WILDLIFE
PHARMACEUTICALS

SEDATING THE WILD: EXPLORING THE USE OF MIDAZOLAM IN ZOO AND WILDLIFE MANAGEMENT

DR COBUS RAATH

WILDLIFE
PHARMACEUTICALS

CLASSIFICATION

TRANQUILISERS

- also called neuroleptics
- modify CNS function
- generally have no antidotes
- ↑ dose does not ↑ the effects
- no analgesia or immobilisation
- behaviour modifiers

SEDATIVES

- also called hypnotics
- causes CNS depression
- have antidotes available
- ↑ dose ↑ the effect

WILDLIFE PHARMACEUTICALS

CLASSIFICATION

TRANQUILISERS

Phenothiazine derivatives

- acepromazine
- perphenazine

Butyrophenones

- azaperone
- haloperidol

Thioxanthenes

- zuclopenthixol

SEDATIVES

Benzodiazepines

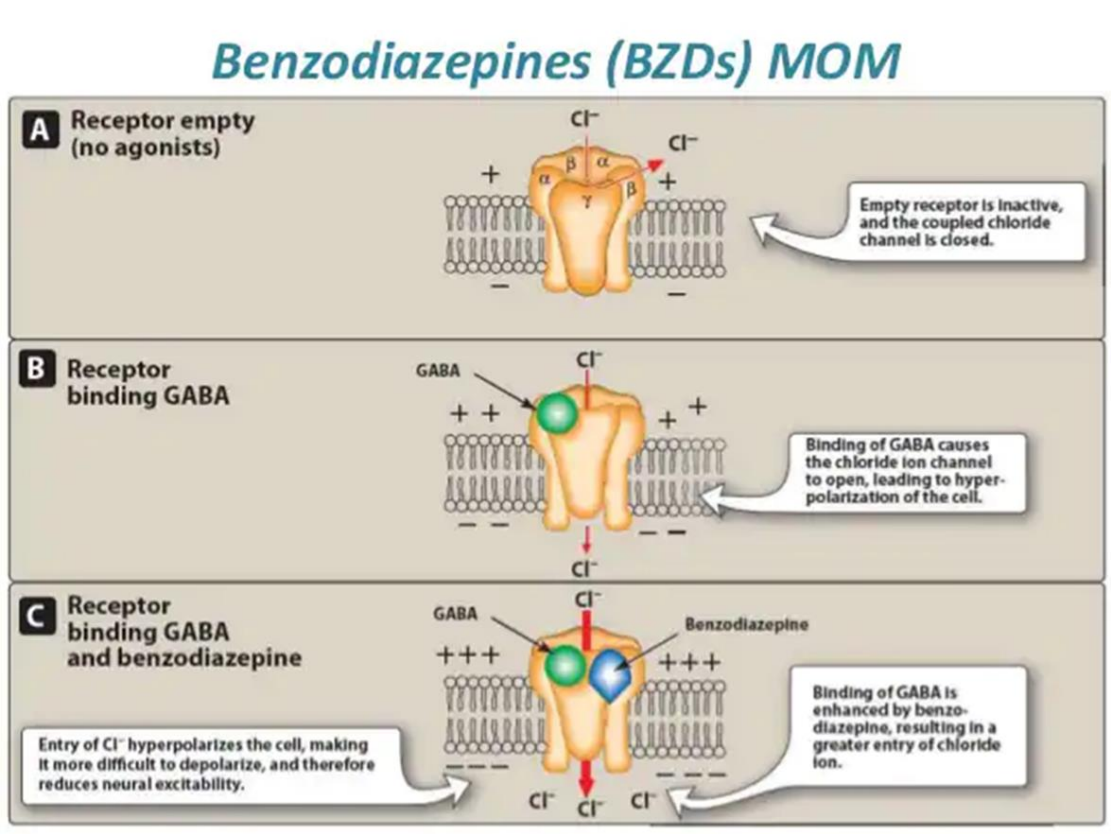
- diazepam
- midazolam

Alpha$_2$-adrenoreceptor agonists

- xylazine
- detomidine
- medetomidine / dexmedetomidine

