Second National Doctors of Nursing Practice Conference: Defining Ourselves

Sugammadex Sodium:
A Synthesis of the Evidence Regarding Neuromuscular Blockade Reversal

Mark Welliver, CRNA, DNP, ARNP
Associate Professor of Professional Practice
Harris College of Nursing and Health Sciences.
Doctor of Nursing Practice Program.
Texas Christian University.

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Mark Welliver is a member of the CRNA advisory council on neuromuscular blockade reversal and has been a paid consultant for Organon/ Schering-Plough. He is also an investigator in a phase III clinical trial of sugammadex sodium. He has received no financial or material incentives related to this project or presentation.

Outline

- Complexity Theoretical framework
- Evidence-based practice model
- Problem identification
  - Cholinesterase inhibitor NMB reversal
- New drug Sugammadex Sodium
- Synthesis of evidence
- Recommendations for practice
  - Direct clinical application
  - Indirect practice improvement
  - Further study
- Practice incorporation
  - Decision making
  - Stakeholder
  - Barriers
- Conclusion

Objectives

1. Critically appraise current neuromuscular blockade reversal methodologies in patients receiving muscle relaxant drugs.

2. Analyze current research finding regarding new pharmacology to restore muscle function.

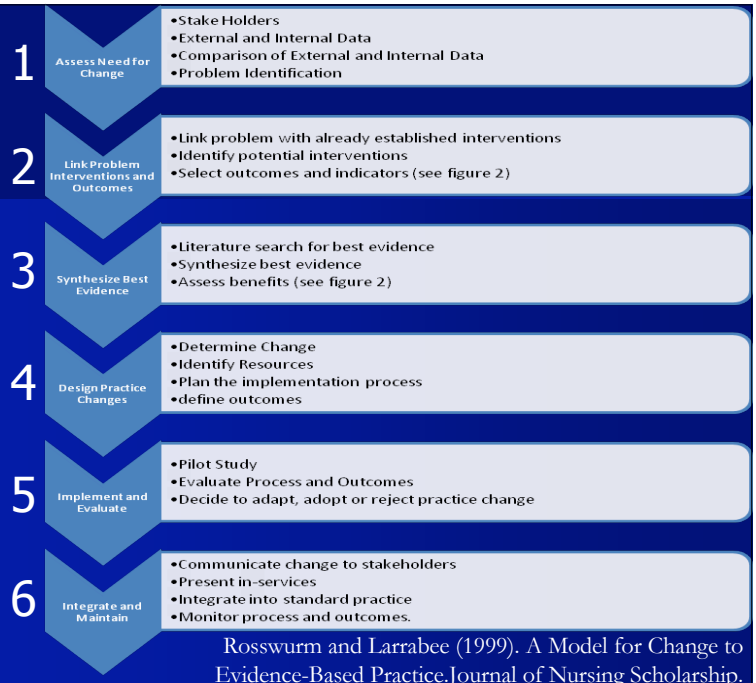
3. Interpret evidence-based recommendations for best clinical practices.

Complexity Theory

"The nursing profession exemplifies the assimilation of both dualist (holist) and materialist (reductionist) perspectives in a comfortable holistic coexistence. It is the nursing profession's encompassing views of mind, body, and spirit that encourage the use of reductionism, without disregard for holism, in the pursuit of understanding complexity."

Welliver M & Kean R. (2008). A Nursing Argument for Incorporating Reduction in Complexity Study. Unpublished manuscript.

Evidence-based Practice Model



Rosswurm and Larrabee (1999). A Model for Change to Evidence-Based Practice.Journal of Nursing Scholarship. 31:317-322.

1 Assess Need for Change

Problem identification.
External and internal data.
Comparison of external and internal data.
Stake holders.

