The Health Risks of Gadolinium-Based Contrast Agents Used in MRIs

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Executive Summary

Magnetic resonance imaging (MRI) is a common diagnostic procedure that can improve the quality of medical care and save lives. Gadolinium-based contrast agents (GBCAs) are used to improve the detail of some types of tissues visible with an MRI (known as contrast-enhanced MRI), thereby improving diagnostic accuracy. There have been nine GBCAs approved by the FDA since 1988.

In 2006, safety concerns were raised when it was determined that patients with severe kidney dysfunction who underwent MRIs with contrast could develop nephrogenic systemic fibrosis (NSF) if their MRIs were performed with certain GBCAs. Since then, by following FDA and medical society recommendations that limit the types and general use of contrast-enhanced MRI for patients with poor kidney function, the incidence of NSF was almost eliminated.

Safety concerns about GBCAs were raised for patients with normal kidney function in 2014, when researchers discovered that gadolinium could remain in patients' brains and could accumulate with each dose of contrast that they received. In addition, gadolinium has been found in bone, skin, and other organs and tissues of patients with normal or impaired kidney function. However, while it is well-established that gadolinium from either linear or macrocyclic GBCAs can be retained and accumulate in at least some patients, there is considerable uncertainty about how this affects patients' health.

Four conditions have been described by researchers and clinicians as due to the long-term retention and accumulation of gadolinium in a patient's body. The most well-known and accepted condition is NSF in patients with poor kidney-function. Gadolinium deposition disease and gadolinium-associated plaques are two conditions that share certain symptoms with NSF, but can also occur in patients with normal kidney function and have symptoms that are typically less severe. The fourth condition, gadolinium storage condition, describes patients with long-term accumulation but who may not have symptoms related to the gadolinium. However, these three latter conditions are not recognized by the FDA, WHO, or major medical societies.

Studies have found mixed results on the effects of GBCA exposure in utero and the effects on brain health. However, limitations in these studies, such as small number of individuals, inadequate study design, or difficulties of controlling for differences between groups, complicate the interpretation of these studies.

Based on the limited data concerning the health effects of gadolinium remaining in the body, FDA required a warning on the labels for GBCAs concerning retention and encouraged additional information be provided to most patients prior to their MRIs. Medical societies developed guidelines to encourage additional consideration of when, what type, and which dose of GBCA should be used.

Hopefully, these recommendations will limit contrast-enhanced MRIs to situations in which the benefits substantially outweigh the risks. However, there are currently many patients with gadolinium in their

[i] Cover image: MRI brain sagittal section; courtesy of Wikimedia Commons https://commons.wikimedia.org/wiki/File:MRI_brain_sagittal_section.jpg

bodies and who have symptoms, and that number is likely to increase. More forceful FDA regulations are needed to ensure better information for doctors and patients about risks and benefits.

There is little research on treatments for gadolinium retention or accumulation and related symptoms. While numerous treatments have been reported on in studies, these have typically included only a small number of patients and lack control groups of patients who were not exposed. Some therapies show promise, such as chelation therapy, but these treatments have risks that can be serious and the benefits are uncertain.

In addition to the health concerns for patients who have contrast-enhanced MRIs, there is a growing concern about GBCAs as well as gadolinium in the environment. As the vast majority of GBCAs pass through patients intact, they also pass through wastewater treatment plants, into surface water, and eventually into tap water. Fortunately, the amounts of gadolinium found in tap water are extremely low. However, as with the lack of solid data regarding the health effects of gadolinium accumulation resulting from MRIs, there is a lack of data about the effects of lifelong exposure to low levels of gadolinium from the environment, particularly with exposures during critical periods of life, especially in utero or early childhood.

The bottom line is that while there is strong evidence that gadolinium can be retained and accumulate in patients, there are many unanswered questions about who develops health problems related to gadolinium, how to determine if symptoms are due to gadolinium, and how to prevent or treat gadolinium-related conditions. New studies with carefully selected populations and study designs are needed to address these questions.

In the meantime, patients and clinicians should consider the benefits and risks of each contrast-enhanced MRI, along with which GBCA and dosage is most appropriate. Contrast-enhanced MRIs with GBCAs are important diagnostic procedures, but they have known and unknown risks, so their use should be cautiously evaluated for each patient and situation, and all patients should be informed of the known and unknown risks. In our experience, that is not currently the case in most medical centers.

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Introduction

Magnetic resonance imaging (MRI) is a common diagnostic procedure that has been credited with saving lives and improving the quality of medical care. Gadolinium-based contrast agents (GBCA; sometimes called contrast media, contrast agents, or 'dyes') are chemical substances that allow the radiologist to see more details in the MRI, which can improve diagnostic accuracy. For example, it improves the visibility of inflammation, tumors, blood vessels, and blood supply of some organs. Millions of contrast-enhanced MRIs using GBCAs are performed in the U.S. every year.

MRI was developed in the mid-1900s. The first whole-body MRI was developed in the 1970s as a method to detect cancer in live humans.[1,2] Soon after, research into methods to improve the quality of the image through enhancing the contrast began. Metals, such as copper, iron, magnesium, chromium, and gadolinium were attached to large molecules to make a stable complex that could be used as a contrast-enhancing agent. (For more information, see Chemistry section, below.) Although gadolinium-based complexes are the only contrast-enhancing agents for MRI currently marketed in the United States, there are contrast-enhancing agents based around iodine, barium-sulfate, microbubbles, and microspheres used for x-ray, computed tomography (CT), or ultrasound imaging.[3] Iron oxide (ferumoxides) was used for contrast-enhanced MRI in the U.S. over a decade, but is no longer used.[4]

In 2006, it was discovered that gadolinium from at least some types of GBCAs could harm patients with impaired kidney function. As a result, FDA and medical societies' guidelines now recommend against the use of some types of GBCAs in patients with poor kidney function. Since 2014, concerns have been raised about GBCAs for patients with healthy kidneys as well. This has resulted in guidelines recommending more careful consideration of the benefits and the risks of various GBCAs for each individual patient and situation.

The goal of this article is to review the published research on GBCAs to determine what is known and not known about long-term risks. We include patient-reported health problems from gadolinium exposure to better understand research results and to inform the need for well-designed research in the future.

