Fate of GBCAs and Gd in the liver, bone, and skin: an overview of animal and human data

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Conflicts of Interest

No conflicts of interest reported.

Overview

- **Gadolinium retention**
  - **Amount, distribution, delayed clearance**
- Gadolinium fate/toxicity in skin, bone, liver
- Chronic symptoms attributed to GBCA exposure

GBCA Pharmacokinetics

- 2 phases:
  - distributed in the extracellular fluid
  - eliminated unchanged by the kidney.
- Elimination half-life of GBCAs in healthy adults is about 90 minutes
- <u>Prescribing information does not provide data for the percentage of retained Gd beyond 24h</u>

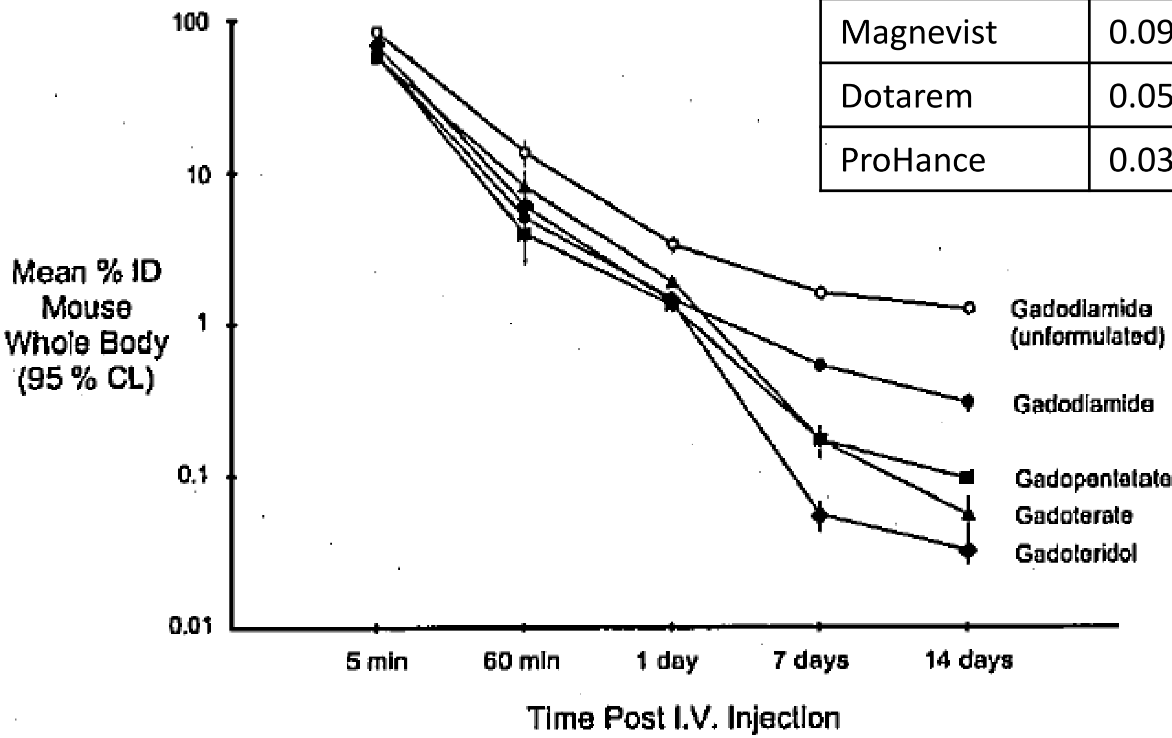
Pharmacokinetics of GBCAs		
	Elimination half-life (min)	% Injected Dose eliminated 24hrs
Omniscan	77.8 ±16	95.4 ±5.5%
Magnevist	96 ±7.8	91 ±13%
Multihance	70.2 ±16 – 121 ±36	80-98%
Eovist	54.6 - 57	<LOD
ProHance	94.2 ±4.8	94.4 ±4.8%
Gadavist	108 (72-393)	>90%[1]
Dotarem	84 ±12 (F) 120 ±42 (M)	72.9 ±17.0%(F) 84.4 ±9.7% (M)

[1]At 12 hours

- Presence of a long-lasting residual excretion phase from a deep compartment (Hirano 1996, Lancelot 2016 (Guerbet))
  - Much slower than the conventional elimination phase
  - Dependent on the stability of the GBCA

Biodistribution Study: Radiolabeled Omniscan, Magnevist, Dotarem, ProHance

% ID remaining at day 14	
Omniscan	0.30%
Magnevist	0.095%
Dotarem	0.055%
ProHance	0.032%



Mouse – whole body

After 24hrs, separation of data occurred in the order of GBCA stability

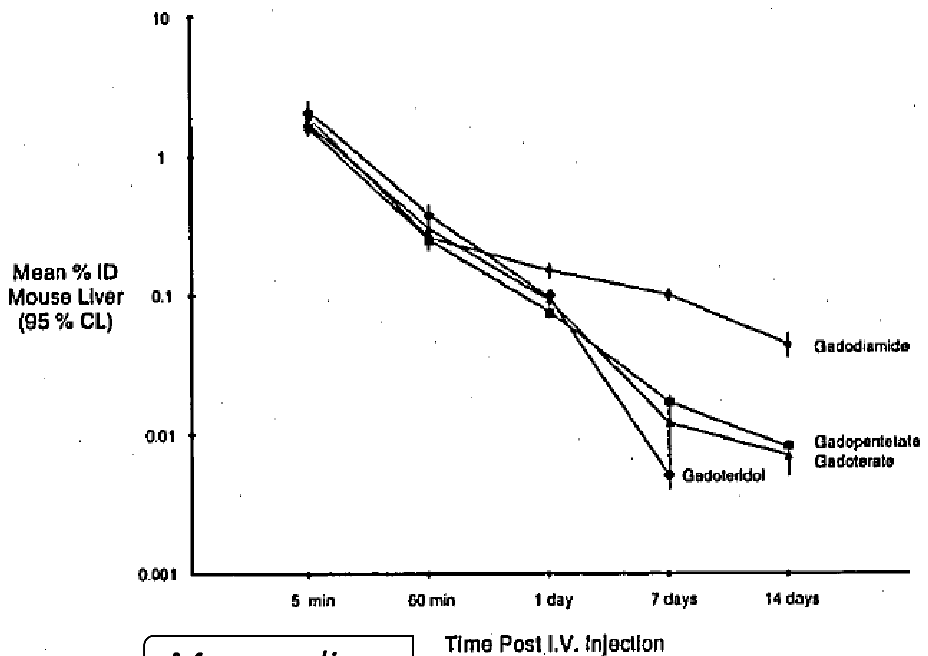
Study could not identify the form of retained Gd

Differences in delayed biodistribution suggest different degrees of Gd dissociation between the GBCAs

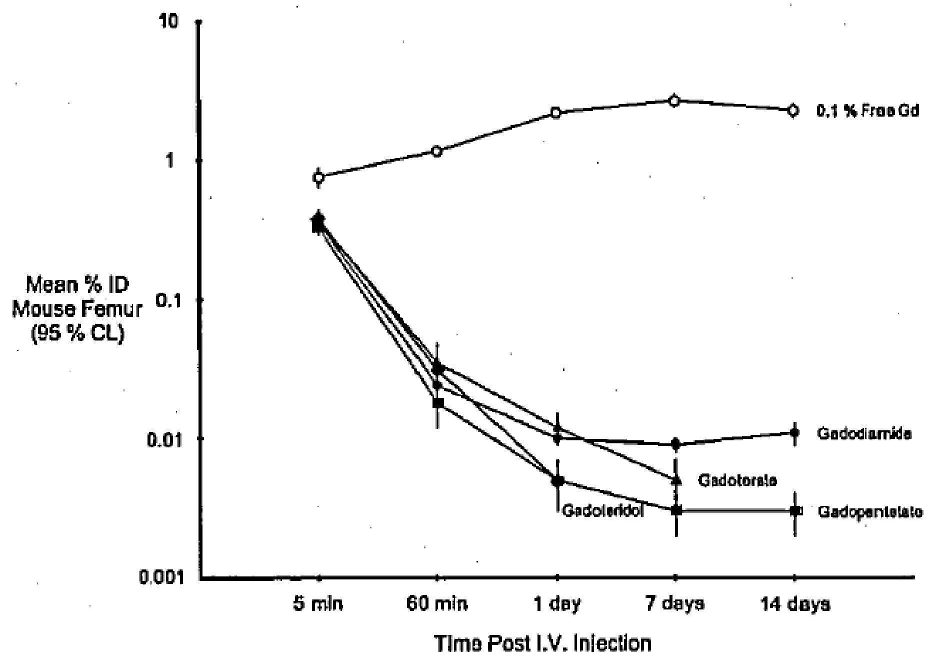
- 5 mice per group
- 1 IV injection of 0.48 mmol/kg of GBCA

