Presenting information for effective communication

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Making informed consent more effective

Strategies

- Mandated “key information” section
- Explaining the study and randomization
- Anticipate misconceptions
- Presentation of side effects

Challenges

- FDA "breakthrough" designation for promising drugs
- Cancer center advertising

Key information

Widely recognized that informed consent forms are too long, hard to read or understand.

Many calls – and some randomized trial evidence - for how to get to better forms.

- Health literacy principles (e. g., reading level, simplified text) improve comprehension; shorter forms - comprehension and trust not worse
- Limitations: largely hypothetical experiments, hard to compare strategies (heterogeneous populations and outcome measures)

DHHS mandates key information at start of consent form

- To help people understand why they might or might not want to participate in the research
- Now part of the NCI informed consent template

Why is this study being done?

What is the science behind this study?

The new idea is to start chemotherapy at the same time as hormone-blocking instead of just when the cancer progresses.

Why it might help? A small trial found that starting chemotherapy with hormone-blocking slowed down the time until progression (PSA increased), yet did not prolong life.

Why it might not help? Some researchers worry that starting them both together may make chemotherapy less effective.

The purpose of this study is to see if starting a chemotherapy (a different drug - docetaxel) at the same time as hormone-blocking helps men live longer than starting hormone-blocking alone. Docetaxel has been proven to prolong life when given at the time of progression.

Bottom line: **No one knows the answer – that's why the trial is being done**

What are the tradeoffs for you?

Why would you <u>not</u> want to be in the study?

If you or your doctor has a strong feeling about starting chemotherapy now or later, you might not want to take part. Your doctor can start hormone blocking with chemotherapy now or later even if you are not in the study.

Other reasons for not taking part are:

- Having important life events in the next 6 months and you don't want to be tired from chemotherapy
- Being much older or have other serious medical problems and are more concerned with quality of life right now

What are the tradeoffs for you?

Why would you want to be in the study?

Starting hormone blocking alone means it's likely that your cancer will progress over the next few years at which point you will need chemotherapy. The time until progression depends on how much the cancer has already spread: usually about 1 year with a lot of spread and 2-3 years with less spread.

Docetaxel chemotherapy has side effects including some very bothersome or even life-threatening. It's also inconvenient: travel time, tests, and the infusion every 3 weeks.

Starting hormone-blocking and chemotherapy means giving up some quality time now – about 5-6 months for chemotherapy and recovery.

If starting chemotherapy right away helps, it may be worth it: the cancer would take longer to progress and you would live longer. But it might not help – or make quality of life worse because of rare long-lasting side effects.

If you and your doctor would be okay with either treatment, you might want to be in the trial.