WILDLIFE PHARMACEUTICALS

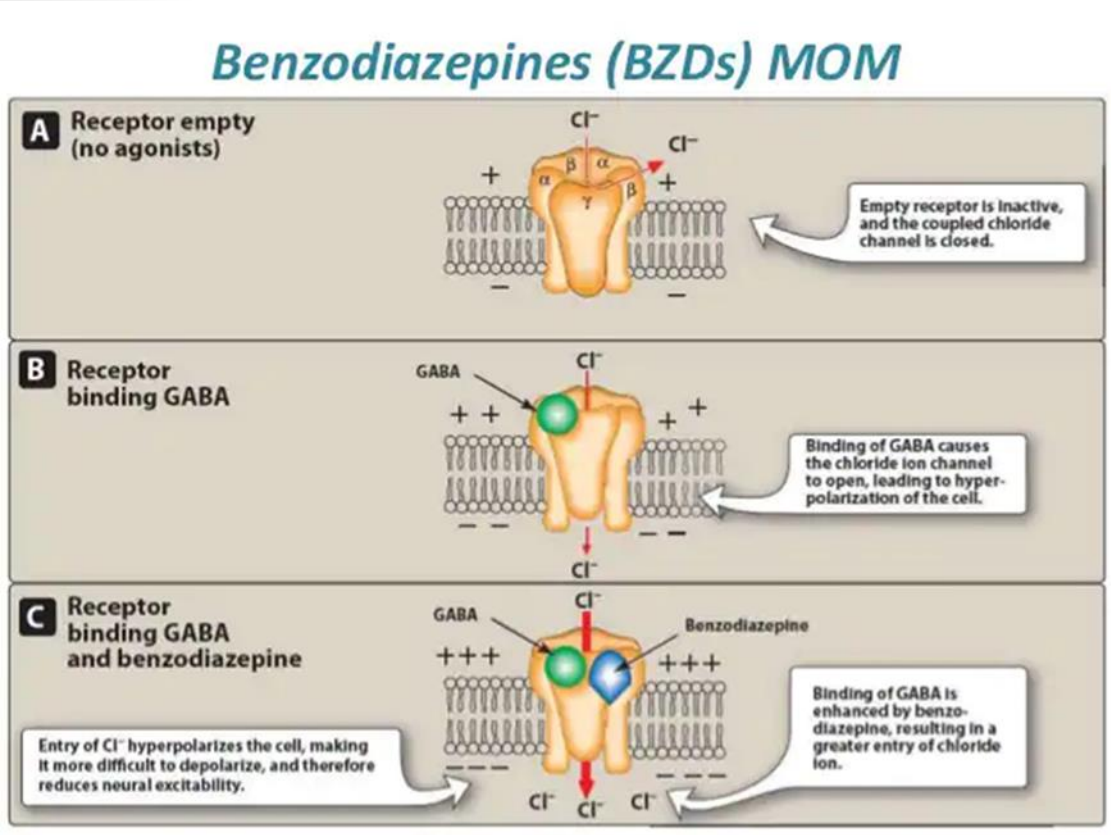
FUNCTIONING OF MIDAZOLAM



- Gamma-aminobutyric acid (GABA) is the primary physiological inhibitory neurotransmitter in the CNS
- Benzodiazepines are GABA agonists that enhance the GABA-receptor's affinity for endogenous GABA (increased effect)
- GABA results in:
  - Sedation
  - Anxiolysis
  - Muscle relaxation
  - Anticonvulsant effects

WILDLIFE
PHARMACEUTICALS

FUNCTIONING OF MIDAZOLAM



- Recent evidence suggests a 10 kDa protein named `Diazepam binding inhibitor' (DBI) is the brain's endogenous BZD (endozepine).
- Depending on the brain region, DBI can potentiate or inhibit GABAR activity suggesting that the brain can modulate GABAR-mediated neuronal inhibition by controlling the levels of DBI and its cleavage products.