History of Gadolinium Regulation

The first gadolinium-based contrast agent (GBCA), Magnevist (gadopentetate dimeglumine), was developed during the 1980s and was approved by the FDA in 1988.[5] Since then, eight other GBCAs have been approved by the FDA: ProHance (gadoteridol), Omniscan (gadodiamide), OptiMark (gadoversetamide), MultiHance (gadobenate dimeglumine), Eovist (gadoxetate disodium), Ablavar (gadofosveset trisodium), Gadavist (gadobutrol), and Dotarem (gadoterate meglumine). Ablavar was removed from the market by February 2018[6] and OptiMark by February 2019.[7]

Safety concerns began to be recognized in 2006, when it was determined that nephrogenic systemic fibrosis (NSF) could develop in patients with severe kidney problems who had undergone MRIs with GBCA.[8,9] The FDA released a Public Health Advisory in June 2006, announcing that it was investigating

reports of NSF and recommending that GBCAs be avoided when patients have advanced kidney dysfunction.[10] The Advisory also suggested that such patients consider closely following exposure to GBCAs with dialysis. The following year, the FDA requested that manufacturers include a black box warning, which is FDA's most urgent warning, to bring attention to the risk of NSF on the labels for all GBCAs.[11]

In December 2009, the FDA convened an Advisory Committee Meeting to discuss GBCAs and NSF. The committee concluded that the evidence demonstrated that at least some GBCAs could cause NSF and discussed label changes and other options to reduce this risk.[12,13] As a result, the FDA issued a Safety Communication warning of the risk of NSF for patients with poor kidney function in September 2010. The communication also announced that the labels for all GBCAs must be changed to reduce the risk for NSF as follows:[14]

- Not to use Magnevist, Omniscan, or OptiMark in patients with kidney problems
- Screen patients or use clinical history to identify patients with kidney problems (glomerular filtration rate or GFR < 30 mL/min/1.73m2)
- Avoid GBCAs in patients with reduced ability to rid the body of drugs
- Watch for NSF signs or symptoms in patients who may have a reduced ability to rid the body of the drug
- Not to provide multiple administrations during an MRI session

All labels were updated by the end of 2010.

In December 2013, the safety of GBCAs was again called into question when a study was published showing that patients who had previously had contrast-enhanced MRI(s) with GBCA continued to have contrast enhancement on a later MRI that had not used a GBCA.[15] This suggested that some gadolinium had been retained in the body. Retained gadolinium had previously been detected in bone and has since been found in other organs and tissues as well. This prompted another Safety Communication from the FDA in July 2015, stating that it would look into the issue.[16]

In May 2017, the FDA announced an Advisory Committee meeting to address this concern, stating: "All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because we identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time."[17]

The Advisory Committee meeting mentioned above was held in September 2017 to discuss the evidence for gadolinium retention, their concerns about it, and FDA's plans for addressing this issue. In general, the Committee recognized that gadolinium could be retained in the body for years, but did not believe it had enough evidence to assess the effects or determine which types of patients were at highest risk.[18,19] Even with the lack of evidence and the need for further research, committee members stressed that the "absence of evidence does not prove that there is no risk" and that additional attention should be given to some types of patients, such as children and pregnant women.[18] The Committee agreed with the FDA's plan to require a warning on the labels of all GBCAs about the risk of retention, specifically that the risk differs among GBCAs, and agreed with the FDA's plan to recommend steps for reducing risk for some

types of patients. They also agreed that the FDA should consider requiring additional studies be conducted by GBCA manufacturers.

The FDA does not always follow the recommendations of their Advisory Committees, but this new warning requirement for all GBCAs was announced in December 2017.[20] The announcement also stated, "To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. We have also received reports of adverse events involving multiple organ systems in patients with normal kidney function. A causal association between these adverse events and gadolinium retention could not be established."

At the same time FDA stated that they were requiring the development of new medication guides for patients that provided "educational information that every patient will be asked to read before receiving a GBCA." [20] The agency also stated that they would be requiring GBCA manufacturers to conduct further safety studies.

By May 2018, the labels had been updated and medication guides for each GBCA had been developed.[20] However, the FDA changed the recommendation from providing medication guides to <u>all</u> patients before receiving a GBCA to "All MRI centers should provide a Medication Guide the first time an outpatient receives a GBCA injection or when the information is substantially changed. In general, hospital inpatients are not required to receive a Medication Guide unless the patient or caregiver requests it. A health care professional who determines that it is not in a patient's best interest to receive a Medication Guide because of significant concerns about its effects may direct that it not be provided to that patient; however, the Medication Guide should be provided to any patient who requests the information." [20]

The clear intent of the changed requirement was to prevent patients from having concerns that could result in their deciding not to undergo an MRI with contrast. Most patients would not know that they have an option to request a Medication Guide for GBCA, since they would consider an MRI a diagnostic test, not a medication. This change in warnings to patients undermined the intent of providing informed consent to patients about the potential risks of GBCA.

Compared to the FDA, the European Medicines Agency and European Commission have moved more quickly and proactively to reduce exposure to gadolinium. On the recommendation of the European Medicines Agency, in 2017 the European Commission suspended marketing authorization for Magnevist, Omniscan, and OptiMark.[21] They also limited the use of MultiHance to imaging of the liver. The European Medicines Agency stated, "There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however, EMA has recommended restrictions and suspensions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition."

An international meeting was convened by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health (NIH) in February 2018 to discuss the research issues concerning gadolinium retention, accumulation and health.[22] It was cosponsored by the NIH and two medical societies, American College of Radiology (ACR) and Radiological Society of North America

(RSNA). They developed a roadmap to prioritize the research needed to determine the clinical effects of gadolinium retention.

Chemistry

Gadolinium is a toxic, heavy metal. To keep the gadolinium from causing toxicity when used to enhance contrast in an MRI, it is attached to a large molecule, which may be called a chelate, ligand, or carrier. GBCAs are typically categorized by their structure because this affects their stability and likelihood of causing complications.

The chelate on a linear GBCA has a tail that wraps partially around the gadolinium atom, while the chelate on a macrocyclic GBCA forms a rigid cage-like structure around the gadolinium. The linear forms are more likely to release gadolinium compared to macrocyclic forms. Linear GBCAs are more likely to be stored or form deposits.

GBCAs are also described as ionic or non-ionic. This affects how linear GBCAs interact with other proteins and chemicals, which affects their stability. Linear ionic GBCAs are more stable than linear non-ionic GBCAs, so are less likely to release gadolinium or deposit in the body.