Problem identification

Cholinesterase Inhibitor NMB Reversal

- Indirect mode of action
- Numerous side effects
- Limited ability to reverse NMB
- Requires "antidote"
- Antidote side effects
- Limits NMB options

Side Effects of Cholinesterase Inhibitors

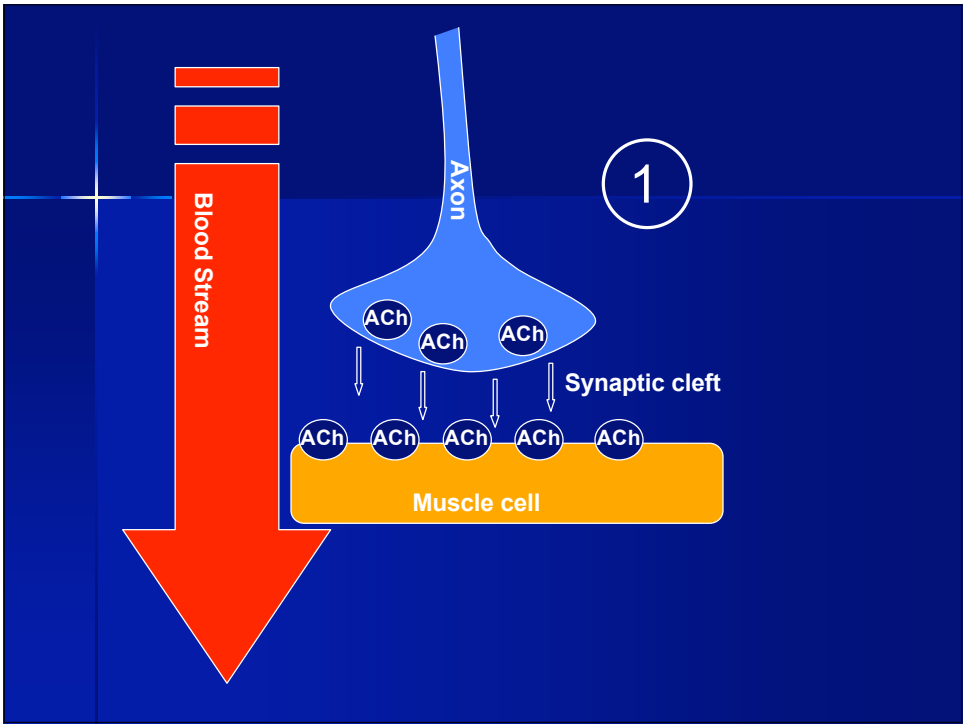
- Bradycardia
- Bronchospasm
- Increased airway secretions
- Nausea
- Vomiting
- Abdominal cramping
- Miosis
- Vision disturbances
- Micturation

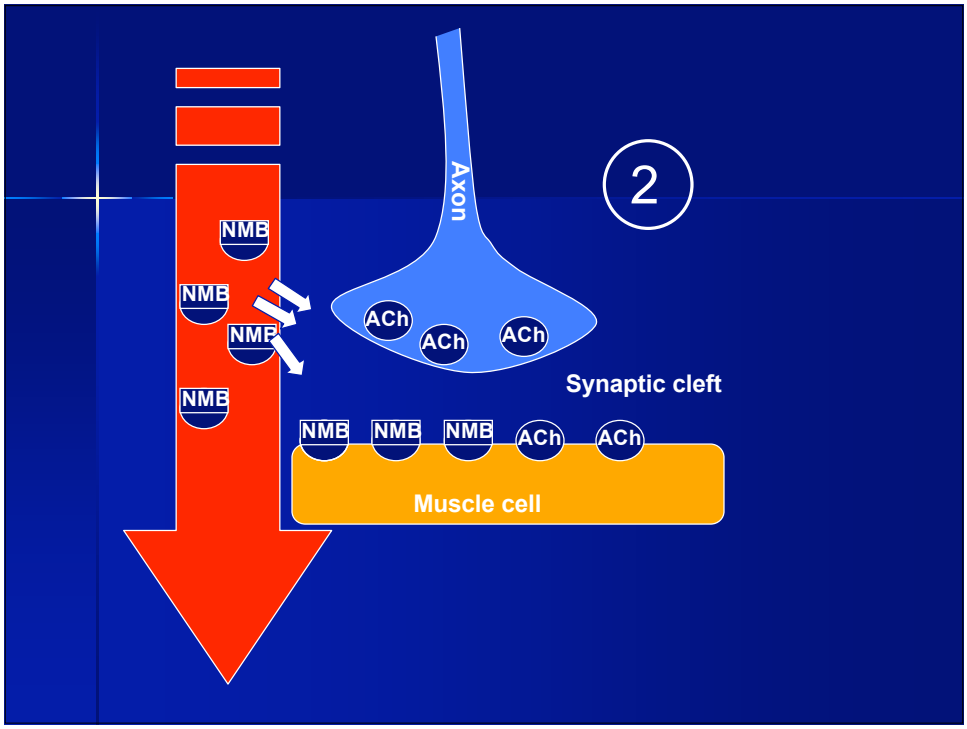
Anti-Cholinergics "The "Antidotes"