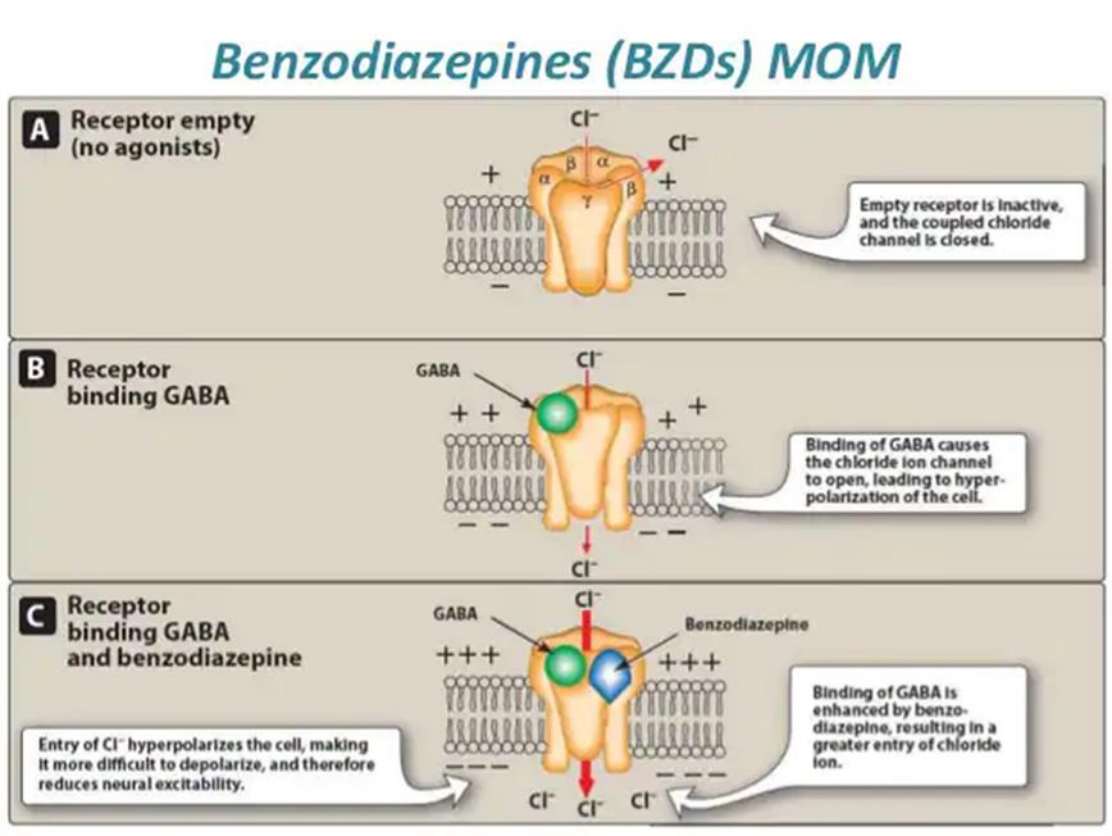
WILDLIFE
PHARMACEUTICALS

FUNCTIONING OF MIDAZOLAM

- Little, however, is known about how DBI levels are regulated, how it is processed, or how DBI exerts its positive versus negative effects on GABAR activity.
- Decreases in GABAergic neurotransmission are linked to numerous neurological and mental health disorders such as insomnia, epilepsy, anxiety, autism, Fragile X syndrome and schizophrenia