Tweedle 1995 (Bracco)

Biodistribution: Radiolabeled Omniscan, Magnevist, Dotarem, ProHance



Mouse - liver



Mouse - femur

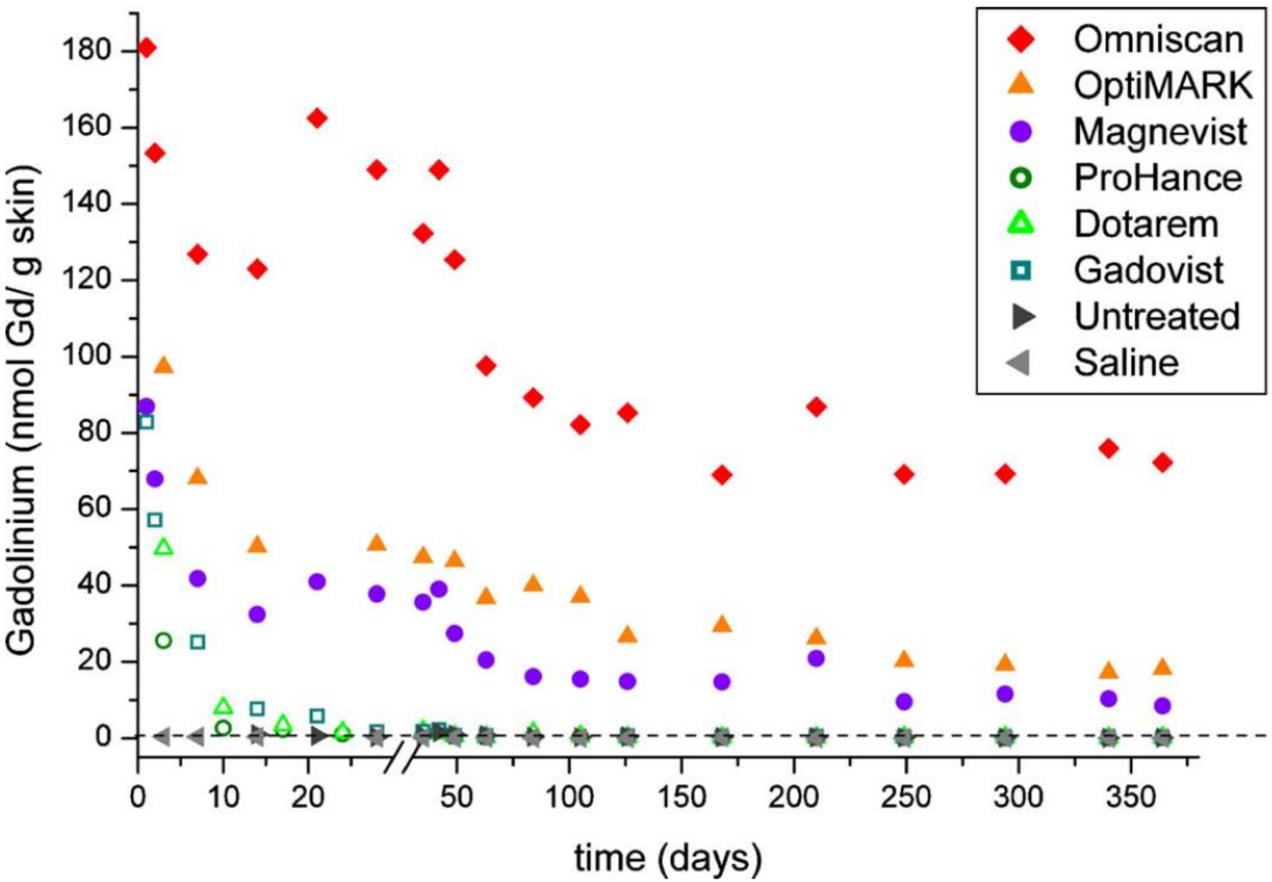
Liver and bone had greatest detected residual Gd at 14 days, %ID remaining correlated with GBCA stability

% ID remaining at d. 14	
Omniscan	0.044%
Magnevist	0.008%
Dotarem	0.007%
ProHance	<LOD

% ID remaining at d. 14	
Omniscan	0.011%
Magnevist	0.003%
Dotarem	<LOD
ProHance	<LOD

Tweedle 1995 (Bracco)

Correlation between GBCA stability and the amount of retention



Gd was measured in sequential skin biopsies over a year

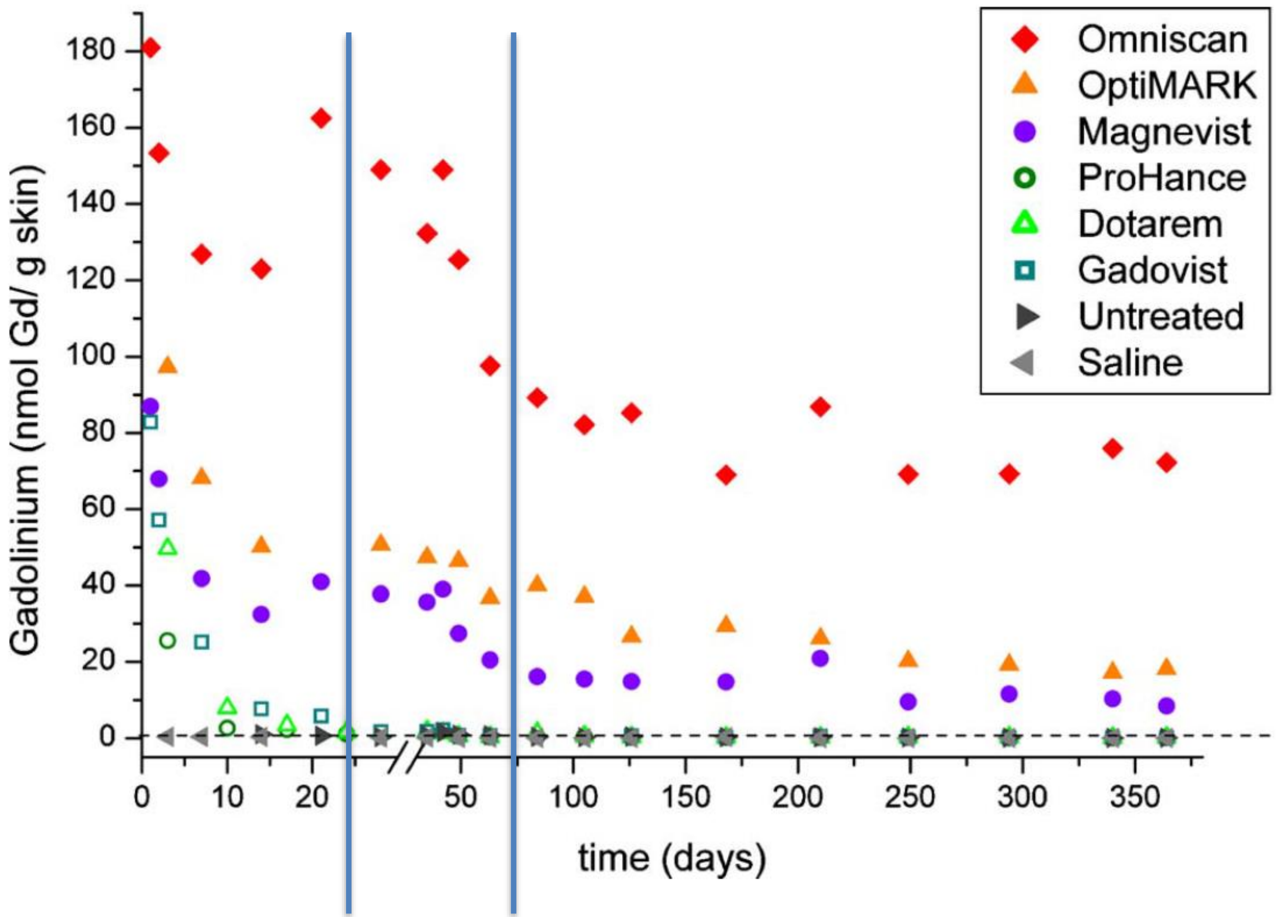
The less stable GBCAs resulted in higher Gd concentrations in the skin at all time points compared to the macrocyclic GBCAs