Under normal conditions in the body, gadolinium naturally separates from the chelate at a rate that depends on its structure. It can then rebind to the chelate or it can bind to another nearby protein or chemical. Other minerals, such as iron, magnesium, copper, zinc, or calcium, can also bind to the chelate after the gadolinium is released. This is called transmetallation, which means that one of these other chemicals switches position with gadolinium. Anything that reduces the stability of the GBCA or delays excretion of GBCA increases the chance that gadolinium separates from the chelate and binds to something that will be retained in the body. If gadolinium separates from the GBCA, it is more likely to be retained in the body, collect in tissues, and cause symptoms. On the other hand, gadolinium that remains attached to a chelate (intact GBCA) is more likely to be excreted from the body.

Eliminating GBCA from the Body

All of the GBCAs on the market in the U.S. are delivered intravenously.[23,24,25,26,27,28,29] They are removed from the body primarily or exclusively by the kidneys. Consequently, as noted earlier in this report, patients with poorly functioning kidneys have slower clearance or removal rates, and thus, more time for the molecules to break down and for gadolinium to deposit in bone and other tissues. Two linear GBCAs, MultiHance and Eovist, are removed via the liver as well as the kidneys, so are considered safer than other linear GBCAs for patients with poor kidney function.

The amount of time that it takes for a healthy individual to excrete half of the GBCA is approximately 2 hours or less for all GBCA currently on the market. For patients with severe kidney impairment, this time increases dramatically. For the linear GBCAs that are of most concern (Magnevist, Omniscan, and OptiMark), the time it takes to excrete half of the GBCA is increased to up to about 34 hours.[26,30,31] This

allows more time for gadolinium to separate from the chelate and it can therefore be retained for months or years.

Even though most of the GBCA is eliminated rapidly, the remaining GBCA or gadolinium that has separated from the GBCA is removed from the body much more slowly. About 90% of the GBCA is removed within 24 hours in individuals with normal renal function, although this varies among GBCAs.[22] However, the GBCA that remains takes much longer to be eliminated, which increase the risk of gadolinium accumulation.[ii] A small study by Alwasiyah et al. of 13 patients with healthy kidneys found elevated levels of gadolinium in the urine 30 days after MRI contrast procedures for all patients.[32] The study suggested that after exposure there is a rapid reduction in GBCA and then additional elimination occurs more slowly. A study published as a white paper by Grimm and Williams found the same pattern of elimination based on 218 urine samples submitted by 135 members of a gadolinium-toxicity support group, and also found elevated levels of gadolinium years after exposure.[33]

Although most of the GBCA is excreted from the body within a few days, the concern is that a small amount of GBCA or gadolinium from a contrast-enhanced MRI can remain for months or years. Gadolinium can accumulate from multiple contrast-enhanced MRIs and some types of patients may retain more than others. These individual differences in terms of patient characteristics and number of MRIs, are the main controversies about the risks of gadolinium accumulation and the potential harm from GBCAs.

Evidence of Gadolinium Accumulation

Brain

Accumulation in the Brain

In humans, the most common method for studying gadolinium retention is through MRI of the brain without providing additional contrast agent. Gadolinium that has been retained in the brain from one or more previous contrast MRIs causes brain tissue to continue to have a low level of contrast enhancement. This increased (more intense) signal on images from an MRI appear as brighter areas and is called hyperintensity. This increased signal can be seen in many areas of the brain, but two areas tend to have a much more intense signal than other parts of the brain: the dentate nucleus and globus pallidus.[34] Most studies of gadolinium accumulation using MRIs without GBCAs focus on these two areas with higher levels of hyperintensity.

The type of GBCA used in a patient's previous MRI affects how much contrast enhancement is seen in these non-GBCA MRIs.[35] The retention of gadolinium from linear GBCAs are clearly shown in these studies, whereas some studies have found similar results with macrocyclic GBCAs, but other studies have not.

[ii] For the purposes of this paper, the use of the term accumulation also includes retention from a single exposure.

However, gadolinium retention is not the only possible reason why contrast enhancement can be seen in subsequent non-GBCA MRIs. High levels of minerals such as manganese from environmental exposure, as well as underlying conditions, such as neurofibromatosis type I, metabolic disorders, and hypoxia-induced brain damage, can also cause hyperintensity on an unenhanced MRI.[36,37]

While other exposures and conditions can cause contrast enhancement, studies that directly measured gadolinium in brain tissue obtained from cadavers or from tissue taken during surgery to remove brain tumors demonstrate that gadolinium accumulation in the brain from previous contrast-enhanced MRIs affects the hyperintensity seen in subsequent non-GBCA MRIs. For example, gadolinium was detected in the areas that have strong hyperintensity on an unenhanced MRI and in areas that did not show hyperintensity.[38,39,40,41,42,43] Higher levels of hyperintensity could reflect higher amounts of gadolinium, as was confirmed in one study.[41,43] In addition, gadolinium was found following either linear GBCAs, such as Omniscan, and macrocyclic GBCAs, such as ProHance and Gadavist. This indicates that all GBCAs can be deposited in many areas of the brain.

It is important to note that relatively high levels of gadolinium were found in the brains of patients who had normal kidney function. This demonstrated that the early belief that gadolinium retention was only a problem for patients with kidney dysfunction was not correct.

In addition, researchers had suspected gadolinium could only enter the brain if the blood-brain barrier was damaged, but these studies found gadolinium in the brains of patients who did not have damage to the blood-brain barrier.

It is of particular concern that gadolinium was found in the blood-brain barrier, the space between neurons, and in the nucleus of some cells. The latter two findings mean that gadolinium could directly affect the health and function of these cells.[39,41] However, the tissue in these areas appeared normal and did not have noticeable loss of cells, which suggests that gadolinium may not cause much cell death.

Effects on Brain Function

Four studies have attempted to determine if gadolinium could affect brain function or the health of cells in the brain.

Forslin et al. compared 23 patients with multiple sclerosis (MS) who had received 3-12 GBCA exposures and 23 age- and sex-matched healthy controls who had never been exposed to GBCA.[44] Patients had received linear non-ionic Omniscan and linear ionic Magnevist, and some had received macrocyclic Dotarem one time.

This study used hyperintensity (continued contrast signal) on an unenhanced MRI as an indicator for the amount of gadolinium accumulation in the brain. Like other studies of hyperintensity on an unenhanced MRI, the amount of hyperintensity in the two brain areas examined correlated with number of exposures to GBCAs when controlling for disease severity.

