



# NORA- NEW TOOLS FOR THE JOB? ANOTHER ROAD TO ROME

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# Disclosures

- No financial disclosures
- OFF-Label use of medication **WILL** be discussed – clearly labelled



## Goals and objectives

- By the end of this conference, participants should be able to:
- Recognize the unique pharmacokinetic and pharmacodynamic properties of Remimazolam
- Distinguish which clinical applications will best suit the pharmacological profile of Remimazolam

# NORA: Challenges

- Airway Management
- Useful Help
- Limited PACU / Recovery resources
- Time Pressure
- Production Pressure
- Transitions to higher level of care
- Distance from higher level of care (miles, not meters?)

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## NORA

### Formulation Wish List

- Rapid onset
- Predictable
- Rapid offset
- Minimal Respiratory effects
- Minimal CV effects
- Multiple routes of administration
- Cheap
- Available

# Drug Development:

- Phase I trials: 2012
- Phase II 2015
- Phase III: 2018
  
- Remimazolam approved for use in Japan 2020
  - Approved for use in US: July 2020
  - Approved for use in EU: March 2021
  
- First use at Mayo clinic: July 2021

# PHARMACOLOGY



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# Remimazolam

## Formulation

- 20mg lyophilized powder
- Reconstitute in saline 8.2mL - >2.5mg/mL
- For IV injection
- Reconstituted in vial: stable 8 hrs room temp



Byfavo.com

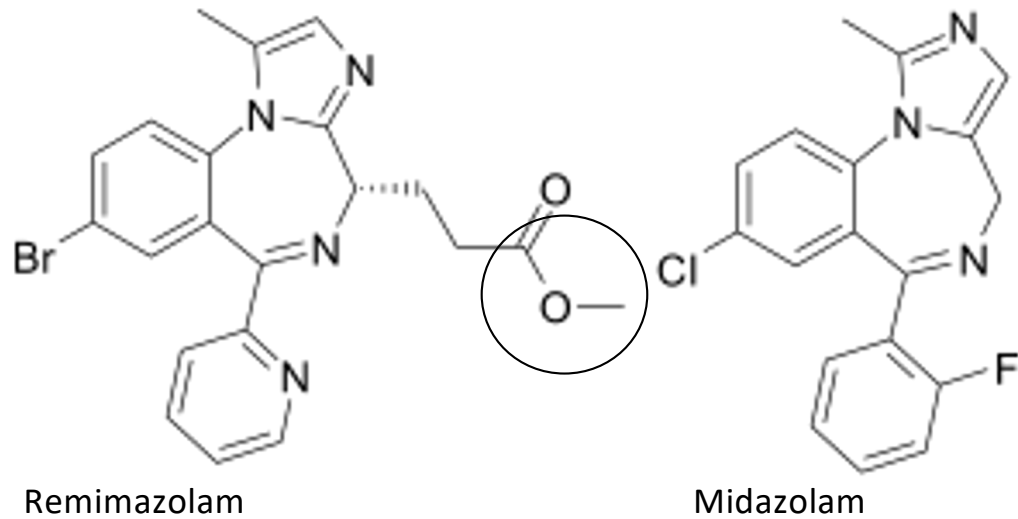


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# Remimazolam:

Physiochemical Properties

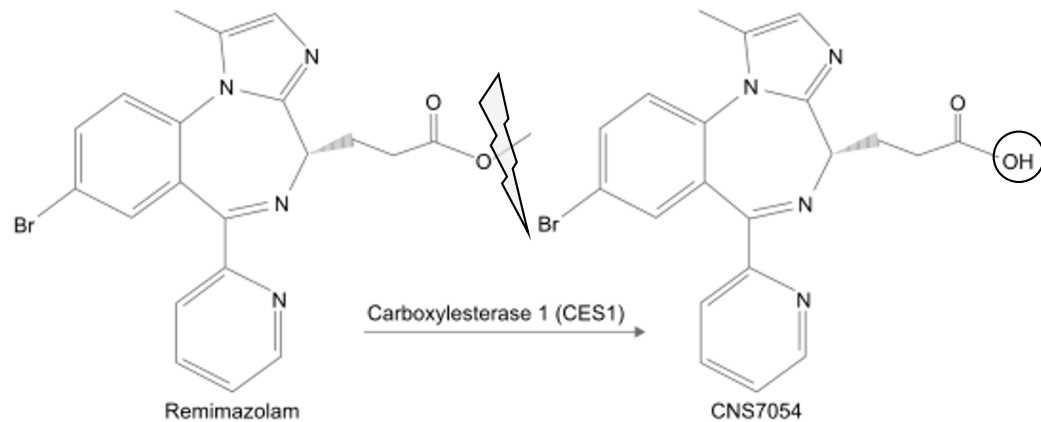
- Additional Ester linkage
- pH 2.9-3.9 in saline



British Journal of Anaesthesia, 127 (1):  
41e55 (2021)

# Remimazolam:

## Metabolism



- Ester linkage hydrolyzed:
  - Tissue esterase
  - Carboxylesterase1 (CES1)
    - Hepatic
- Inactive metabolite:
  - CNS 7054

# Remimazolam

## Formal Pharmacokinetics

- Volume of distribution:  $34 \pm 9.4L$
- Terminal Half-life:  $45\text{min} \pm 9\text{min}$
- Clearance time independent of body mass

## Practical Pharmacokinetics

- Onset and offset:
  - 1-2 minutes for onset
  - Offset: dose dependent.
  - single dose: 10 min
  - Infusion(**off label**): 10-20 min

# Remimazolam

## Pharmacology: Bioavailability

- PO
  - 100% absorption as a liquid
  - 1.2% bioavailability PO
    - 1<sup>st</sup> pass metabolism
    - Even 480mg of PO remimaz had minimal CNS effects (24vials...)
    - Bitter taste
- Low likelihood to be used in drug facilitated sexual assault

# Remimazolam

Pharmacology: Bioavailability

- Study: 12 male volunteers “...*only with experience of intranasal drug administration included*”
  - Intranasal: **Powder**: 10, 20, 40mg
    - 50% bioavailable
    - Elimination: 0.7-0.9hr
  - Intranasal **Solution**(2.5mg/mL):
    - 47% (low volume) 26%(high volume)
- Nasal/Sinus pain prohibitive

# Remimazolam

## Administration

- Dosing:
  - ASA 1-2: 5mg IV with 2.5mg Q2min PRN
  - ASA 3+: 2.5mg with 1.25-2.5 Q2 PRN
- Induction for GA:
  - 0.1-0.3mg/kg (OFF LABEL)
- Contraindications:
  - Allergy to dextran 40 (part of the formulation)