- 6 rats per group
- 5 IV injections each at a dose of 2.5 mmol Gd/kg for 5 consecutive days

Rat - Skin

Pietsch 2009 (Bayer)

Correlation between GBCA stability and the amount of retention
Correlation between GBCA stability and delayed clearance



Linear GBCAs:
Plateau Gd conc reached at ~d60

Macrocyclic GBCAs:
Plateau Gd conc reached at ~d24

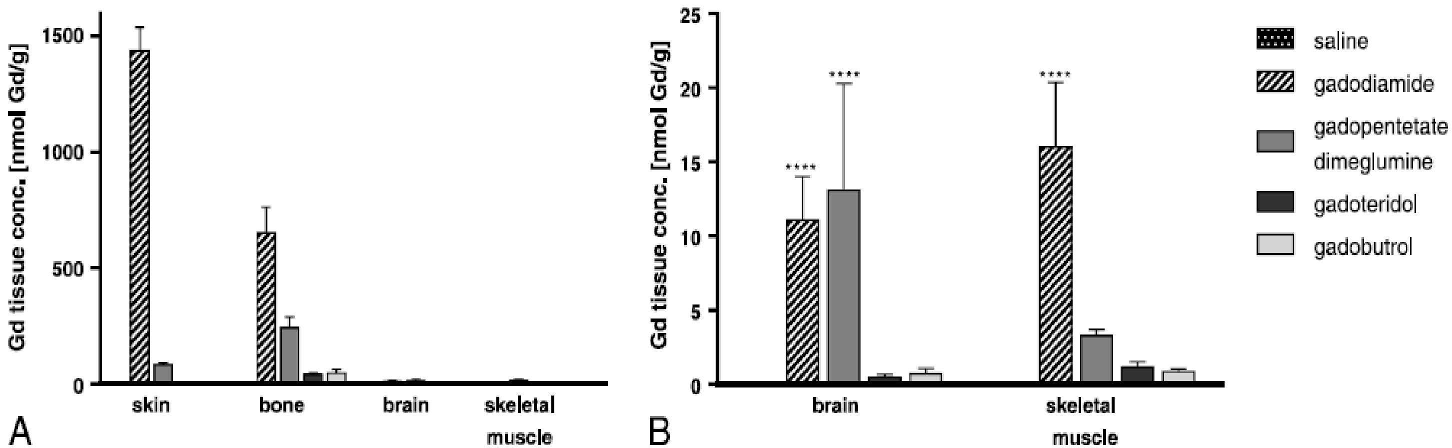
Correlation between GBCA stability and retention suggests that dechelation is important in retention

Long term retention of intact GBCA molecules identified in human skin (Birka 2015, Roberts 2016)

Rat - Skin

Variability between the individual GBCAs

Standardized studies for reliable cross-product comparisons have not been done



- 10 rats per group
- 20 IV injections each at a dose of 2.5 mmol Gd/kg for 5 consecutive days per week over period of 4 weeks
- 8 weeks after the last injection, necroscopy and sample collection

Gadolinium concentrations in rat organs after repeat high dose GBCAs (nmol/g)

GBCA	Skin	Bone	Brain	Muscle
Omniscan	1472 ±115	653 ±111	11.1 ±5.1	16 ±4
Magnevist	81 ±6	242 ±46	13.1 ±7.3	3.3 ±0.4
ProHance	1.7 ±0.8	40 ±7	0.5 ±0.2	1.1 ±0.4
Gadavist	1.1 ±0.5	46 ±17	0.7 ±0.4	0.9 ±0.2

At 8 weeks after dosing with Omniscan, the highest Gd concentration is in the skin

At 8 weeks after dosing with Magnevist, ProHance, and Gadavist, the highest Gd concentration is in the bone

Rat – skin, bone, brain, muscle

Lohrke 2017 (Bayer)

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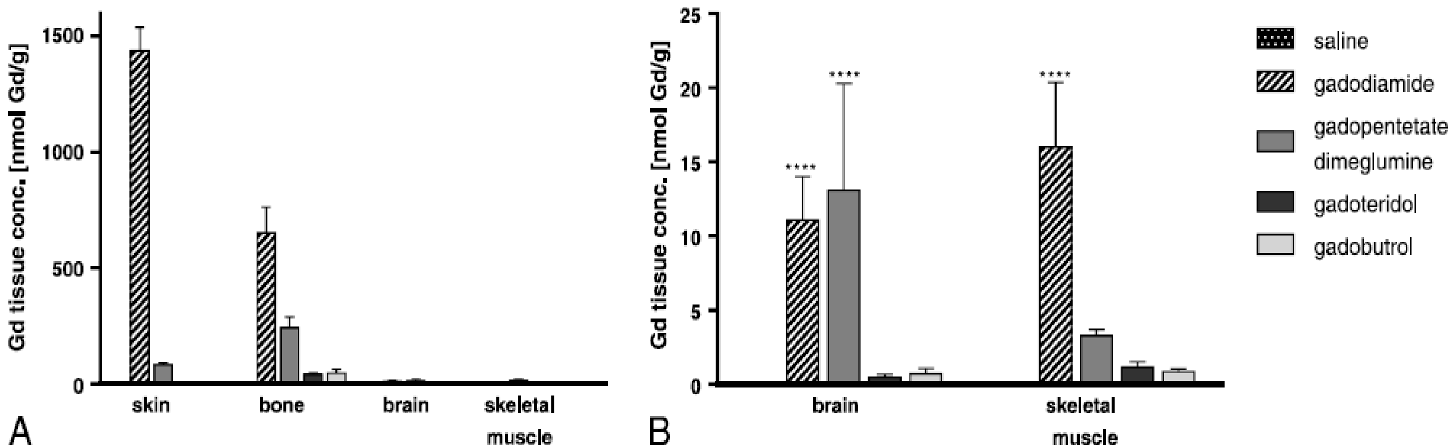

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Despite significant differences in the thermodynamic stability between non-ionic Omniscan and ionic Magnevist, the Gd concentrations were about the same in the brain.

Rat – skin, bone, brain, muscle

Lohrke 2017 (Bayer)

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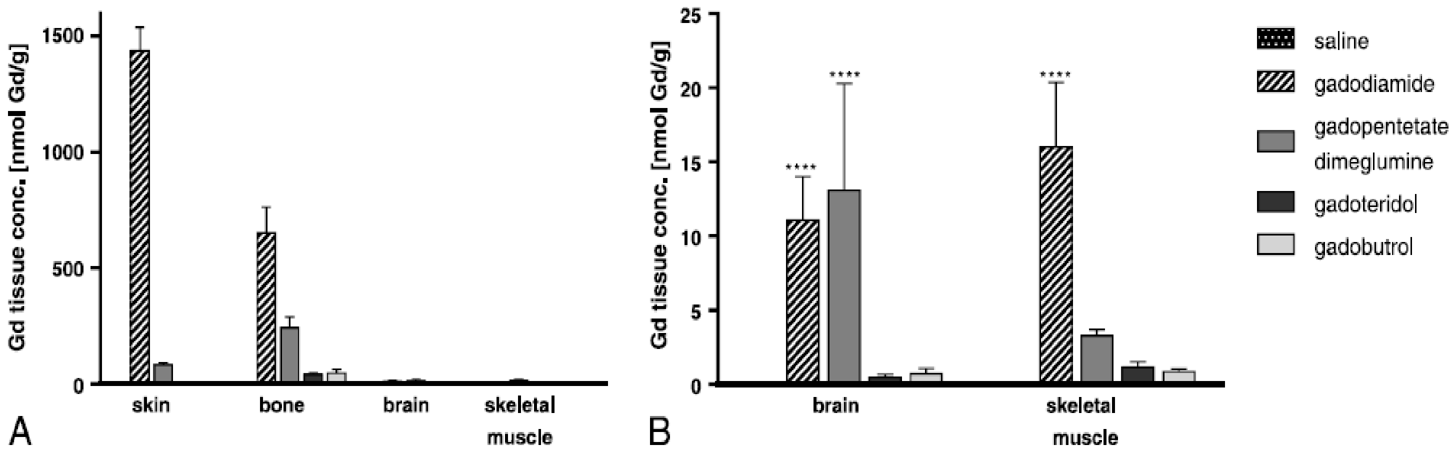

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There is a large difference in the skin/brain gadolinium concentration ratio after the linears, but much less so after the macrocyclics.

