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Use of Real-Life Safety Data From International Pharmacovigilance Databases to Assess the Importance of Symptoms Associated With Gadolinium Exposure

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Objective: Recent scientific publications have reported cases of patients who complained from a variety of symptoms after they received a gadolinium-based contrast agent (GBCA). The aim of this study was to appreciate the importance of these clinical manifestations in the overall population by assessing the weight of "symptoms associated with gadolinium exposure" (SAGE) among the bulk of safety experiences reported to major health authorities.

Materials and Methods: Symptoms associated with gadolinium exposure were identified from a review of the scientific literature, and the corresponding preferred terms were searched in each system organ class (SOC) category recorded in the European and North American pharmacovigilance databases EudraVigilance (EV) and FDA Adverse Event Reporting System (FAERS), respectively. The numbers of SAGE per preferred term, and cumulatively per SOC, were recorded and their weights in the overall spectrum of adverse events (AEs) were determined for each GBCA.

Results: The analysis of the selected AEs revealed a significantly higher SAGE weight for gadobenate dimeglumine (EV: 25.83%, FAERS: 32.24%) than for gadoteridol (EV: 15.51%; FAERS: 21.13%) and significantly lower SAGE weights for gadobutrol (EV: 7.75%; FAERS: 13.31%) and gadoterate meglumine (EV: 8.66%; FAERS: 12.99%). A similar ranking was found for most of the SOCs except for "nervous system disorders," probably owing to a limitation in the methods of data selection. Furthermore, this analysis showed a greater percentage of reports mentioning a decrease in the quality of life of the patients when they were exposed to gadobenate dimeglumine or gadoteridol than to gadobutrol or gadoterate meglumine.

Conclusion: This study showed that SAGE represent a significant percentage of the bulk of AEs reported to the health authorities for each GBCA. It provided real-life arguments suggesting that SAGE may be more prevalent with linear than macrocyclic GBCAs and that gadoteridol may present a higher SAGE risk than the other macrocyclic contrast agents.

Key Words: gadolinium-based contrast agent, gadolinium deposition disease, symptoms associated with gadolinium exposure, pharmacovigilance, database

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Gadolinium-based contrast agents (GBCAs) play a pivotal role in contrast-enhanced magnetic resonance imaging (CE-MRI) procedures. Since their approval in the late 1980s, more than 500 million doses have been administered worldwide and it is estimated that about 50 million doses are administered annually.[1] However, as free gadolinium is toxic, ligands have been used to create gadolinium chelates allowing safe use of GBCAs in humans.[2] These agents are generally classified on the basis of their corresponding chelates as linear or macrocyclic (Fig. 1). Since their use in CE-MRI, GBCAs have shown an excellent safety profile with a low incidence of mild adverse events (AEs), rare cases of severe hypersensitivity reactions, and infrequent episodes of neurotoxic reactions. Nausea is seen in approximately 1.5% of patients, hives in 0.2%, and severe reactions in less than 0.001%.[3] Among the late AE category, nephrogenic systemic fibrosis (NSF) has also been associated with GBCAs, especially the linear chelates.[4–8] Thermodynamic and kinetic stability studies have shown linear chelates to possess a higher propensity to release free gadolinium as compared with macrocyclic chelates, which led the European Medicines Agency (EMA) to categorize them as high-risk agents for their potential to cause NSF.[2,9–11]

In 2014, Kanda and colleagues[12] reported the presence of hyperintensities in the dentate nucleus and globus pallidus of GBCA-exposed patients on unenhanced T1-weighted brain MRI scans. They assumed that these hyperintensities were caused by gadolinium retained in the brain areas due to multiple administrations of GBCAs. This hypothesis was confirmed by 2 studies that demonstrated the presence of elemental gadolinium in brain tissues of deceased patients who received multiple doses of GBCAs over their lifetime.[13,14] Additional studies further demonstrated that a small fraction of gadolinium could be retained over months or years, in a dose-dependent manner, within these neural tissues, even in patients with normal kidney function and intact blood-brain barrier.[15,16] Moreover, the degree of tissue retention corresponded to the stability profile of the contrast agents, with macrocyclic GBCAs exhibiting significantly less retention than linear GBCAs.[17–19] Studies have also shown detectable gadolinium in other cerebral regions, however, with significantly lower levels as compared with the dentate nucleus and globus pallidus.[20–22] Because of this growing safety concern, the EMA suspended the marketing authorizations of linear GBCAs (except for hepatic imaging) in November 2017 as a preventive measure.[23,24] The Food and Drug Administration (FDA) of the United States made a different decision and requested contrast media companies to change the product safety labeling of their GBCAs and undertake both preclinical and clinical studies to determine the potential long-term consequences of repeated GBCA administrations on neural functions.[24,25]

Some preclinical studies have reported a significant accumulation of gadolinium in the skin, bones, liver, kidneys, and spleen in animals exposed to GBCAs.[26–30] At that time, these observations did not raise much concern as most of the contrast agent molecules were rapidly eliminated via the kidneys without any noticeable toxic effects in the exposed animals.[26–31] There were a few clinical studies also showing accumulation of gadolinium in human skin,[32,33] in human bones,[34–36] and more recently in human globus pallidus and dentate nucleus.[12–25] Hence, gadolinium retention in human tissues is a known phenomenon in the scientific community that only became a safety concern after the report published by Kanda and colleagues.[12]

In 2016, the term "gadolinium deposition disease" (GDD) was first proposed by Semelka and colleagues[37] to describe a series of

