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SUMMARY WITH CRITICAL APPRAISAL

Macrocyclic and Linear Gadolinium Based Contrast Agents for Adults Undergoing Magnetic Resonance Imaging: A Review of Safety

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Authors: Tara Cowling, Nina Frey

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Abbreviations

ACROBAT-NRSI	A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions
AMSTAR-2	A MeaSurement Tool to Assess systematic Reviews
CASP	Critical Appraisal Skills Programme
CCr	Creatine Clearance Rate
CIN	Contrast-induced nephropathy
CKD	Chronic kidney disease
CNS	Central nervous system
CRD	University of York Centre for Reviews and Dissemination
FDA	Food and Drug Administration
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GBCA	Gadolinium-based contrast agents
MRI	Magnetic resonance imaging
RCT	Randomized controlled trial
ROBINS-I	Risk of Bias in Non-Randomized Studies – of Interventions
USA	United States of America

Context and Policy Issues

Contrast agents are widely used for magnetic resonance imaging (MRI) and angiography.[1,2] These agents are administered intravenously and enhance the detail and clarity of images for more precise diagnoses.[1,2] Although generally considered to be safe, the use of contrast agents may result in mild to severe adverse effects.[3]

Gadolinium-based contrast agents (GBCAs) have been approved for clinical use for over 20 years and remain a standard contrast-enhanced MRI technique that further improves the detection and visualization of morphologic features.[4-6] There are two structurally different categories of GBCAs available; linear contrast agents and macrocylic contrast agents, which are considered to be the most stable since they have lower dissociation constants.[1,2] In recent years, GBCAs have been highlighted due concerns associated with potential adverse events. Recent studies have found that GBCAs may have nephrotoxic potential, raising questions about the renal safety of these agents.[1,7,8] In addition, questions about the retention of gadolinium in the body, particularly in the brain after MRI, prompted evaluations from various regulatory organizations. For instance, the Food and Drug Administration (FDA) reviewed GBCAs and found that while gadolinium retention has not been directly linked to adverse effects in patients with normal renal function, a new class warning was required.[9] A similar review by the European Medicines Agency (EMA) resulted in recommendations to restrict the use of some linear GBCAs and the suspended authorization of others.[10] Similarly, Health Canada states that the use of macrocylic agents may be preferable in certain patients, especially those for whom repeated doses of GBCAs may be required, as well as vulnerable patients including pregnant women and children.[11]

The current Rapid Response report will seek to identify and synthesize the evidence around the risks and safety of macrocyclic and linear GBCAs for adults undergoing MRI.

Research Questions

1. What are the risks and safety of macrocyclic gadolinium based contrast agents for adults undergoing magnetic resonance imaging?
2. What are the risks and safety of linear gadolinium based contrast agents for adults undergoing magnetic resonance imaging?
3. What are the comparative risks and safety of macrocyclic versus linear gadolinium based contrast agents for adults undergoing magnetic resonance imaging?

Key Findings

Overall, ten publications met the selection criteria for this review and included: two systematic reviews, six randomized controlled trials, and two non-randomized clinical studies.

Three of the included studies examined the risks and safety of macrocyclic gadolinium-based contrast agents, including gadobutrol and gadoteridol. All three studies reported that these contrast agents were well-tolerated with a good safety profile.

Two studies examined the risks and safety of linear gadolinium-based contrast agents, including gadodiamide, gadopentetate dimeglumine and gadoxetate disodium. One study found that that gadopentetate dimeglumine had no nephrotoxic effects, and gadodiamide had slight, though clinically insignificant, nephrotoxic effects. The second study, comparing the safety of gadoxetate disodium and gadobenate dimeglumine, found that both agents had a similar safety profile, with approximately 6% of patients in both groups experiencing adverse events.

Five of the included studies, including a meta-analysis, a systematic review, and three randomized controlled trials, provided a comparison of the risks and safety of macrocyclic and linear gadolinium-based contrast agents. The meta-analysis found that protein binding, macrocyclic structure, and ionicity were associated with a higher rate of allergic-like adverse events in patients injected with gadolinium-based contrast agents. The systematic review reported that signal intensity on unenhanced T1-weighted magnetic resonance images was positively correlated with exposure to gadolinium-based contrast agents, and this was greater after serial administrations of linear nonionic versus cyclic contract agents. Finally, three randomized control trials found both macrocyclic and linear gadolinium-based contrast agents were well tolerated.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs), non-randomized studies, health technology assessments, systematic reviews, meta-analyses, and safety. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2010 and March 5, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Any adult undergoing MRI examination (including those with conditions such as renal failure, cardiac disease)
Intervention	Q1 and Q3: macrocyclic gadolinium based contrast agent – at any dose (including off label dosing) Q2: linear gadolinium based contrast agent – at any dose (including off-label dosing)
Comparator	Q1, Q2: non-gadolinium based contrast, no comparator Q3: linear gadolinium based contrast
Outcomes	Adverse events related to gadolinium contrast such as: - nephrogenic systemic fibrosis (particularly an issue for those with an estimated glomerular filtration rate <30mL/min) - toxicity associated with accumulation of gadolinium (such as nephrotoxicity, pancreatitis, necrosis and apoptosis, neurotoxicity, hematoxicity, hepatotoxicity) - deposition of gadolinium in brain tissue Dose-response for adverse events
Study Designs	HTA/Systematic Reviews/Meta-Analyses; Randomized Controlled Trials; Non-Randomized Clinical Studies

HTA = Health Technology Assessment, MRI = magnetic resonance imaging

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Reviews with unclear methodology were excluded. After the search was completed, observational study designs without clinical interventions, such as surveys, were also excluded due to the high volume of studies identified.

Critical Appraisal of Individual Studies

The included studies were critically appraised by one reviewer using the appropriate tool for the associated study design: A Measurement Tool To Assess Systematic Reviews (AMSTAR-2),[12] the Critical Appraisal Skills Programme (CASP)[13] checklist for RCTs, and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I)[14]. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 273 citations were identified in the literature search. Following screening of titles and abstracts, 182 citations were excluded and 91 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 83 publications were excluded for not meeting the predefined selection

criteria, and 10 publications were included in this report. The included studies comprised two systematic reviews, six RCTs, and two non-randomized studies. Appendix 1 presents the PRISMA[15] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Overall, 10 publications met the inclusion criteria and were included in this report: two systematic reviews, six RCTs, and two non-randomized studies.

Additional details regarding the characteristics of included publications are provided Appendix 2.

Study Design

Two systematic reviews met the inclusion criteria listed in Table 1 and were included in the current Rapid Response report: a systematic review and meta-analysis examining immediate allergic reactions to GBCAs and a systematic review examining the presence of GBCA depositions in the brain and neurotoxicity.

The systematic review and meta-analysis of immediate allergic reactions to GBCAs was published in 2018 and included nine non-randomized studies. The authors searched PubMed and Google Scholar for published studies until February 2017. The included studies were published from 2011 onwards, with study periods ranging from 2000 to 2016.[16]

The systematic review of GBCA depositions in the brain was published in 2017 and included 25 publications (19 MRI analyses, three case reports, and three autopsy reports), The authors did not report their search date range; however, the search was completed in July 2016 and the included studies dated back to 2014.[17]

There was no overlap in the included studies of the two systematic reviews, as outlined in Appendix 5.