- Cholinesterase inhibitors require an anticholinergic antidote
- Used to attenuate the muscarinic effects of cholinesterase inhibitors
- Glycopyrrolate
- Atropine
- Scopalamine
  - Rarely used due to significant central effects

Anti-Cholinergics Side Effects

- Tachycardia
- Dry mouth
- Mydriasis
- Vision disturbances
- Confusion*




2
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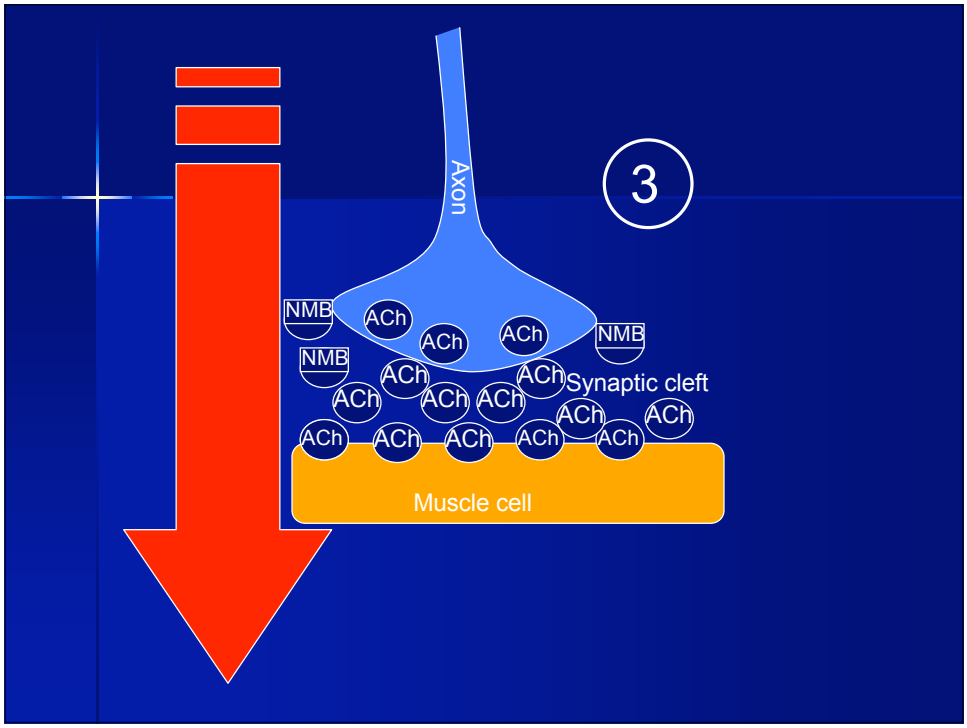
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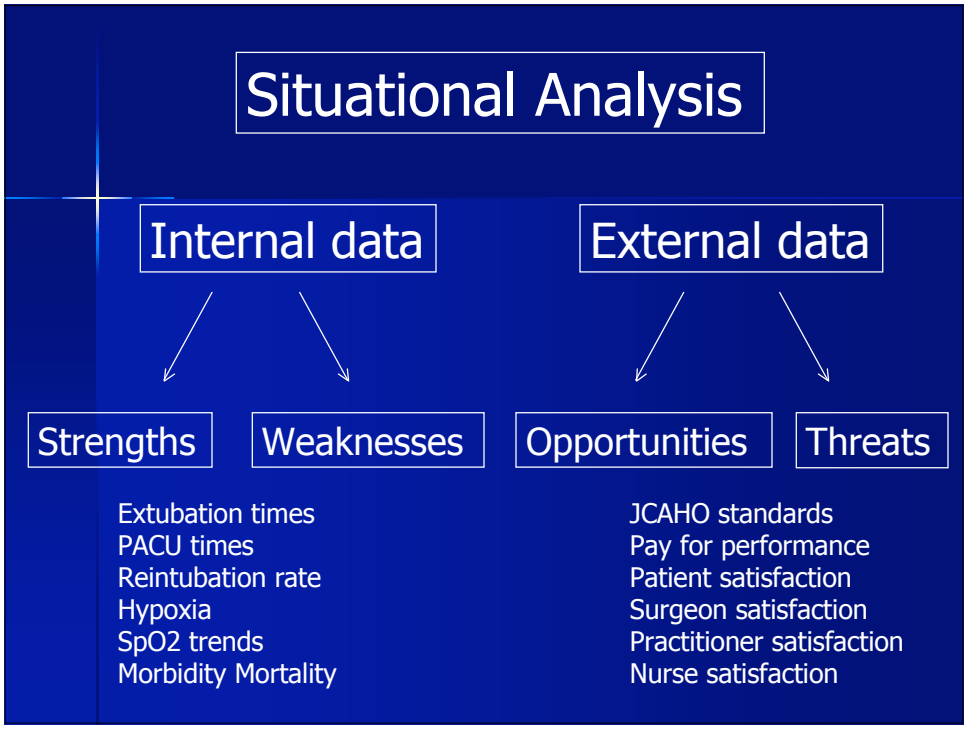