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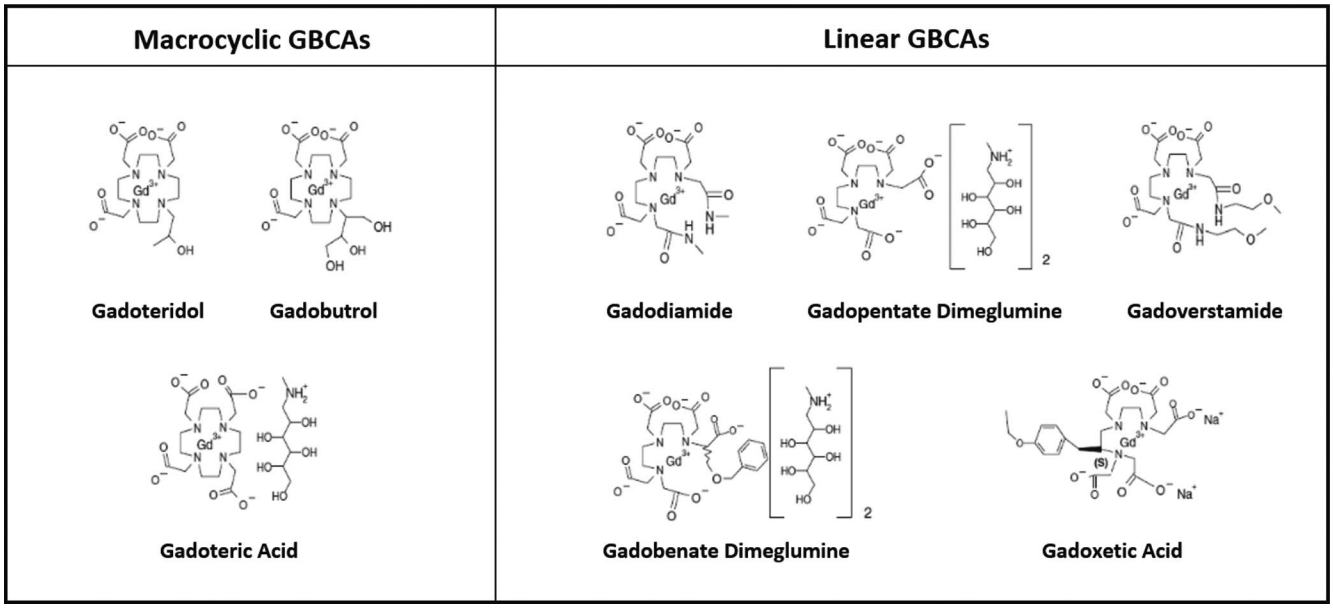

FIGURE 1. Structure of routinely used GBCAs classified on the basis of the type of chelate.

symptoms reported by patients with normal renal function after exposure to GBCAs. They suggested diagnostic criteria for this new type of disease, which should include at least 3 of the following symptoms: (i) central torso pain, (ii) headache and clouded mentation, (iii) peripheral leg and arm pain, (iv) peripheral leg and arm thickening and discoloration, and (v) bone pain. Some of the patients who were assumed to suffer from GDD also presented evidence of long-term body retention and persistent urinary excretion of gadolinium.[38]

In 2021, members of the American College of Radiology Committee on Drugs and Contrast Media proposed to use the term "symptoms associated with gadolinium exposure" (SAGE) in place of GDD, gadolinium storage disease, gadolinium storage condition, and other GDD-equivalent terminologies.[39] It refers to symptoms that may occur irrespective of kidney function and are unrelated to established early-onset AEs (occurring <24 hours after GBCA exposure, such as acute allergic-like and physiologic reactions) and late-onset AEs (occurring >24 hours after GBCA exposure, such as NSF). Potential examples of symptoms meeting the SAGE definition include headache, bone and joint pain, joint stiffness, muscle spasms, fatigue, clouded mentation, brain fog, distal extremity and skin thickening, skin discoloration, skin pain, painful tendons and ligaments, tightness in the hands and feet, and peripheral neuropathic pain. The main difference with GDD is that SAGE does not necessarily imply a causal relationship between the AEs and the exposure to a GBCA. In the absence of a prospective, randomized, and double-blind clinical study, a causal relationship between SAGE and gadolinium retention cannot be proven scientifically, and the term SAGE seems more appropriate than GDD to describe this association. It is worth noting, however, that such a study has been considered unethical by the EMA and the FDA because of the higher risk taken by the group of patients who would receive multiple GBCA injections for the sole purpose of assessing the occurrence of SAGE. For that reason, alternative approaches must be devised to bring some light on this safety concern.

We conducted an extensive analysis of the AEs that have been associated with the use of the GBCAs and recorded in the EMA and FDA databases of suspected adverse drug reaction reports. The aim of this study was to appreciate the reality and determine the weight of SAGE in the bulk of safety experiences reported to the EMA and FDA for the GBCAs currently approved in the European and North American markets.

MATERIALS AND METHODS

This study assessed the spontaneous reports of AEs in the publicly available EMA and FDA databases, EudraVigilance (EV) and FDA Adverse Event Reporting System (FAERS), respectively. EudraVigilance contains reports of undesirable side effects potentially associated with the use of medicines authorized in the European Economic Area, which have been collected and reported by health care professionals (HCPs), patients, and marketing authorization holders (MAHs) since 1995. The FAERS database also contains AE reports to medicinal products since 1968. All the events received by the EMA and FDA have been coded using the Medical Dictionary for Regulatory Activities (MedDRA), assigned a preferred term (PT) and grouped by system organ classes (SOCs) in EV and FAERS databases.

To determine the SOCs and PTs of the AEs specifically associated with GDD or SAGE, a preliminary search was undertaken in electronic databases of scientific and medical journals (PubMed and EMBASE) up to December 23, 2021. The aim was to identify all the published articles (clinical studies or case reports) that evaluated the clinical signs or symptoms of potential gadolinium toxicity in GBCA-exposed subjects with a normal or near-to-normal renal function. The key words used for the search were "gadolinium deposition disease," "gadolinium disease," "gadolinium poisoning," "gadolinium and chelation therapy," "symptoms associated with gadolinium exposure," and "SAGE." The strategy for including or rejecting a study was the following: (i) studies describing AEs suggestive of an allergic-like reaction (eg, nausea, vomiting, rash) or a physiologic reaction (eg, feeling of warmth) were excluded from the analysis; (ii) those mentioning common AEs were included only if the events were reported in the SAGE list of symptoms (eg, headaches); and (iii) those presenting uncommon AEs were included if the events were reported in at least 2 publications (eg, insomnia, muscle weakness, peripheral pain). The AEs selected from the retained articles were then searched for in the appropriate SOCs and PTs in both pharmacovigilance databases. The data extraction was performed, for each GBCA of interest, on September 30 and December 25, 2021, from the FAERS and EV databases, respectively.

