Testimony to the FDA Medical Imaging Drugs Advisory Committee

Gadolinium Retention after Gadolinium Based Contrast MRI in Patients with Normal Renal Function

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Sammy Almashat, MD, MPH

Michael Carome, MD

Public Citizen Health Research Group

(We have no financial conflicts of interest)

European Medicines Agency (EMA) vs. FDA

EMA

There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however EMA has recommended restrictions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition.

FDA

However, because we identified no evidence to date that gadolinium retention in the brain from any of the GBCAs [gadolinium-based contrast agents], including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time.

Do linear GBCAs provide a unique clinical benefit?

- Among other questions, the EMA's PRAC asked manufacturers of GBCAs to provide the following information:

  Please specify (and provide evidence to justify) if there are groups of patients (e.g. diseases, age groups, demographics) or specific circumstances where use of your product has particular clinical advantages, relative to other products in the class.

EMA: Unique benefit for just a few linear GBCAs, for certain uses; all others banned

The intravenous linear agents gadoxetic acid [EOVIST] and gadobenic acid [MULTIHANCE] can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need. In addition, gadopentetic acid [MAGNEVIST] given intra-articularly (into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low.

All other intravenous linear products (gadodiamide [OMNISCAN], gadopentetic acid [MAGNEVIST] and gadoversetamide [OPTIMARK]) should be suspended in the EU.

EMA: Onus on companies to prove unique benefit of linear products

The suspensions or restrictions on linear agents can be lifted if the companies concerned provide evidence of new benefits in an identified patient group that outweigh the risk of brain deposition or if the companies can modify their products so they do not release gadolinium significantly or cause its retention in tissues.

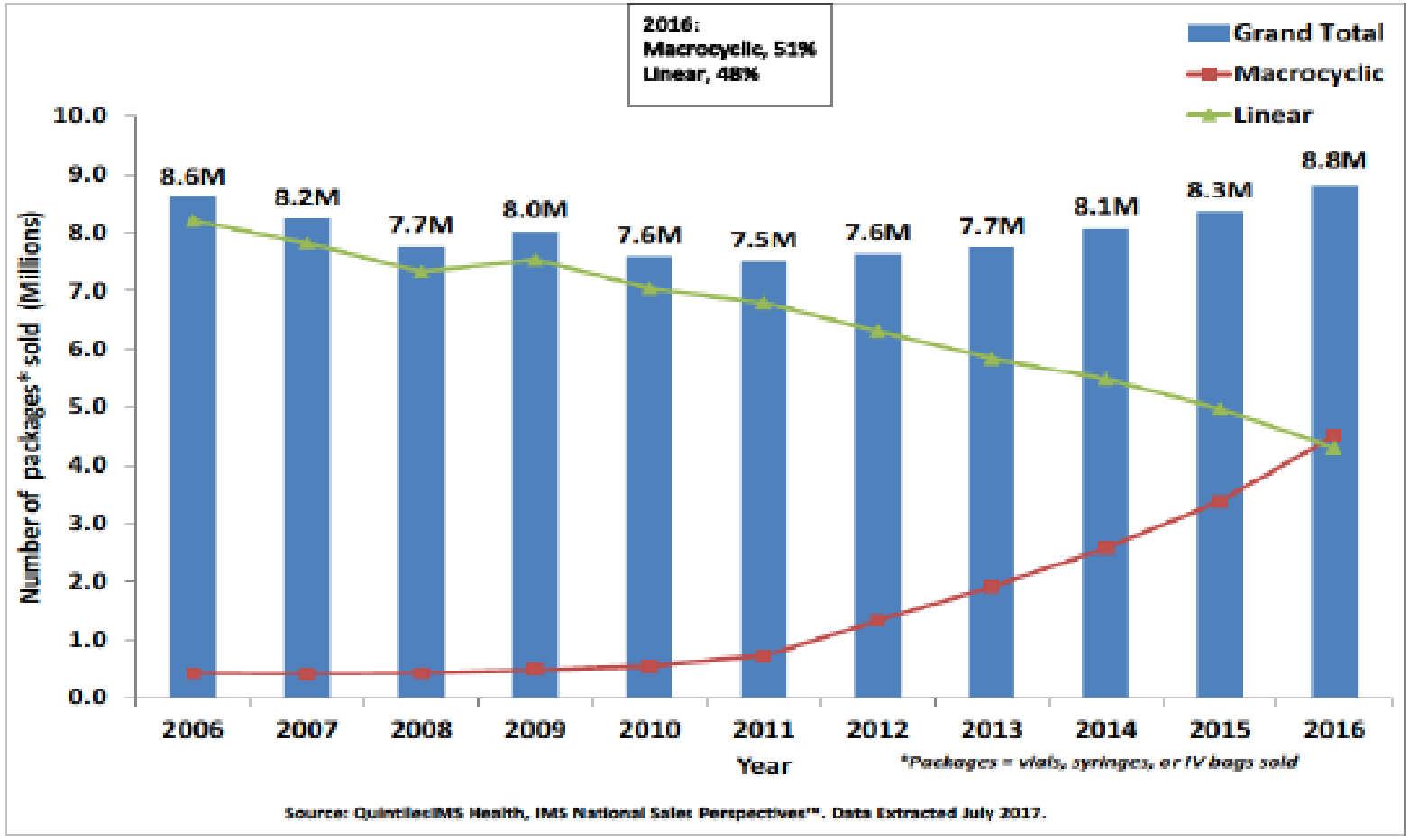
NIH Conclusion (2017)

The references summarized in this report conclude that increased signal intensity within certain regions of the brain parenchyma occurred with the use of linear (ionic and non-ionic) contrast agents and have not been conclusively reported with the use of macrocyclic contrast agents. Autopsy studies, albeit only exploratory in nature with a small number of patients, support the notion that the increased signal intensity is due to gadolinium deposition. Although further investigation is warranted, it appears prudent at this time to revisit institutional protocols for GBCA administration until additional information is obtained.