Rat – skin, bone, brain, muscle

Lohrke 2017 (Bayer)

Understanding retention from macrocyclic GBCAs

What to make of the small numbers

"below the limit of quantification"

Day 60 Gd concentrations in juvenile rats
All animals received Dotarem (Giorgi 2015 (Guerbet))

Tissue	Dose (mmol/kg	Subgroup A	Subgroup C
Bone	0.6	N = 8 < LOQ[1] N = 4 < LOQ[2]	< LOQ[2]
	1.25	N = 6 < LOQ[1] N = 6 < LOQ[2]	< LOQ[2]
	2.5	N = 6 < LOQ[1] N = 6 < LOQ[2]	N = 8 < LOQ[2] **0.4 ± 0.6**
Skin	0.6	< LOQ[1]	< LOQ[1]
	1.25	< LOQ[1]	< LOQ[1]
	2.5	< LOQ[1]	< LOQ[1]
Liver	0.6	< LOQ[1]	< LOQ[1]
	1.25	< LOQ[1]	< LOQ[1]
	2.5	< LOQ[1]	N = 10 < LOQ[1] **0.2 ± 0.5**
Kidneys	0.6	N = 8 < LOQ[1] **0.3 ± 0.5**	N = 3 < LOQ[1] **1.4 ± 1.6**
	1.25	N = 7 < LOQ[1] **0.4 ± 0.6**	N = 1 < LOQ[1] **2.7 ± 1.8**
	2.5	N = 2 < LOQ[1] **1.0 ± 0.6**	**9.8 ± 6.2**

LOQ[1] = 0.509 nmol/g; LOQ[2] = 1.02 nmol/g

Juvenile rat – bone, skin, liver, kidneys

"in the same range as controls"

Day 364 skin Gd concentration in rats
(Pietsch 2009 (Bayer))

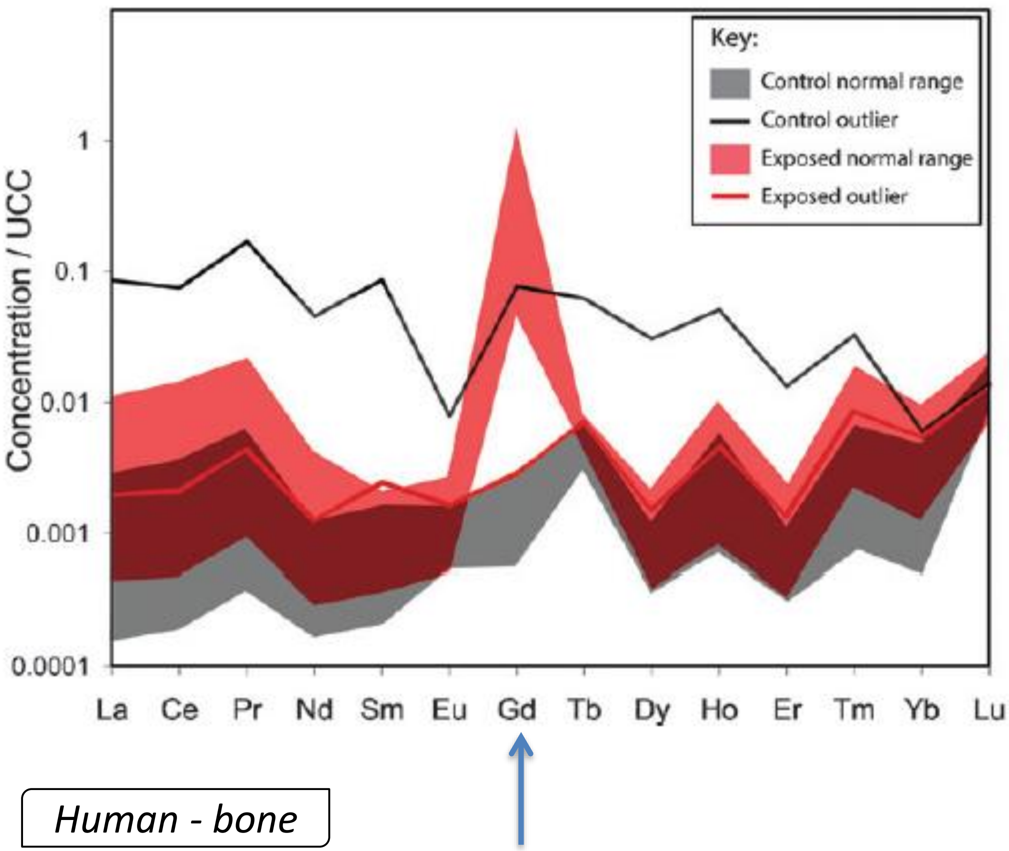
	nmol Gd/g skin
Omniscan	72 ±12
Magnevist	9 ±2
Multihance	1.4 ±0.4
ProHance	0.08 ±0.02
Dotarem	0.22 ±0.17
Gadavist	0.06 ±0.03
Untreated control	0.06 ±0.03
Saline control	0.18 ±0.07

LOQ 0.05 nmol/g skin

Rat - Skin

Is there a number below which we would consider that administered GBCA had washed out completely?

Background Gd exposure



Human - bone

Femoral head resections from 13 patients exposed to GBCA and 18 patients not exposed to GBCA

Figure shows the concentrations for all REEs in the bone samples, normalized to the average Rochester, NY soil composition

Gray band representing the REE pattern for control patients demonstrates the normal pattern of REE uptake relative to natural abundance in soils, food, water

Gd incorporation from natural sources:
0.03 nmol/g cortical bone
(95% CI: 0.023, 0.041 nmol/g)
0.08 nmol/g trabecular tissue
(95% CI: 0.054, 0.107 nmol/g)

Darrah 2009

Human Gd retention is less well characterized than rat

Human autopsy data (Murata 2016)

Subject	GBCA, # doses	Days since last dose	Brain, DN or GP (nmol Gd/g)	Skin (nmol Gd/g)	Bone (nmol Gd/g)
1	Gadavist, 1	5	6.8	na	na
2	Gadavist, 2	392	0.71	na	33.58
3	ProHance, 1	15	0.50	na	4.80
4	ProHance, 11	19	0.25	na	10.30
5	ProHance, 3	53	0.15	na	2.72
6	ProHance, 1	118	0.05	0.03	0.62
7	ProHance, 1	90	<0.03	0.01	0.60
8	Eovist, 10	90	0.94	na	8.27
9	Multihance, 1	83	0.50	0.36	15.14

Gd concentration in bone was on average 23x higher than brain levels

In the cases with skin bx, the Gd concentration in brain was similar to skin

Human – skin, bone, brain

Human Gd retention may differ from rat

Rat dentate nucleus data (McDonald 2017)

Rats	Omniscan, # doses	Days since last dose	Brain, DN (nmol Gd/g)
5	80[1]	7	38.8 – 44.5

[1]Human equivalent of rat dosing 20 x 2.5 mmol Gd/kg

20 x 2.5 mmol Gd/kg over 26 days, necropsy at 7 days after last dose

Rat – brain (DN)

Patients who received high doses of Omniscan had higher Gd concentrations in the DN than rats given very high doses

Rat brain may not experience the same Gd exposures as humans

Human autopsy data (McDonald 2015)

Subject	Omniscan, # doses	Days since last dose	Brain, DN (nmol Gd/g)
1	4	18	0.6
2	5	13	28.0
3	6	86	1.9
4	7	29	13.4
5	8	511	22.9
6	9	197	52.1
7	10	44	24.8
8	11	523	54.1
9	11	20	42.0
10	14	17	74.4
11	17	53	161
12	28	62	254
13	29	106	374

Human – brain (DN)

The Bone Study

Evaluated retention in human skin and bone from all of the GBCAs, using a standardized protocol

- Title: "Exploratory evaluation of the potential for long-term retention of gadolinium in the bones of patients who have received GBCAs according to their medical history"
- Start date/End date: May 2013/October 2017
- Enrollment: Patients with h/o GBCA administration (one administration or multiple administrations of the same GBCA) at least one month prior to orthopedic procedure; with stable normal or moderately impaired renal function
- Outcome measures:
  - Concentration of Gd in bone
  - Concentration of Gd in skin
  - Concentrations of calcium, phosphorus, sodium, iron, zinc, and potassium in skin and bone samples
  - Histopathological evaluation of skin samples for findings associated with NSF

Overview

- Gadolinium retention
- **Gadolinium fate/toxicity in skin, bone, liver**
- Chronic symptoms attributed to GBCA exposure

Skin Gd in NSF

- Insoluble extracellular Gd deposits identified in skin (Abraham 2008, Thakral 2009) → Gd → colloidal precipitates with tissue anions such as phosphates, hydroxides, or carbonates → deposited in skin
- Insoluble intracellular Gd deposits identified in skin fibroblasts and macrophages (Thakral 2009) → Intact GBCA/Gd phosphates → taken up by macrophages → GBCA localizes in lysosome → acidic environment → insoluble phosphates in the lysosome
- Intact ProHance, Multihance and Magnevist identified in skin up to 8 years after exposure (Birka 2015, Roberts 2016) → Soluble?