To ensure the comparability of the data between GBCAs and between EV and FAERS databases, the products included in the analysis should (i) be approved in both Europe and the United States, (ii) be indicated for intravenous administration, and (iii) behave mostly as

extracellular contrast agents. These criteria led to only select the products that have been present on major markets since the outcome of the regulatory debate on GDD in 2017 and that bear a similar probability of triggering SAGE based on the similarity of their pharmacokinetic profiles. Accordingly, all the macrocyclic GBCAs approved for intravenous administration were included in the current analysis, namely gadoteridol (Prohance, Bracco), gadobutrol (Gadovist/Gadavist, Bayer Healthcare), and gadoterate meglumine (Dotarem, Guerbet; Clariscan, GE Healthcare). The linear agent gadobenate dimeglumine (Multihance, Bracco) was also included as it is currently in use for liver CE-MRI in Europe and for CE-MRI of the central nervous system and magnetic resonance peripheral angiography in the United States.[23,24] On the other hand, the linear agents gadopentetate dimeglumine (Magnevist, Bayer Healthcare), gadodiamide (Omniscan, GE Healthcare), and gadoversetamide (Optimark, Guerbet) were excluded because of the suspension or the nonrenewal of their marketing authorizations in Europe since November 2017. Gadoxetate disodium (Primovist/Eovist, Bayer Healthcare) was excluded as it is a liver-specific GBCA administered at a 4-times lower dose than the other compounds and that accumulates into liver cells, thus exhibiting a highly different pharmacokinetic profile than the extracellular GBCAs. Other agents that were excluded from the current analysis are the diluted formulations of the macrocyclic agent gadoterate meglumine (Artirem, Guerbet) and of the linear agent gadopentetate dimeglumine (Magnevist 2 mmol/L, Bayer Healthcare) approved for magnetic resonance arthrography owing to their use at very low doses and exclusively for administration into the joints.

A standard approach in pharmacovigilance to appreciate the potential impact on patients of a safety concern is to estimate the incidence of AEs that have been reported to regulatory authorities during a certain period or cumulatively. Incidence figures are calculated as the ratio between the number of reported AEs and the number of patients exposed to the medicinal product. The main difficulty of using pharmacovigilance databases to assess and compare the safety of different products is that the numbers of exposed patients, which are usually extrapolated from market share data, are not publicly available. Moreover, the recorded AEs are a mix of serious and nonserious AEs from the countries which own these databases (eg, from the United States in FAERS) and of serious AEs from other countries where the products are registered. It means that these databases miss all the nonserious AEs that occurred outside their own country. As a consequence, incidence data cannot be derived from the analysis of AEs recorded in international pharmacovigilance databases owing to the impossible access to patient exposure data and to the impossible segregation of country-specific AEs. The alternative approach developed in this study was to calculate the weight represented by some types of AEs among the total number of AEs reported for a medicinal product. More specifically, we determined the SAGE weights from both EV and FAERS databases to appreciate the proclivity of the GBCAs for SAGE occurrence in the global population. To that end, for each relevant PT, we registered the number of AEs recorded in the database. Then, we determined the SAGE weight per PT by calculating the ratio between the number of AEs in the PT and the total number of AEs recorded in the database. Similarly, we determined the SAGE weight per SOC by calculating the ratio between the number of AEs in the relevant PTs of this SOC and the total number of AEs. All SAGE weights were presented as percentages. Descriptive statistics were applied to compare the SAGE weights per SOC between the different GBCAs.

Both databases also enabled recording, for each relevant PT, the number of AEs that had been reported by HCPs. Thus, HCP reporting rates were determined by calculating, for each SOC, the fraction of SAGE notifications made by HCPs out of the total SAGE notifications. Descriptive statistics were used to compare the HCP reporting rates between SOCs and GBCAs.

RESULTS

Figure 2 describes the search strategy followed in the selection of articles. Overall, 99 publications of interest were identified in the scientific and medical literature. After a preliminary exclusion of papers not focusing on the GDD topic, as assessed from the abstracts, 23 potentially relevant articles were examined, from which 10 clinical studies and case reports were finally selected.[38,40–48] The recently published review article by McDonald and colleagues[39] introducing the topic of SAGE was also included owing to its value for the current analysis. The remaining 12 articles were reviews on the GDD topic. However,

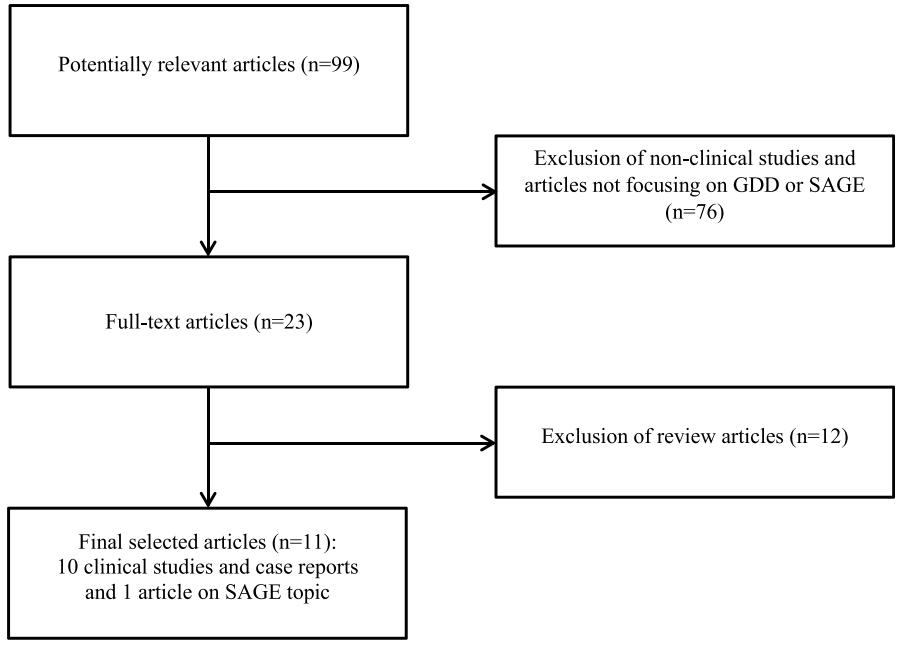

FIGURE 2. Flowchart summarizing study selection.

as they dealt with the results of the clinical studies already mentioned above, they were excluded from the analysis.

Among the 10 clinical studies and case reports retained for the analysis, 1 was a prospective cohort study comparing the symptoms associated with either gadodiamide or gadoterate meglumine in 1088 patients,[43] another one was a case report in a patient exposed to gadobutrol,[44] whereas the 8 other publications were small-sized observational studies and case series from Semelka and colleagues.[38,40–42,45–48] Overall, 1270 patients (677 women and 540 men), with age ranging between 17 and 90 years, were included. Both linear and macrocyclic GBCAs were injected as single or multiple administrations. Gadobutrol was reported in 8 studies and was administered to 21 patients, followed by gadobenate dimeglumine (7 studies; 30 patients), gadoterate meglumine (4 studies; 392 patients), and gadoteridol (1 study; 2 patients). The period for the manifestation of GDD symptoms after GBCA exposure ranged between 1 day and 9 years. Headache was the most common symptom reported in most of the clinical studies as well as in the SAGE review article (n = 10), followed by skin discoloration (n = 8); bone pain and muscle fatigue (or fatigue) (n = 7 each); skin thickening and clouded mentation (or brain fog) (n = 6 each); paraesthesia, pain of skin, joint pain/stiffness, muscle spasms/pain, and arthralgia (n = 4 each); and finally a few other symptoms that were reported 2 or 3 times each. Moreover, probing the EV and FAERS databases for GDD symptoms led to the identification of additional PTs that were considered to be relevant for the analysis, such as skin burning sensation and skin tightness. The full list of PTs retained for the analysis can be found in Table 1.