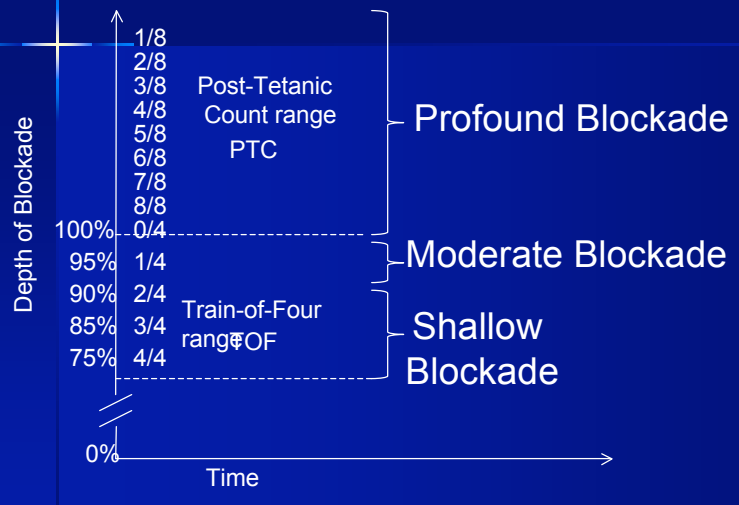
Stakeholders

- Stakeholders:
  - Anesthesia providers
  - Surgeons
  - Pharmacy
  - Purchasing administrators
  - Operating room & Recovery room Nurses
  - Patients
- Barriers:
  - Practitioner resistance to change
  - Drug Acquisition Committee
  - Cost
  - Drug availability

