Media analysis: Tysabri case study

Lisa M. Schwartz, MD, MS
Steven Woloshin, MD, MS

Rebecca English, MPH, Program officer, IOM
Ellen Kimmel, Medical librarian, IOM

The Dartmouth Institute for Health Policy and Clinical Practice,
Dartmouth Medical School, Hanover, NH

THE DARTMOUTH INSTITUTE
FOR HEALTH POLICY & CLINICAL PRACTICE
Where Knowledge Informs Change™

GEISEL SCHOOL OF MEDICINE
AT DARTMOUTH

Media coverage of Tysabri

To describe media coverage of selected milestones in the Tysabri saga --from approval through availability of improved PML risk prediction.

Compare FDA press releases and news stories on presentation of drug benefits, harms and uncertainties (stemming from accelerated approval and the risk of PML).

Media coverage

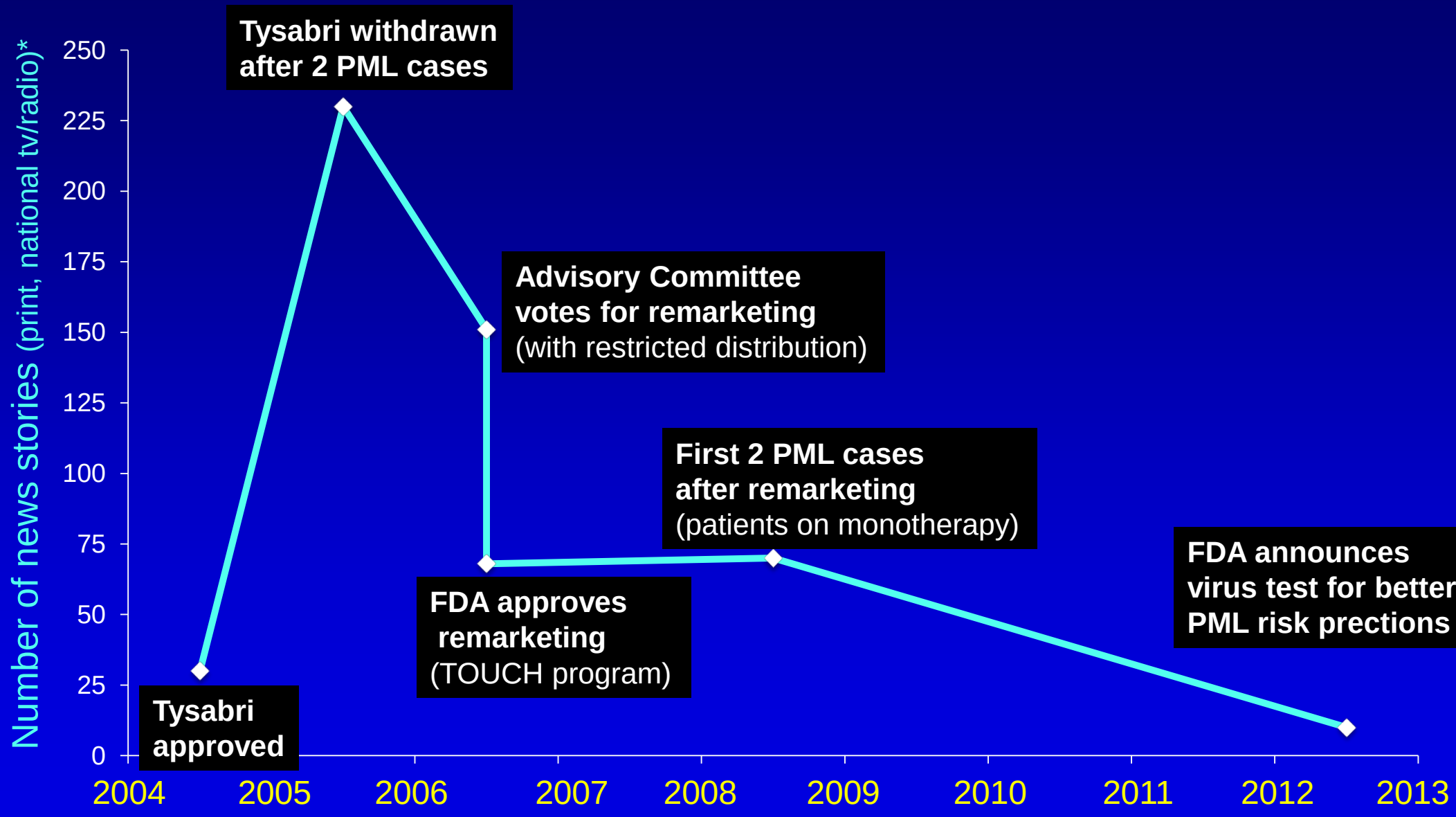
How much coverage?