J Am Coll Radiol. 2016; 13(3): 237–241.

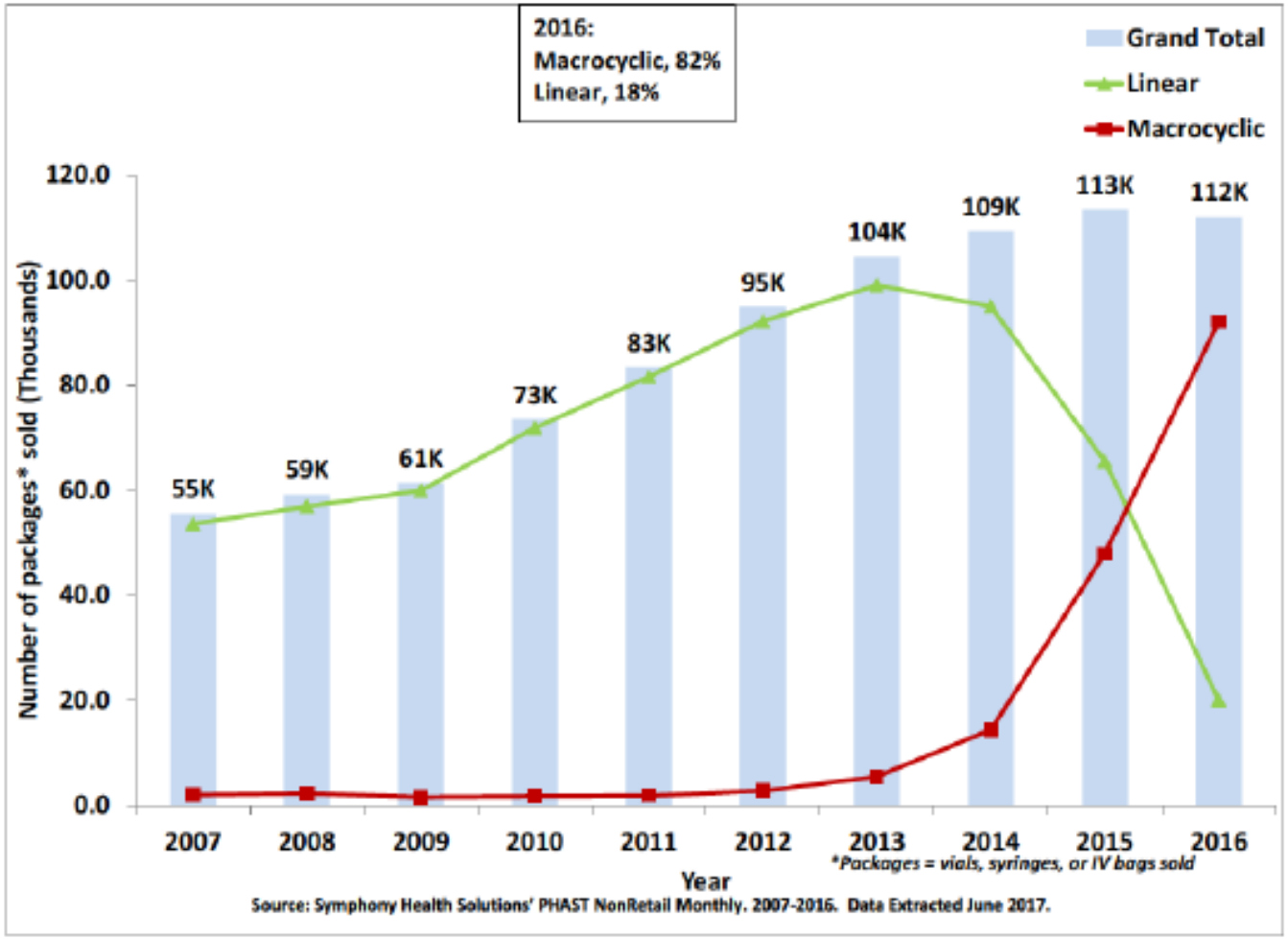
Use of linear GBCAs falling in favor of macrocyclic products

Figure 1. National estimates of sales (in packages[1] sold) by macrocyclic vs. linear gadolinium-based contrast agents (GBCAs) from US manufacturers to non-retail channels of distribution, 2006 – 2016



Use of linear GBCAs in pediatric patients dropping precipitously

Figure 4. Sales (in packages[1] sold) by macrocyclic or linear gadolinium-based contrast agents from US manufacturers and wholesalers to pediatric hospitals and clinics, 2007 – 2016*



* Sales distribution data of the volume of GBCAs sold from manufacturers to 50 pediatric specialty hospitals and 5 pediatric specialty clinics were captured in this data source

Conclusion

The FDA's proposed plan for addressing gadolinium retention in the brain is inadequate. With certain exceptions, linear GBCAs offer no clinical advantage, and only the potential for long-term harm, when compared with macrocyclic GBCAs. With the use of macrocyclic GBCAs already rising rapidly in the U.S., there is no logical reason for the FDA not to follow the lead of the EMA and protect American patients from the possibility of long-term, potentially irreversible brain damage from linear GBCAs. We strongly urge the committee to recommend that the FDA adopt the EMA's bans and restrictions on linear GBCAs, based on the precautionary principle.