WILDLIFE PHARMACEUTICALS

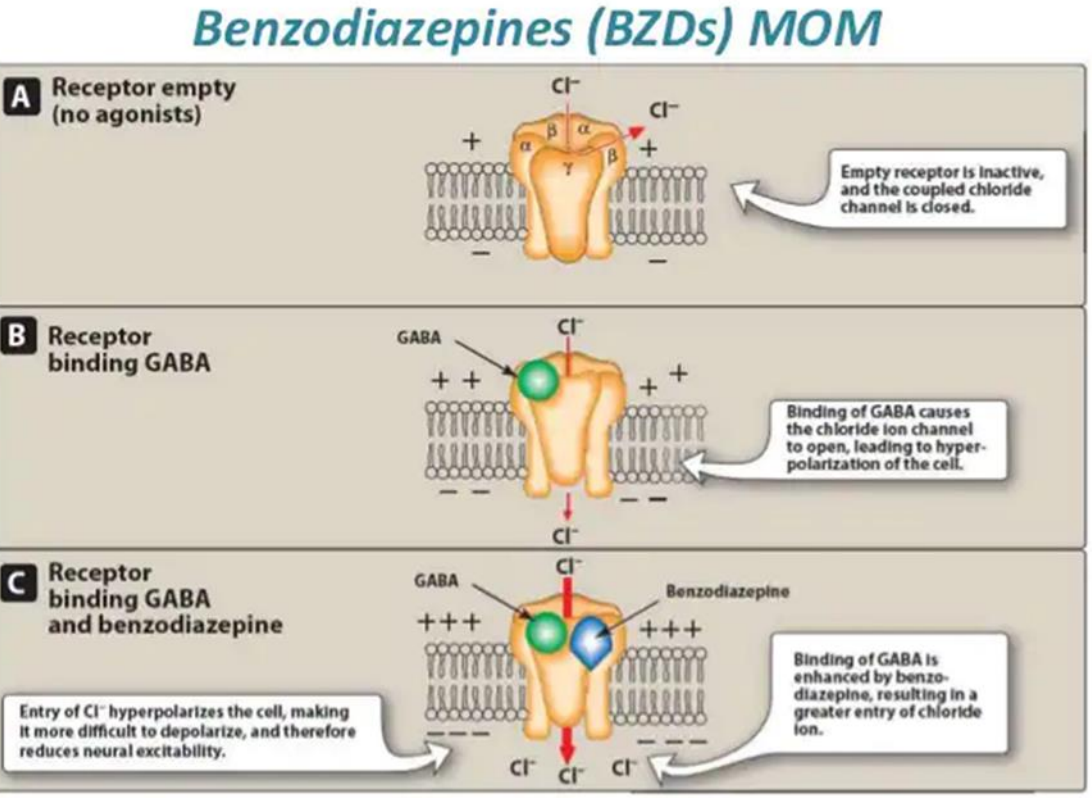
FUNCTIONING OF MIDAZOLAM



- Simply put, GABA sends its inhibitory message by binding at special sites called GABA-A receptors on the outside of the receiving neuron.
- Once GABA is bound to the GABA-A receptor, the neuron opens a channel which allows chloride ions to pass inside of the neuron.
- These negative chloride ions make the neuron less responsive to other neurotransmitters (norepinephrine [noradrenaline], serotonin, acetylcholine and dopamine) which would normally excite it.

WILDLIFE
PHARMACEUTICALS

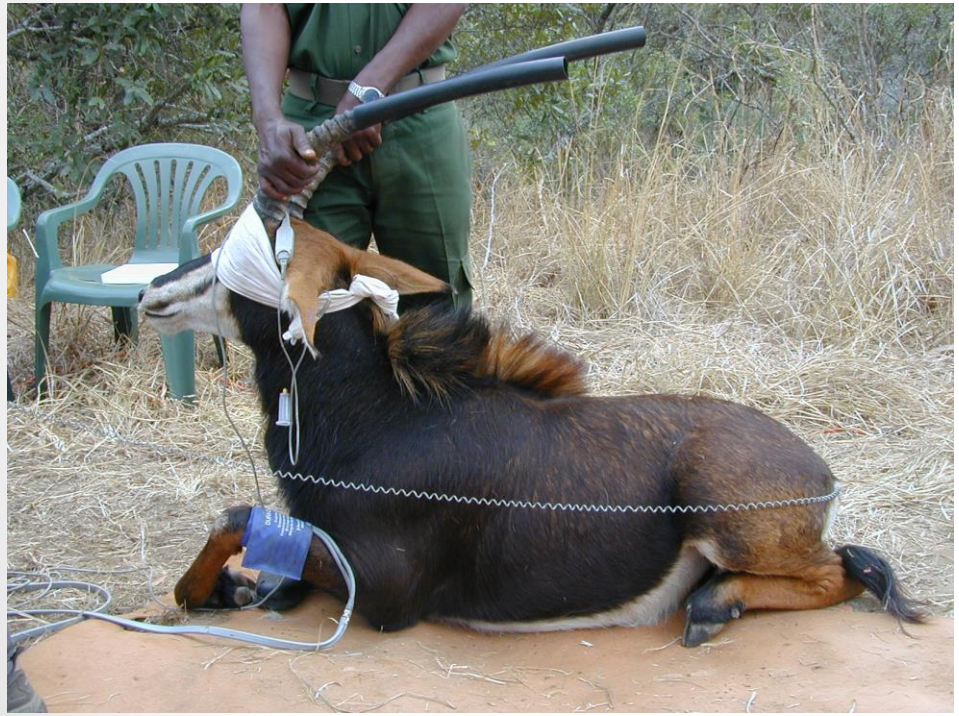
FUNCTIONING OF MIDAZOLAM



- Benzodiazepines also bind to their own receptors (benzodiazepine receptors) that are situated on the GABA-A receptor.
- Combination of a benzodiazepine at this site acts as a booster to the actions of GABA, allowing more chloride ions to enter the neuron, making it even more resistant to excitation.