Major newspapers, National radio & TV transcripts

Lexis-Nexis and Proquest searches for "Tysabri" or "natalizumab" for 2 months after 6 milestones

559 stories

News coverage of Tysabri saga



Media coverage

How much coverage?

Major newspapers, National radio & TV transcripts

Lexis-Nexis and Proquest searches for "Tysabri" or "natalizumab" for 2 months after 6 milestones (or FDA press release)

559 stories

What did the media report?

Top 20 circulation US newspapers

96 stories

Too short (<100 words)
Milestone NOT main focus
Pure business or stock news

76 stories

Structured coding scheme

Benefit: Magnitude, uncertainty

Harm: Others, PML, uncertainty

Sources quoted or mentioned

Overall impression

1. News story description

1.1 Name of news source _____

1.2 Section of paper ☐ News ☐ Business ☐ Health ☐ Op-Ed ☐ Press release ☐ Not stated

2.1 **How was benefit described?**

Anecdote (how drug helped a named patient)	☐ Yes	☐ No
Breathless language (eg. hope, miracle, breakthrough, gamechanger, etc.) for patients	☐ Yes	☐ No

2.2 Any benefit of Tysabri mentioned? ☐ Yes ☐ No

If yes, which benefit?

Less relapse	☐ Yes	☐ No
Fewer MRI brain lesions	☐ Yes	☐ No
Less disability	☐ Yes	☐ No

2.3 Tysabri's benefit on relapse rate **quantified** (anywhere)? ☐ Yes ☐ No

If quantified, how?

Chance of relapse for Tysabri and placebo groups (e.g. 25 vs 74 per 100 patients per year had relapses, 76% vs 53% relapse free)	☐ Yes	☐ No
Relative decrease in relapse rate (e.g. relapses reduced by two-thirds or 66% lower with Tysabri)	☐ Yes	☐ No

2.4 Benefit of Tysabri compared to other MS drugs ☐ Bigger ☐ Same ☐ Smaller ☐ Not stated

Uncertainty

2.5 **Was topic mentioned?**

Accelerated approval (or concept of conditional approval)?	☐=Uncertainty ☐ Fact ☐ No ☐=Extra promise
Benefit based on interim 1 year results	☐=Uncertainty ☐ Fact ☐ No

3.1 **How was harm described?**

Other Tysabri side effects (e.g. immunosuppression) mentioned	☐ Yes		☐ No
TOUCH program mentioned	☐ General	☐ Restricted dist.	☐ No
PML (or viral brain infection) mentioned explicitly	☐ Yes		☐ No

3.2 **If PML mentioned, how?**

Number of cases	☐ Yes		☐ No
Number of deaths	☐ Yes		☐ No
Called potentially deadly, life-threatening, etc disease	☐ Yes		☐ No
Patient/Family anecdote of someone with PML	☐ Yes		☐ No
PML explicitly weighed against benefit (relapse/disability)	☐ Yes		☐ No
Risk of PML with Tysabri quantified?	☐ Yes		☐ No ☐ Says unknown

3.3 **If quantified, how?**

Absolute risk of PML (e.g. 1 in 1,000)	☐ Yes	☐ No
Relative increase (e.g. increased by 300% or four fold)	☐ Yes	☐ No