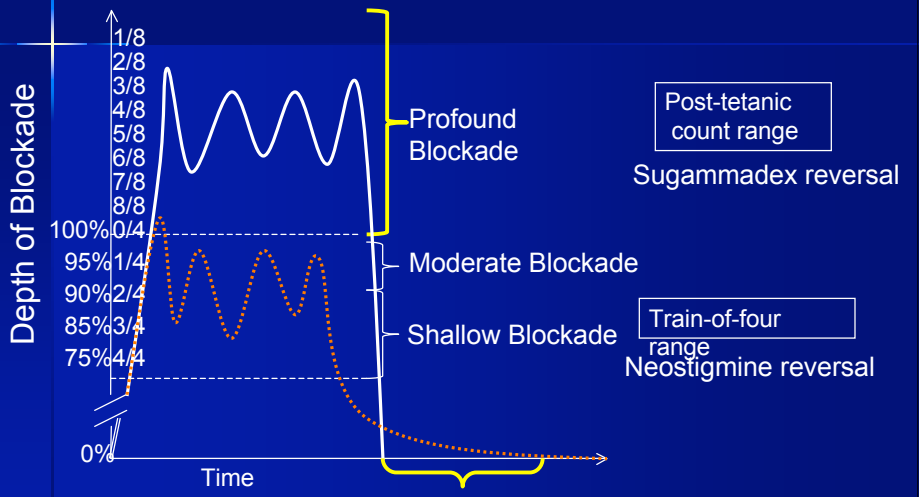
2 Link Problem Interventions & Outcomes

Link problem with already established interventions.
Identify potential interventions.
Select outcomes and indicators.

NMB Depth Ranges



Old & New NMB Management



Potential Interventions

- Methods used to overcome barriers:
  - Knowledge dissemination/empowerment
  - Departmental collaboration
  - Phase III clinical trial participation
  - Inter-departmental collaboration
    - Anesthesia
    - Pharmacy
    - Surgery

Clinical Practice Considerations

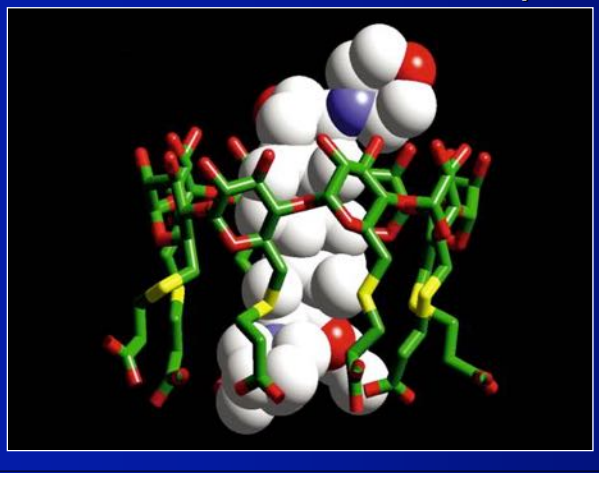
- Muscle relaxation vs muscle paralysis
- Shallow/Moderate vs Profound (Deep) blockade
- Reversability
- Degree reversal
- Residual paralysis
- RSI options
  - Competitive Antagonism
  - Encapsulation Termination