Off Label in US: Infusion Kinetics

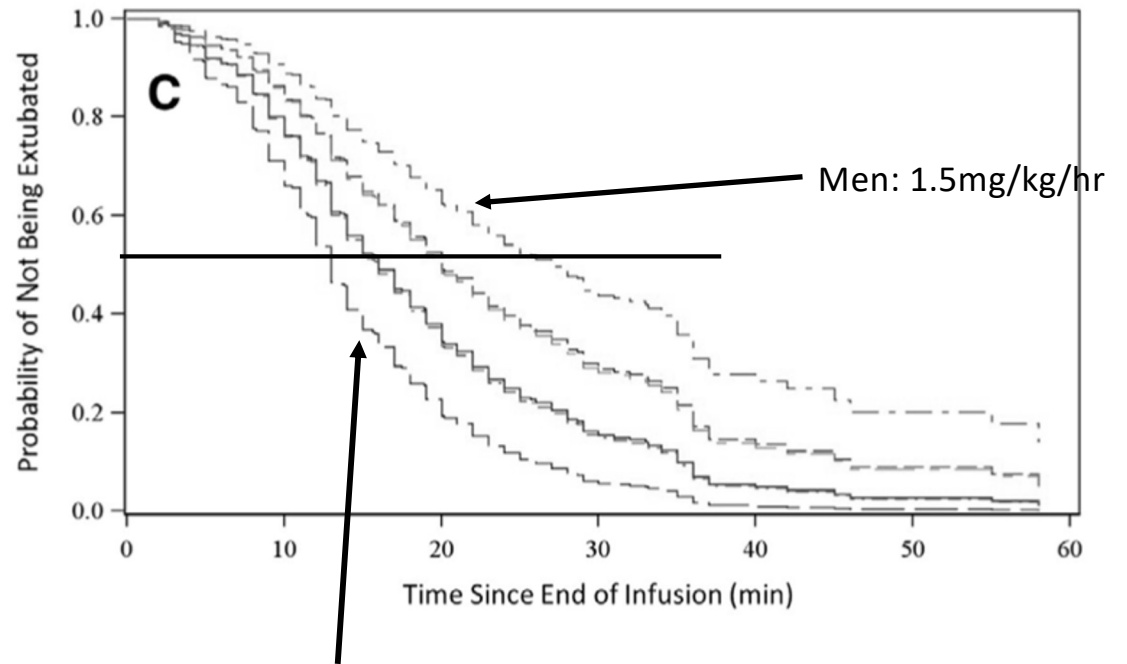
- Infusion for general anesthesia

- Induction:

- 12mg/kg/hr
    - 6mg/kg/hr (15-20s slower)

- Maintenance:

- 1-3mg/kg/hr



Women: 0.5mg/kg/hr +  
BIS 60

# Patient Subsets:

The unknowns:

- Pediatrics –no published studies on pediatric patients
- Obstetrics: unknown placental transfer
- Lactating Women- no published data on presence of remimazolam in breast milk or nursing infant
- Extremes of hepatic dysfunction -
  - European packaging recommends dose reduction
  - Case report of prolonged sedation with Child-Pugh score of 11

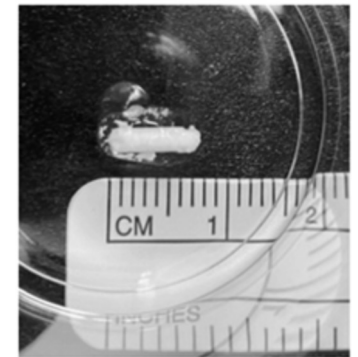
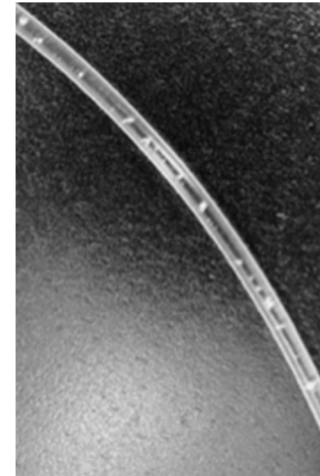


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# Unusual Complications

IV compatibility

- Remimazolam forms precipitates in:
  - Lactated Ringer's
  - Acetated Ringer's
- Concentration 5mg/ml
  - -US concentration 2-2.5mg/mL
- pH dependent