3.4 Harm of Tysabri compared to other MS drugs ☐ Bigger ☐ Same ☐ Smaller ☐ Not stated

Uncertainty

3.5 **Was topic mentioned?**

Harm/Side effects based interim 1 year results	☐=Uncertainty ☐ Fact ☐ No ☐ N/A (2yr avail)
It is a new drug	☐=Uncertainty (i.e. inherent from limited experience) ☐=Extra promise ☐ Fact ☐ No
Magnitude of PML risk	☐ Unknown ☐ Fact ☐ No ☐ Known
PML risk factors (e.g. duration of use, other drugs)	☐ Uncertain ☐ Fact ☐ No ☐ Certain
FDA view of PML risk	☐ Unknown ☐ Fact ☐ No ☐ Known

4.1 **Was FDA official quoted?** ☐ Yes ☐ No ☐ "No comment"

If yes about benefit	☐ Yes	☐ No			
about PML	☐ Reassuring	☐ Mixed	☐ Alarming	☐ Facts	☐ No
portrayal of drug's net benefit	☐ Positive	☐ Mixed	☐ Negative	☐ Facts	

4.2 **Did story cite information "according to FDA"?** ☐ Yes ☐ No

If yes about benefit	☐ Yes	☐ No			
about PML	☐ Reassuring	☐ Mixed	☐ Alarming	☐ Facts	☐ No
portrayal of drug's net benefit	☐ Positive	☐ Mixed	☐ Negative	☐ Facts	

4.3 **Was company** (named/spokesman/per company) **quoted?** ☐ Yes ☐ No ☐ "No comment"

If yes about benefit	☐ Yes	☐ No			
about PML	☐ Reassuring	☐ Mixed	☐ Alarming	☐ Facts	☐ No
portrayal of drug's net benefit	☐ Positive	☐ Mixed	☐ Negative	☐ Facts	

4.4 **Was physician quoted?** ☐ Yes ☐ No

If yes about benefit	☐ Yes	☐ No			
about PML	☐ Reassuring	☐ Mixed	☐ Alarming	☐ Facts	☐ No
portrayal of drug's net benefit	☐ Positive	☐ Mixed	☐ Negative	☐ Facts	

4.5 **Was MS patient quoted?** ☐ Yes ☐ No

If yes about benefit	☐ Yes	☐ No			
about PML	☐ Reassuring	☐ Mixed	☐ Alarming	☐ Facts	☐ No

should...

- ☐ Probably be on market
- ☐ Story neutral
- ☐ Probably **not** be on market
- ☐ Definitely **not** be on market

5.2 **Given what was known about Tysabri at the time of this story, do you think this news story would have helped a person with MS decide if Tysabri would be a good treatment option for them?**

- ☐ Definitely yes
- ☐ Probably yes
- ☐ Probably no
- ☐ Definitely no

"Top 20" US print news stories

	Number of stories	Newspaper section		
		News or Health	Business	Op-Ed
Approval	5	80%	20%	0%
Withdrawal after PML	30	47%	50%	3%
Advisory committee votes for remarketing	24	63%	33%	4%
FDA approves remarketing	7	29%	57%	14%
2 PML cases after remarketing	4	0%	100%	0%
Better PML risk prediction	0			

FDA press release about Tysabri approval

"This innovative treatment for multiple sclerosis represents a new approach to treating MS -- exciting news for patients with this serious disease…..while we eagerly await long-term results from ongoing clinical trials, we have reason to believe that Tysabri will significantly reduce relapses in MS”

Enthusiasm without any reminder about uncertainty inherent with all new drugs given limited track record

"This innovative treatment for multiple sclerosis represents a new approach to treating MS -- exciting news for patients with this serious disease…..while we eagerly await long-term results from ongoing clinical trials, we have reason to believe that Tysabri will significantly reduce relapses in MS”

FDA press release Tysabri approval

"This innovative treatment for multiple sclerosis represents a new approach to treating MS -- exciting news for patients with this serious disease…..while we eagerly await long-term results from ongoing clinical trials, we have reason to believe that Tysabri will significantly reduce relapses in MS"

"The approval of Tysabri is based on positive results seen in patients after one year of treatment. This product received accelerated approval because it appears to provide substantial benefit for patients with a serious disease. As part of that approval, the manufacturer has committed to continuing its trials of this product for another year"

FDA press release about approval of Tysabri

"This innovative treatment for multiple sclerosis represents a new approach to treating MS -- exciting news for patients with this serious disease…..while we eagerly await long-term results from ongoing