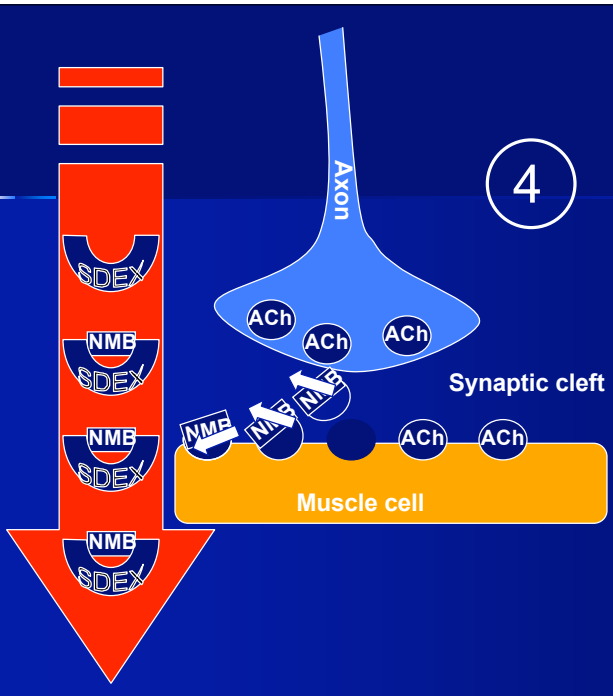
Synthesize Best Evidence

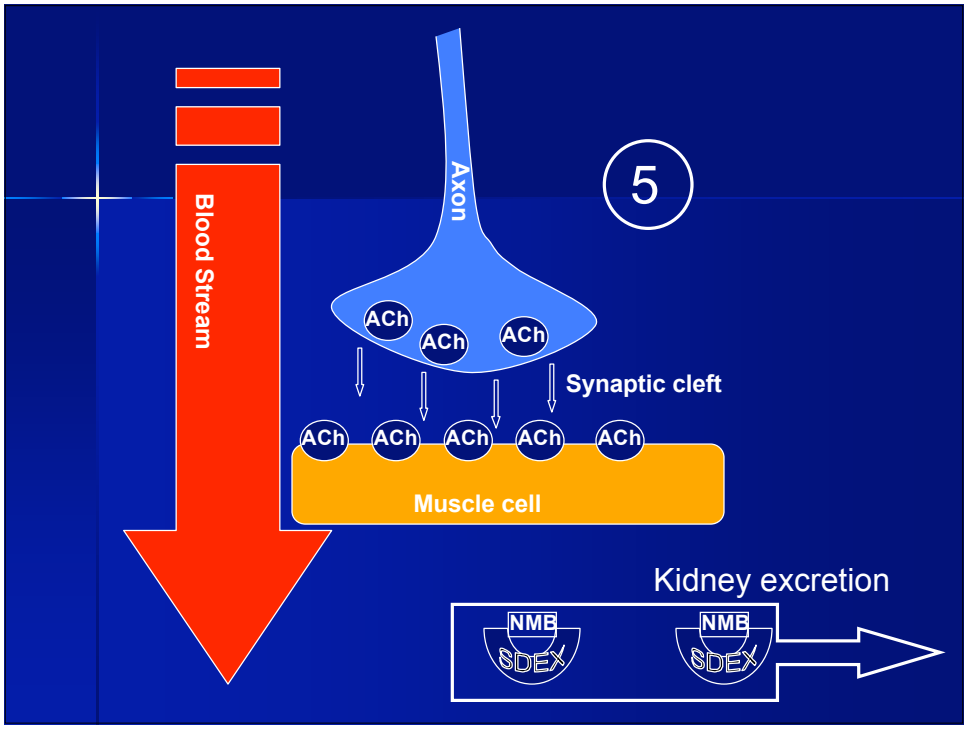
Literature search for best evidence.
Synthesize best evidence.
Assess benefits.

Sugammadex Sodium

- Modified Gamma (8 glucose ring) Cyclodextrin







Capstone Project Synthesis

Cochrane Systematic Format

- 1. Summary
- 2. Structured Abstract
- 3. Background
- 4. Objectives
- 5. Selection criteria Types of studies, Types of participants, Types of interventions, Types of outcome measures
- 6. Search strategy for identification of studies
- 7. Methods of the review
- 8. Description of studies
- 9. Methodological quality of included studies
- 10. Results
- 11. Discussion
- 12. Authors' conclusions

Literature selection

- Inclusion criteria:
  - Peer reviewed
  - Bench studies
  - RCTs
  - Human studies
  - Animal studies
- Exclusion criteria:
  - Expert opinion
  - Drug reviews

Sugammadex

- All animal and Clinical Phase I, II, III (to date n≈2000) have shown:
  - Fast dose-dependent reversal of rocuronium- & vecuronium-induced blockade. Roc. ≤ 3 min. Vec. ≤ 5min.
  - Complete reversal of all levels blockade.
  - No hemodynamic alterations
  - No recurarization
  - Minimal side effects
  - Mild adverse events

Animal Study Conclusions:

- Rapid reversal of rocuronium
- No re-curarization
- Reversal unaffected by acidosis or alkalosis
- Mechanism of action d/t encapsulation and concentration gradient shift away from nicotinic junction.
- Rocuronium blockade after sugammadex reversal only after sugammadex cleared from body

Clinical Study Conclusions

- Reverses rocuronium & vecuronium NMB.
- Reverses All levels of blockade including profound block.
- Dose dependant rapid time to full reversal.
- No Re-curarization
- No significant side effects*
- Reversal unaffected by sevoflurane or propofol.
- Sugammadex-rocuronium complex excretion mirrors GFR.
- Sugammadex-rocuronium complex dialysable.

