

# Comparison of pharmacokinetics and efficacy of oral and injectable medicine



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# Outline

- Background
- Results
  - Antibiotics
  - Non steroidal anti-inflammatory drugs (NSAIDs)
  - Vitamins
- Conclusions and recommendations



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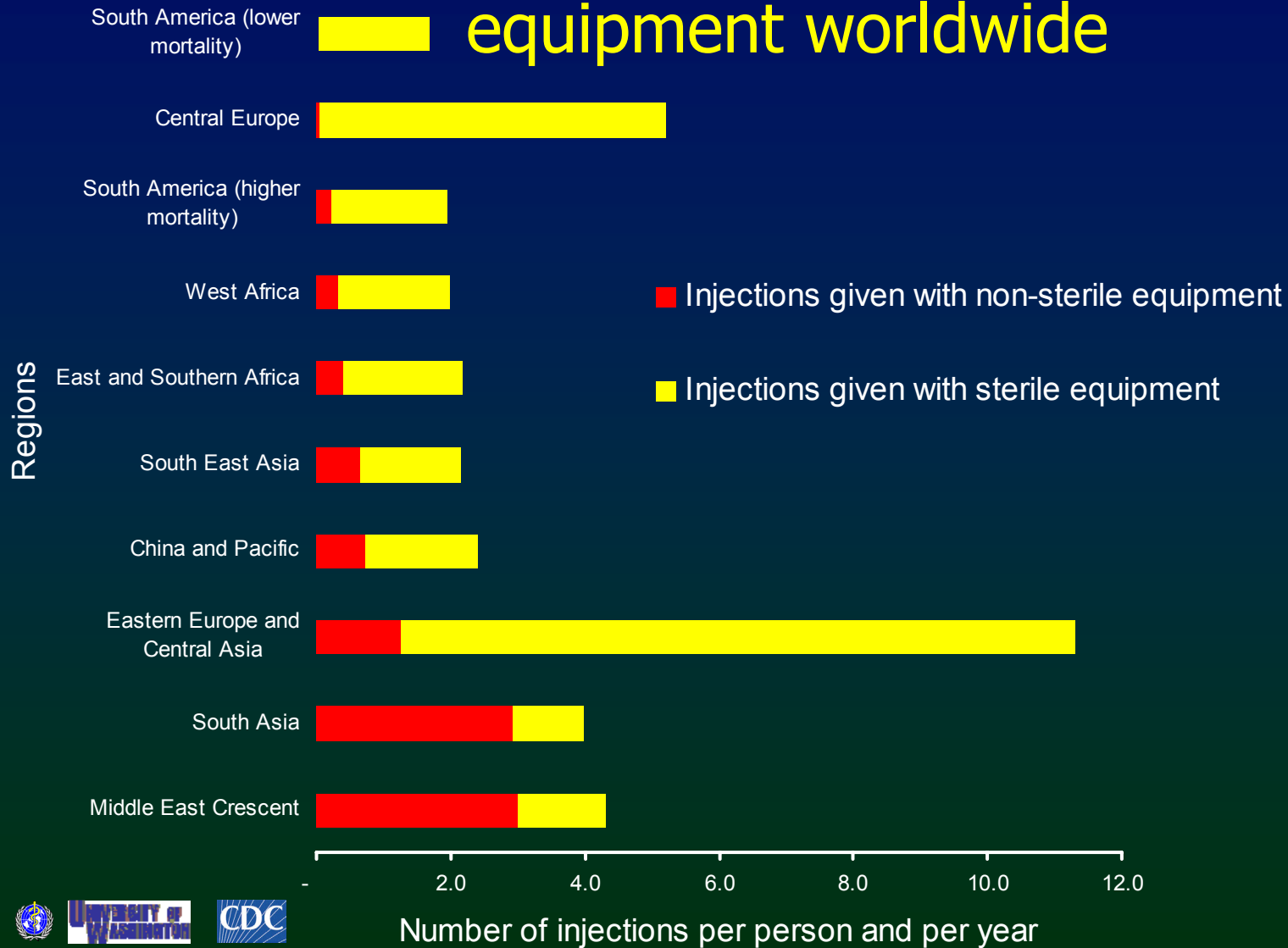