No explanation that all previous MS drugs approved on 2 year results

reduce relapses in MS"

"The approval of Tysabri is based on positive results seen in patients after one year of treatment. This product received accelerated approval because it appears to provide substantial benefit for patients with a serious disease. As part of that approval, the manufacturer has committed to continuing its trials of this product for another year"

No acknowledgment that Tysabri's effect on disability progression unknown (and basis of post-marketing requirement)

FDA press release about Tysabri approval

Tysabri was evaluated for safety and efficacy in two ongoing randomized, double-blind, placebo-controlled trialsin patients with relapsing forms of MS. In the first clinical trial of the product's safety and efficacy, the drug reduced the frequency of relapses by 66 percent relative to placebo

FDA press release about Tysabri approval

Tysabri was evaluated for safety and efficacy in two ongoing randomized, double-blind, placebo-controlled trialsin patients with relapsing forms of MS. In the first clinical trial of the product's safety and efficacy, the drug reduced the frequency of relapses by 66 percent relative to placebo

Relative changes without base rate exaggerate perceived benefit

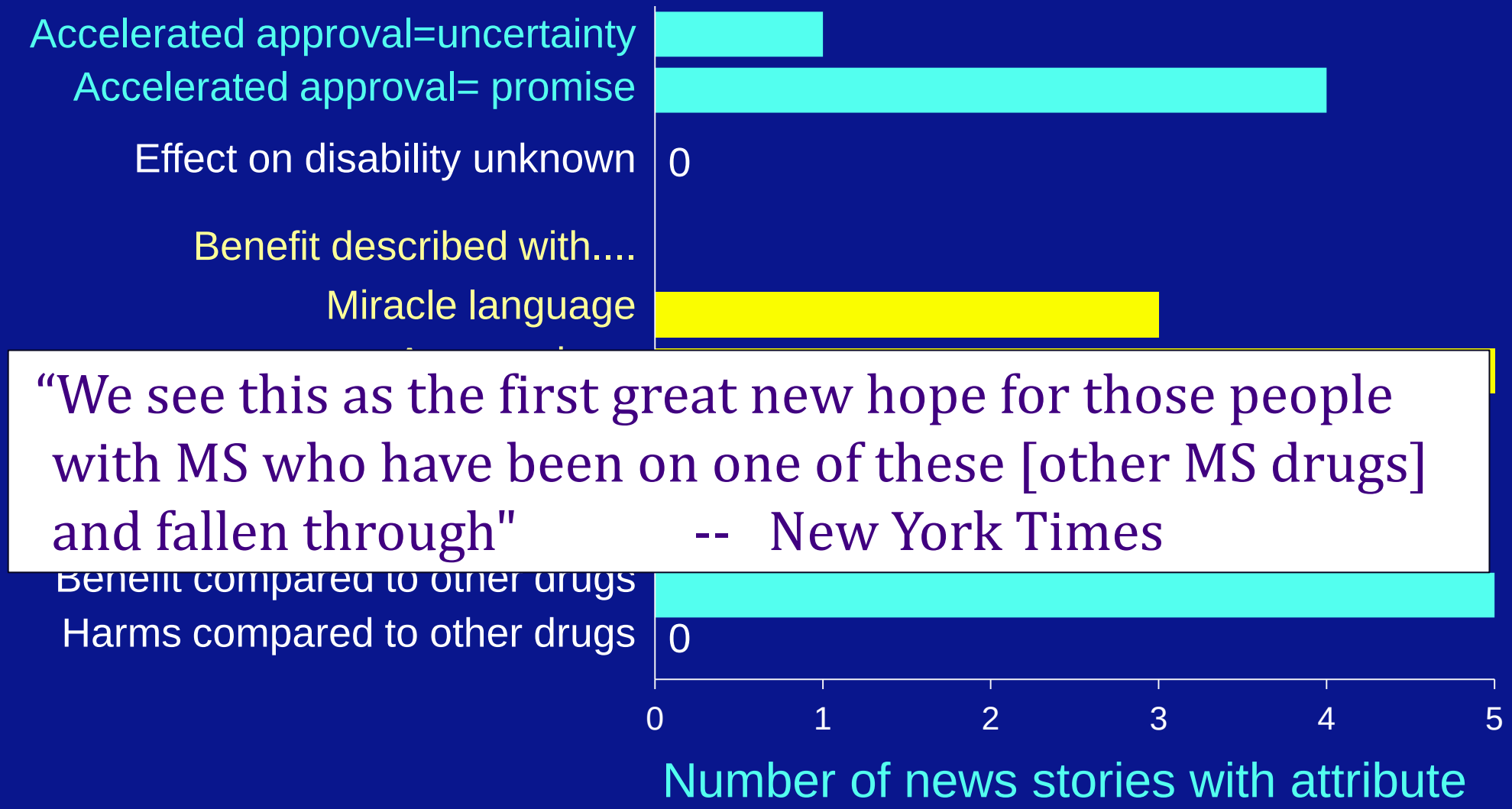
Tysabri (natalizumab) monotherapy for relapsing multiple sclerosis