In addition, eight clinical studies also met the inclusion criteria outlined in Table 1. The first study was a multicenter, double-blind RCT that utilized a crossover design.[6] Another five studies were RCTs,[4,7,18-20] and the remaining two studies were non-randomized, open-label clinical trials.[5,21] Three of the five RCTs were multicenter RCTs, and the remaining two were conducted at single centers.[7,20] Furthermore, two RCTs were double-blinded,[19,20] two were single-blinded,[4,18] and one RCT did not specify any blinding procedure.[7] The non-randomized trials obtained two sets of MRIs from each patient, the first being unenhanced (i.e. with no contrast agent administered), and the second enhanced with contrast agent.[5,21]

Country of Origin

The first author of the systematic review and meta-analysis of allergic reactions to GBCAs was from the United States of America (USA)[16] and the first author of the systematic review of GBCA depositions in the brain was from Poland.[17]

Of the eight clinical trials, three were conducted in the USA,[5,6,20] three were conducted in Japan, [4,7,21] one was conducted in China,[18] and one was conducted in Switzerland.[19]

Patient Population

The systematic review and meta-analysis of allergic reactions included studies where rates of immediate (timeframe not defined) allergic reactions to GBCAs were reported; details of the patient population for the nine included studies were limited to the type of GBCA administered.[16] The systematic review of GBCA depositions in the brain included patients who had MRI examinations with GBCAs. Among the 19 studies and autopsy reports included in the review, the authors presented the number of GBCA administrations as well as the contrast agent.[17]

In the study that utilized a randomized crossover trial design, men and women at least 18 years of age who were referred for contrast-enhanced MRI of the central nervous system (CNS) were recruited from 51 centers worldwide. Patients who were pregnant, breastfeeding, had a history of severe allergic reaction, or had underlying diseases (such as cardiovascular, kidney or liver diseases) were excluded from the study. Additionally, any patient who had been administered any contrast agent within 24 hours of the study MRI or were taking medications that may have interfered with the study were excluded.[6]

One RCT involved male and female patients at least 20 years of age who were referred for contrast-enhanced MRI based on their current clinical symptoms, or the results of a previous imaging procedure. Included patients had to be clinically stable. The exclusion criteria were patients who were pregnant, breastfeeding, had a history of severe allergic reaction, severe cardiovascular disease or chronic renal failure. Patients who had participated in any gadobutrol studies, had received or were to receive a contrast agent within 24 hours of the first contrast agent administration, and those who had contraindications to the MRI procedures or gadolinium-based contrast agent use were also excluded.[4]

The RCT conducted in China recruited patients from four centers. The patients were between 18 and 65 years of age, had known or suspected CNS lesions (cranial and/or spinal) and were referred for a contrast-enhanced MRI. Patients who were pregnant, breastfeeding, had hypersensitivity to contrast media, or had severely impaired liver or kidney function (or other underlying diseases) were excluded from the study. Patients were also excluded from the study if they had received or were to receive a contrast agent within 24 hours of the first contrast agent administration or had contraindications to the MRI procedures or the contrast agent used.[18]

The Japanese RCT included patients between 20 to 85 years of age, weighing 45 to 70 kg and were scheduled for a contrast-enhanced MRI of the brain at Kitasato University Hospital between November 2007 and February 2010. Patients were excluded from the study if their serum-creatinine levels were ≥ 1.6 mg/dL within 3 months prior to the MRI procedure, or if they were unable to comply with the study protocol.[7]

In one RCT conducted by Semelka et al., the patient population was not well described. The 59 included patients were described as having an age range of 5 to 85 years, with a mean age of 52 years. The patients were comprised of 31 men and 28 women.[20]

The RCT conducted in Switzerland studied patients who were at least 18 years of age, had suspected or known focal liver lesions, and required a contrast-enhanced liver MRI. Patients were excluded if they had received an investigational drug within 30 days prior to entering the study or were contraindicated for contrast-enhanced MRI.[19]

The first non-randomized clinical trial, conducted by Gutierrez et al., recruited patients from 22 centers in Argentina, China, Colombia, South Korea and the USA between December 2007 and December 2008. The study examined patients at least 18 years of age, who were referred for a contrast-enhanced MRI of the CNS. Patients were excluded if they were pregnant, breastfeeding, had a history of severe allergic reactions, or had any underlying diseases (including liver or kidney diseases/injuries). Patients who had participated in any clinical studies 30 days prior to enrollment (including any gadobutrol studies), had received a contrast agent within 24 hours of the first contrast agent administration, and those who had contraindications to the MRI procedures or gadolinium-based contrast agent use were also excluded. Additionally, patients who were taking medications that may have interfered with the study were excluded, as well as any patients who were scheduled to receive a contrast agent or any therapeutic procedure 72 hours after their study MRI.[5]

The second non-randomized clinical trial examined men and women at least 18 years of age with any indication who were referred for a contrast-enhanced MRI of the CNS. Like the non-randomized study performed by Gutierrez et al., patients who were pregnant, breastfeeding, had a history of severe allergic reactions, received a contrast agent 24 hours prior to the study MRI, or participated in any clinical studies 30 days prior to enrollment (including any gadobutrol studies) were excluded. The patients in this study also had to be clinically stable, and patients with severe cardiovascular diseases or hepato-renal diseases were excluded.[21]

Interventions and Comparators

In the systematic review and meta-analysis of allergic reactions, the GBCAs used in the included studies were: gadodiamide, gadopentetate, gadobutrol, gadoxetate, gadoterate, gadobenate, gadoteridol, and gadofosveset. The GBCAs were grouped as linear or macrocylic, as well as by ionicity for analysis.[16]

The systematic review of GBCA depositions in the brain included patients who had undergone GBCA-enhanced MRI. As noted in the systematic review, the contrast agents of the included publications were: gadopentetate dimeglumine, linear GBCA, gabobutrol, gadodiamide (Omniscan), gadoteridol, gadodiamide, gadoterate meglumine, gadobenate dimeglumine.[17]

In the RCT that utilized a crossover study design, patients were randomized 1:1 to receive either gadobutrol followed by gadoteridol, or gadoteridol followed by gadobutrol. The agents were administered on separate days, with a mean of 4.6 days between injections. After patients had crossed over to their respective second contrast agent (Period 2), patients were monitored for at least 72 hours for adverse events.[6] Both agents were administered as a single intravenous injection at the standard dose of 0.1 mmol/kg body weight and at a rate of 2 mL/s. All injections were followed by a 20 mL 0.9% saline flush at the same rate.