The MS patients were tested for verbal fluency, visuospatial ability, test information-processing speed, and episodic auditory-verbal memory. When the researchers statistically controlled for two measures of MS severity (disease duration and physical disability), the patients with more hyperintesnisty in one or both brain areas in their non-GBCA MRI had poorer verbal fluency and poorer auditory verbal learning and retention. When the researchers statistically controlled for additional measures of disease severity, such as the size of lesions and brain atrophy, only the correlation between hyperintensity and verbal fluency remained statistically significant. Although this suggests that gadolinium accumulation could harm the brain, the researchers cautioned that patients who have received more doses of GBCAs could have more severe disease in ways that were not statistically controlled, which could have resulted in poorer performance on these tests.

A second study by Baure et al. examined the health of the cells in the two brain areas that have the highest hyperintensity on an unenhanced MRI (the dentate nucleus and globus pallidus).[45] Glucose use was measured using a PET/CT scan to look at metabolic activity. This retrospective study examined 15 people with previous GBCA exposure (3-6 contrast-enhanced MRs) and 15 controls who underwent a non-contrast-enhanced MRI and PET/CT at their facility. Researchers found that patients with GBCA-exposure had a statistically significant decrease in metabolic activity in both brain areas compared to controls. This could mean that gadolinium deposition harmed these tissues; however, there were only 15 patients in each group and there were age differences between the GBCA-exposed patients and controls that could have affected the metabolic activity of these brain areas. In addition, some of the GBCA-exposed patients had cancer but none of the controls had cancer and some cancer treatments can harm the brain. Moreover, the protocol used to perform the PET/CT scans differed between the two groups, including the amount of scan time for the brain. The study did not look for evidence that there were gadolinium deposits in these patients or provide any information about the type of GBCA used.

Welk et al. that looked for a connection between GBCA exposure and a new diagnosis of Parkinson's disease found none.[46] The brain area affected by Parkinson's disease, the substantia nigra, directs voluntary movement through the globus pallidus, which is one of the areas with higher levels of gadolinium accumulation. Researchers looked at a Canadian database for patients older than 66 years who had an MRI of the brain or spinal cord between April 2003 to March 2013 and did not have prior Parkinson's disease or neurosurgery. They used diagnosis codes and Parkinson disease-specific medication to correlate contrast-enhanced MRIs to Parkinson disease. They compared 99,739 patients who had received GBCA to 146,818 who had a non-contrast-enhanced MRI. The incidence of parkinsonism was 1.2% for GBCA-exposed patients and for controls.

Freedman et al. re-evaluated the data from a failed clinical trial of patients with secondary progressive multiple sclerosis.[47,48] The trial had enrolled 612 patients, who received between 1 and 11 contrast-enhanced MRIs over the course of the two-year study. The researchers divided patients into "infrequent" group if they had 1-4 MRIs and "frequent" group if they had 5-11. There were no differences between the two groups in the severity of the MS disease.

Bone

Gadolinium accumulation in bones has been primarily studied in two ways: 1) by giving GBCA to patients before hip replacement surgery, and evaluating the removed bone and 2) evaluating bones removed from cadavers with known medical histories. These studies show that the amount of gadolinium in bone was much higher (23x) than in brain tissue, indicating that bones may store more gadolinium long-term.[35,40]

Gadolinium from linear and macrocyclic GBCAs was detected in bone after only 3-8 days as well as after at least 8 years.[40,49,50,51] Studies comparing the linear Omniscan with the macrocyclic ProHance, showed that patients who had received Omniscan had much higher levels of gadolinium in their bones after 3-8 days. No difference between these two GBCAs was observed when bone was studied 8 years after exposure. These studies were too small to make conclusions about a possible correlation between gadolinium levels and time since exposure, but suggest that the long-term storage may not vary much, at least for these two GBCAs.

Skin

Gadolinium accumulation can also be studied using skin biopsies from patients diagnosed with NSF. Levels of gadolinium were higher in deeper layers of the skin, so superficial biopsies may not detect it.[52] Gadolinium remained in skin for years, and under some circumstances the amount of gadolinium in skin increased over time. The amount of gadolinium was much higher in tissue affected by NSF than unaffected tissue, and it was higher in skin tissue of patients with NSF compared to GBCA-exposed patients who did not have NSF.[53]

High levels of gadolinium in the skin have been found in patients without kidney impairment. In one case, a patient had high levels of gadolinium in skin biopsies following 61 contrast-enhanced MRIs.[54] The patients in most of these studies on gadolinium found in the skin had been exposed to the linear GBCAs for their contrast-enhanced MRI that have since been determined to be more likely to remain and to cause NSF. However, gadolinium has been found following exposure to a GBCA that was considered unlikely to cause NSF (macrocyclic ProHance or linear MultiHance).[40]

Unexpectedly, a few case studies found intact GBCA in skin months or years after exposure.[54,55] Because most studies tested for gadolinium without trying to identify if the GBCA was still present, it is unclear how much of gadolinium accumulation is in the form of intact GBCA or separated gadolinium. It is possible that symptoms could be caused by either intact GBCA or separated gadolinium or both. [56]

Other Organs

There is limited research on gadolinium accumulation in other human organs. In case studies of patients with NSF, gadolinium has been found in numerous tissues, including eyes, lungs, intestines, and muscles.[57,58,59] Gadolinium has also been found in the liver in patients with normal or near normal kidney function.[60]

Detection in People without MRI Exposure to GBCAs

Several studies found trace amounts of gadolinium in brain tissue and bone in some or all patients in the study who had never received a GBCA.[40,51] However, the amount of gadolinium detected was extremely low and was likely due to environmental exposure.

Gadolinium Toxicity and Clinical Effects

Several conditions have been described as related to continued retention of gadolinium in patients' bodies: NSF, gadolinium deposition disease, gadolinium storage condition, and gadolinium-associated plaques. The descriptions of these conditions are based on a relatively small number of case studies, clinicians'/researchers' experience, and/or surveys of patients that believe that GBCAs caused their symptoms. These conditions demonstrate that the small amount of gadolinium that remains in the body may cause long-term problems for some patients. It is not yet clear if these conditions are all part of the same pathophysiological process or if they are distinct conditions. Nor is there enough information to determine the risk factors or rates of occurrence. In addition, studies have looked at the effects on the survival and health of fetuses exposed to contrast-enhanced MRI in utero.