Study Findings

942 people with relapsing multiple sclerosis who had at least 1 relapse in the past year were randomized to TYSABRI or PLACEBO for 2 years. Here's what happened at the end of **1 year**:

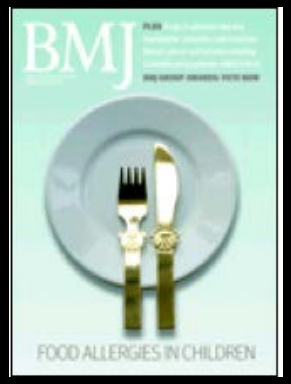
	TYSABRI (300mg IV every 4 weeks)	**PLACEBO**
How did Tysabri help?		
One-year relapse rate (4.9 fewer relapse per 100 people)	2.5 relapses per 100 people	7.4 relapses per 100 people
Percent of people with no relapses (23% more had no relapses)	76%	53%
Change in disability	Unknown	

What did the newspapers say at approval?



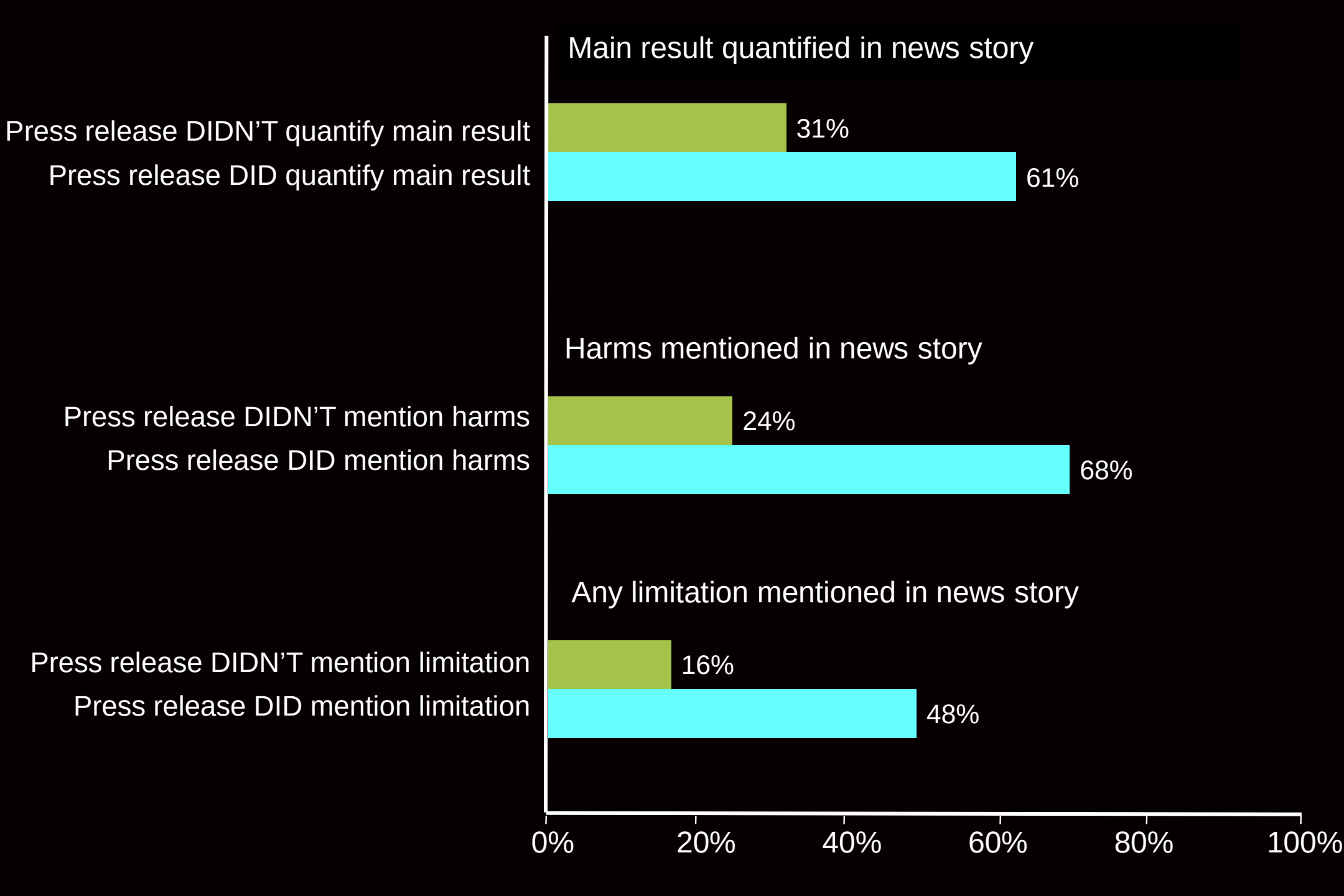
"We see this as the first great new hope for those people with MS who have been on one of these [other MS drugs] and fallen through" -- New York Times