One of the Japanese RCTs randomized patients 1:1 to either gadobutrol or gadopentetate dimeglumine. The patients received one intravenous standard dose of 0.1 mmol/kg body weight of their assigned contrast agent by bolus administration, using a power injector via a peripheral vein. To ensure that the injection duration was comparable, gadobutrol was administered at a rate of 1.5 to 2 mL/s and gadopentetate dimeglumine was administered at a rate of 2 to 3 mL/s. Administrations were followed by a 10 mL 0.9% saline flush at the same rate as the contrast agent.[4]

Similarly, the Chinese RCT randomized patients 1:1 to receive either gadobutrol or gadopentetate dimeglumine at a dose of 0.1 mmol/kg body weight. Gadobutrol was

administered as a single intravenous bolus injection at a rate of 1.0 mL/s using a power injector and followed by a 20 mL saline flush. Gadopentetate was administered in the same fashion, but at a rate of 2.0 mL/s.[18]

The second, single-center Japanese RCT compared patients who were randomly assigned to receive gadodiamide or gadopentetate dimeglumine, each at 0.1 mmol/kg. Details on the method of injection were not given.[7]

The single-center RCT conducted in the USA noted that patients were randomized to receive gadobutrol or gadobenate dimeglumine. Similar to the other RCTs, the contrast agents were administered as a bolus via power injector at a rate of 2 mL/s, followed by a 20 mL saline flush. However, while gadobutrol was administered at 0.1 mmol/kg, a half-dose of gadobenate dimeglumine was used (i.e. 0.05 mmol/kg). The authors stated that this dosage was routinely used at the institution in an effort to reduce the risk of nephrogenic systemic fibrosis and produced the same diagnostic imaging quality as a full dose.[20]

The RCT conducted in Switzerland randomized patients to receive 0.025 mmol/kg body weight of gadoxetate disodium, or 0.05 mmol/kg body weight of gadobenate dimeglumine. Both contrast agents were administered as single intravenous injections at 2 mL/s, followed by a 20 mL 0.9% saline flush.[19]

Both non-randomized clinical trials administered first an unenhanced MRI, then a gadobutrol-enhanced MRI to each patient. The study investigators in each study administered 0.1 mmol/kg body weight of gadobutrol as a single intravenous injection at 2 mL/s, followed by a 20 mL 0.9% saline flush.[5,21]

Outcomes

The systematic review and meta-analysis examined immediate allergic reactions to GBCAs, which were defined using the American College of Radiology Classification system, whereby acute reactions are classified as mild, moderate or severe.[16] The systematic review of GBCA depositions in the brain examined the signal intensity within the dentate nucleus and globus pallidus on MR images in patients who had undergone MRI with GBCA, as well as short- and long-term consequences of gadolinium use; however, the authors did not report how these were outcomes measured or extracted.[17]

The included RCTs examined a variety of outcomes. The crossover trial examined the occurrence of adverse events.[6] Whereas, the Japanese RCT monitored the occurrence of adverse events, as well as clinical laboratory parameters, vital signs and physical examinations at specified time points post-administration.[4] In addition, Liang et al. conducted a safety analysis as part of the RCT, which consisted of reporting adverse events and their associated intensity, as well as adverse events related to the contrast agent administered.[18] The second Japanese RCT examined only safety outcomes, including the effects of contrast agents on renal function, such as serum-creatinine, serum cystatin-C, estimated glomerular filtration rate (eGFR) and creatinine clearance rate (CCr) levels, to examine subgroups with chronic kidney disease (CKD) and the development of contrast-induced nephropathy (CIN).[7] The single-center RCT from the USA reported the occurrence and severity of visually apparent adverse events, specifically emesis and hives.[20] The final RCT by Zech et al., evaluated adverse events using the patient response to the question “How do you feel?”, where responses were determined by the investigators to be related or unrelated to the contrast agent administered.[19]

In the non-randomized trials clinical laboratory parameters, vital signs and results of physical examinations were compared at baseline and during the 72-hour follow-up periods of each trial.[5,21]

Summary of Critical Appraisal

Systematic Reviews

The two systematic reviews were critically appraised using AMSTAR-II.[12] The following is a summary highlighting the strengths and limitations of each study; additional details are provided in Appendix 3.

Strengths of the systematic review and meta-analysis included: data extraction completed in duplicate, author assessment of the risk of bias of the included studies using A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) and discussion of the impacts of the risk of bias on the results of each study in the review, such as sources of funding. The authors detail the heterogeneity of the included studies in the review and utilized appropriate statistics in their analysis. Finally, the authors reported any potential sources of conflict. The limitations of the systematic review included a poorly defined research question and inclusion criteria, and it was unclear to what extent a protocol was developed prior to the completion of the review. Likewise, the details of the search strategy were limited and were executed only in PubMed and Google Scholar. The authors do not explicitly state whether study selection was completed in duplicate and the included studies were not described in detail.[16]

Strengths of the systematic review of GBCA depositions in the brain included the following: the research question, inclusion criteria and key search terms were presented in the article; the search strategy was executed in PubMed and Medline databases; the authors hand searched the bibliographies of included studies; and study selection (title/abstract and full text screening) was reported to be conducted in duplicate, with a third reviewer consulted as necessary to resolve disputes. The limitations of the review included: limited details on the process for conducting the literature search, including the extent to which the review methods were established prior to the completion of the review (e.g. a protocol); the selection criteria for study designs; the process for data extraction; and details of the included or excluded studies. Finally, the authors did not complete any risk of bias assessment and did not report sources of funding for the included studies.[17]

Randomized Studies

The six included RCTs were critically appraised utilizing the CASP checklist for RCTs. The following is a summary that highlights the strengths and limitations from each study. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

The strengths of the RCT with a crossover design included the following: patients were randomly assigned to the treatment groups, a double-blind study design was utilized, all patients were properly accounted for at the trial's conclusion, the study had sufficiently large sample size and power and both groups had similar characteristics at baseline and were treated equally for the duration of the trial. One limitation of the study was the variable precision (i.e. the size of the standard deviations varied by outcome). The study was double-blinded, however, due to the nature of the crossover study design, the initial injection was administered by an unblinded nurse or technologist to ensure the fully blinded administration of the second injection. Although this was a large multicenter study, with

many countries represented, patients with underlying conditions were excluded from the study population. Hence, the generalizability of these results may be limited.[6]

Kuwatsuru et al.[4] conducted an RCT with strengths that are comparable to the cross-over RCT[6], in that the patients were randomly assigned to treatment groups, all patients were properly accounted for at the trial's conclusion, both groups had similar characteristics at the beginning of the trial and were treated equally for the duration of the trial. The study had sufficiently large sample size and power, as demonstrated by a power calculation. In addition, the patients were blinded to which treatment they received, however the investigators were not blinded. The limitations of this RCT[4] were also similar to the cross-over RCT[6], including: variable precision estimates (i.e. the size of the standard deviations varied by outcome); all patients were of Asian descent, which may limit the generalizability to more diverse populations; and patients were clinically stable, limiting the generalizability of the results to real-world populations.

The strengths of Liang et al.[18] RCT include the random assignment of patients to the treatment groups, all patients were properly accounted for at the trial's conclusion, and both groups had similar characteristics at the beginning of the trial. Similar to the Kuwatsuru et al.[4] RCT, the trial had a single-blind design, where investigators were not blinded to the treatment groups; however since the two contrast agents had different molarity (gadobutrol was 1.0 M and gadopentetate was 0.5 M) and were administered at different rates, the investigators could not be blinded. Limitations of this study include small treatment effects with large standard deviations, and the study included only Chinese patients.[18]

Naito et al.[7] performed a single-center RCT. The strengths of the study include the random assignment of patients to the treatment groups and the proper accounting for all patients at the end of the trial. Additionally, both treatment groups had similar characteristics at the beginning of the trial and were treated equally for the duration of the trial. Limitations included a lack of details on blinding procedures and generalizability due to the study being conducted at a single center in Japan.