WILDLIFE
PHARMACEUTICALS

FUNCTIONING OF MIDAZOLAM



- Lack of direct agonistic activity = very wide safety margin
- The highest concentration of GABA A receptors is found in the cerebral cortex, very few receptor sites found outside the CNS, hence minimal cardiopulmonary effects
- They cause a reduction in cerebral blood flow and an even greater reduction in oxygen consumption – useful in CNS disease
- They do not provide analgesia

WILDLIFE
PHARMACEUTICALS

FUNCTIONING OF MIDAZOLAM

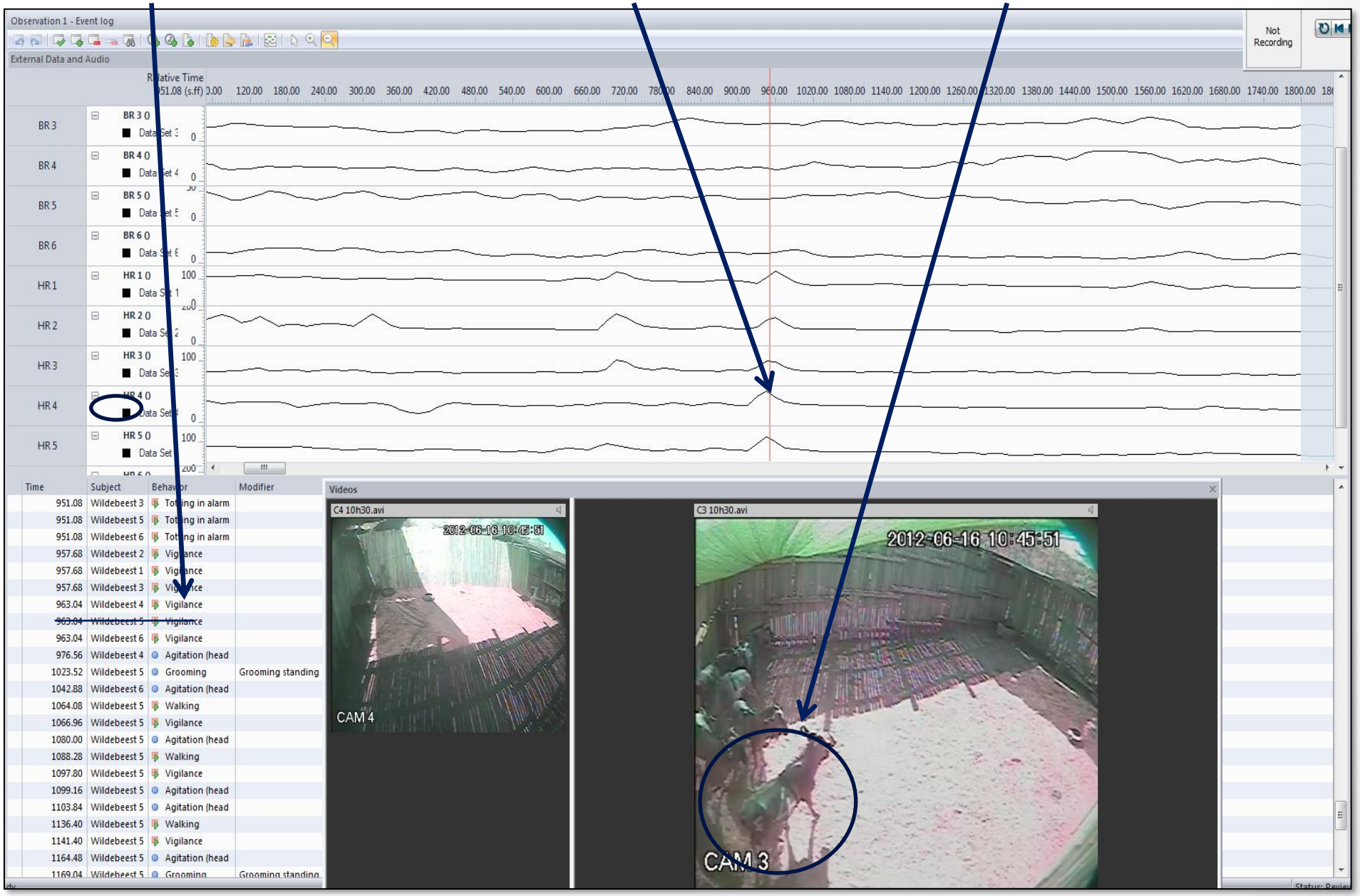
- Clinical effects of benzodiazepines
  - Good muscle relaxation
  - Minimal respiratory and cardiovascular effect at normal doses
  - Anticonvulsant properties
  - Anxiolysis (relaxed but awake)
  - Appetite-stimulating effects
  - Midazolam has a profound amnesic effect

