

A few words on dosing

"One should be aware of manufacturers suggested dosing recommendations for other uses, but be prepared to use clinically effective doses for the management of this condition"

- ACEP Exicited Delirium Task Force White Paper Report on Excited Delirium Syndrome, 2009

Benzodiazepines

- Facilitate GABA transmission
- Sedating and anxiolytic (calming)
- Very safe
  - no EPS or arrhythmogenic side effects
- Drug of choice for sympathomimetic intoxication & alcohol withdrawl/DT's
- Can be mixed with haldol in same syringe
- Some research shows that if one agent is not effective, another might be

Benzodiazepines

- Can be unpredictable when given IM
- Often require multiple doses
- Major side effects are dose-dependent
  - Respiratory depression, excessive sedation
  - Sedative effects are additive with other CNS depressants
  - May cause ataxia
- Paradoxical disinhibition
  - More common in patients with underlying structural brain problems

How Much Should We Give?

"Often benzodiazepine doses many times the traditional suggested dose for sedation are required, and there is likely no maximum dose limit for benzodiazepines when facilities for respiratory and blood pressure support are available."

- ACEP Exicited Delirium Task Force White Paper Report on Excited Delirium Syndrome, 2009

- More, More, More
- Creedence Clearwater Revival

Lorazepam

- Consistent, rapid IM absorption
- 1-2mg PO, IM, or IV
  - IV/IM forms require refrigeration
- Onset 15-30 minutes IM, 2-5 minutes IV
- Duration 8-10 hours
- 2-4mg of lorazepam has been shown to be equal to 5mg haldol in controlling agitated patients

Midazolam

- More rapid absorption & onset of action than lorazepam when given IM
- Available as an intranasal spray
- Typical dose 2-5mg IV; 5mg INH or IM
- Onset 3-5min INH or IV; 10-15min IM
- Short duration – may wear off in as little as 30 minutes
- Diazepam – great IV, not so hot IM

Typical Antipsychotics

- Inhibit dopaminergic transmissions
- **All** typical antipsychotics prolong QT
  - But then again, so does cocaine
- All can theoretically lower seizure threshold
- May cause extrapyramidal symptoms
  - Dystonia, akathisia, Parkinson-like effects
  - Prophylactic anticholinergic is NOT recommended
- Some risk for NMS
- Many patients do not like how TA's make them feel & prefer other agents

Haloperidol

- Can be given PO, IM, or IV;
  - IV use is off-label; FDA issued a warning/reminder of this in September 2007
- Typical Dose – 5-10mg every 10-30minutes
  - Doses up to 600mg/24h have been given safely
  - That's 5mg q5min in case you're wondering
- Onset ~30min IM, 10-15min IV
- Can last ~24 hours

FDA Alert: Haloperidol

The Food and Drug Administration issued this alert in September 2007.

This alert highlights revisions to the labeling for haloperidol (marketed as Haldol, Haldol Decanoate, and Haldol Lactate). The updated labeling includes WARNINGS stating that Torsades de Pointes and QT prolongation have been observed in patients receiving haloperidol, especially when the drug is administered intravenously or in higher doses than recommended. Haloperidol is not approved for intravenous use.

Haloperidol

- QT prolongation is minimal, clinically insignificant
  - Haldol is less problematic than other antipsychotics
- Dystonic reactions more common with haloperidol than other typical antipsychotics
- NMS does happen

Droperidol

- The infamous “black box” in 2001 led to a drastic decrease in use
  - Concerns about QT prolongation
  - 2 studies, looking at over 14,000 patients showed no difference in mortality/morbidity
- IM or IV, 2.5-10mg
- Faster onset of action, shorter duration than haloperidol
- Outperformed haldol in patients with increased BAL

Atypical Antipsychotics

- Block serotonin and dopamine
- Fewer side effects than either benzodiazepines or typical antipsychotics
- More “calming,” less sedating
- Can prolong the QT –
  - Less than the typicals; “clinically insignificant”
- Co-administration with benzos is not recommended
- Have mostly been studied in non-intoxicated, medically stable patients
  - A few smaller studies have looked at broader populations

Ziprasadone

- Typical dose 10-20mg, IM or PO
- Rapid onset, ~15min IM
  - Both ziprasadone and olazepine have faster onset than IM haldol or IM lorazepam
- Duration ~4 hours
- One study (110 patients) treated undifferentiated patients, including
  - Nonspecific & drug induced psychoses
  - Alcohol intoxication
  - Our typical patients

Olanzapine

- Also rapid onset; much longer duration of action – up to 24h
- Typical dose 10mg IM
- Actually decreased the QTc (3ms) in one study
- May cause hypotension, bradycardia, and cardiorespiratory depression
- In trials, fantastic for schizophrenic, manic, and demented patients