Strengths of Semelka et al.[20] include the randomization of treatment assignment, blinding of patients and study personnel to treatment, and the similarity of groups at the start of the trial. The main limitation of the study was the lack of quantitative evidence provided, thus the quality of the results could not be evaluated. Additionally, Semelka et al. did not define the patient population well, and a mixed population of children and adults (ages 5 – 85) was included. This limits the generalizability to the population of interest (i.e. adults undergoing MRI). Adverse event outcomes of interest were limited to those that were visually apparent, specifically emesis and hives. Finally, gadobenate dimeglumine was administered at half-dose as per hospital protocol (gadobutrol was administered at full dose), thus the groups were not treated equally in the trial.

The strengths of the multicenter RCT performed by Zech et al.[19] include randomization of patients to the treatment groups, and the double-blinded study design (though the paper does not explicitly state that the investigators were blinded). The treatment groups were not similar at the start of the trial, as more patients assigned to receive gadoxetate disodium had signs of diffuse liver disease or liver cancer. Additionally, the treatment groups received different concentrations of contrast agents (0.025 mmol/kg of gadoxetate disodium, and 0.05 mmol/kg of gadobenate dimeglumine), which may have compromised blinding and resulted in unequal treatment of the groups. Adverse events were addressed by the study investigators as an open question: "How do you feel?", thus measurement of the safety

outcome was subjective. Finally, the study population was comprised of 95% Caucasians, limiting the generalizability to more heterogeneous populations.

Non-Randomized Studies

The two included non-randomized clinical trials were critically appraised utilizing the Cochrane ROBINS-I tool.[14] The following summary highlights the strengths and limitations from each study, with additional details provided in Appendix 3.

Overall, Gutierrez et al.[5] and Tanaka et al.[21] were similar in study design and analysis, and both were found to be comparable to a well-performed randomized trial: no bias due to confounding was expected, all eligible patients were included, the follow-up and start of intervention coincided for all patients, the intervention was well defined, and assessors were blinded and thus the outcome measures were not influenced by knowledge of the intervention. In Gutierrez et al.[5], while it was reported in some cases that the intervention deviated from usual practice, these patients were excluded from analysis and thus the outcome was not affected. Tanaka et al.[21] did not provide any information regarding deviations from the intended intervention.

Summary of Findings

The summary of findings below are presented according to the research questions posed by this Rapid Response report. Appendix 4 presents a table of the main study findings and authors' conclusions.

Safety of Macrocyclic GBCAs

Gutierrez et al.[6] conducted an RCT utilizing a crossover design to determine the safety profile of gadobutrol in comparison to gadoteridol, which are both macrocyclic gadolinium-based contrast agents. The main study findings with regards to safety were that gadobutrol and gadoteridol have similar safety profiles, and a similar number of patients in the trial experienced treatment-emergent adverse events in each group (approximately 10% of patients in each group). However, less than 1% of patients experienced a serious treatment-emergent adverse event, none of which were related to gadobutrol or gadoteridol as assessed by the study investigators.[6]

Gutierrez et al.[5] also performed a non-randomized, open-label clinical trial to determine the safety of gadobutrol. Approximately 5% of patients experienced an adverse event, and only one patient experienced a serious adverse event, which was deemed to be unrelated to gadobutrol. Gadobutrol also did not cause any clinically relevant changes to vital signs, laboratory or hematological parameters in the study population. The authors concluded that gadobutrol has a very good safety profile.[5]

The second non-randomized study design by Tanaka et al. also examined the safety of gadobutrol using an open-label clinical trial study design. Less than 10% of patients experienced at least one treatment-emergent adverse event, and 2.7% experienced an adverse event that was related to gadobutrol. No severe adverse events were reported with the use of gadobutrol. The study authors concluded that gadobutrol is a well-tolerated contrast agent.[21]

Safety of Linear GBCAs

In a single-blind RCT conducted at Kitasano University Hospital in Japan, Naito et al. [7] examined the renal safety of gadodiamide and gadopentetate dimeglumine. No patients developed contrast-induced nephropathy in either group. Kidney function parameters such as serum-creatinine, eGFR and CCr did not change significantly after receiving either gadolinium-based contrast agent, but serum cystatin-C levels were significantly higher after exposure to gadodiamide. Subgroups of patients with stage 1, 2 or 3 CKD were also examined. It was found that serum cystatin-C levels in patients with stage 1 CKD, and serum creatinine levels in patients with stage 2 CKD significantly increased after exposure to gadodiamide. The authors concluded that gadopentetate dimeglumine has no nephrotoxic effects, and gadodiamide has slight (but clinically insignificant) nephrotoxic effects. Since this study was conducted at only one center, a follow-up study on a larger scale is needed to confirm these findings.[7]

Zech et al.[19] compared the safety of gadoxetate disodium and gadobenate dimeglumine, two linear contrast agents, in a multicenter, double-blind RCT. Adverse events were reported for each contrast agent, with approximately 6% of patients in both groups experiencing adverse events. No serious adverse events or deaths were reported. The majority of the adverse events (which were considered not serious in nature) were determined to be either “possibly” or “probably” related to the contrast agent administration, by the study investigators. However, the authors found that both agents have a similar safety profile, and this evidence was consistent with other studies.[19]

Comparative Risks and Safety of Macrocyclic and Linear GBCAs

The systematic review and meta-analysis of immediate allergic reactions to GBCAs found that the rate of overall and severe allergic-like reactions was 9.2 and 0.52 per 10000 administrations, respectively. The authors reported that the nonionic linear GBCA gadodiamide had the lowest overall rate of immediate adverse reactions compared to linear ionic GBCAs and nonionic macrocylic GBCAs. Nonionic linear GBCA was reported to have the lowest rate of moderate and severe adverse reactions compared to linear ionic GBCAs. The authors also reported that linear agents without protein binding had a lower reaction rate per 10000 injections when compared to macrocyclics without protein binding. In a model controlling for both ionicity and protein binding, the authors reported that nonionic linear GBCA had a lower relative risk for all reactions (0.12, 95% confidence interval [CI]: 0.05 to 0.31; $P < .0001$) as well as moderate and severe reactions (0.19, 95% CI: 0.05 to 0.66; $P = .009$) when compared with macrocyclic GBCAs. Finally, the authors reported that all GBCAs with protein binding, which included the linear GBCAs gadoxetate, gadofosveset, and gadobenate, were associated with a greater risk of reactions compared to gadopentetate dimeflumine, an ionic linear agent without protein binding. Based on these findings, the authors conclude that protein binding, macrocyclic structure, and ionicity were associated with a higher rate of allergic-like adverse events in patients injected with GBCAs. This meta-analysis was based on the findings of nine studies, and results may be limited by the retrospective analysis of data, selection bias and data accuracy.[16]

In the systematic review examining the presence of GBCA depositions in the brain and symptoms of gadolinium neurotoxicity looked at 25 publications (including 19 MRI analyses, 3 case reports and 3 autopsies) the authors conclude that signal intensity on unenhanced T1-weighted MR images (an indicator of brain accumulation) was correlated positively with exposure to GBCAs, and was found to be greater after serial administrations of linear nonionic versus cyclic contrast agents. However, limited data on the populations of the

included studies was included in the systematic review and only a narrative description of study findings was provided.[17]