Table 1 provides an overview of the numbers of SAGE per GBCA found in the EV and FAERS databases for each SOC and globally.

TABLE 1. SAGE Weights and SAGE Numbers Determined From EV and FAERS Databases

GBCAs	Gadobenate Dimeglumine		Gadoteridol		Gadobutrol		Gadoterate Meglumine	
Databases Containing AE Reports	**EV**	**FAERS**	**EV**	**FAERS**	**EV**	**FAERS**	**EV**	**FAERS**
Years of marketing authorization in Europe (for EV) and in the United States for (FAERS)	1997	2004	1992	2003	2003	2011	1989	2013
Total number of AEs	9,582	9,705	8,833	8,569	13,904	9,241	10,598	6,227
SAGE weights (SAGE numbers) in the SOC "Skin and subcutaneous tissue disorders"[a]	4.32% (414)	5.22% (507)	4.38% (387)	5.36% (459)	0.55% (77)	0.98% (91)	0.45% (48)	0.92% (57)
SAGE weights (SAGE numbers) in the SOC "Musculoskeletal and connective tissue disorders"[b]	8.06% (772)	9.78% (949)	4.75% (420)	6.10% (523)	2.27% (316)	4.58% (423)	2.40% (254)	4.38% (273)
SAGE weights (SAGE numbers) in the SOC "General disorders and administration site conditions"[c]	8.58% (822)	10.91% (1059)	4.02% (355)	6.52% (559)	1.75% (244)	2.97% (274)	2.00% (212)	2.91% (181)
SAGE weights (SAGE numbers) in the SOC "Nervous system disorders"[d]	3.21% (308)	3.96% (384)	1.99% (176)	2.47% (212)	2.80% (389)	4.11% (380)	3.50% (371)	4.21% (262)
SAGE weights (SAGE numbers) in the SOC "Psychiatric disorders"[e]	1.87% (179)	2.14% (208)	0.24% (21)	0.46% (39)	0.34% (47)	0.56% (52)	0.26% (28)	0.47% (29)
SAGE weights (SAGE numbers) in the SOC "Investigations"[f]	0.13% (12)	0.23% (22)	0.12% (11)	0.22% (19)	0.04% (5)	0.11% (10)	0.05% (5)	0.11% (7)
Total SAGE weights (SAGE numbers) in the databases	**25.83% (2507)**	**32.24% (3129)**	**15.51% (1370)**	**21.13% (1811)**	**7.75% (1078)**	**13.31% (1230)**	**8.66% (918)**	**12.99% (809)**

Bold emphasis as it represents the grand total of SAGE weights.

SAGE indicates symptoms associated to gadolinium exposure; EV, Eudravigilance; FAERS, FDA Adverse Event Reporting System; GBCA, gadolinium-based contrast agent; AE: adverse event; SOC, system organ class.

[a] Pain of skin, skin burning sensation, skin discoloration, skin induration, skin tightness.

[b] Arthralgia, bone pain, fibromyalgia, joint stiffness, ligament and tendon pain, muscle fatigue, muscle spasms, muscle tightness, muscle twitching, muscular weakness, musculoskeletal chest (wall) pain, musculoskeletal pain, pain in extremity.

[c] Asthenia, fatigue, pain.

[d] Cognitive disorder, headache, paraesthesia, peripheral pain/neuropathy.

[e] Confusional state, insomnia.

[f] Quality of life decreased.

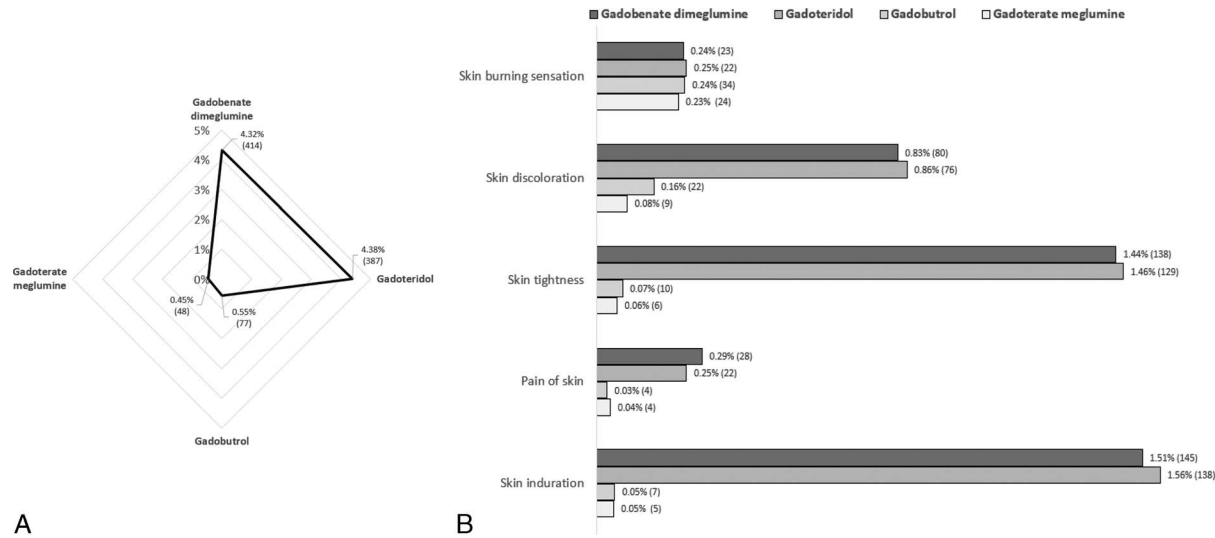

FIGURE 3. Radar chart of SAGE weight in the SOC "skin and subcutaneous tissue disorders" in EV (A), and bar charts showing a breakdown of these data by relevant PTs for this SOC (B). The figures on the graphs represent SAGE weights (numbers of SAGE).