Gadolinium Toxicity in Patients with Kidney Impairment - Nephrogenic Systemic Fibrosis (NSF)

NSF is a rare debilitating condition that can be fatal.[61,62] It can occur in patients with severe chronic kidney disease or acute kidney injury following exposure to GBCA. Reports suggest that most NSF patients develop symptoms within 6 months of GBCA exposure, but a few patients have been described who first developed symptoms 8 or 10 years after their last contrast-enhanced MRI. Reduced kidney function is a requirement for this condition.

Early symptoms typically affect the skin on the arms and legs, particularly the hands and feet.[61,63] Patches of skin may become thick, hard, or discolored, and there may be swelling. Later symptoms include reduced ability to move due to the tendons and muscles thickening and hardening. Over time, organs can be similarly affected. Patients may also experience severe pain, itching, abnormal response to touch (including increased pain sensitivity), hair loss, and digestive system problems.[64]

Most patients developed NSF following exposure to Omniscan, OptiMark, and Magnevist.[61] All three of these are linear GBCAs, and Omniscan and OptiMark are non-ionic. Again, linear GBCAs, and especially non-ionic linear GBCAs, are the most unstable GBCAs and are the most likely to stay in the body. The other two linear GBCAs are removed by the liver as well as kidneys, which may reduce the likelihood of accumulation and harm.

In most cases, NSF occurred following a large dose of GBCA or multiple doses.[61] However, some patients have developed NSF after a single standard dose.

FDA and medical societies recommend the following steps to reduce the risk for NSF:[3,14]

- Using the lowest possible dose
- Avoiding multiple exposures within short period of time for patients with acute kidney injury or chronic kidney disease stage 4 or 5.
- Avoiding GBCAs with highest risk
- Test for renal function (serum creatinine [eGFR] or questionnaire ["age >60, years, history of hypertension requiring medical therapy, diabetes mellitus, dialysis, kidney transplant, single kidney, single kidney, kidney surgery, history of known cancer involving the kidney, etc."]) and assess for acute kidney injury
- Undergoing haemodialysis within 2 hours, with additional sessions over the next few days for those that undergo haemodialysis. However, there is no strong evidence to support prompt haemodialysis. In addition, haemodialysis has risks, which are higher than risk for NSF for some GBCAs.

Since these steps have been implemented, few new NSF cases have been described,[65,66,67,68,69] although there have been a small number of new cases of NSF reported to FDA.[70] However, some experts believe NSF is underdiagnosed and under-reported.[62]

NSF-like Symptoms in Patients with Normal Kidney Function – Gadolinium Deposition Disease

There are also reports of patients without kidney problems developing some or many of the same symptoms of NSF. Gadolinium deposition disease is the term that has been proposed by researchers to describe patients with normal or near normal kidney function that develop long-lasting symptoms several hours to 2 months after GBCA exposure, where alternative conditions and causes are excluded.[71,72]

Many of the symptoms are similar to NSF, but less severe. The skin and deeper tissues of the hands and feet may thicken or feel like very tight gloves or socks. The deep tissue layer (subcutaneous soft-tissue) may appear rubbery or spongy. Pain can be severe. It is most common in the hands or feet, but can also occur in the torso or other areas. Symptoms often include persistent headaches and "brain fog." This last symptom is not considered a symptom for NSF, but this may be because cognitive impairment is common for patients with severe kidney disease.[73]

One case study by Semelka et al. described four patients who had pain, skin symptoms, and other health problems following exposure to GBCAs.[74] These patients had between one and six exposures to GBCAs. All patients had received a linear GBCA at least once. Patients were between 29 and 58 years old. For three of the four cases, symptoms started within 24 hours of exposure, whereas the fourth started after a few weeks. At the time of the study, patients had experienced symptoms for 2 months to 8 years. All four had detectable levels of gadolinium in blood serum, urine, hair and/or skin at least 1 month after the contrast-enhanced MRI.

A small study by Lord et al. measured the amount of gadolinium in the urine and bone (using X-ray fluorescence) in four participants who had symptoms that they believed were due to gadolinium, 11 non-symptomatic participants who had had a contrast-enhanced MRI, and 15 participants who had not had a contrast-enhanced MRI.[75] The amount of gadolinium in the bone of participants who had received GBCA was statistically significantly greater than participants who had not had a contrast-enhanced MRI. Interestingly, the amount of gadolinium in the urine of the non-symptomatic participants and never-exposed participants was statistically significantly smaller than the amount in the four symptomatic participants. It is inappropriate to draw conclusions based on four participants who believed that their symptoms were caused by gadolinium, but this study suggests that symptoms may correlated with higher levels of gadolinium.

Three studies of patients who were participating in online gadolinium-toxicity support groups found similar symptoms. Two of these studies were conducted by the same research group; the first asked about general symptoms and the second asked more detailed questions. The third study was smaller and conducted by a support group and also focused on similar symptoms. Because participants were from a self-selected group of patients who had previously communicated with each other about their symptoms, the similarity of symptoms could be influenced by the inherent bias of support group members sharing their experiences with each other.

The first survey by Burke et al. included 50 participants who had received between 1 and 23 contrast-enhanced MRIs.[76] Seventy-eight percent of participants had bone and/or joint pain; 78% had head or neck problems such as headache, vision change, hearing change; and 59% had skin changes. Other symptoms that patients reported include flu-like symptoms; digestive symptoms such as nausea, vomiting, or diarrhea; and chest symptoms such as difficulty in breathing.

The second study by Semelka et al. included 42 participants without kidney problems at the time of the MRI who were between 28 and 69 years old.[77] Forty-one reported to the researchers that they had detectable levels of gadolinium in their urine at least one month after administration. Forty percent had received only a single exposure to a GBCA.

Pain was a common problem; 74% still had pain at the time of the survey, including in the hands, feet, trunk, or bone. Half of participants reported that the skin on their hands or feet had thickened and had pain in these areas, while 67% of participants reported skin discoloration. In addition, 79% had joint stiffness, 85% reported fatigue, and 69% reported problems with mental function and headache for longer than 3 months. All participants reported that symptoms diminished over time, but had not disappeared.