Clinical Study Conclusions

- Reverses shallow pancuronium blockade.
- Re-curarization, Rebound paralysis with too low dose 0.5 mg/kg
- QT prolongation not r/t sugammadex
- Effective in renal patients.
- Effective in pediatrics.
- Effective in elderly but slightly slower onset r/t slower circulation time.

Preliminary Phase III results

Sugammadex Benefits

- Reverses Rocuronium & Vecuronium
- Rapid reversal < 3 min (dose dependant)
- No residual block, No recurarization
- Reverses Profound blockade
- Higher degree reversal than present
- Rescue of residual paralysis from cholinesterase inhibitors
- Renal clearance and dialysable
- Reverses independent of renal function, acidosis, alkalosis
- Re-paralysis possible w/isoquinolones or aminosteroids after sugammadex clearance
- No cardiovascular side-effects
- No cholinergic side-effects
- RSI induction w/large dose NDMR
- Neuromuscular Monitoring? Yes.

4 Design Practice Changes

Determine change.
Identify resources.
Plan the implementation process.
Define outcomes.

Change Practice Recommendations

- Sugammadex used to reverse rocuronium- and vecuronium-induced NMB:
  - Whenever profound NMB is present
  - Hemodynamic and pulmonary parasympathetic effects are undesirable
  - Any degree of residual paralysis will be detrimental to the patient
  - "Can not ventilate, can not intubate" scenario d/t NMB.

Identify Resources

- Academic institution
- Research facility
- DNP practitioners
- High risk populations
- Large patient populations
- We have a Need

Implementation Process

- Complexity theory- one little action may reflect dramatic change.
- Actions:
  - Knowledge dissemination
  - Stakeholder "buy in"
    - Academic institution/endeavor-*done*
    - Co-author publication-*done*
    - Co-investigate clinical trial-*underway*
    - Inter-departmental collaboration- *underway*
    - Inter-departmental funding- *done*

Implementation Stakeholders

- Institutional stakeholders:
  - Patients
  - Anesthesia providers
  - Operating room & Recovery room Nurses
  - Surgeons
  - Pharmacy
  - Purchasing administrators

Define Outcomes

- Reversal of NMB of any depth at any time within 3 minutes.
- No recurarization, no residual paralysis.
- Minimal to no side effects compared to CIs.
- Safer & more efficacious.

5 Implement & Evaluate

Pilot study.
Evaluate process and outcomes.
Decide to adapt, adopt, or reject practice change.

"Pilot" Study

- Utilize phase III clinical trial to incorporate new drug into academic hospital system.
- Pre-purchase drug acquisition & assessment.
- Formal new drug request upon FDA approval.

Decision to adapt, adopt, or reject

- Drug Purchasing committee.
  - Members already involved with publication, clinical trial. "vested interest"
- Formal data presentation (slide and handouts) to Purchasing committee.
- Expected "adopt" determination…

Adapt Change

- Official policy draft of Sugammadex Clinical Guidelines evidence-based capstone project …

"Decreasing complexity of the protocol increases the likelihood of acceptance"

Rosswurm and Larrabee (1999). A Model for Change to Evidence-Based Practice. Journal of Nursing Scholarship. 31:320.

Practice Change

Grades of Recommendation

A	Consistent level 1 studies (RCTs)
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Phillips B, Ball C, Sackett D, Badenoch D Straus, Haynes B, Dawes M. (Nov. 1998). Oxford Centre for Evidence-based Medicine. Available at www.cebm.net/?o=125. Assessed December 12, 2007.