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# Injections given with sterile and reused equipment worldwide



# Injections: A dangerous engine of disease

- Hepatitis B
  - Highly infectious virus
  - Highest number of infections (21 million annually)
  - 32% of HBV infections
- Hepatitis C
  - More than 2 million infections each year
  - More than 40% of HCV infections
- HIV
  - More than 260 000 infections
  - Approximately 5% of HIV infections



# Reported common conditions leading to injection prescription

- Infections
  - Fever
  - Upper Respiratory Infection/ Ear Infection
  - Pneumonia
  - Tonsillitis
  - Pelvic Inflammatory Disease
  - Skin Infections
  - Diarrhea
  - Urinary tract infection
- Asthma
- Other
  - Malaise
  - Fatigue
  - Old Age



Simonsen et al. WHO 1999



# Reported injectable medicines commonly used

- Antibiotics
- Anti-inflammatory agents / Analgesics
- Vitamins



Simonsen et al. WHO 1999



# Reported factors leading to injection overuse

- Prescriber-associated factors
  - Perceptions regarding injections
  - Assumptions about patient`s expectations
- Patient-associated factors
  - Perceptions regarding injections
  - Therapeutic expectation
- System issues
  - Lack of effective oral medications
  - Financial implications



Reeler et. al. WHO 2000



# Reported prescribers' reasons for the use of injections

- Pharmacokinetics
  - “Strength” of injectables
  - Rapid onset of action
  - Poor intestinal absorption of oral medications
  - Absence of effective oral medications
- Other
  - Recommendations by Professors/Ministry of Health
  - Direct observed therapy
- Patient care issues
  - Inability of patient to take medications by mouth
  - Patient’s desire for injection
  - Chronic condition of patient ( illness, malnutrition or alcohol abuse)



# Misconceptions about injections among prescribers

- Oral absorption is variable, whereas parenteral administration assures high drug levels
- Injectable drugs are “stronger” than oral drugs
- Injectable drugs have more rapid onset of action
- Chronic conditions (malnutrition) of patients leads to poor oral absorption of drugs