It also provides the SAGE weights calculated for each SOC and globally. These SAGE weights are presented as percentages of the total numbers of AEs recorded in the databases. Gadobenate dimeglumine showed the highest global SAGE weight among the 4 GBCAs included in this study (EV: 25.83%, FAERS: 32.24%). This was followed by gadoteridol (EV: 15.51%; FAERS: 21.13%), gadobutrol (EV: 7.75%; FAERS: 13.31%), and gadoterate meglumine (EV: 8.66%; FAERS: 12.99%).

With regard to the SOC "skin and subcutaneous tissue disorders," the highest SAGE weights were displayed by gadoteridol and gadobenate dimeglumine. Those of gadobutrol and gadoterate meglumine were significantly lower and in the same level of magnitude. The most prevalent PTs in the safety experiences recorded for gadoteridol and gadobenate dimeglumine were "skin induration," "skin tightness," "skin discoloration," and "pain of skin" (Fig. 3). There was no difference in "skin burning sensation" among the 4 GBCAs.

For the SOCs "musculoskeletal and connective tissue disorders" and "general disorders and administration site conditions," the highest SAGE weights were reported for gadobenate dimeglumine, followed by gadoteridol. Again, the SAGE weights of gadobutrol and gadoterate meglumine were significantly lower and in the same range. Figures 4 and 5 show the most prevalent PTs in the safety experiences recorded for gadobenate dimeglumine and gadoteridol in both SOCs.

As shown in Figure 6, there was no obvious difference in SAGE weights for the SOC "nervous system disorders" among gadobenate dimeglumine, gadobutrol, and gadoterate meglumine. The scores of gadoteridol were slightly below those of the other GBCAs. "Headache" and "paraesthesia" were the most frequently used PTs for the 4 GBCAs.

The SOC "psychiatric disorders" was slightly less represented than the previous SOCs. Gadobenate dimeglumine was associated with the highest SAGE weights in this SOC, whereas the 3 macrocyclic GBCAs yielded lower and comparable scores (Fig. 7).

Finally, as shown in Table 1, the PT "quality of life decreased" in the SOC "investigations" was significantly more present in the bulk of AEs recorded for gadobenate dimeglumine and gadoteridol than in those of gadobutrol and gadoterate meglumine.

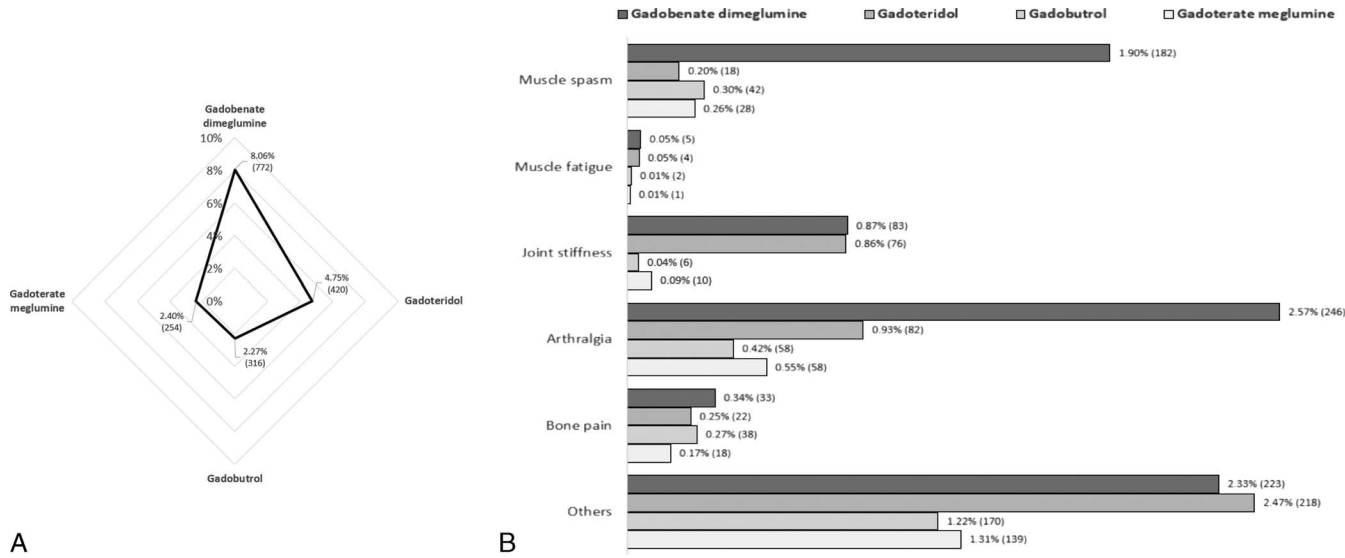

FIGURE 4. Radar chart of SAGE weight in the SOC "musculoskeletal and connective tissue disorders" in EV (A), and bar charts showing a breakdown of these data by relevant PTs for this SOC (B). The figures on the graphs represent SAGE weights (numbers of SAGE).

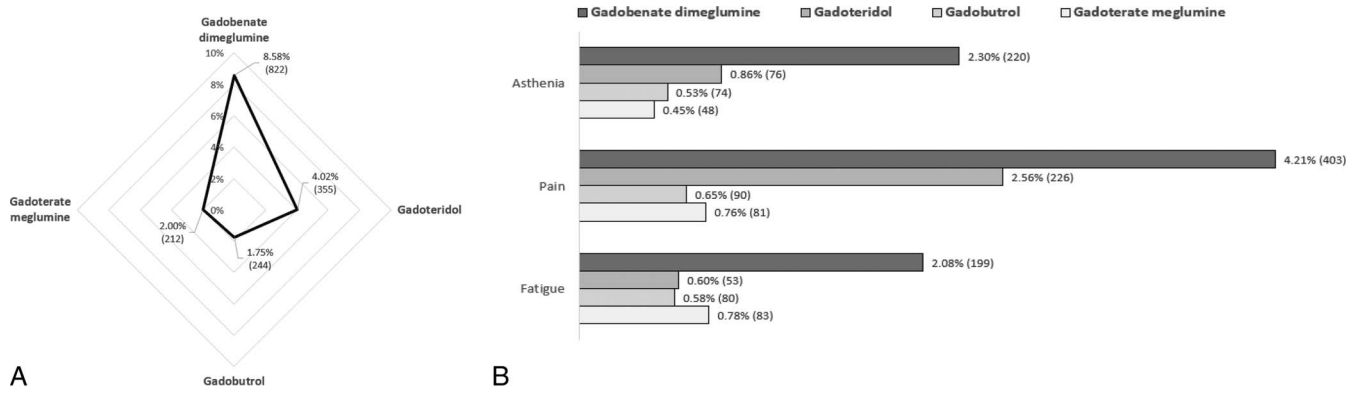

FIGURE 5. Radar chart of SAGE weight in the SOC "general disorders and administration site conditions" in EV (A), and bar charts showing a breakdown of these data by relevant PTs for this SOC (B). The figures on the graphs represent SAGE weights (numbers of SAGE).