Olanzapine

- In one study of dementia patients, olanzapine decreased agitation more quickly than lorazempam
- Another study found olanzapine to be a safe alternative to haldol in delirious ICU patients
  - No dystonia
  - Safe for Parkinson's patients
  - No QTc prolongation seen

Combinations

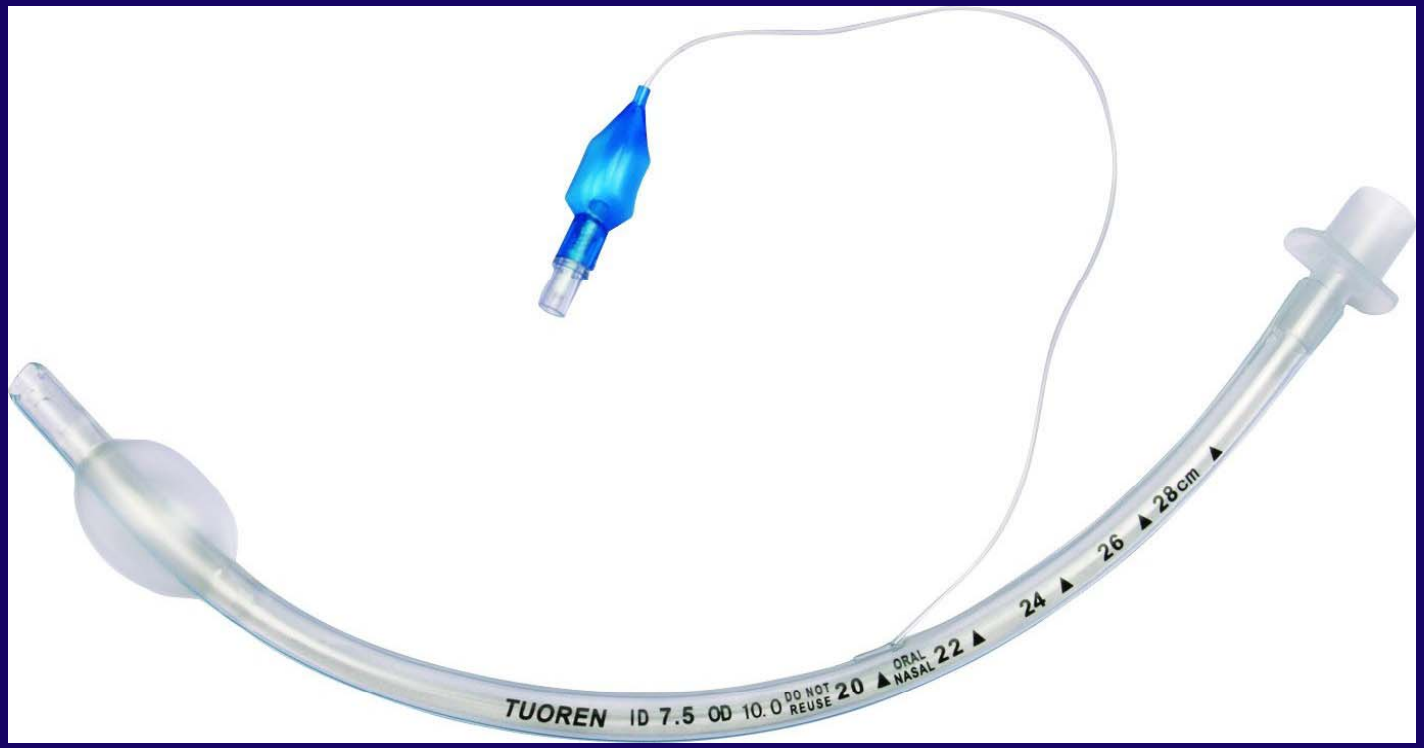
- The most studied combination is haldol/lorazepam
- All studies have shown superiority of the combination to either agent alone
  - Faster reduction in agitation
  - Less time in restraints
  - Fewer side effects

The Psychiatrists Weigh In

- Survey of 50 emergency psychiatrists
- Overall, atypical antipsychotic agents are preferred for agitation for primary psychiatric illness, while benzodiazepines are preferred in other situations.
  - Undifferentiated patient, alcohol/drug related
- BUT “no specific atypical antipsychotic agent is preferred over haloperidol.”
- Haloperidol is best combined with a benzodiazepine unless the patient is medically compromised.

- J Psychiatr Pract 2005;11[supp 1]:5.