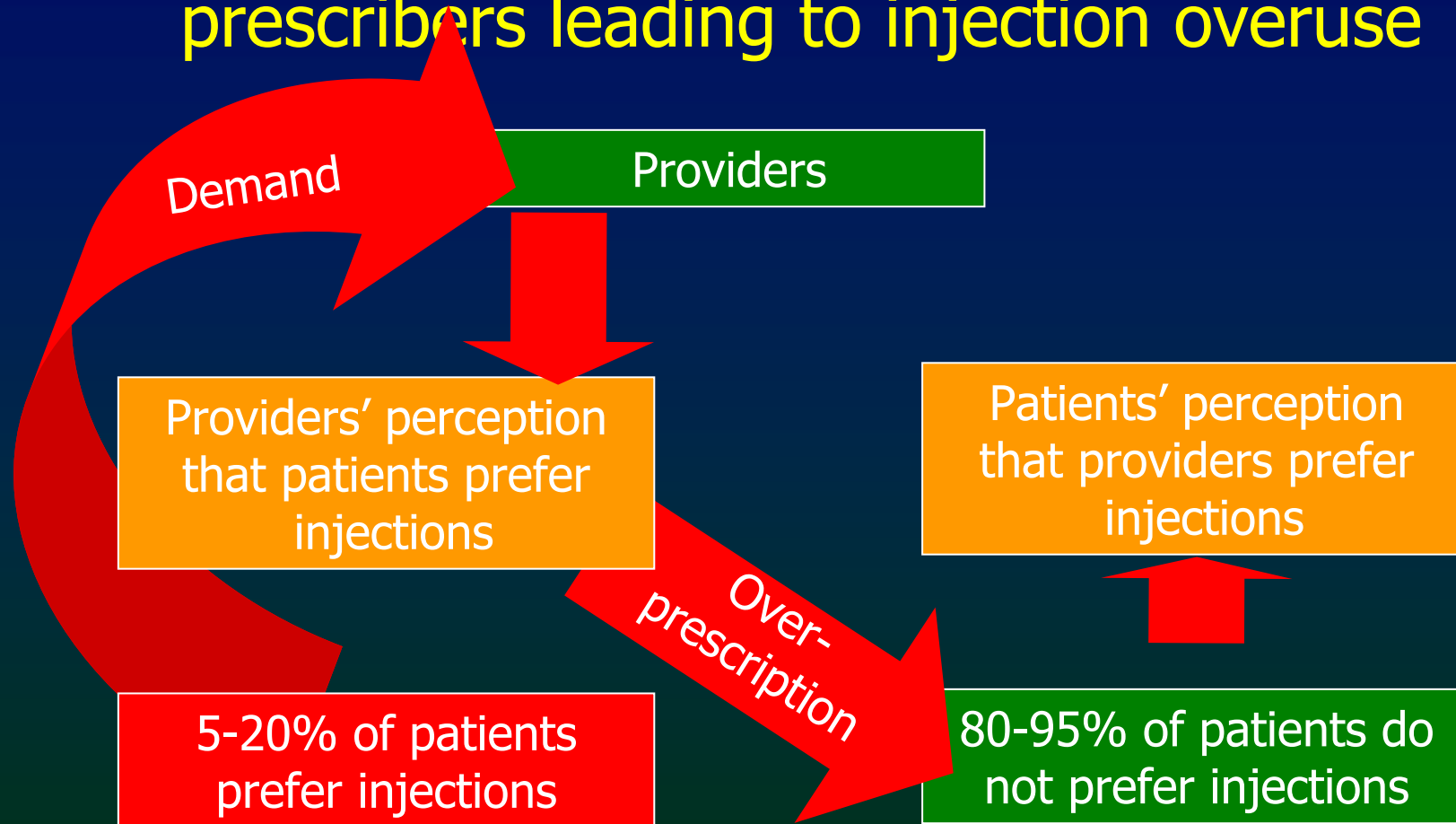


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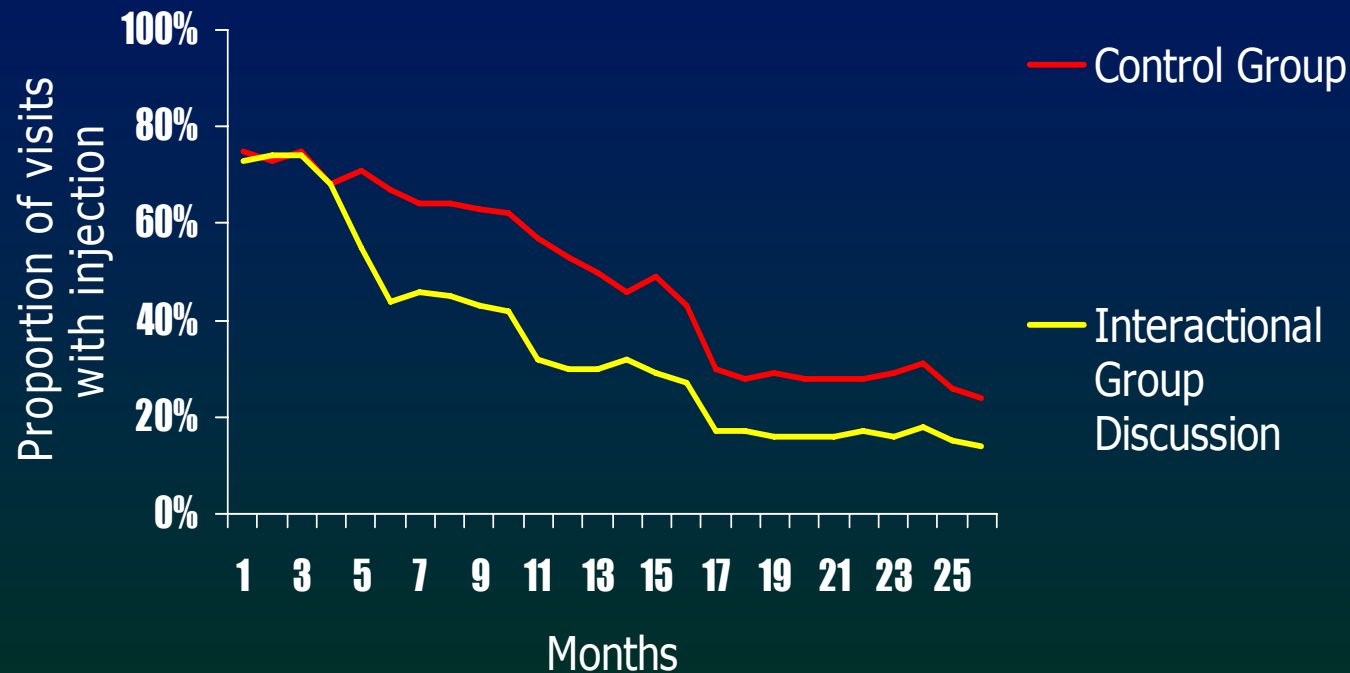
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# Misunderstanding between patients and prescribers leading to injection overuse