A third survey of 17 participants with urine tests for gadolinium was published as a white paper.[33] All participants reported pain, most in the extremities, but some in hips, joints, or ribs. Pain typically began within a month of a contrast-enhanced MRI. In addition, 71% had chronic skin changes including “tight skin” and skin lesions, most of which started within a month of last administration. Of the 5 patients without chronic skin problems, three reported an acute rash. Of the participants, 88% had muscle problems such as twitching or weakness, and most of these symptoms began within a month of a contrast-enhanced MRI. Other symptoms include chronic eye symptoms (worsening vision dry eyes, or bloodshot eyes), cognitive symptoms, ringing in ears, swallowing problems, itchy skin, balance problems, and

fatigue. Some symptoms increased in frequency, becoming a chronic problem between the initial and follow up surveys, including tight skin, low body temperature, ringing in ears, worsening vision.

Finally, a case study, described by Roberts et al, of a patient that had undergone 61 contrast-enhanced MRIs between the ages of 19 and 30 years described rigid joints in the neck, arms, and legs similar to patients with NSF.[54] The contrast-enhanced MRIs had been used to initially diagnose glioblastoma and were continued to monitor for recurrence. High levels of gadolinium were measured in skin biopsies from an arm and leg.

Gadolinium Accumulation Conditions in Patients with Normal or Impaired Kidney function

Gadolinium Storage Condition

Gadolinium storage condition is the term that has been proposed by researchers to describe gadolinium accumulation in tissues of patients.[71,72] Patients may have normal or impaired kidney function. In addition, patients may not have any identified symptoms related to gadolinium.

Due to the unknown risks for retention for patients, the American College of Radiology (ACR) and the American Society of Neuroradiology (ASNR) recommend that physicians consider the benefits and risks for each patient for every contrast-enhanced MRI in terms of whether it is needed, which GBCA to use, and the dose.[78] They note that there should be additional consideration for pediatric patients or patients who may receive many contrast-enhanced MRIs. The Radiological Society of North America (RSNA) similarly recommends consideration of the benefits and risks for each patient.[79] However, as noted in this report, the risks are unknown, making it difficult to weigh the ratio of risks to benefits.

Gadolinium-Associated Plaques

Gadolinium-associated plaques is the term that has been proposed by researchers to describe sclerotic bodies with calcification in skin, which are plaques or hardened tissue caused by an immune system reaction to a foreign body.[71,80,81,82] These plaques had only been identified in patients with NSF after multiple exposures to GBCAs, however several case studies have described four patients without NSF who developed these plaques. One patient did not have any kidney problems and the plaques were associated with an itchy, burning rash. The other three patients had chronic kidney dysfunction, but did not have any other symptoms characteristic of NSF. These plaques were associated with thickened, darkened skin in one patient, darkened skin in a second patient and near squamous cell carcinoma in the third patient.

Impact of Prenatal Exposure

As with most drugs, there is limited research on the safety of GBCAs during pregnancy. GBCAs are classified as a class C drug by the FDA.[23,24,25,26,27,28,29] This means that animal studies have found harm for fetal development and that there are not adequate, well-controlled studies in humans. GBCAs can cross the placenta to expose the fetus; the immaturity of fetal organs and their rapid development puts a fetus at

increased risk for harm due to drug exposure. Indeed, animal studies have shown harm to fetuses when GBCAs were given at doses much higher than recommended. Nevertheless, if the benefits of an MRI with contrast are substantial, they may outweigh the risks.

A retrospective study by Ray et al. of all births at an Ontario hospital from April 2003 to March 2015 compared 393 pregnancies exposed to a GBCA-enhanced MRI to more than 1.4 million pregnancies not exposed to any MRI.[83] The study found a significantly greater percentage of stillbirths or neonatal deaths after GBCA-enhanced MRI compared to no MRI. However, this increased risk for death was not observed in 1,720 pregnancies exposed to any (enhanced or unenhanced) MRI during the first trimester. The study also found significantly more young children exposed to GBCA during the first trimester in utero had a rheumatological, inflammatory, or infiltrative skin condition; however, the fact that the risk was limited to the first trimester may be due to the fact that most enhanced MRIs occurred during first trimester.

The findings of this study may be due to the risks of having a pregnancy that required an enhanced MRI instead of the risks of GBCAs, because it did not control for the reasons why women needed MRIs. Only 1 in 3000 pregnant women received a GBCA MRI, and these pregnancies are likely to be different in ways that might affect birth outcomes. Although the researchers used statistical methods to try to control for these expected differences, they may have over- or under-estimated differences.

Another study by Amin et al. examined health status for preterm infants born at a single medical center over an 18-month period.[84] Only 4 of the 104 mothers had been exposed to GBCA during the 3 years prior to the birth, all before pregnancy. It is unclear how many babies were exposed to higher levels of gadolinium in utero, but it appears to be a small number. They did not find any associations between higher levels of gadolinium in cord blood and health outcomes at birth or during time in the neonatal intensive care unit; however, with only 4 exposed infants, these results are not conclusive.

There are a few other case studies that found no overall or lasting effects of GBCA exposure for babies born after exposure to GBCA in utero or around conception.[85,86,87] However, these studies included very few exposed infants, looked at few outcomes, and did not compare outcomes to similar unexposed babies. Therefore, they were not well-designed to detect effects of gadolinium exposure.

Due to concerns over risks associated with GBCAs, the American College of Obstetricians and Gynecologists (ACOG) recommends that contrast-enhanced MRIs should be limited to situations where there is a clear benefit that would outweigh the risks.[88] However, contrast-enhanced MRI is not a specific concern for breastfeeding women because very little gadolinium is transferred to breast milk.

Possible Treatments

There is little research evaluating treatments for those affected by gadolinium accumulation and its reported side effects. Most treatments were studied on just a few patients, usually those with NSF. As a result, none of these treatments are well supported by clinical evidence. In addition, most of these studies evaluated the effect on symptoms of NSF without attempting to cure it. Moreover, most treatments are

based on the off-label use of treatments approved for other health problems and not previously evaluated by the FDA specifically for GBCA exposure. Below are many of the therapies that have been discussed in more than one study.

Chelation therapy is an often-discussed option for patients with gadolinium accumulation. It uses chelating agents to remove excess metal. Like the extra chelate included in many GBCAs, chelating agents can bind free metal atoms, preventing toxicity and allowing more rapid excretion. Chelation therapy is used to reduce high levels of lead from children who were exposed to dangerous levels.[89] It therefore seems plausible that chelation treatment could possibly remove gadolinium.[72]

Early studies described chelation therapy in eight patients with previous GBCA exposure.[60,90,91] In most of these cases, chelation therapy was given to reduce high levels of another metal (iron or zinc) and reducing gadolinium was a side effect. Three different chelation treatments were discussed in these studies and a reduction of gadolinium was found with two treatments. These studies demonstrated that some types of chelation therapy help eliminate gadolinium in specific tissues or through urine. However, these studies cannot demonstrate what percentage of gadolinium is removed from the body nor did they demonstrate that treatment affected patients' symptoms.