An RCT by Kuwatsuru et al.[4] compared the safety of gadobutrol (a macrocyclic agent) to gadopentetate dimeglumine (a linear agent). In this trial, no significant changes were noted in vital signs, physical examinations or clinical laboratory parameters in either group, 24 hours after administration. Both agents were well-tolerated, with less than 10% of patients in both groups experiencing treatment-emergent adverse events. All adverse events reported in this study were of mild severity, and no serious adverse events or deaths were reported. In conclusion, the study found that both the macrocyclic and linear agent had good safety and tolerability.[4]

Liang et al.[18] also compared the safety of gadobutrol to gadopentetate dimeglumine. The investigators found similar results to Kuwatsuru et al. regarding the safety profiles of both agents. Less than 5% of patients reported adverse events, and all adverse events were of mild intensity, according to the study investigators. One mild adverse event was deemed to be related to gadobutrol, and all other adverse events were unrelated to the study agents. Like Kuwatsuru et al., no significant changes were noted in vital signs, physical examinations or clinical laboratory parameters in either group.[18]

Finally, Semelka et al.[20] compared gadobutrol to gadobenate dimeglumine, a linear contrast agent. The occurrence of mild adverse events was examined for both agents, particularly those that were visually apparent (emesis and hives). No patients included in the study experienced any adverse events, regardless of severity. The authors state that this study was a small-scale, pilot study designed to test the feasibility of addressing the safety of gadolinium-based contrast agents in a randomized fashion. Given the significant limitations of the study design, the results should be considered with caution, but are not dissimilar to other studies comparing macrocyclic and linear contrast agents.[20]

Limitations

There are several limitations that should be noted. For instance, a limited volume of evidence was available to answer the first two research question: three studies examining macrocyclic GBCAs, and two examining linear GBCAs. Five studies were identified which compared linear and macrocyclic GBCAs, including two systematic reviews. In some cases, authors urged caution in the interpretation and generalizability of results, as they were conducted in single centres or needed replication with larger populations. While the results included a meta-analysis and a systematic review, lack of details on the patient populations of included studies limited the generalizability of these studies. It was also the case in some studies that more vulnerable populations, such as those with renal or cardiovascular complications, were excluded. Overall the current Rapid Response report included studies with diverse patient populations, adverse events and outcomes which limits the interpretation of results.

Conclusions and Implications for Decision or Policy Making

Overall, ten studies examining the risks and safety of GBCAs were included in this report: two systematic reviews, six RCTs, and two non-randomized clinical studies.

Three of the included studies examined the risks and safety of macrocyclic GBCAs, including gadobutrol and gadoteridol, and two examined the risks and safety of linear GBCAs, including gadodiamide, gadopentetate dimeglumine and gadoxetate disodium. Overall, these studies reported that macrocyclic and linear contrast agents have good safety profiles, when examined separately and compared to each other. The studies reported that few patients (< 10% of patients in all studies) experienced mild adverse events after exposure to macrocyclic or linear contrast agents, and the likelihood of developing a serious adverse event due to a macrocyclic or linear contrast agent was very low, based on the evidence provided. As reported by one study, conducted in a single Japanese center, linear contrast agents have minimal nephrotoxic effects.[7]

Five of the included studies, including a meta-analysis, a systematic review, and three randomized controlled trials, provided a comparison of the risks and safety of macrocyclic and linear GBCAs. The meta-analysis found that protein binding, macrocyclic structure, and ionicity were associated with a higher rate of allergic-like adverse events in patients injected with GBCAs. A systematic review examining the presence of GBCA depositions in the brain and symptoms of gadolinium neurotoxicity reported that signal intensity on unenhanced T1-weighted magnetic resonance images was correlated positively with exposure to GBCAs; and that this was found to be greater after serial administrations of linear nonionic versus cyclic contract agents. Three randomized control trials comparing macrocyclic and linear GBCAs and reported that both agents were well tolerated.

Overall, the evidence from studies published since January 1, 2010 suggests that, overall, linear and macrocyclic GBCAs are well-tolerated by patients. As highlighted in both the systematic review and meta-analysis of allergic reactions and the systematic review of GBCA depositions in the brain, the risks and safety of GBCAs appear to vary across properties of the GBCA, including whether they are linear or macrocyclic agents, protein binding or non-protein binding, and ionic or nonionic.[16,17] Future research focusing on properties which may impact the safety profile of these agents and additional research across various patient populations (e.g. pregnant or breast feeding women, or patients with cardiac and kidney disease) would strengthen the evidence base surrounding the risks and safety of GBCAs.

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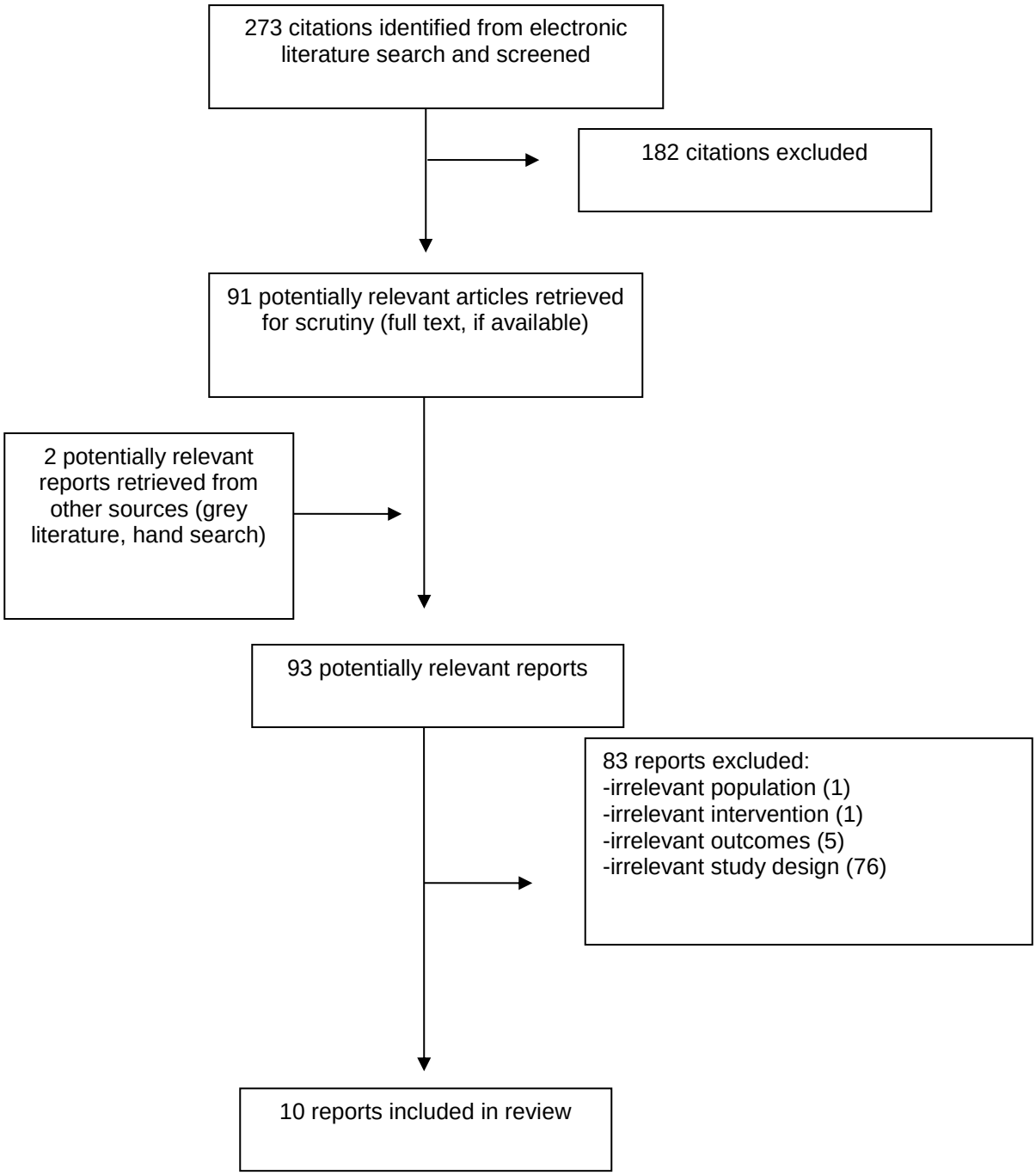
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Behzadi, 2018, USA USA	Non-randomized studies of interventions, n=9	NR	• GBCAs	• Number of administrations; • Number of mild, moderate, and severe reactions; • Number of deaths for each GBCA
Olchowy, 2017, Poland Poland	Original studies, n=19 Case Reports, n=3 Autopsy Examinations, n=3	Studies included patients who had undergone MRI using GBCAs	• GBCAs	• "signal intensity in the dentate nucleus and globus pallidus in the brain of patients with a history of GBCA administrations." (p. 2) • Short term consequences of gadolinium use • Long-term consequences of gadolinium use