WILDLIFE
PHARMACEUTICALS

Behaviour animal 4 = vigilance

Peak in heart rate of animal 4

Corresponds to video



WILDLIFE
PHARMACEUTICALS

FUNCTIONING OF MIDAZOLAM

- Side effects of benzodiazepines:
  - Paradoxical excitation in young healthy animals
  - At very high doses, relaxation of striated muscles in the diaphragm – accentuation of respiratory depression
  - Can produce a severe sedation in sick or old animals
  - Prolonged recovery in elephants and rhinos

WILDLIFE PHARMACEUTICALS

BENZODIAZEPINES CLASSIFIED BY HALF LIFE

Short Acting < 1 to 12 h	Intermediate Acting: 12 – 40 h	Long Acting: 40 – 250 h
Alprazolam	Flunitrazepam	Clorazepate
Triazolam	Clonazepam	Diazepam
Oxazepam	Lorazepam	Chlordiazepoxide
Midazolam	Temazepam	Flurazepam

Benzodiazepine metabolism:

- Metabolised by the liver, then excreted by urine after process of glucuronidation.
- EXCEPTIONS (no liver metabolism): oxazepam, temazepam, lorazepam

WILDLIFE PHARMACEUTICALS

BENZODIAZEPINES USED IN WILDLIFE

DIAZEPAM

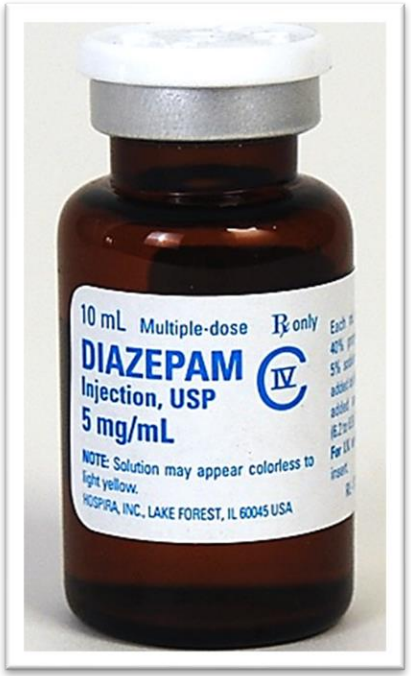
MIDAZOLAM

Both are classified as “short-acting” – lasting < 6 hours in comparison to other benzos

WILDLIFE PHARMACEUTICALS

PROPERTIES OF BENZOS AS WILDLIFE SEDATIVES

DIAZEPAM



PROPERTIES & EFFECTS

- Good muscle relaxant
- Minimal respiratory and cardiovascular effect
- Anticonvulsant
- Can be used to control severe extrapyramidal effects
- Anxiolytic
- Appetite-stimulating effect
- Excellent tranquilization in ostriches
- Not recommended for IM administration (oil-based)
- Often used orally (powder mixed with maizemeal / pills dissolved in liquid)

PROPERTIES OF BENZOS AS WILDLIFE SEDATIVES

MIDAZOLAM

PROPERTIES & EFFECTS

- More potent than diazepam
- Tolerated if given IM
- Profound amnesic effect
- Better anticonvulsant, anxiolytic & amnesic than diazepam
- Often used for *per os* administration in meat for large carnivores or as a premedication for primates
- Shorter duration of action - 30 minutes
- Used in rhinos
- Used for prolonged anaesthesia to decrease the dose of general anaesthetics (dental procedures in carnivores and primates)

WILDLIFE PHARMACEUTICALS

BENZODIAZEPINE ANTAGONISTS

FLUMAZENIL

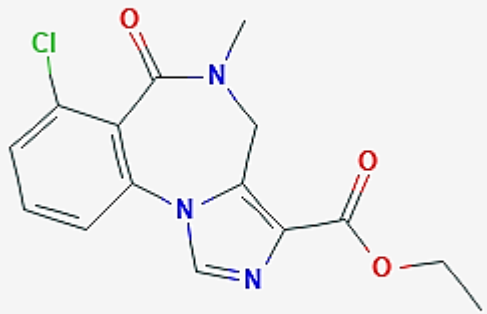
PROPERTIES & EFFECTS

- Binds competitively to the benzodiazepine site on the GABA A Receptor
- High affinity
- Virtually no agonistic activity
- Safe and effective
- Short acting = re-sedation possible
- Expensive
- At high doses (> 0.08 mg/kg) doses severe shivering, muscle rigidity, opisthotonos and seizures can occur
- Dose: re-sedation has been observed at 0.01-0.03 mg/kg dose → recently recommended dose is 0.04 – 0.06 mg/kg