How much dissociated Gd (more dissociated Gd → more retention)

Number of macrophages/inflammatory cells/activation status (more immune activation → more retention)

Role of blood vessel integrity (blood vessel dysfunction → more retention)

Correlation between skin gd concentration and the presence of skin lesions

- Skin biopsies from NSF skin lesions, NSF normal skin, and no renal disease

	GBCA, # of doses	# of pts	Mean (range) nmol Gd/g skin
NSF, affected skin			
High 2007	unknown	4 pts	445 (153-675)
Khurana 2008	Omniscan, 1 – 4	6 pts	2036 (364 – 4565)
Christensen 2011	unknown	13 pts	454 (40-2218)
NSF, unaffected skin			
High 2007	Unknown	1 pt	30.5
Christensen 2011	Unknown	13 pts	65 (3.8 – 434)
No renal disease, unaffected skin			
Khurana 2008	Omniscan, 3-5 doses	2 pts	0.64
Christensen 2011	Unknown, 1 dose	2 pts	0.64
Roberts 2016	Multiple, 61 doses	1 pt	92

Rat skin Gd (nmol/g) (Lohrke 2017 (Bayer))	
Omniscan	1472 ±115
Magnevist	81 ±6
ProHance	1.7 ±0.8
Gadavist	1.1 ±0.5

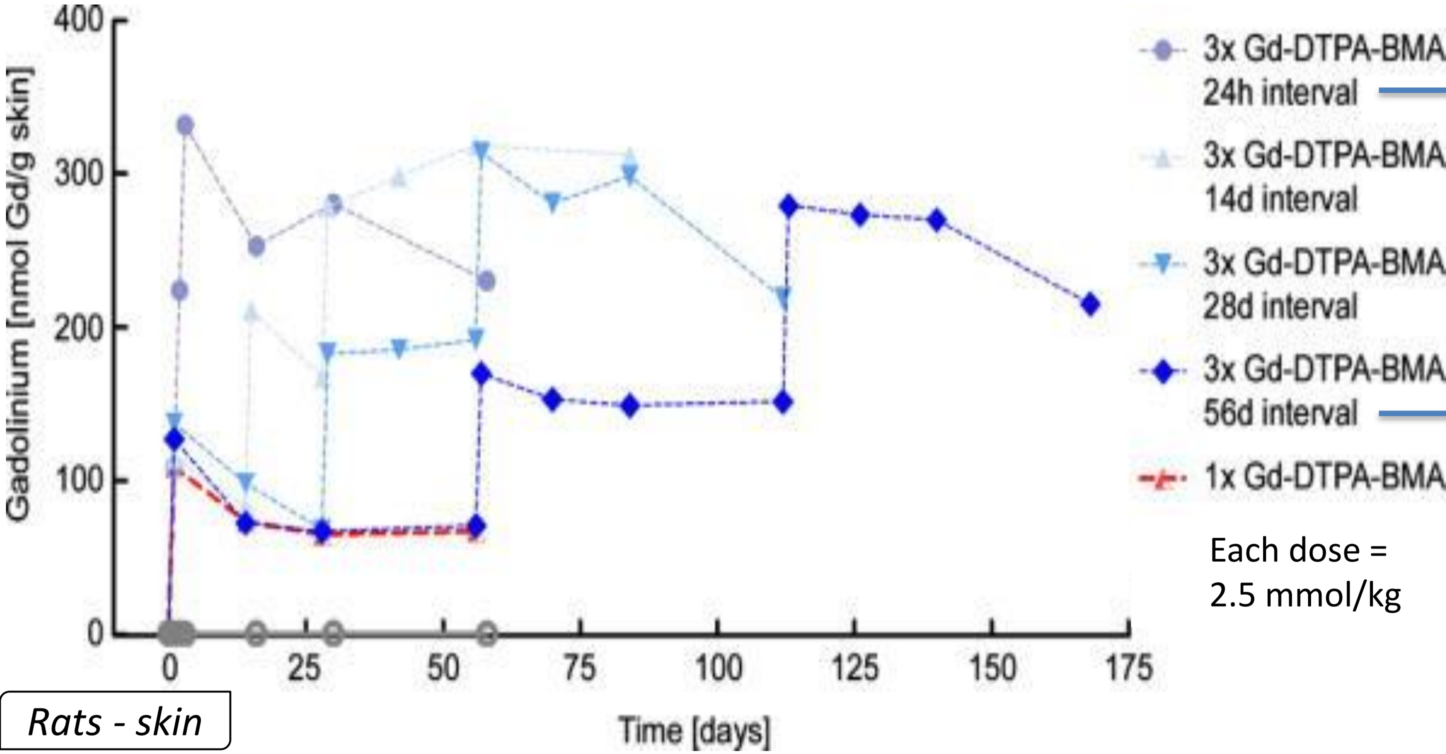
Rat - Skin

Are the skin deposits toxic?

- Unknown Gd skin concentration:
  - Gadolinium-associated plaques reported in 3 patients without NSF, one with normal renal function, 2 on HD (Gathings 2015, Bhawan 2013)
  - 4 pts with skin thickening/rubbery subcutaneous tissue (Semelka 2016)

Skin deposit toxicity/dose timing

Gd concentration in rat skin over time (Pietsch 2011 (Bayer))



Rats - skin

6/6 rats had skin lesions from d3, persisted in 3/5 d175

4/6 rats had mild skin lesions after first dose, no additional lesions after 2nd and 3rd dose, all lesions resolved at d175

Each dose = 2.5 mmol/kg

Doses given over a long period of time result in the same levels of long-term Gd skin retention as the doses give over a shorter period of time

Skin lesions were more severe when doses given in shorter period of time

Allowing for a certain period of time between doses, the Gd measured in skin may be inert

Toxicity to Gd may represent an ongoing response to an acute exposure, rather than toxicity to chronic presence of gd

Stable GBCAs

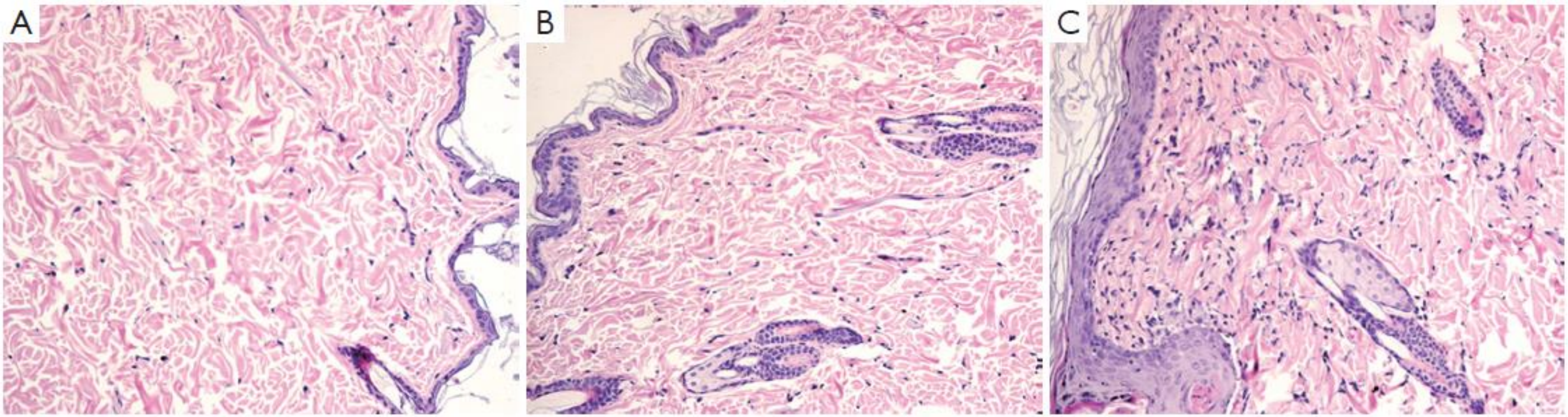


Figure 2 Phase 1 study. HE histology (original magnification, ×200). (A) Saline-treated rats showed normal collagen fibril density; (B) gadoteric acid and (C) gadodiamide induced spindle cell and stellate cell hyperplasia, and resulted in denser collagen fibril. The gadodiamide-treated rats show thicker epidermis layer and more abundant and denser collagen fibril than the gadoteric acid treated rats.