# Addressing Cognitive Dissonance Using Patient-Provider Interactional Group Discussions, Indonesia, 1993



Source: Long-term impact of small group interventions, Santoso et al., 1996



# Objectives of the Study

- Primary objective
  - Provide an evidence base for decision making in prescribing injections
- Secondary objective
  - Compare pharmacokinetics of oral and injectable drugs
  - Describe the impact of malnutrition on drug pharmacokinetics
  - Compare the effectivenesss of oral and injectable drugs in randomized clinical trials
  - Compare the cost of oral and injectable drugs



# Literature review methods

- Medline
- Cochrane reviews
- Pharmacology textbook reviews
- Micromedex



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# Parameters commonly used in pharmacokinetics

- Parameters affected by mode of administration
  - Absorption
  - Bio-availability
  - Peak serum concentration
  - Time to peak serum concentration
- Parameters unaffected by mode of administration
  - Half-life
  - Clearance
  - Distribution
  - Metabolism
  - Protein binding



# Factors influencing absorption and bioavailability of medications

- Oral route
  - Food consumption
  - Cation interaction
  - Gastric pH
  - Intrinsic absorptive capabilities of digestive tract
  - First pass hepatic metabolism
- IM route
  - Injection site
  - Diluent
  - Solubility of drug
  - Concentration of drug
  - Total surface area for diffusion
  - Blood flow to muscle injected

IV 100% bioavailable



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## Peak serum concentration of selected oral, IM and IV antibiotics

Class of Antibiotic	Oral	IM	IV
Natural Penicillin	++	-	+++++
Aminopenicillin	+	++	+++
Fluoroquinolones	+	NA	+
Chloramphenicol	++	+	++
Sulfonamides	+	NA	+
Rifampin	+	NA	++



Source: Micromedex

# Time to peak serum concentration by different modes of administration

- Oral
  - 30min – 6hrs
- IM
  - 30min – 3hrs\*
- IV
  - End of infusion

\* Natural penicillin time to peak serum concentration 4-24 hrs



# Effect of malnutrition on the pharmacokinetics of antibiotics

- Children
  - Decreased clearance
  - Larger area under the curve
  - Potential toxicity
- Adults
  - Lower absorption (may be overcome by larger doses)
  - Increased clearance
  - Potential need for more frequent administration



# Injected and oral antibiotics in the treatment of mild to moderate infections

	No. of studies	<u>Clinical outcome</u>		<u>Bacterial outcome</u>	
		Studies reporting equivalence	Studies reporting parenteral benefit	Studies reporting equivalence	Studies reporting parenteral benefit
Otitis media	4	4/4	0/4	NA	NA
Pneumonia	3	2/3	1/3*	0/1	1/1*
STD	13	2/2	0/2	12/12	0/12
UTI	5	3/3	0/3	2/3	0/3
Osteomyelitis	2	1/1	0/1	2/2	0/2