When All Else Fails…



The “attitube”

Class	Agent (Trade Name)	Available Routes	Dosing (mg)*	Onset (min)	Duration (min)
Midazolam (Versed)		IN	5	3-5	30-60
		IM	5	10-15	120-360
		IV	2 - 5	3-5	30-60
Lorazepam (Ativan)		IM	4	15-30	60-120
		IV	2 - 4	2-5	60-120
Diazepam (Valium)		IM	10	15-30	15-60
		IV	5 - 10	2-5	15-60
†Haloperidol (Haldol)		IM	10– 20	15	180-360
		††IV	5 – 10	10	180-360
†Droperidol (Inapsine)		IM	5	20	120-240
		IV	2.5	10	120-240
Ziprasidone (Geodon)		IM	10– 20	10	240
Olanzapine (Zyprexa)		IM	10	15-30	24 hrs
Ketamine (Ketaset, Ketalar)		IM	4-5 mg/kg	3-5	60-90
		IV	2 mg/kg)	1	20-30

Drugs - Summary

- Benzos are the agent of choice for the undifferentiated patient
- This may change as we learn more about EXDS
  - If dopamine really is the key, antipsychotics may be a better choice
- Whatever your choice, give enough.
- Oversedation may be less of a risk than continued struggle in patients with EXDS

Case 1

- 24 y.o. male, drinking heavily at a party
  - Possibly other substances on board
- Becomes a bit too rambunctious, falls, breaks through glass-topped table with his head
- Multiple lacerations to scalp
- Does not want EMS transport; fights vigorously

Case 1 - Resolution

- Pt was “sandwiched” between 2 backboards and transported to ED, kicking and fighting the whole way
- Once he realized he was in ED, he begged to be freed – “I’ll behave, I promise!”
- Restraints loosened & pt was very cooperative
- Turns out he was afraid of the bill…
- Lacs repaired, metabolized to freedom

Case 2

- Mom calls EMS because her 19 y.o. son is acting strangely – thinks people are after him, is concerned his stepfather is trying to kill him.
- Has been talking to his sister, who died 6 months ago
- No psychiatric history
- Is calm and cooperative until you attempt to check his BP, at which point he becomes extremely agitated and is convinced you are trying to kill him, too

Case 2 - Resolution

- Police arrived & restrained patient
  - Prolonged struggle
- Pt given 2mg ativan IM x 2
- Sleepy but arousable by ED arrival
- Labs notable for WBC 18k
  - Also had a metabolic acidosis, which resolved quickly; likely due to struggle
- LP with 1800 WBC's
- Admitted to medicine for meningitis

Case 3

- 30 y.o. male on a narrow ledge on the wrong side of a 6’ fence above a highway overpass, threatening to jump. 30’ to the road surface.
- No shirt, glistening with sweat…at night, in spring, in Minnesota
- Brandishing a sharpened stick and a broken bottle; has cut himself with the bottle
- Threatens anyone & everyone who gets near

Case 3 – Resolution

- Police grabbed the patient through the fence
- Pt was given 300mg Ketamine IM, through the fence, and another 150mg IM 4 minutes later;
- Pt was limp within 5 minutes
  - Still breathing spontaneously
- Firefighters in an aerial bucket got the patient onto a backboard & lowered him to the ground
- Intubated on arrival at the ED, spent the night in the ICU & was extubated 12 hours later.
- Went uneventfully to the pyschiatric service

Ketamine?

- Extremely rapid onset
  - 3-5 minutes IM, <1 minute IV
- No cardiac or respiratory depression, no loss of airway protective reflexes
  - 886 surgical cases in the Pacific Islands, without monitoring – no complications
- Does not lower seizure threshold
- May cause bronchorrhea

Ketamine

- Some data with flight programs in the US
  - WI, 40 cases, age 2m – 75y, over 3 years
  - Doses from 1-5mg/kg, given IM and IV
  - Given without IV access in several cases
  - Given for pain control in hypotensive patients, combative patients, asthma patients
  - No complications – "All maintained airway responsiveness and oxygen saturations."
  - Svenson, et al. Ketamine for prehospital use: new look at an old drug. *Am J Emerg Med* 2007; 25:997

Ketamine

- May increase ICP
  - Head injury is a relative contraindication
  - Israeli series of 11 combative trauma patients with prolonged transport times; 3 had TBI
  - No complications during transport
    - Melamed E, et al *Euro J Emerg Med* 2007;14(5):265
- Emergence reaction
  - Treatable with benzodiazepines
- Biggest risk?

Summary

- We’re not sure how common EXDS is
  - Other causes of agitation are much more common
- EXDS can be fatal
- Sedation is a good thing
- Don’t be afraid to give more drugs
- Think about ketamine for special situations

Key References

- ACEP Exicited Delirium Task Force, White Paper Report on Excited Delirium Syndrome, 2009
- Battaglia, J. Pharmacological Management of Acute Agitation. *Drugs* 2005; 65 (9):1207-1222
- Takeuchi, A, Ahern, T, Henderson, S. Excited Delirium. *West J Emerg Med* 2011; 12(1):77-83