GBCA = gadolinium-based contrast agent; MRI = magnetic resonance imaging; USA = United States of America

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Gutierrez, 2015, USA	Phase III, prospective, multicenter, double-blind, crossover trial	Men and women aged ≥ 18 years, referred for contrast-enhanced MRI of the CNS	• Gadobutrol followed by gadoteridol • Gadoteridol followed by gadobutrol	Clinical Outcomes: • Adverse events Length of Follow-up: • Adverse events were monitored >72 hours following the crossover MRI study with the second contrast agent
Gutierrez, 2015, USA	International, multicenter, open-label controlled Phase III study	Men and women aged ≥ 18 years, referred for contrast-enhanced MRI of the CNS	Intervention • Gadobutrol Comparator	Clinical Outcomes • Monitoring vital signs • Adverse events

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			• No agent	• Physical examinations • Laboratory parameters • Comparison to baseline safety parameters obtained before MR imaging Length of Follow-up • 72 hours
Kuwatsuru, 2015, Japan	Multicenter, randomized, controlled single-blind, parallel-group comparison Phase III study	Male and female patients, age 20 years or older, referred for contrast-enhanced MRI of regions in the body and/or extremities	Intervention • Gadobutrol Comparator • Gadopentetate dimeglumine	Clinical Outcomes • Adverse events • Delayed drug reactions • Clinical laboratory parameters • Vital signs • Physical examinations Length of Follow-up • 24 ± 4 hours
Liang, 2012, China	Multicenter, single-blind, randomized comparative study	Chinese patients aged 18 – 65 years with known or suspected cranial and/or spinal CNS lesions requiring contrast-enhanced MRI	Intervention • Gadobutrol Comparator • Gadopentetate dimeglumine	Clinical Outcomes • Incidence and severity of adverse events following injection Length of Follow-up • 24 hours
Naito, 2017, Japan	Prospective, randomized study	Patients aged 20 to 85 years weighing 45 to 70 kg with normal or mildly-diminished renal function (serum creatinine < 1.6 mg/dL in the 3 months prior to MRI), who were scheduled for contrast-enhanced MRI of the brain at Kitasato University Hospital	Intervention • Gadodiamide Comparator • Gadopentetate dimeglumine	Clinical Outcomes • Renal function before and after administration of contrast media • Contrast-induced nephropathy (CIN)
Semelka, 2013, USA	Randomized, controlled, blinded study	Patients who had clinical MR studies ordered of the brain or	Intervention • Gadobutrol	Clinical Outcomes • Acute, visually apparent adverse

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		abdomen	Comparator • Gadobenate dimeglumine	events
Tanaka, 2016, Japan	Multicenter, open-label, controlled study with blinded image evaluation	Men and women aged ≥ 18 years referred for a contrast-enhanced MRI of the CNS with any indication	Intervention • Gadobutrol Comparator • No agent	Clinical Outcomes • Occurrence of adverse events • Vital signs • Physical examinations • Clinical laboratory parameters Length of Follow-up • 72 hours
Zech, 2019, Switzerland	Prospective, multicenter, double-blind, randomized, inter-individual Phase III study	Patients ≥ 18 years of age with suspected or known focal liver lesions, scheduled for contrast-enhanced liver MRI	Intervention • Gadoxetate disodium Comparator • Gadobenate dimeglumine	Clinical Outcomes • Adverse events

CIN = contrast-induced nephropathy; CNS = central nervous system; MR = magnetic resonance; MRI = magnetic resonance imaging; USA = United States of America

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR-2[12]

Strengths	Limitations
Behzadi, 2018[16]	
• The authors completed data extraction in duplicate; however, no consensus process was detailed. • The authors assessed the risk of bias for the included studies using ACROBAT-NRSI • The authors reported on the sources of funding for the studies included in the review in the Discussion section of the systematic review. • The authors provided adequate detail for the methods used in the meta-analysis. • The authors discussed the potential impact of risk of bias in the individual studies on the results of the meta-analysis. • The authors accounted for risk of bias in individual studies in the discussion of the results of the review. • The authors described the heterogeneity in the results of review. • The authors reported any potential sources of conflict.	• The research question and inclusion criteria (PICO) were not well defined in the systematic review • It was unclear to what extent the review methods were established prior to the completion of the review (e.g. a protocol) • The selection of study designs for inclusion in the review was unclear • The literature search strategy was not well reported. The authors note that PubMed and Google Scholar databases were searched and provide the key words searched. • The article does not explicitly state whether study selection was completed in duplicate, or what type of consensus strategy was used. • A list of excluded studies was not provided. • The authors did not describe the included studies in detail. • The authors did not provide a discussion of publication bias and its possible impact on the results of the review.
Olchowy, 2017[17]	
• The research question and inclusion criteria (PICO) can be discerned through the systematic review. • The literature search strategy was presented in the systematic review and included PubMed and Medline databases. These searches were supplemented with grey literature. • Study selection was performed in duplicate. • The authors note that heterogeneity of study samples may be a sources of bias in the systematic review as a technical consideration. • The authors reported any potential sources of conflict.	• It was unclear to what extent the review methods were established prior to the completion of the review (e.g. a protocol) • The selection of study designs for inclusion in the review was unclear • Process for data extraction was unclear in the systematic review • A list of excluded studies was not provided. • The authors did not describe the included studies in detail. • The authors did not perform any risk of bias assessment • The review did not report sources of funding for the included studies

ACROBAT-NRSI = A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions; PICO = Population, Intervention, Comparator, Outcome

Table 5: Strengths and Limitations of Clinical Studies using CASP[13]

Strengths	Limitations
Gutierrez, 2015a[6]	
• The trial addressed a clearly focused issue • The assignment of patients to treatments was randomized • All patients who entered the trial were properly accounted for at its conclusion • Patients, health workers and study personnel were blind to	• The treatment effects were not consistently precise

Table 5: Strengths and Limitations of Clinical Studies using CASP[13]