Furthermore, Table 2 shows the fraction of SAGE notifications made by HCPs in each relevant SOC. Interestingly, the reporting rates of such AEs by HCPs were significantly lower in FAERS than in EV, which means that non-HCPs reported more frequently this type of symptoms to the FDA than to the EMA. When focusing on the most prevalent SOCs for SAGE (ie, skin, musculoskeletal, general, and nervous system disorders in Table 1), it seems that the highest HCP reporting rates were found in the SOC "nervous system disorders" for gadobutrol and gadoterate meglumine and in the SOC "skin and subcutaneous tissue disorders" for gadobenate dimeglumine and gadoteridol. The HCP reporting rates for gadobenate dimeglumine were unexpectedly low in the SOC "General disorders and administration site conditions," although the SAGE of this SOC were the most frequently reported overall and they represented the greatest SAGE weight of all the analyzed data (Table 1).

DISCUSSION

International pharmacovigilance databases like EV and FAERS contain suspected adverse drug reaction reports that have been submitted to national health authorities by HCPs, patients/consumers, or MAHs of the medicines. Such reports result from spontaneous notifications, which means that a lot of adverse events are not included in these databases owing to underreporting. On the other hand, the cumulative data recorded in these databases represent an interesting source of information owing to the large numbers of reports collected so far (range: from 2220 individual cases in EV for gadoterate meglumine to 3964 for gadobenate dimeglumine) and the even larger numbers of adverse events (range: from 8,333 AEs in EV for gadoteridol to 13,904 for gadobutrol). Another limitation to the use of such data is the fact that there is no available information about the exposure of the patients to the medicinal products of interest. As a consequence, the figures written in these databases cannot be used to calculate the incidence of certain types of adverse events in the exposed population, and comparisons between products are not possible. An alternative way to use these data is to determine the weights represented by some adverse events in the overall spectrum of safety experiences recorded for the medicines. These weights are not directly affected by the numbers of administrations nor by the durations of commercialization of the medicines, and thus are independent from patient exposure. They provide an opportunity to compare different products and appreciate whether some risks may be more prominent with one product or another.

We applied this methodology in an attempt to assess whether SAGE have been reported to health authorities and whether the proclivity of the selected GBCAs for SAGE occurrence differed between the products. In 2016, Semelka and colleagues[37] proposed the term "gadolinium deposition disease" to describe a condition in which patients with normal kidney function develop long-lasting symptoms after

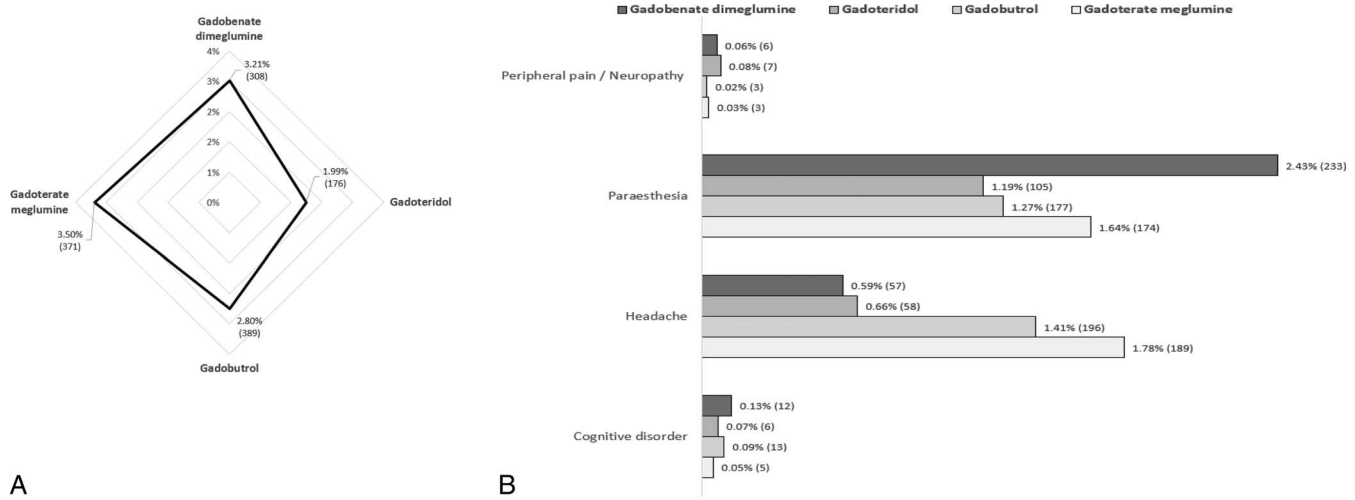

FIGURE 6. Radar chart of SAGE weight in the SOC "nervous system disorders" in EV (A), and bar charts showing a breakdown of these data by relevant PTs for this SOC (B). The figures on the graphs represent SAGE weights (numbers of SAGE).

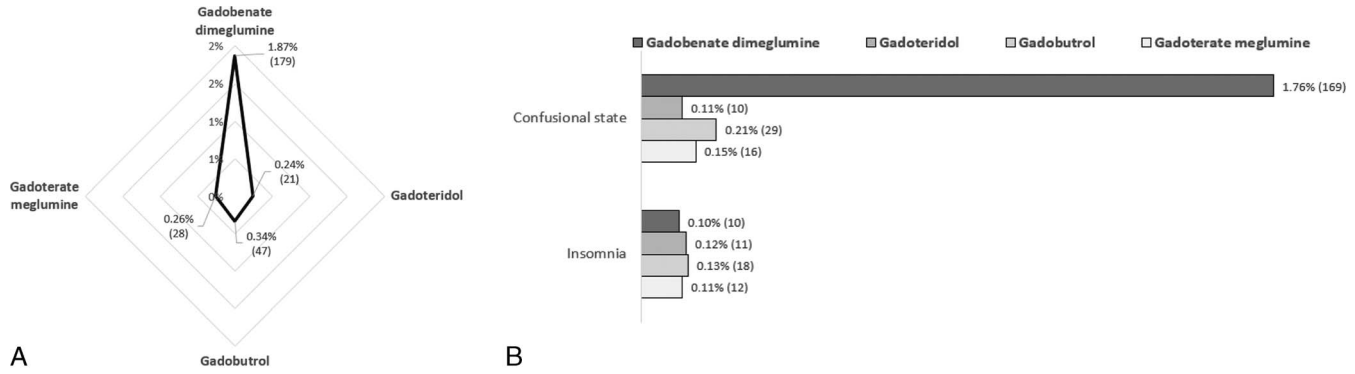

FIGURE 7. Radar chart of SAGE weight in the SOC "psychiatric disorders" in EV (A), and bar charts showing a breakdown of these data by relevant PTs for this SOC (B). The figures on the graphs represent SAGE weights (numbers of SAGE).