Study group	Cellularity/×200 view*	Epidermis thickness (μm)**
Baseline	89±10	22±4
Saline	90±7	25±5
Gadoteric acid	104±10[#]	33±4[Δ]
Gadodiamide	120±9[§]	46±9[Δ]

Rats - skin

Omniscan	45 nmol Gd/g skin
Dotarem	0.25 nmol Gd/g skin

- 8 rats per group
- 5 IV injections each at a dose of 3.5 mmol Gd/kg for 5 consecutive days
- 10 weeks after the last injection, necroscopy and sample collection

Wang 2015 (Guerbet)

NSF - Muscles, fascia, tendons, nerves, vessels

- Muscles/fascia/tendons
  - Muscle most common organ involved besides skin in NSF cases (Sanyal 2011)
  - Skeletal muscle with CD34-positive cellular fibrosis (Sanyal 2011)
  - Muscle biopsies range from mild myopathic changes to severe fibrosis, correlated with degree of muscle hardening and immobility; muscle involvement includes atrophy, infiltration with fibrous tissue, increased collagen deposition (Levine 2004)
  - Fibrosis of muscles, involving subcutaneous fascia, and striated muscles, thickening of the tendons and peri-articular tissues (Mendoza 2006)
  - Histology - subcutaneous septa markedly thickened with fibrosis extending through the lobular septa into the underlying fascia and muscle (Thakral 2009)
  - Contractures due to skin and muscle fibrosis (Wahba 2007)
- Nerves
  - Sensory-motor axonal neuropathy - fibrous bands of collagen invade deeper structures, invading nerves as well as muscle fibers causing neuropathies with both neurogenic and myopathic features (Keyrouz 2007)
  - Sensory-motor polyneuropathy: burning pain and clinical and/or electrophyiological findings of neuropathy. (Levine 2004)
- Vessels
  - Increased vascular calcification (Song 2009)
  - Gd-Ca-P co-deposition along the basement membranes of blood vessels (Boyd 2007)
  - Perivascular Gd deposition (Schroeder 2008, Singh 2008)
  - Predominant site of Gd deposits in vessel walls (Sanyal 2011)

Gadolinium toxicity - Bone

- Mechanism of retention in bone
  - There are well-known pathways whereby Gd ions (and metals in general) may be taken up into bone
    - active incorporation during osteoblast-mediated bone mineralization
    - passive ionic exchange into the bone mineral lattice
  - Gd incorporation into bone – can replace calcium in the hydroxyapatite (Vidaud 2012, Abraham 2008)

- Potential toxicity
  - Could negatively impact bone health similar to other toxic metals (Pb, Cd) which alter bone cellular processes (Darrah 2009)
    - Toxicity to cells within bone tissue – osteoblasts, osteoclasts, endothelial cells, hematopoietic bone marrow
    - Altering bone cell signaling and molecular pathways (Carmouche 2005)
    - Inhibit fracture healing (Carmouche 2005)
    - Alter the metabolism of osteoblasts and osteoclasts responsible for remodeling bone tissue (Puzas 1992, Dowd 2001)

Long term reservoir - Bone

- Mechanism
  - Long term retention of Gd is thought to be highest in bone, probably related to Gd replacing calcium in the hydroxyapatite of bone
  - Documented for as long as 8 years after exposure (Darrah 2009)

- Potential toxicity to other tissues
  - Metals are released from bone during normal and abnormal bone resorption and remodeling
  - Whether initially incorporated in the form of a GBCA, other Gd complexes, or ionic Gd3+, the normal resorption process (which involves the secretion of HCl by osteoclasts to dissolve existing bone mineral) may release ionic Gd3+, due to the lower thermodynamic stability of GBCAs at lower pH (Darrah 2009)

- Clinical manifestations
  - Increased skin Gd concentration over time (without additional GBCA exposure) on sequential skin biopsies from NSF (Abraham 2008, Thakral 2009, Bennett 2012)
  - Delayed onset NSF cases up to 5 years after exposure (Abraham 2008, Grebe 2008, Heinz-Peer 2010)

Long term reservoir – Vulnerable populations

- Patients with increased rates of bone resorption may have increased risk of exposure to endogenous Gd release
  - Post menopausal women
    - Rates for resorption of the trabecular bone in post menopausal women are 19-26%; normal bone turnover in adults is 5-15% per year (Eriksen 1990, Darrah 2009)
  - Pregnant, lactating women
    - Pregnant and lactating women had increased plasma lead concentrations from increased bone resorption (Rothenberg 1994, Gilson 1997)
  - Osteoporosis

- Children – increased bone formation – risk of accumulating larger reservoir of Gd

- Patients exposed to large doses of GBCAs – chronic illness, high risk screening populations.

Case report: Young man, 61 CE MRIs over 11 years

- Dx with glioblastoma (Roberts 2016)
  - 2 years of treatment chemo/radiation
  - Continued MRI surveillance
  - About 8 yrs after diagnosis, underwent cholecystectomy
  - After surgery, he developed joint contractures which progressed to severe and incapacitating and pt became nonambulatory
- Skin biopsy (no gross skin abnormality)
  - Skin gd concentration 92 nmol/g - similar to those reported in the unaffected skin in patients with NSF
  - Increased CD34 immunoreactivity in the connective tissue septations of the subcutaneous tissue
  - Did not meet criteria for NSF
- Joint contractures
  - Muscle/joint biopsy declined
  - Cause unknown, possibly multifactorial

High levels of Gd in skin

Contractures developed after surgery (pro-inflammatory event)

"a definite association of the joint contractures with the high levels of gadolinium could not be confirmed or excluded"

Highlights the concern for potential toxicity from very high lifetime GBCA exposure

Gadolinium toxicity- Liver

- Preclinical studies – Gd accumulates significantly in the liver
  - 14d rat Gd biodistribution data: femur > kidney > liver (Tweedle 1995)
  - 10w Gd concentration data: bone > skin > liver (Wang 2015)
- NSF human autopsy – no defined hepatic toxicity
  - Extracellular Gd deposits in the form of insoluble phosphates
  - Intracellular Gd deposits in a hepatocyte (Sanyal 2011)
- Recent human liver gd data

- $GdCl_3$ (releases Gd ions in solution)
  - Profoundly hepatoxic; hepatic necrosis (Spencer 1997, Hirano 1993)
  - Exposure to Gd from dechelation of GBCA – potential for hepatoxicity

Overview

- Gadolinium retention
- Gadolinium fate/toxicity in organs
- **Chronic symptoms attributed to GBCA exposure**

Chronic symptoms attributed to GBCA exposure

- FDA DPV reviewed FAERS database and literature for evidence of toxicity related to gadolinium retention
  - 132 cases total
    - 34 FAERS cases, 98 literature cases
    - Review found no apparent causal association between reported AEs and Gd retention
  - Limitations of DPV review
    Nonspecific symptoms, particularly delayed in onset could be overlooked or not attributed to the GBCA exposure resulting in an underestimation of a potentially more common adverse event

Chronic symptoms attributed to GBCA exposure

- Clustering of AEs around cutaneous, MSK, neurological/cognitive, and pain syndromes