Strengths	Limitations
treatment • The groups were similar at the start of the trial • Aside from the experimental intervention, the groups were treated equally • The results can be applied to the local population, in this context • A power calculation was completed, and the sample size was sufficiently large • All clinically important outcomes were considered • The benefits are worth the harms and costs	
Kuwatsuru, 2015[4]	
• The trial addressed a clearly focused issue • The assignment of patients to treatments was randomized • All patients who entered the trial were properly accounted for at its conclusion • Patients, health workers and study personnel were blind to treatment • The groups were similar at the start of the trial • Aside from the experimental intervention, the groups were treated equally • A power calculation was completed, and the sample size was sufficiently large • All clinically important outcomes were considered • The benefits are worth the harms and costs	• The treatment effects were not consistently precise • The results cannot be applied to the local population, or in this context, as all patients included in the study were of Asian descent and clinically stable
Liang, 2012[18]	
• The trial addressed a clearly focused issue • The assignment of patients to treatments was randomized • All patients who entered the trial were properly accounted for at its conclusion ○ Attrition from the trial was minimal; one patient (randomized to receive gadobutrol) withdrew consent • The groups were similar at the start of the trial • All clinically important outcomes were considered • The benefits are worth the harms and costs	• Patients were blind to the treatment, but the on-site investigators were not blind (i.e. single-blind design) • The groups were not treated equally, as the two contrast agents were administered in different volumes • The treatment effect was not large; most results of the clearly-specified outcomes were not statistically significant • The treatment effects were not precise • The results cannot be applied to the local population, or in this context, as all patients included in the study were of Chinese descent
Naito, 2017[7]	
• The trial addressed a clearly focused issue • The assignment of patients to treatments was randomized • All patients who entered the trial were properly accounted for at its conclusion • The groups were similar at the start of the trial • Aside from the experimental intervention, the groups were treated equally • The treatment effects were precise • All clinically important outcomes were considered	• It is unclear if patients, health workers and study personnel were blind to treatment • The treatment effect was not large; most results of the clearly-specified outcomes were not statistically significant • It is unclear if the results can be applied to the local population, or in this context, as limited details were provided on the study population

Table 5: Strengths and Limitations of Clinical Studies using CASP[13]

Strengths	Limitations
• The benefits are worth the harms and costs	
Semelka, 2013[20]	
• The assignment of patients to treatments was randomized • Patients, health workers and study personnel were blind to treatment • The groups were similar at the start of the trial	• The trial did not address a clearly focused issue, as the patient population and outcomes were not well defined • It is unclear whether all patients who entered the trial were properly accounted for at its conclusion • The groups were not treated equally, as gadobenate dimeglumine was administered at half-dose according to hospital protocol • No quantitative results were reported • The results cannot be applied to the local population, or in this context, as limited details on patient characteristics were reported • Not all clinically important outcomes were considered, as the study only focused on mild, acute adverse events • It is unclear if the benefits are worth the harms and costs
Zech, 2019[19]	
• The trial addressed a clearly focused issue • The assignment of patients to treatments was randomized • Patients, health workers and study personnel were blind to treatment • All clinically important outcomes were considered • The benefits are worth the harms and costs	• It is unclear whether all patients who entered the trial were properly accounted for at its conclusion • The outcome was subjectively measured as an open question to the patients • The groups were not similar at the start of the trial, as more patients in the gadoxetate disodium group showed signs of liver disease • The groups were not treated equally, as gadoxetate disodium was administered at half of the dose of gadobenate dimeglumine • The treatment effects were not consistently large • The treatment effects were not consistently precise • The results cannot be applied to the local population, or in this context, as approximately 95% of the trial participants were Caucasian

Table 6: Strengths and Limitations of Clinical Studies using ROBINS-I[13]

Strengths	Limitations
Gutierrez, 2015b[5]	
• No bias due to confounding was expected • All patients who would have been eligible for the study were included and the follow-up and start of intervention coincided for all patients. • The intervention was well defined, and all patients received the same interventions • Missing data was handled appropriately • Assessors were blinded and thus outcome measures were not influenced by knowledge of the intervention • The analysis was consistent with an a priori plan • All patients who entered the trial were properly accounted for at its conclusion • Aside from the experimental intervention, the groups were treated equally • The treatment effects were statistically significantly large. • The results can be applied to the local population, in this context • All clinically important outcomes were considered • The benefits are worth the harms and costs	• Although there were some reported cases of deviations from usual practice, the effect on the outcomes is expected to be slight as these patients were excluded • The assignment of patients to treatments was not randomized • Patients, health workers and study personnel were not blind to treatment • The groups were not similar at the start of the trial, as all patients received both the control and treatment • The estimates of treatment effects were not precise, as some outcomes had relatively large standard deviations
Tanaka, 2016[21]	
• No bias due to confounding was expected • All patients who would have been eligible for the study were included and the follow-up and start of intervention coincided for all patients. • The intervention was well defined, and all patients received the same interventions • Missing data was handled appropriately • Assessors were blinded and thus outcome measures were not influenced by knowledge of the intervention • The analysis was consistent with an a priori plan • The trial addressed a clearly focused issue • Aside from the experimental intervention, the groups were treated equally • The treatment effect was large • The treatment effect was precise • The results can be applied to the local population, or in this context • All clinically important outcomes were considered • The benefits are worth the harms and costs	• There was no information available regarding deviations from the intended interventions • The assignment of patients to treatments was not randomized, as all patients received both the control and treatment • It is unclear whether all patients who entered the trial were properly accounted for at its conclusion • Patients, health workers and study personnel were not blind to treatment • The groups were not similar at the start of the trial, as all patients received both the control and treatment

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Behzadi, 2018[16]	
• Overall rate of GBCA allergic-like adverse events: 9.2 per 10 000 administrations • Severe rates of GBCA allergic-like adverse events: 0.52 per 10 000 administrations, • 81% (539 of 662) were mild, 13% (86 of 662) were moderate, and 6% (37 of 662) were severe reactions. **Reaction Risk per 10^4 injections** *Linear nonionic vs Linear ionic:* • 1.5 (95% CI: 0.74, 2.4) per 10 000 administrations vs 8.3 (95% CI: 7.5, 9.2) per 10 000 administrations • Relative risk, 0.19 [95% CI: 0.10, 0.36]; p<.00001 *Linear nonionic vs linear ionic (non-protein binding)* • 1.5 (95% CI: 0.74, 2.4) per 10 000 administrations vs 5.2 (95% CI : 4.5, 6.0) • Relative risk: 0.28 (95% CI: 0.14, 0.55), p=0.0002 *Non-protein binding linear ionic vs protein binding linear ionic* • 5.2 (95% CI : 4.5, 6.0) per 10 000 administrations vs 17 (95% CI: 15, 20) • Relative risk : 0.33 (95% CI : 0.26, 0.41), p<0.0001 *Non-protein binding linear vs macrocyclic* • 4.4 (95% CI : 3.8, 5.1) per 10 000 administrations vs 14 (95% CI : 12, 16) • Relative Risk : 0.46 (95% CI : 0.26, 0.83), p=0.01 *Linear nonionic vs macrocyclic nonionic* • 1.5 (95% CI: 0.74, 2.4) per 10 000 administrations vs 16 (95% CI: 14, 19) per 10 000 administrations • Relative risk: 0.12 (95% CI: 0.05, 0.31); p<.0001	• "In conclusion, by combining data from nine studies of immediate reactions to GBCA we showed that protein binding, macrocyclic structure, and ionicity are associated with higher rates of allergic-like adverse events." (p. 481)
Olchowy, 2017[17]	
• 19 MRI analyses, 3 case reports, and 3 autopsy studies were included in the systematic review • Magnetic resonance images of 1247 patients with increased signal intensity of unenhanced T1-weighted MR images were analyzed; Tissue specimens from 27 patients were analyzed • High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted magnetic resonance images was correlated with exposure to GBCAs and was	• "Literature review confirms that increased signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images is associated with previous administrations of GBCAs, predominantly linear, and corresponds with the concentration of gadolinium in the brain tissue. Despite of rapidly growing number of published papers, the level of knowledge about gadolinium depositions in the brain and their clinical significance remains insufficient; therefore, it seems to be reasonable to choose the most stable types of GBCAs and avoid higher doses especially in children and young patients even with