WILDLIFE PHARMACEUTICALS

BENZODIAZEPINE ANTAGONISTS

SARMEZENIL



PROPERTIES & EFFECTS

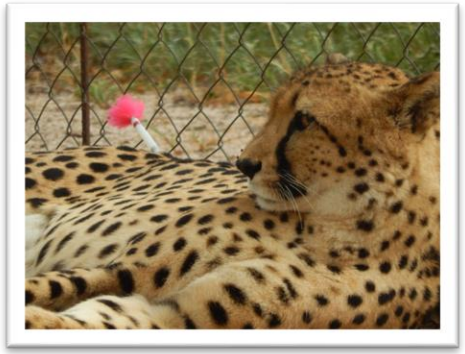
- Successfully used to antagonize effects of zolazepam in cheetahs & lions (*Stander & Morkel 1991; Walzer & Huber 2002)*
- Should be a valuable alternative to flumazenil (*Walzer & Huber 2002)*
- Dose: 0.1 mg/kg

WILDLIFE PHARMACEUTICALS

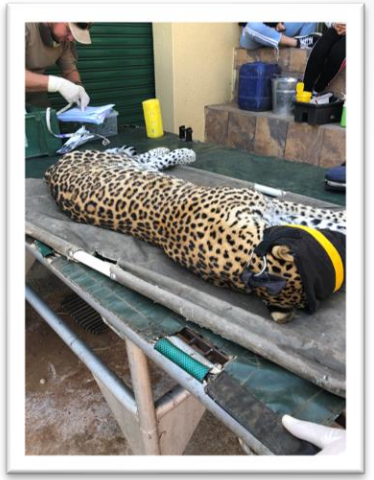
MIDAZOLAM AS PREMEDICATION

Species	Dose	Route
Primates	0.5 mg/kg	Oral
Ungulates	0.2 mg/kg	IM
Predators	0.4 – 0.5 mg/kg	Oral (bait)

WILDLIFE PHARMACEUTICALS



COMBINATIONS USED IN PREDATORS



	Dose (mg/kg)			
Species	Midazolam	Medetomidine	Butorphanol	Ketamine
African leopard	0.2	0.06	0.3	
African lion	0.2	0.025-0.05	0.2-0.3	
	0.1	0.04-0.04		2.2-2.7
Black-footed cat (*captive*)	0.1	0.05	0.2	
Black-footed cat (*wild*)	0.2	0.1	0.4	
Cheetah	0.15	0.035	0.2	
Spotted hyena (*higher dose for juvenile animals*)	0.25-0.5	0.07-0.13	0.25-0.8	

WILDLIFE
PHARMACEUTICALS

COMBINATIONS USED IN UNGULATES

	Dose (mg/kg)	
Species	Midazolam	Thiafentanil OR Etorphine
General ungulates immobilisation	0.2	0.01-0.03
General ungulates sedation	0.2	

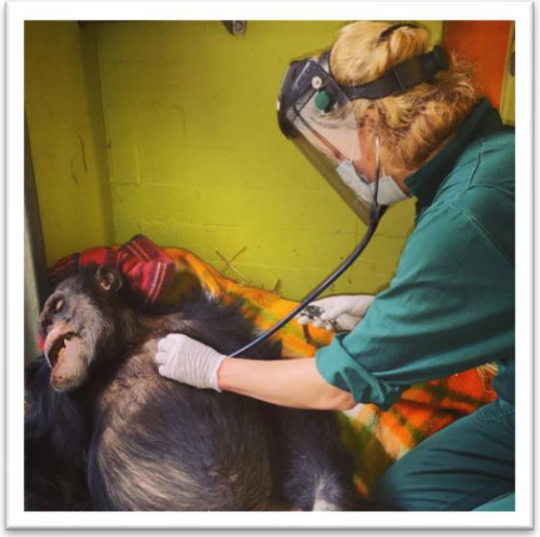
WILDLIFE PHARMACEUTICALS

COMBINATIONS USED IN EQUINE SPECIES

	Dose (mg/kg)				
Species	Midazolam	Etorphine	Ketamine	Medetomidine	Azaperone
Hartmann's mountain zebra	0.2	0.2-0.3			
Mountain zebra	0.2	0.01-0.02			0.1-0.25
Plains zebra	0.2	0.01-0.03			
	0.1-0.2	0.02-0.03			0.2-0.5
	0.1		2.7	0.06	*Standing sedation*