Adverse Events by Clinical Category Occurring in ≥10 Cases

Pain syndromes	Neurological	Cutaneous	Musculoskeletal	Other
limb or central torso nociceptive paresthesias/ dysesthesias (53)	**clouded mentation (31)**	**skin discoloration (30)**	**bone pain (40)**	**fatigue/asthenia (51)**
headache (37)	non-nociceptive paresthesias/ dysesthesias (14)	**skin changes (29)**	**bone/joint pain (38)**	head & neck including headache, vision changes, and hearing changes (38)
unspecified pain (10)	cognitive impairment (13)	**skin thickening (25)**	muscle spasms (36)	other unspecified (37)
		rash/erythema (14)	joint stiffness (33)	generalized whole body symptoms (30)
			arthralgia (12)	digestive symptoms including nausea, vomiting, and diarrhea (27)
			muscular weakness (10)	chest symptoms/dyspnea (26)
				buzzing sensation (24)
				metallic taste (20)

Reported symptoms overlap with NSF, raising the concern that there could be an association between the reported symptoms and GBCA exposure

DPV Review 2017

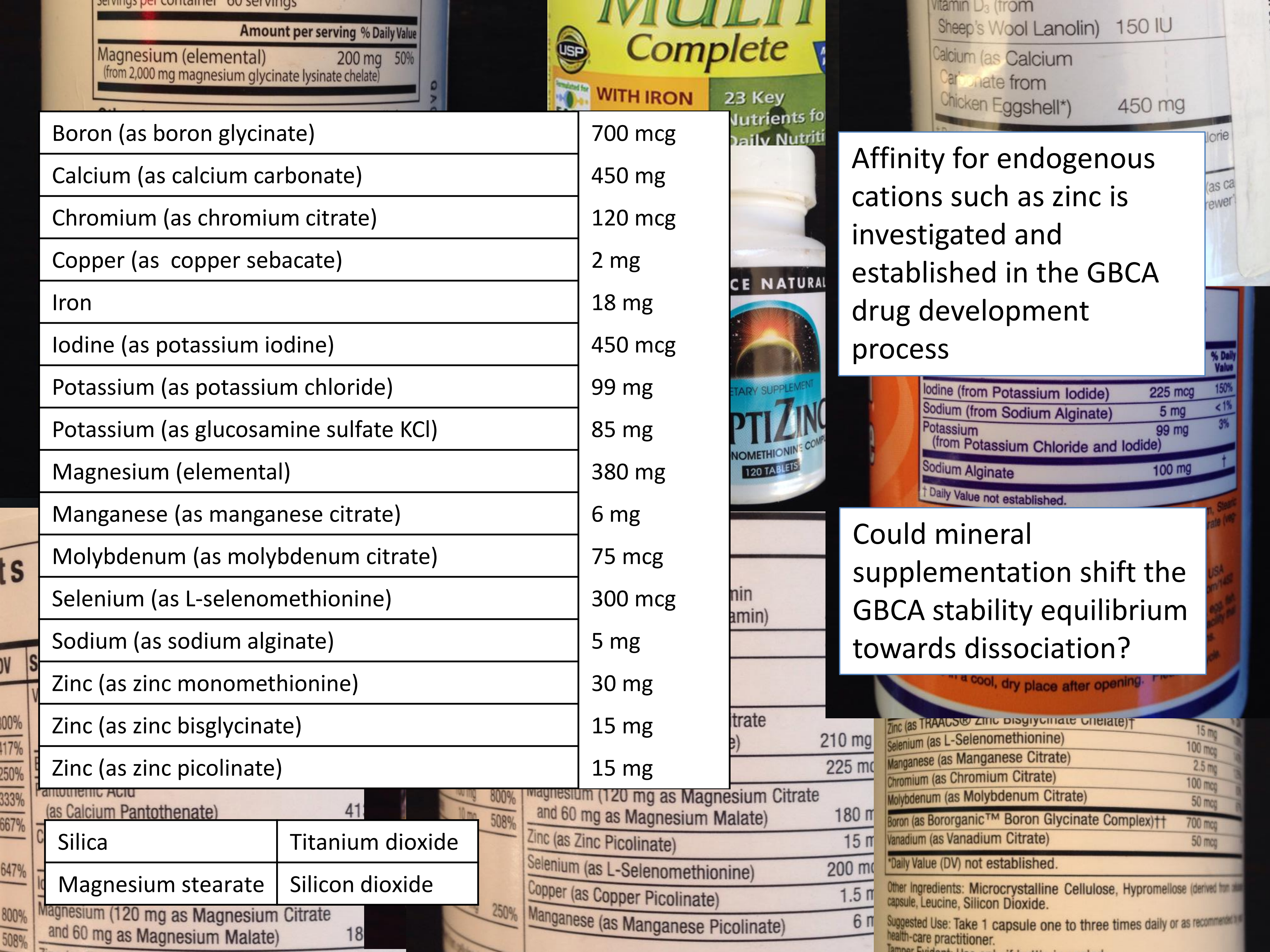
Chronic symptoms attributed to GBCA exposure

- Chelate dissociation hypothesis
  - What factors could favor GBCA dissociation in the setting of normal renal function?
  - Could a drug interaction favor transmetalation?
    - Case report – Patient with chronic zinc poisoning from denture cream (30 mg zinc/g) was found to have retained at least 0.59% of the ID of Gd at D29 after Magnevist, which is at least 6 times expected based on the mouse biodistribution data (Greenberg 2010)

“Patients with elevated zinc exposure may be at increased risk of Gd retention”

Evaluate within the framework of NSF

The prevailing theory is that NSF is caused by dechelation of the GBCA molecule, related to delayed renal clearance, and subsequent exposure to Gd^{3+}



Boron (as boron glycinate)	700 mcg
Calcium (as calcium carbonate)	450 mg
Chromium (as chromium citrate)	120 mcg
Copper (as copper sebacate)	2 mg
Iron	18 mg
Iodine (as potassium iodine)	450 mcg
Potassium (as potassium chloride)	99 mg
Potassium (as glucosamine sulfate KCl)	85 mg
Magnesium (elemental)	380 mg
Manganese (as manganese citrate)	6 mg
Molybdenum (as molybdenum citrate)	75 mcg
Selenium (as L-selenomethionine)	300 mcg
Sodium (as sodium alginate)	5 mg
Zinc (as zinc monomethionine)	30 mg
Zinc (as zinc bisglycinate)	15 mg
Zinc (as zinc picolinate)	15 mg

Silica	Titanium dioxide
Magnesium stearate	Silicon dioxide

Affinity for endogenous cations such as zinc is investigated and established in the GBCA drug development process

Could mineral supplementation shift the GBCA stability equilibrium towards dissociation?

Chronic symptoms attributed to GBCA exposure

- Chelate dissociation hypothesis
  - Potential causes in the setting of normal renal function
    - Medication/supplement interaction
      - » competing metals (Ca, Zn, Fe, Cu) which may favor transmetalation
    - Other factors that influence dissociation –pH, other causes of elevated serum calcium, serum phosphate, and pro-inflammatory conditions

→ May be able to measure chelate dissociation by comparing urine/serum assays to normative extended excretion curves for each GBCA

- Other co-factor(s) or causative factor(s)
  - Proinflammatory state/condition
  - Genetic
    - Variable immune response
    - Genetic abnormality in metabolizing heavy metals
  - Vascular dysfunction

→ Many co-factors have been proposed to explain the low incidence of NSF, may also explain extremely small numbers of reported chronic symptoms in 100s of millions of GBCA doses administered

- Reaction to intact GBCA

Key points

- Gadolinium retention
  - Human GBCA elimination data are incomplete, and known to vary among GBCAs after 24 hours
  - In preclinical models, standardized methods are needed particularly for quantifying and comparing retention after macrocyclics
- Gadolinium fate/toxicity in organs
  - Dose timing may play an important role
  - Local bone toxicity is known to occur in the setting of other metals, and would be potentially most significant for pts exposed to GBCAs as children or fetus as they may incorporate more Gd in the setting of a growing skeleton.
  - A reservoir of bone and/or total body gadolinium could result in significant morbidity in certain clinical scenarios – proinflammatory event, increased bone turnover
  - The liver may be a sensitive organ in terms of chronic exposure to Gd from bone stores
- Chronic symptoms attributed to GBCA exposure
  - In the population of patients with chronic symptoms attributed to GBCAs, no causal association has been identified, but overlap of symptoms with NSF is concerning and warrants urgent study
  - Consider factors that may shift the GBCA stability equilibrium towards dissociation