Sasaki et al. Br J Anaesth.2021 Mar;126(3):e87-e89

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Procedural Use



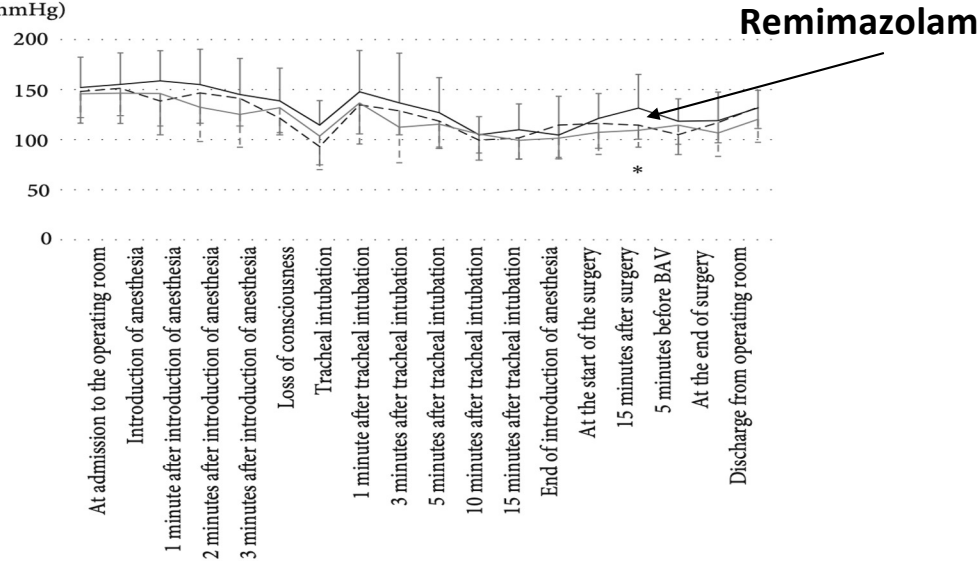
## Remimazolam in Cardiac Surgery TAVR

- Myoshi et al:
- 42 TAVR pts under GA
  - Remimaz + Remifentanil
  - Prop/sevo + Remifentanil
  - Midaz/prop TIVA + Remifentanil

Miyoshi et al. Biomed Res Int. 2022 Oct 22;2022

# Remimazolam in TAVI

Systolic Blood Pressure (mmHg)



Less Norepinephrine in Remimazolam group

HR lower in Remimazolam group

Note: R: remimazolam, P: propofol, S: sevoflurane, M: midazolam, BAV: balloon aortic valvuloplasty. \* $p < 0.05$

- Group R/R
- - - Group P/S
- · · Group M/P

Miyoshi et al. Biomed Res Int. 2022 Oct 22;2022

## What about delirium?

- Aoki et al:
  - 200 CV surgery pt
    - 78 remimaz infusion +remifentanil
    - 122 TIVA/volatile
    - CPB, AAA, endovascular

### **Results:**

No changes in MMSE  
No difference in delirium

Caveat: small, observational,  
potential confounders

# Remimazolam

## Procedural Uses

- GI endoscopy
  - LVAD patients
  - ALS PEG tube patients
  - Feeding tube w/ odynophagia
- Cardiac Cath Lab:
  - Cardioversion
  - Congenital Percutaneous interventions
  - Trans-carotid TAVR
- Interventional Radiology
  - - vascular access w/ poor CV status
  - vascular stenting, angiography
- PICC/HD catheter placement
- ultrasound guided procedures needing quick sedation
- - CT guided quicker procedures (bone biopsies, etc)
- Neurosurgical/ Neuro IR outpatient procedures:
  - - trigeminal ablations

# Remimazolam

## Procedural Advantages

- Very hemodynamically stable:
  - Minimal changes to SVR
  - Minimal Changes to HR
  - No rhythm disturbances
- Minimal respiratory depression
  - Spontaneous respiration preserved
- Rapid emergence
- Easily titrated due to short duration
- Reversible with flumazenil if needed

# Remimazolam

## Procedural Disadvantages

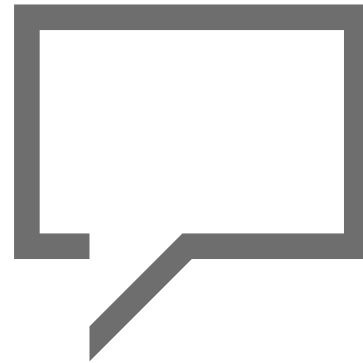
- Short duration = frequent dosing
  - Manage provider expectations
- IV compatibility issues
- \$\$



## Conclusions:

- Pros and Cons: Context dependent
- Con: \$
- Very titratable
- Reversible
- Quick wakeup with minimal grogginess
- Good hemodynamic profile
- Minimal respiratory depression when used as solo agent

QUESTIONS  
& ANSWERS



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