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
greater after serial administrations of linear nonionic than cyclic contrast agents • Gadolinium was detected in all tissue examinations; though the clinical significance remains unclear	normal renal function." (p.11)

CI = confidence interval; GBCA = gadolinium-based contrast agent; MRI = magnetic resonance imaging

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Gutierrez, 2015a[6]	

• 40 patients that received gadobutrol-enhanced MRI (n = 399) experienced at least one treatment-related adverse event
  ○ Two patients experienced two serious adverse events that were unrelated to gadobutrol
  ○ Three patients discontinued the trial due to adverse events (allergic reactions)
• 38 patients that received gadoteridol-enhanced MRI (n = 393) reported at least one treatment-related adverse event
  ○ One patient experienced two serious adverse events that were unrelated to gadoteridol
  ○ One patient discontinued the trial due to adverse events (allergic reactions)
• No relevant changes to clinical laboratory parameters were observed
	• Gadobutrol was found to have a similar safety profile to other MRI contrast agents
	• The findings were consistent with previous studies, with respect to safety

Gutierrez, 2015b[5]	
• 67 patients in the study (n = 343) reported at least one adverse event, 14 of which were gadobutrol-related but not serious • One patient reported a serious adverse event that was determined to be unrelated to gadobutrol • No deaths or discontinuations were reported • No significant changes in vital signs, clinical laboratory values or hematological parameters were reported	• Gadobutrol has a very good safety profile • The findings are consistent with previous studies, with respect to safety
Kuwatsuru, 2015[4]	
• 13 patients that received gadobutrol-enhanced MRI (n = 178) experienced 12 mild treatment-emergent adverse events ○ Seven patients experienced seven drug-related treatment-emergent adverse events	• Gadobutrol and gadopentetate are similar in safety and tolerability • The observed incidence of treatment-emergent adverse events is similar to previously-reported findings

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
○ One patient experienced one severe treatment-emergent adverse event, which resolved after 15 minutes • 16 patients that received gadopentetate dimeglumine-enhanced MRI (n = 185) experienced 13 mild treatment-emergent adverse events ○ Three patients experienced seven drug-related treatment-emergent adverse events • When compared to the baseline values, there were no significant changes in clinical laboratory values, vital signs or physical examinations up to 24 hours after injection • No serious adverse events, deaths or discontinuations were reported for gadobutrol or gadopentetate dimeglumine	
Liang, 2012[18]	
• Six out of 146 patients included in the safety analysis reported mild adverse events; one adverse event was determined to be related to the treatment • Four adverse events were experienced by two patients in the gadobutrol group; four adverse events were experienced by four patients in the gadopentetate dimeglumine group	• Gadobutrol and gadopentetate dimeglumine are similar with regards to safety
Naito, 2017[7]	
• Patients who received gadodiamide or gadopentetate dimeglumine did not experience contrast-induced nephropathy (CIN) • Gadodiamide significantly increased serum cystatin-C levels from 0.74 to 0.79 (p = 0.028) • In patients with stage 1 CKD who received gadodiamide, serum cystatin-C levels significantly increased from 0.69 to 0.72 (p = 0.047) • In patients with stage 2 CKD who received gadodiamide, serum-creatinine levels significantly increased from 0.74 to 0.77 (p = 0.049); CCr levels significantly decreased from 80.5 to 78.5 (p = 0.039); and eGFR levels significantly decreased from 79.3 to 77.1 (p = 0.039)	• Small amounts of gadolinium are safe for patients with normal or mildly-diminished renal failure • Administration of gadopentetate dimeglumine has no effect on renal function • Gadodiamide has slight nephrotoxicity in patients with stage 1 or 2 CKD, however, this finding is not clinically important
Semelka, 2013[20]	
• No patients experienced mild (specifically emesis or hives), moderate or severe adverse events • All images were rated as having "good" overall enhancement adequacy (from "poor", "fair", or "good")	• Adverse events were not noted amongst the 59 patients who received gadobutrol and gadobenate dimeglumine • It is feasible to objectively evaluate adverse events and image quality

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Tanaka, 2016[21]	
• 19 patients (out of n = 223) reported at least one treatment-emergent adverse event, of which 6 were gadobutrol-related • The most common gadobutrol-related treatment-emergent adverse event was hot flush, experienced by 2 patients • No severe adverse events or deaths were reported	• Gadobutrol demonstrated good tolerability, with only 2.7% of the study population experiencing a mild adverse event
Zech, 2019[19]	
• 9 patients in each group experienced at least 1 adverse event (n = 146 received gadoxetate disodium, n = 149 received gadobenate dimeglumine) • 9 of 12 adverse events in the gadoxetate disodium group were probably related to the contrast administration • 7 of 14 adverse events in the gadobenate dimeglumine group were possibly or probably related to the contrast administration	• The safety profiles of gadoxetate disodium and gadobenate dimeglumine are similar regarding adverse events • The findings are most meaningful for daily practice in examining focal liver lesions

CCr = creatinine clearance; CKD = chronic kidney disease; CIN = contrast-induced nephropathy; eGFR = estimated glomerular filtration rate; MRI = magnetic resonance imaging

Appendix 5: Overlap between Included Systematic Reviews

Table 9: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Behzadi 2018[16]	Olchowy, 2017[17]
Prince et al, 2011	X	
Morgan et al, 2011	X	
Jung et al, 2012	X	
Davenport et al, 2013	X	
Okigawa et al, 2014	X	
Bruder et al, 2015	X	
Aran et al, 2015	X	
Power et al, 2016	X	
Granata et al, 2016	X	
Adin et al, 2015		X
Cao et al, 2016 (1)		X
Cao et al, 2016 (2)		X
Errante, 2014		X
Flood 2016		X
Hu 2016		X
Kanda 2014		X
Kanda 2015		X
Kromrey 2016		X
Quattrocchi 2015		X
Radbruch 2015 (1)		X
Radbruch 2015 (2)		X
Ramalho 2015 (1)		X
Ramalho 2015 (2)		X
Stojanov 2015		X
Tanaka 2016		X
Tedeschi 2016		X
Weberling 2015		X
Barbieri 2016		X
Roberts 2016		X
Miller 2015		X
McDonald 2015		X

Table 9: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Behzadi 2018[16]	Olchowy, 2017[17]
Kanda 2015		X
Murata 2016		X

Appendix 6: Additional References of Potential Interest

Observational Studies

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