\*Only in subset of study patients



# Sequential and prolonged parenteral antibiotics in the treatment of severe infections

	No. of studies	<u>Clinical outcome</u>		<u>Bacterial outcome</u>	
		Studies reporting equivalence	Studies reporting parenteral benefit	Studies reporting equivalence	Studies reporting parenteral benefit
UTI	2	2/2	0/2	1/2	0/2
Pneumonia	3	3/3	0/3	2/2	0/2
Skin infection	2	1/2	0/2	2/2	0/2
Febrile cytopenia	2	2/2	0/2	1/1	0/1
Mixed	4	4/4	0/4	4/4	0/2



# Compared cost of selected oral and parenteral antibiotics

Drug	Relative cost of parenteral:oral per equivalent Dose
Ampicillin	3:1
Cloxacillin	4:1
Chloramphenicol	5:1



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# Comparison of the pharmacokinetics of different NSAIDs by route of administration

Class	NSAID	Bioavailability (%)		Time to serum peak (hours)	
		Oral	IM	Oral	IM
Salicylic	Aspirin	80-100	NA <sup>1</sup>	0.5-3	NA
	Lysine	---	NA	1-2	0.25
	Acetylsalicylate	---	NA	1-2	0.25
Indolic	Indometacin	90-100	NA	0.5-2	NA
Aryl-carboxylic	Ketoprofen	95-100	NA	0.5-2	0.3-0.5
	Ibuprofen	80	---	2	---
	Diclofenac Na	100	100	1.5-3	0.3
	Ketorolac	80-100	100	0.3-1	0.5-1
Oxicam	Naproxen	100	---	1-2	---
	Piroxicam	100	---	3-5	NA
	Isoxicam	100	100	10	3
Fenamates	Meloxicam	89	---	1	NA
	Niflumic ac.	---	---	2	---
Pyrazolic	Phenylbutazone	100	---	2-5	NA



# Randomized clinical trials comparing the outcome of oral and injectable NSAIDs in various clinical situations

Authors	Diagnosis	Oral dosage and frequency	Injectable dosage and frequency	Conclusions
Comb	Rheumatoid arthritis	Meloxicam	Meloxicam IM	Both effective and well-tolerated
Auvinet	Acute Sciatica	Meloxicam	Meloxicam IM	Both effective
Turner	Pain after surgery	R. indometacin	Ketorolac IM	No significant difference in pain
Shresta	Acute gout	Indometacin	Ketorolac IM	Both similar in the relief
Kumara	Molar surgery	Tenoxicam	Tenoxicam IV	Both equally effective
Tuomilehto	Adenoidectomy	Ketoprofen	Ketoprofen	No differences in pain scores,
Supervia	Renal colic	Piroxicam,	Diclofenac IM	No significant difference
Evans	Ductus arteriosus	Indometacin	Indometacin IV	Intravenous form superior



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# Pharmacokinetics of selected vitamins

	<u>Oral Administration</u>		<u>IM Administration</u>	
	Absorption	Time to peak serum conc.	Absorption	Time to peak serum conc.
Vitamin B6	Well	1.25hrs	?	?
Vitamin B12	Well	8-12 hrs	?	1 hr
Vitamin K	Well	6-12 hrs	Well	1-2 hrs



Source: Micromedex



## Compared outcomes of oral and IM administration for selected vitamins

Vitamin	Number of Studies	Outcome Equal Oral and IM
B6	0	NA
B12	1	1/1 @
K	2	1 / 2 *

@ clinical outcome

\*Markers of Vitamin K status



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## Conclusions (1)

- There is minimal to no benefit of IM versus oral administration of drugs in terms of pharmacokinetics
- IV administration results in shorter onset of action and for some drugs higher bioavailability and peak serum levels
- The issue of onset of action is clinically relevant only in life threatening illness



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## Conclusions (2)

- Normal drug dosing in malnourished children may lead to toxic drug levels
- Undernourished adults may need drug dosing at the high end of the therapeutic range given more frequently
- The pharmacokinetic advantage of parenteral over oral drugs does not translate to better clinical outcomes in mild-moderate illness
- Even in serious illnesses, sequential therapy within 2-5 days can be as effective as prolonged parenteral courses