GBCA exposure. Thereafter, they published several case series of patients who complained of intense pain and burning sensation, headache, and clouded mentation, as well as erythematous and thickened skin and subcutaneous tissue.[40,41,46] Most of these reactions were severe, persistent, and worsening after multiple injections; some of them were similar to the symptoms described for NSF; some had a detrimental impact on the patients' daily activity and ability to work. These reports naturally led to the question whether GBCAs are actually responsible for these clinical manifestations, and to which extent the exposed population is actually affected.

Until recently, only spontaneous notifications from patients have fuelled the bag of evidence supporting the GDD theory. In 2021, however, Semelka and Ramalho[46] published a case series of physicians who reported their experience with self-diagnosed GDD. Because these patients were educated reporters on diseases, the authors considered that they had the medical knowledge to establish an association between the administration of a GBCA and their symptoms. However, evidence of long-term gadolinium retention in human tissues and consistency in the chronology of events with symptoms occurring after exposure to a GBCA cannot be taken as a demonstration that the medicine caused the disease. Moreover, there are multiple unanswered questions such as the underlying pathophysiological mechanisms, whether risk factors may contribute to the expression of the disease, whether it is time and/or dose dependent, and whether all GBCAs are equally susceptible to trigger GDD symptoms, which require clarification before a stronger relationship can be established. More recently, McDonald and colleagues[39] proposed the term "symptoms associated with gadolinium exposure" (SAGE) to be used in place of GDD. They considered that there is no sufficiently compelling evidence to date to assert that this coincidental relationship is actually a causal relationship. They also proposed to define SAGE as symptoms that are unrelated to established early-onset (ie, acute allergic-like and physiologic reactions) and late-onset (ie, NSF) AEs from GBCAs.

In their review article, McDonald and colleagues[39] explained that the FDA requested GBCA manufacturers to conduct a multicenter, prospective trial to detect any effect of repeated GBCA administrations on motor and cognitive functions in normal adults. As a 5-year follow-up assessment is required for all the patients included in the study, it is unlikely that a clear outcome becomes available soon. Thus, pharmacovigilance databases like EV and FAERS represent an alternative solution to appreciate the extent of SAGE in the spectrum of AEs potentially associated with the use of GBCAs. No conclusion can be drawn in

TABLE 2. Percentages of SAGE Reported by HCPs in EV and FAERS Databases

GBCAs	Gadobenate Dimeglumine		Gadoteridol		Gadobutrol		Gadoterate Meglumine	
Databases Containing AE Reports	**EV**	**FAERS**	**EV**	**FAERS**	**EV**	**FAERS**	**EV**	**FAERS**
% of SAGE reported by HCPs in the SOC "Skin and subcutaneous tissue disorders"[a]	92	33	94	35	64	17	54	32
% of SAGE reported by HCPs in the SOC "Musculoskeletal and connective tissue disorders"[b]	53	21	86	27	53	28	46	24
% of SAGE reported by HCPs in the SOC "General disorders and administration site conditions"[c]	30	13	87	26	56	31	61	35
% of SAGE reported by HCPs in the SOC "Nervous system disorders"[d]	41	28	72	32	73	41	73	42
% of SAGE reported by HCPs in the SOC "Psychiatric disorders"[e]	12	12	67	33	66	52	75	41
% of SAGE reported by HCPs in the SOC "Investigations"[f]	83	23	82	21	40	10	40	43

SAGE indicates symptoms associated to gadolinium exposure; HCP, health care professional; EV, Eudravigilance; FAERS, FDA Adverse Event Reporting System; GBCA, gadolinium-based contrast agent; AE: adverse event; SOC, system organ class.

[a]Pain of skin, skin burning sensation, skin discoloration, skin induration, skin tightness.

[b]Arthralgia, bone pain, fibromyalgia, joint stiffness, ligament and tendon pain, muscle fatigue, muscle spasms, muscle tightness, muscle twitching, muscular weakness, musculoskeletal chest (wall) pain, musculoskeletal pain, pain in extremity.

[c]Asthenia, fatigue, pain.

[d]Cognitive disorder, headache, paraesthesia, peripheral pain/neuropathy.

[e]Confusional state, insomnia.

[f]Quality of life decreased.

causality from this type of analysis, but trends may be established to identify the predominant SOCs containing SAGE and to assess whether the prevalence of these AEs correlates with the GBCA categorization into linear and macrocyclic agents.

Our analysis of safety data in both pharmacovigilance databases showed that the proportion of SAGE among all suspected adverse reactions was not negligible and that it was significantly greater for gadobenate dimeglumine than for gadoteridol and lower for gadobutrol and gadoterate meglumine (26%, 16%, 8%, and 9% in EV, respectively). The same ranking was observed in FAERS despite different durations of commercialization and different numbers of safety notifications in the United States compared with Europe. As expected from the literature,[38,40–43,45–48] the linear agent displayed a higher SAGE weight than the macrocyclic ones. Unexpectedly, however, a twice greater SAGE weight was found for gadoteridol compared with the other macrocyclic GBCAs. This intermediate position of gadoteridol could not be anticipated from the literature because this product was reported in only a single article.[38]

In-depth investigations showed that gadobenate dimeglumine reached systematically the highest SAGE scores in the most represented SOCs, gadobutrol and gadoterate meglumine the lowest scores, whereas gadoteridol showed either high or intermediate positions. In the SOC dealing with "nervous system disorders," the most prevalent PTs were "paresthesia" (highest weight for gadobenate dimeglumine) and "headache" (highest weights for gadobutrol and gadoterate meglumine). It is noteworthy, however, that headaches are also well-known acute physiologic reactions induced by GBCAs.[39] Segregating SAGE from physiologic reactions for this type of AE is not possible in EV and FAERS. Therefore, the SAGE weights in the SOC "nervous system disorders" must be considered as inaccurate, especially for gadobutrol and gadoterate meglumine, owing to a selection bias on headaches. As can be seen in Figure 6B, should headaches be ignored, then gadobenate dimeglumine would present a higher SAGE weight than the macrocyclic agents. In a prospective cohort study on 1088 patients comparing gadoterate meglumine and the linear GBCA gadodiamide, Parillo and colleagues[43] reported a nonstatistically significant increase of headaches with both products as compared with control patients who underwent an MRI without contrast medium injection. We may assume that the lack of a statistical difference was due to the short period of assessment, which was limited to 24 hours post-MRI. Indeed, in their survey on 42 GDD patients, Semelka and colleagues[38] mentioned that headaches persisted beyond 3 months in 29 subjects. A too short period for AE collection may therefore underestimate the prevalence of persistent headaches that meet the SAGE definition.