Identify medical journal articles that generated news coverage



Medical journal press release

The news


Main result quantified in news story
Press release DIDN’T quantify main result
31%
Press release DID quantify main result
61%
Harms mentioned in news story
Press release DIDN’T mention harms
24%
Press release DID mention harms
68%
Any limitation mentioned in news story
Press release DIDN’T mention limitation
16%
Press release DID mention limitation
48%
0%
20%
40%
60%
80%
100%

FDA press release about Tysabri withdrawal

During the review of Tysabri for marketing approval, FDA conducted an intensive analysis of possible adverse events that might be related to effects of the drug on the immune system. No cases of PML were seen in the clinical trials. However, for any approved therapy, new and unexpected adverse events may occur that were not seen in clinical trials.

FDA press release about Tysabri withdrawal

During the review of Tysabri for marketing approval, FDA conducted an intensive analysis of possible adverse events that might be related to effects of the drug on the immune system. No cases of PML were seen in the clinical trials.

However, for any approved therapy, new and unexpected adverse events may occur that were not seen in clinical trials.

Great new warning! Probably more effective at approval than when the new, unexpected harm – like PML - happens.

The PML story

	PML Facts		PML News Coverage			
	Risk	Risk Factors	Cases	RIsk	Risk factors	"TOUCH"
Withdrawal after PML	???	???	100%	---	57%	---
Advisory committee votes for remarketing	Quantified	??	96%	38%	21%	67%
FDA approves remarketing	Quantified	?	57%	29%	14%	71%
2 PML cases after remarketing	Quantied	??	75%	50%	14%	71%

Limitations

We have not formally assessed reliability of codi… t time frame for project.

Caution! Preliminary results

Dat… to major newspapers

…ano (i.e., likely to be highest quality coverage)

Findings need to be interpreted with caution because some milestone events generated limited high-profile news coverage

Extending analysis to all news coverage will increase sample size

Take-home messages

Media lost interest when became story of reduced uncertainty *More coverage of events like virus test for better risk prediction would help doctors and patients understand safer use of drug.*

Accelerated approval interpreted as "extra promise" not "extra uncertainty" *Explicit acknowledgment – and explanation – of the reasons for conditional approval at the beginning could balance perceptions.*

Coverage reflects general problems with media *Overly enthusiastic early on about benefit (anecdote miracle language, exaggerates statistics) and too quite about harm or uncertainty.*

FDA could help by being more proactive *Better press releases could help journalists do a better job by quantifying benefits and harms with absolute numbers and highlighting uncertainties about all new drugs.*