Goal	**Recommendation**	SOR	LOE
Profound rocuronium NMB (PTC<8) reversal	Sug	A	1b
Moderate rocuronium NMB (TOF 1-2/4) reversal	Sug	A	1b
Shallow rocuronium NMB (TOF 2-4/4) reversal	Sug (*CI)*	A	1b
Profound vecuronium NMB (PTC<8) reversal	Sug	A	1b
Moderate vecuronium NMB (TOF 1-2/4) reversal	Sug	A	1b
Shallow vecuronium NMB (TOF 2-4/4) reversal	Sug (*CI)*	A	1b
Rescue residual paralysis s/p sug (insufficient dose)	Sug	A B	1b 1b
Rescue residual paralysis s/p CI	Sug	C	1b
Rocuronium RSI stat reversal	Sug	A	1b
Full airway / Pharyngeal muscle function	Sug	A	1b

Coexisting condition / disease	Recommendation	SOR	LOE
Cardiac ischemia	Sug	A	1b
Unstable hemodynamics	Sug	A B	1b 1b
Restrictive pulmonary disease	Sug	A	1b
Obstructive pulmonary disease	Sug	A	1b
Renal insufficiency creatinine clearance <30 ml/hr	CI *(Sug)*	A C	1b 1b
Acute renal failure	CI	na	na
Chronic renal failure	CI	na	na
Obesity BMI > 30	Sug	B	1b
Morbid obesity BMI >40	Sug	B	1b

Patient population	Recommendation	SOR	LOE
Infants (<23 months)	CI	D *n=8*	1b
Children (2-11 years)	CI	D *n=24*	1b
Adolescents (12-17years)	CI	D *n=31*	1b
Adults (18-65)	Sug (CI)	A	1b
Geriatric (65+)	Sug CI	A	1b

6 Integrate & Maintain

Communicate change to stakeholders.
Present in-services.
Integrate into standard practice.
Monitor process and outcomes.

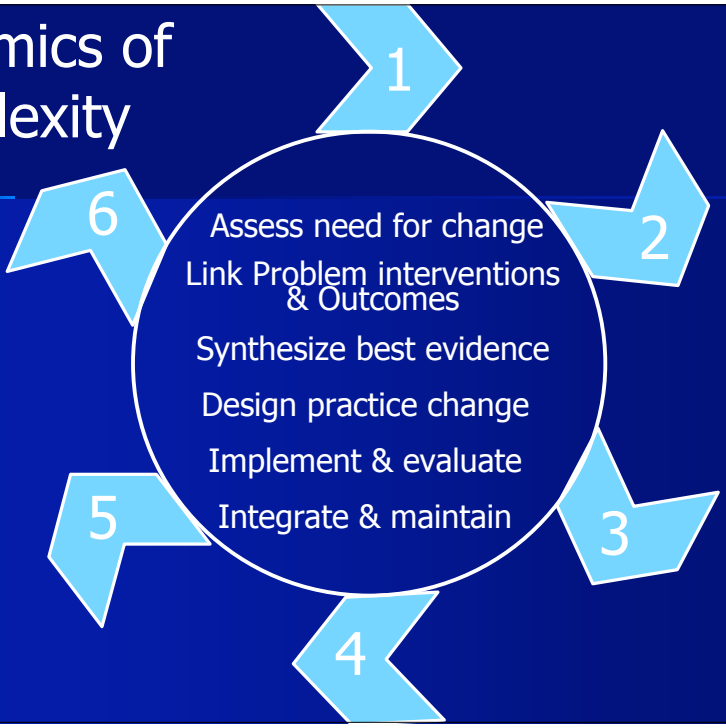
Clinical Change-Guidelines

- Departmental in-service to:
  - Anesthesia department
  - Surgery departments
  - Operating room nurses
  - Recovery Room nurses

Clinical Change

- Sugammadex will be made immediately available on each OR drug cart.
- Phase IV cost & clinical outcome studies will be conducted.
- Knowledge dissemination will continue
  - Institutional presentations- *done*
  - Publication accepted *AANA J. June 2009*
  - National presentation DNP project *NAFA June 2009*

Dynamics of complexity



Conclusion

- The evidence leads to the conclusion that sugammadex is a more effective, safer reversal of rocuronium- and vecuronium-induced NMB at any time and at any depth compared to CIs.
- Practice change recommendation is to use sugammadex instead of CIs using EBP guidelines developed in Capstone project.
- A dynamic EBP model on-going assessment, assimilation, and integration will be initiated.

Questions