The SOC "psychiatric disorders" showed a consistent pattern with gadobenate dimeglumine, reaching a significantly higher ranking than the 3 macrocyclic GBCAs. The main type of AE responsible for this difference was "confusional state." We considered that this medical term, which is listed as a PT in pharmacovigilance databases, was the most appropriate coded term for the symptoms "clouded mentation" and "brain fog," which have been reported in the literature.[37,38,41] In their prospective study, Parillo and colleagues[43] observed a higher incidence of mental confusion in patients exposed to gadoterate meglumine than those exposed to gadodiamide, but again, the short observation time (24 hours after the MRI) precludes any definite conclusion.

In some publications, Semelka and colleagues[38,46] emphasized the fact that GDD-related symptoms interfered with the daily life of the affected patients. In their most recent case series, 9 physicians with self-diagnosed GDD explained that they had to stop or reduce their medical practice because of persistent brain fog, burning sensation, or both. Interestingly, skin burning sensation did not appear as a leading symptom in the SOC "skin and subcutaneous tissue disorders" in EV and FAERS. As for brain fog, this symptom was reported by 3 of the 4 physicians who determined that gadobenate dimeglumine was the precipitating agent, 1 who identified the linear GBCA gadopentetate dimeglumine as the trigger, and 2 of the 3 who mentioned gadobutrol.[46] The last physician who received gadoterate meglumine did not develop brain fog symptoms. Overall, it is likely that the linear agents were more frequently associated with brain fog, which is consistent with the greater weight of "confusional state" in patients exposed to gadobenate dimeglumine, according to EV and FAERS. Furthermore, to appreciate the impact of SAGE on patients' life, we picked up the PT "quality of life decreased" in the SOC "investigations" and calculated its weight among the spectrum of AEs reported for each GBCA. This PT represented a very low weight in the overall safety experiences recorded for the 4 contrast agents. However, gadobenate dimeglumine and gadoteridol displayed a similar score, which was twice greater than that calculated for gadobutrol and gadoterate meglumine.

As most HCPs are medically qualified to detect and assess adverse events in patients, their reports are of great value for this analysis. Adverse events reported by non-HCPs are also quite informative because they come in majority from the patients themselves. Fortunately, a large proportion of the safety reports recorded in EV and FAERS have been validated medically by pharmacovigilance responsible persons working in the national health systems or at MAHs. Both EV and FAERS contain serious pharmacovigilance cases from worldwide origin but they only comprise domestic nonserious cases, that is, nonserious cases from Europe in EV and nonserious cases from the United States in FAERS. With regard to SAGE, it is possible that many nonserious cases were not reported by HCPs because they concerned nonspecific events likely related to the medical condition of their patients. Because the collection of nonserious cases became mandatory in the United States long before in Europe (in force only since November 2017), it may explain why such events were more reported by non-HCPs in FAERS than in EV, as shown in Table 2.

In both databases, the highest HCP reporting rates concerned the SOC "nervous system disorders" for gadobutrol and gadoterate meglumine. This may be explained by the fact that safety concerns dealing with this SOC are always given a greater consideration, and even more so since the demonstration that gadolinium may be retained in patients' brains after repeated GBCA exposure.[12–22] Furthermore, HCPs frequently reported AEs in the SOC "skin and subcutaneous tissue disorders" for gadobenate dimeglumine and gadoteridol, which suggests that the occurrence of these NSF-like symptoms raised their attention. Interestingly, they rarely reported cases of patients presenting with general disorders such as "asthenia," "fatigue," and "pain" after exposure to gadobenate dimeglumine, although these AEs were the most prevalent among all SAGE. This shows how symptoms that are considered subjective are better reported by the patients themselves.

This analysis bears some limitations. First, it did not provide any demonstration of a causal relationship between the reported events and GBCA administration to the patients. However, it brought an overview of the SAGE notifications received by the EMA and FDA and it allowed stratifying the GBCAs in terms of SAGE weight. Second, it would have been interesting to include in the comparison a negative control group of patients who underwent an MRI without receiving a GBCA, but such information is not available in pharmacovigilance databases that deal exclusively with adverse events associated with the use of medicinal products. Third, all the safety reports recorded in the databases are not medically validated. This is especially true for those notified by non-HCPs, but it probably allowed capturing more nonserious AEs and some subjective feelings that would have been lost otherwise. Fourth, as HCPs, patients, and MAHs may notify a case to their health authorities, double reporting may occur and ultimately affect the accuracy of our analysis. However, regulatory authorities and MAHs have set up some processes to minimize this risk. Fifth, as individual patient data are not available in EV and FAERS, we could not assess if multiple GDD-related symptoms occurred in the same patients, as presented in the published case reports,[38,41,46] or whether they were widespread in the exposed population. To compensate for this, we analyzed the

available data of several relevant PTs per SOC. As shown in Figures 3B to 7B, this approach allowed to clearly identify which PTs contributed the most to the overall SAGE weights of the GBCAs. Finally, because the databases do not provide access to patients' medical data, we could not evaluate whether previously injected GBCAs could be associated with the reported symptoms.

In conclusion, we applied a rigorous methodology to determine the relative importance of SAGE in GBCA-exposed patients using the EMA and FDA pharmacovigilance databases as safety data sources. Even though no causal relationship could be established between the administration of a GBCA and the clinical manifestations of SAGE, it is noticeable that gadobenate dimeglumine, and to a lesser extent gadoteridol, presented the highest percentages of such AEs. Contrary to gadobutrol and gadoterate meglumine, both contrast agents showed a high proclivity for the occurrence of skin disorders, musculoskeletal and connective tissue disorders, as well as general disorders. They were also associated with a significantly greater reporting trend of decreased quality of life. Altogether, this analysis suggests that SAGE may be more prevalent with linear than macrocyclic GBCAs, and that gadoteridol may present a higher SAGE risk than the other macrocyclic contrast agents.

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