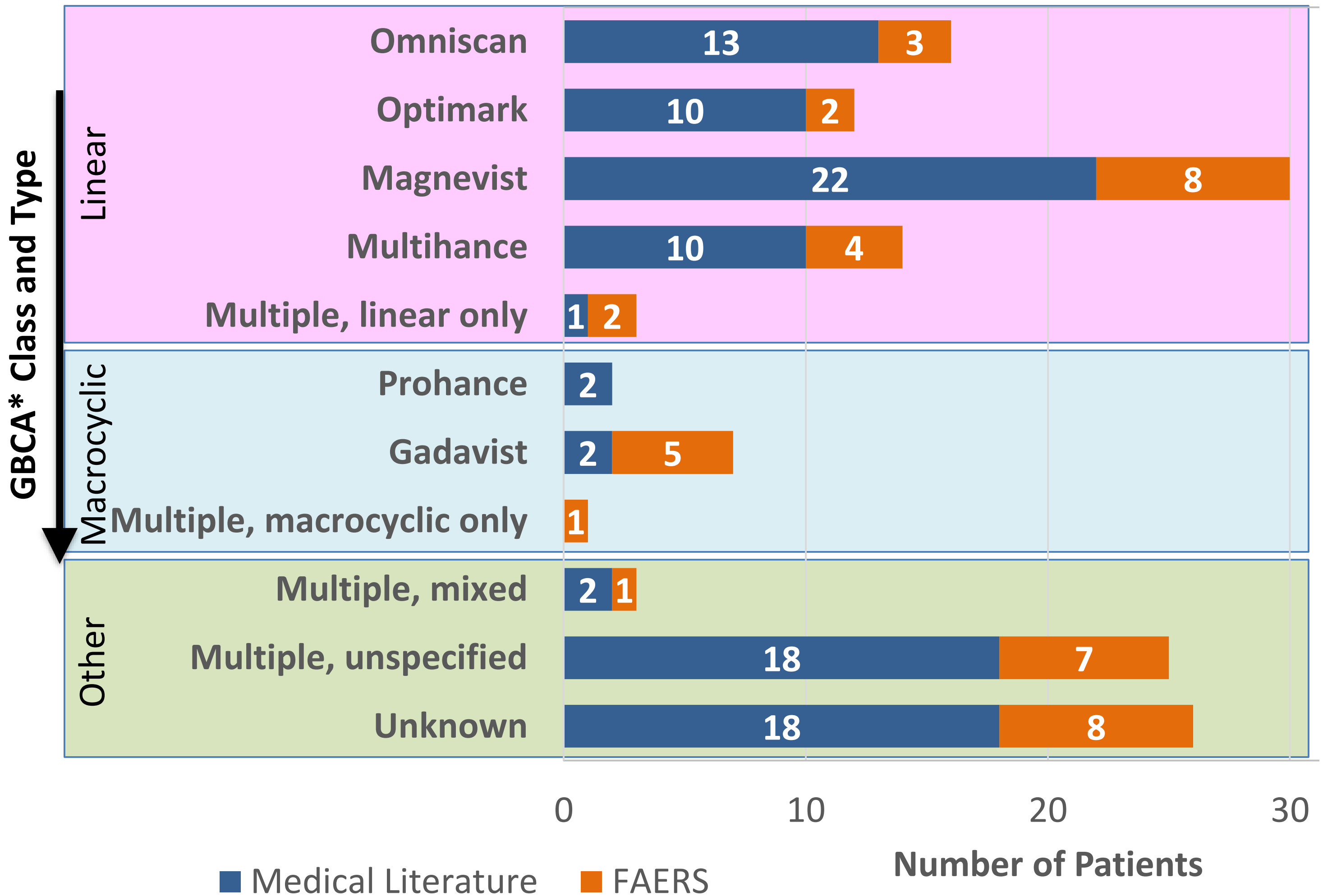
U.S. FOOD & DRUG
ADMINISTRATION

Back up slides

Chronic symptoms attributed to GBCA exposure

FDA

Number of Patients with Reported Adverse Events (FAERS and Medical Literature) (N=139)

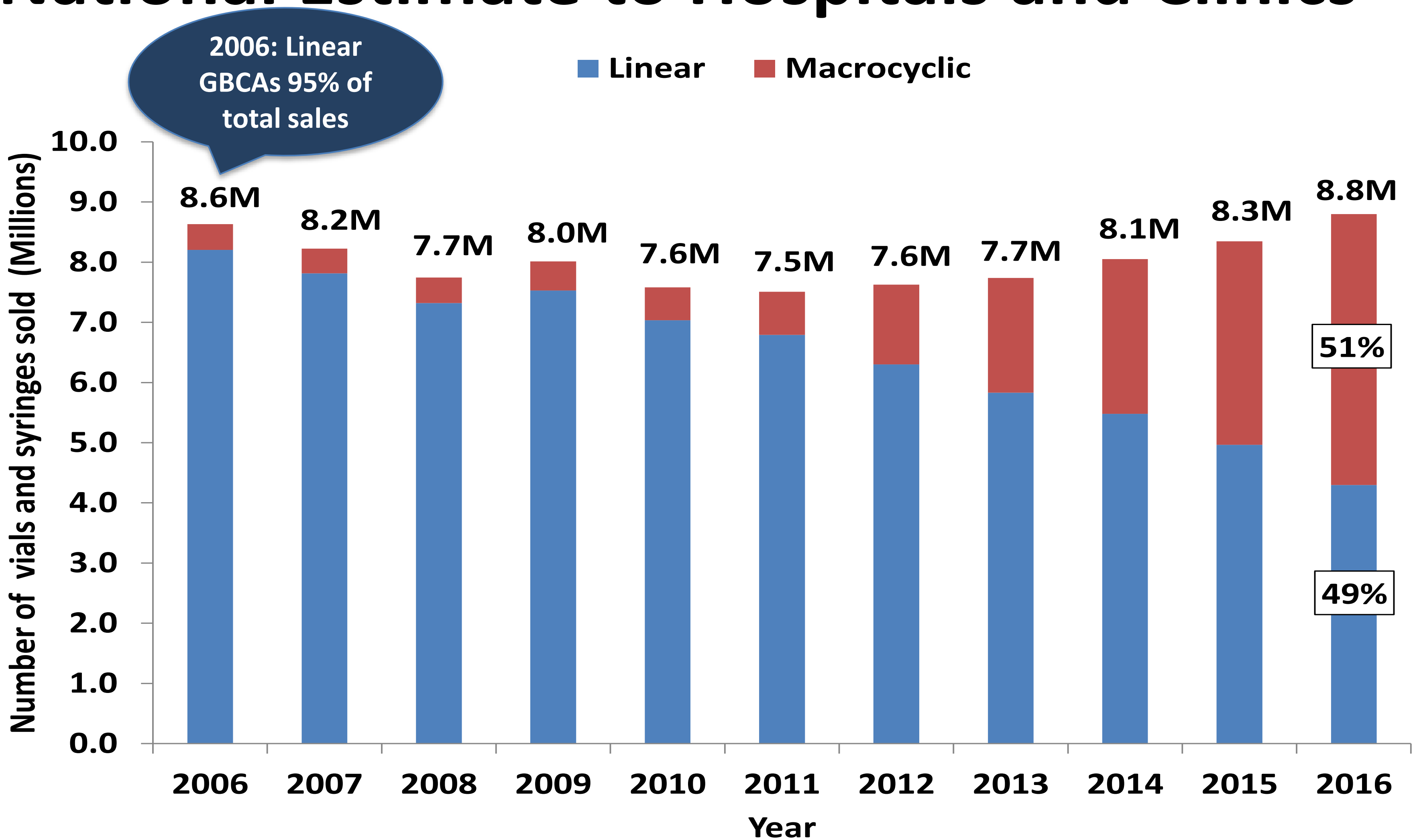


Linear	**75**
Macrocyclic	**10**
Mixed/Unknown	**54**

More reports associated with linear agents, but could be related to use patterns, and numbers are confounded by many mixed/unknown reports

DPV Review 2017

Total U.S. GBCA Sales: National Estimate to Hospitals and Clinics



Source: QuintilesIMS Health, IMS National Sales Perspectives™. Data Extracted July 2017.