Chelation therapy has been studied in only one randomized, open-label, uncontrolled clinical trial by Semelka et al. with 25 patients with gadolinium deposition disease.[92] Patients were treated with a different chelation agent, calcium-/zinc-DTPA, on a weekly or monthly basis for 3 sessions. After each treatment, the amount of gadolinium in patients' urine was statistically significantly increased. Most patients reported improvement in at least one of the following symptoms: torso pain, arm pain, leg pain, headache, brain fog, and bone pain. Some patients experienced worsening for some symptoms. The researchers state that symptom improvement was still present 30 days after the last treatment for patients that reported symptom improvement. This study is encouraging, but because all the patients were aware that they were getting a treatment and there was no other group of patients to compare them to, it is impossible to determine the extent to which the placebo effect contributed to symptom changes.

There are concerns that chelation treatments that only weakly bind gadolinium, such as ethylenediaminetetraacetic acid (EDTA), may just move the gadolinium to a new location within the body.[72] In addition, chelation therapy has risks, including death.[93] It does not seem ethical to recommend these treatments until there is evidence that there is an improvement in symptoms or long-term outcomes. Well-designed prospective studies are needed to determine which, if any, chelation therapies can safely and effectively treat gadolinium retention and associated symptoms.

Kidney transplants have been successful in improving the symptoms of NSF when it improved kidney function, even when improved function was temporary.[94,95,96,97] However, the amount of improvement documented in these case studies varied, and in some cases, symptoms worsened.

Physical therapy can help slow the progression of joint contractures and has been added to the treatment regimen for patients.[98,99,100,101]

Ultraviolet A1 therapy (UV-A1) has been tested for patients with NSF. Patients are treated with a narrow range of ultraviolet light (UV-A with wavelengths of 340–400 nm). This is the type of ultraviolet light with the lowest risk for harm, but UV-A1 treatment has risks, including skin cancer and premature skin aging.[102] One case study by Tran et al. of 4 patients and an uncontrolled, retrospective analysis by Connolly et al. of 17 patients found that UV-A1 treatments improve skin hardness, lesion size, or even joint mobility that could last for a year after treatment completion for some patients.[103,104] However, other studies including 5 patients did not find an improvement in NSF symptoms.[95,102]

Plasmapheresis (plasma exchange) is a process by which a patient's plasma is removed from the blood.[105] Case studies of three NSF patients treated with plasmapheresis have found improvement in joint mobility, skin hardness, swelling, and pain following plasmapheresis.[106,107] For some patients, symptom improvement lasted at least two years. In one case, retreatment after one and two years after symptoms had returned improved symptoms again. However, the lack of a comparison group again raises the possibility of a placebo effect rather than actual benefit.

Extracorporeal photopheresis is a procedure where a patient's white blood cells are treated with UV light and returned. Case reports of three NSF patients treated with extracorporeal photopheresis have shown that some patients have improvements in skin tightening and range of motion.[108,109,110] Side effects can include tenderness at site of the needle, drop in blood pressure and sensitivity to the UV sensitizer methoxsalen or UV light. Again, the lack of comparison group raises the possibility of a placebo effect rather than actual benefit.

Pentoxifylline (Pentoxil) is a drug that can improve blood circulation and increase tissue oxygenation.[111] It can also affect the way the immune system functions and thus affect the development of fibrosis. Chen et al. described significant improvements in skin symptoms for one patient during treatment with pentoxifylline in combination with other treatments.[112] The lack of a comparison group again raises the possibility of a placebo effect rather than actual benefit.

Imatinib (Gleevec) is a drug typically used to treat cancer, and its side effects seem to outweigh its benefits.[113] The use of Gleevec in one patient with worsening NSF improved joint flexibility, improved overall mobility, and skin softening.[114] The patient discontinued its use, however, due to nausea, vomiting, and an increase in a biomarker for inflammation. A follow-up 10 weeks after treatment found that some of the improvements had deteriorated. Other case studies of three patients described improvements in skin symptoms, joint flexibility, and mobility while taking imatinib, but those symptoms returned if treatment was discontinued.[98,115] An open-label, uncontrolled study by Elmholt et al. of four patients found more modest improvements in skin symptoms or joint flexibility.[116] All four of the patients required dose reductions due to side effects, and two patients stopped the study early due to side effects.

Sodium thiosulfate, a drug initially used for the treatment of arsenic and cyanide poisoning is now used to treat inflammation. It has antioxidant and chelating properties and so it has been used with mixed success in treating the symptoms of NSF. In case studies of seven patients, some but not all of the patients experienced significant improvement in skin discoloration, skin thickness, pain, and/or joint stiffness.[100,117] However, a different study of four patients with NSF found minimal to no improvements in the joint flexibility or skin lesions.[118] Nausea and vomiting were major problems for some patients.

Environmental Exposure

In addition to the direct impact on human health, there is growing concern about gadolinium in waterways and drinking water. GBCAs pass through patients into wastewater and then into waterways. Gadolinium or GBCAs have been detected in surface water in Europe, North America, South America, Asia, and Australia.[119,120] The levels of gadolinium (in the form of GBCA or in gadolinium bound to other molecules) are highest in areas with highly developed medical systems.[119,121] The levels of gadolinium in water has been increasing over the last few decades.

This is a health concern because these waterways are sources for tap water. Gadolinium has been found at low levels in tap water in Berlin and London, and the levels have increased over time.[122,123] If similar studies have been completed in the U.S., the information is not public. Fortunately, the levels of gadolinium in drinking water that have been reported are very low. Even at the highest concentrations published (Berlin) a person would need to drink over a several hundred billion glasses of water to consume the same amount of gadolinium that is present in a standard dose of GBCA.

Gadolinium has also been found in plants.[119] Many heavy metals can be stored and concentrated in plants and animals, and thus lead to higher exposures if they are consumed. However, the impact on human health has not been studied.