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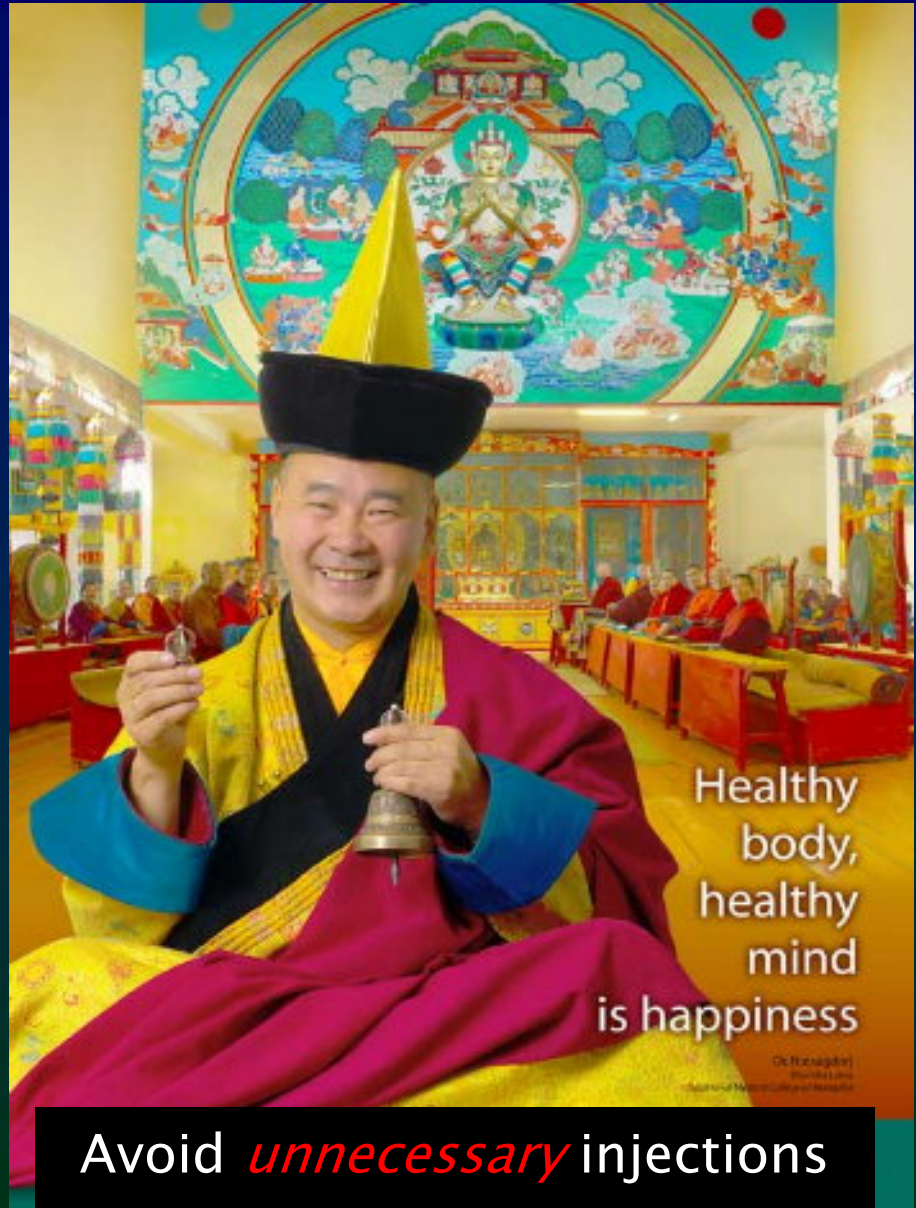
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# Recommendations: indication for therapeutic injections

- Serious and life-threatening illness
- Inability to swallow
- Profuse vomiting
- Absence of effective oral agent
- Significantly altered absorption pattern





Healthy  
body,  
healthy  
mind  
is happiness

Dr. Rinpoche  
Shinsho Lobsang  
Abbot of the Buddhist College of Washington

Avoid *unnecessary* injections

Wise doctors all agree it's safer to take medicine by mouth.