WILDLIFE PHARMACEUTICALS

COMBINATIONS USED IN PRIMATES



	Dose (mg/kg)		
Species	Midazolam	Ketamine	Butorphanol
General primate premedication (*oral*)	0.5		
Chacma baboon	0.035-0.05	10	
Chimpanzee	0.05	5	0.05
Gorilla	0.05	5	0.04

WILDLIFE PHARMACEUTICALS

COMBINATIONS USED IN AVIAN SPECIES

	Dose (mg/kg)			
Species	Midazolam	Ketamine	Butorphanol	Isoflurane
Amazon parrots (intranasal)	1	15		
	2			
Budgerigar (*intranasal*)	13-14			*Deep sedation*
Cockatiels (intranasal)	3		3	
	3			*Mild sedation*
General birds immobilisation	0.5	25	1.5	2.5%
General passeriformes species (intranasal)	5.6			
General psittacidae species (*IM premed*)	0.5		1	
General psittacidae species (*Intranasal sedation*)	2			

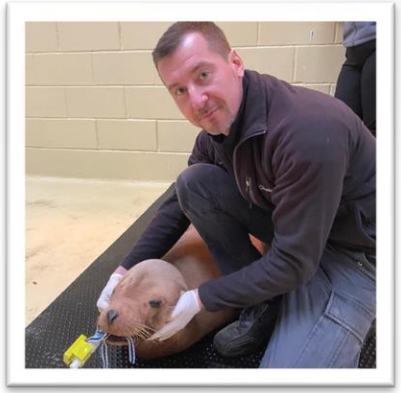
WILDLIFE PHARMACEUTICALS

COMBINATIONS USED IN AVIAN SPECIES *CONT.*

	Dose (mg/kg)			
Species	Midazolam	Ketamine	Butorphanol	Isoflurane
Great white pelican (*IM*)	1		0.5	*5 hrs recovery*
Guinea fowl (*IM*)	0.3	15		+2.5 mg/kg xylazine
Ostrich (*IM*)	0.3	*Only for sedation*		
	0.45	5		
	0.2	8.7	0.4	0.4
Ring-necked parakeets (*intranasal*)	3.7	10		
	7.3			*Deep sedation*

WILDLIFE PHARMACEUTICALS

COMBINATIONS USED IN MARINE MAMMALS



	Dose (mg/kg)			
Species	Midazolam	Ketamine	Butorphanol	Medetomidine
Cape fur seal	0.2		0.2	0.03
California sea lion	0.15		0.1	0.03
	0.25		0.4	0.012
Crabeater seal	0.55			*Moderate sedation*
Harbor seal pups	0.1-0.2		01.-0.2	
North Atlantic right whale	0.1		0.1	*Used for disentanglement*
Weddel seal	0.1	2		
Weddel seal pups	0.2-0.3		0.1-0.2	*Transient apnoea*

WILDLIFE
PHARMACEUTICALS

ADMINISTRATION AFTER RECUMBENCY

- To “smooth out” the anaesthesia
- Stop shivering in rhino or kicking in sable
- Increase muscle relaxation
- Prolong anaesthesia
- Low dose (0,005 mg/kg-0.03 mg/kg) IV
- Smaller animals higher doses.

WILDLIFE PHARMACEUTICALS

PARADOXICAL HYPER EXCITEMENT

- Paradoxical reactions to benzodiazepines, characterized by increased, excitement, and excessive movement, are relatively uncommon and occur in less than 1% of human patients.
- The exact mechanism of paradoxical reactions remains unclear.
- Personal experience in adult black rhino bull – hand reared
- Personal Communication received of repetitive occurrence in the same white rhino calf

WILDLIFE
PHARMACEUTICALS

QUESTIONS ?

REMEMBER TO FOLLOW

Wildlife Pharmaceuticals South Africa

@wildlife_pharmaceuticals

Wildlife Pharmaceuticals South Africa