The low levels of gadolinium detected in patients who had never received a GBCA demonstrate that the general population is exposed to and retains a small amount of gadolinium. These levels are much lower than for patients that receive GBCA for contrast-enhanced MRI(s). However, there is still reason for concern. It is unknown what level of gadolinium accumulation can cause harm. It is also unclear whether long-term exposure to low levels or exposure during critical developmental periods can harm health. Additional exposures from the environment or diet could pose a health risk, particularly for vulnerable populations such as pregnant women and their fetuses.

Advanced water treatment systems that use reverse osmosis have been found to remove 99.85% of gadolinium from wastewater.[124] Improvements in water treatment systems may reduce or remove this risk.

Discussion

In the decades since the GBCA-enhanced MRI became a popular medical procedure, it has become clear that GBCAs could harm patients with impaired kidney function. As the use of high-risk contrast agents was drastically reduced for patients with impaired kidney function, the incidence of NSF has been dramatically reduced. However, more recently, concerns have arisen about GBCA safety for patients with healthy kidneys as well.

It has been well-established that both linear and macrocyclic forms of GBCAs can lead to gadolinium or GBCA remaining in the brain, bones, and other tissues of patients who have undergone contrast-enhanced

MRIs. It is well-accepted that this can cause NSF in patients with poor kidney function. However, there is still uncertainty and controversy concerning other clinical effects of gadolinium accumulation for patients beyond NSF. Due to concerns over gadolinium's long-term effects, MRI guidelines have changed to encourage more careful consideration of whether use of a GBCA is necessary, which dose, and which GBCA should be used. Different countries have responded with a range of recommendations and regulations.

Even with these uncertainties, the research thus far suggests that some patients with healthy kidney function have been harmed by gadolinium. This conclusion is based on the clear evidence of its accumulation and studies correlating its presence with symptoms.

There are major questions concerning GBCAs and potential long-term harm, including:

- What percentage of people have gadolinium in their bodies and at what levels?
- What percentage of people with normal kidney function are likely to have health problems as a result of exposure to a GBCA?
- How is the likelihood of health problems influenced by the number of MRI contrast procedures that an individual undergoes, which GBCA is used, and over what period of time (months or years)?
- Is it possible to determine whether some types of patients are at greater risk of health problems from GBCAs, based on age, health conditions, genetics or other characteristics?
- What form(s) is gadolinium stored in the body, e.g. as intact GBCA or as separated gadolinium, and are there differences in the symptoms caused by different forms?
- What is the best way to determine if gadolinium is causing health problems in an individual?
- Are there medical practices or treatments that reduce the risk for or treat the effects of health problems caused by long-term gadolinium accumulation?

There will be difficulties designing studies to answer these questions.

- Many symptoms reported by patients are quite common (e.g. headache, fatigue, and pain) and could have many other causes.
- Symptoms can occur well after GBCA exposure, and the amount of time between exposure and symptom development is highly variable.
- Different types of patients may be at risk at different times or for different reasons. Some patients may have higher risk for long-term accumulation due to their medical condition and treatments at the time of the contrast-enhanced MRI. Others may be at increased-risk for harm due to the potential for greater severity of effects (e.g. fetus, child). Still others may be at risk for harm well after the contrast-MRI due to changes in bone turnover that lead to higher levels of circulating gadolinium (pregnancy, lactation, osteoporosis).
- The risk for easily recognizable harm may be rare. There are millions of patients who have a contrast-enhanced MRI each year, but a small minority of these have sufficient symptoms to seek out gadolinium-toxicity support groups or treatment. Until the issue gains more public attention, including informed consent for all patients undergoing contrast MRIs, it will be impossible to determine if these symptoms are as rare as they currently seem to be.

Studies will need to be large enough and designed to detect rare but severe events and will need appropriate controls to minimize placebo effects or confounding factors. Because each GBCA has different characteristics in terms of how it moves through the body and how it deteriorates, it will not be appropriate to just extrapolate from one GBCA to all of the same chemical structure. Studies would be more conclusive if they were based on a generalizable sample of patients rather than self-selected groups of harmed patients or the small number of symptomatic patients at a single clinic. Studies need to minimize factors that cause bias, including recall bias from asking participants to talk about symptoms and experiences well after they occurred; bias from researchers with conflicts of interest; and bias caused by beliefs about a treatment by including blinding and a placebo control.

In the meantime, patients and clinicians need to weigh the risks and benefits of contrast-enhanced MRIs using the available GBCAs for each particular patient and condition. Some GBCAs are better for imaging specific tissues, some have higher risks for some types of short-term side effects, and some have higher risks for long-term accumulation and harm. However, research has been inadequate to answer those questions with confidence.

Table of GBCAs Approved in the US

BRAND NAME	GENERIC NAME	SPONSOR	INDICATION	APPROVAL YEAR	CHEMICAL STRUCTURE	ELIMINATION ROUTE	CONTRAINDICATION	ELIMINATION HALF-LIFE (HR)*
MAGNEVIST	gadopentetate dimeglumine	Bayer Healthcare Pharmaceuticals Inc	neuro, body	1988/2000	Linear - ionic	kidneys	Poor kidney function	1.6
PROHANCE	gadoteridol	Bracco Diagnostics Inc	neuro	1992/2003	Macrocyclic	kidneys		1.57
OMNISCAN	gadodiamide	GE Healthcare	neuro, body	1993/2007	Linear - non ionic	kidneys	Poor kidney function	1.3
OPTIMARK	gadoversetamide	Guerbet LLC/ Mallinckrodt Inc	neuro, liver	1999	Linear - non ionic	kidneys	Poor kidney function	1.73
MULTIHANCE	gadobenate dimeglumine	Bracco Diagnostics Inc	neuro, vascular	2004	Linear - ionic	97% kidneys 3% liver		1.17 to 2.02
ABLAVAR	gadofosveset trisodium	Lantheus Medical Imaging, Inc	Vascular	2008	linear - ionic	91% kidneys 9% liver		16.3
EOVIST	gadoxetate disodium	Bayer Healthcare Pharmaceuticals Inc	Liver	2008	Linear - ionic	50% kidneys, 50% liver		0.91 to 0.95
GADAVIST	gadobutrol	Bayer Healthcare Pharmaceuticals Inc	neuro, vascular, breast CA	2011	Macrocyclic	kidneys		1.8
DOTAREM	gadoterate meglumine	Guerbet LLC	neuro	2013	Macrocyclic	kidneys		1.6

Gray – removed from market

* Patients with normal kidney function

All information available from drug labels[23,24,25,26,27,28,29,31,125]

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