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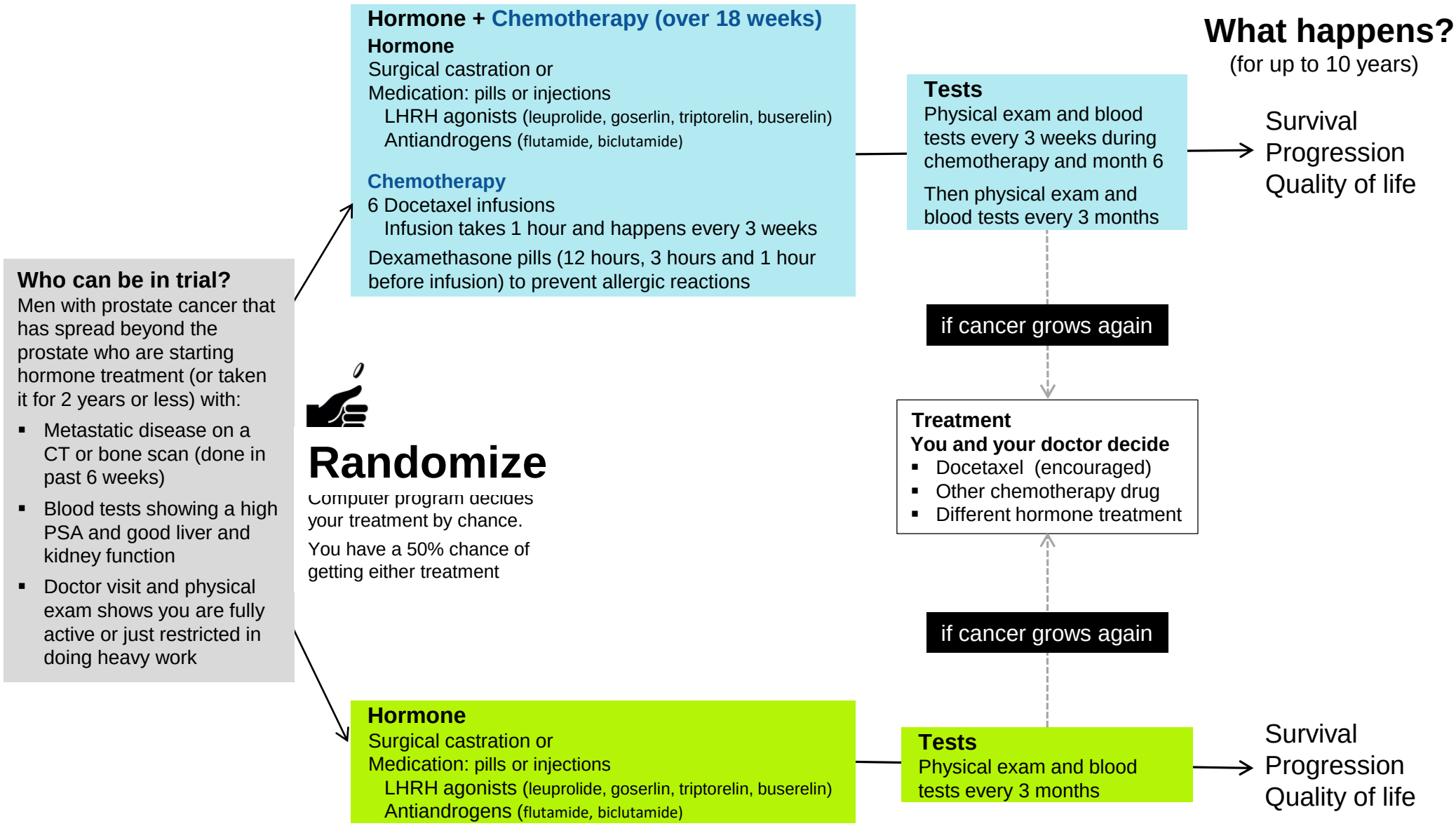

Hormone + Chemotherapy (over 18 weeks)
Hormone
Surgical castration or
Medication: pills or injections
LHRH agonists (leuprolide, goserlin, triptorelin, buserelin)
Antiandrogens (flutamide, biclutamide)
Chemotherapy
6 Docetaxel infusions
Infusion takes 1 hour and happens every 3 weeks
Dexamethasone pills (12 hours, 3 hours and 1 hour before infusion) to prevent allergic reactions
What happens?
(for up to 10 years)
Tests
Physical exam and blood tests every 3 weeks during chemotherapy and month 6
Then physical exam and blood tests every 3 months
Survival
Progression
Quality of life
if cancer grows again
Treatment
You and your doctor decide
Docetaxel (encouraged)
Other chemotherapy drug
Different hormone treatment
if cancer grows again
Who can be in trial?
Men with prostate cancer that has spread beyond the prostate who are starting hormone treatment (or taken it for 2 years or less) with:
Metastatic disease on a CT or bone scan (done in past 6 weeks)
Blood tests showing a high PSA and good liver and kidney function
Doctor visit and physical exam shows you are fully active or just restricted in doing heavy work
Randomize
Computer program decides your treatment by chance.
You have a 50% chance of getting either treatment
Hormone
Surgical castration or
Medication: pills or injections
LHRH agonists (leuprolide, goserlin, triptorelin, buserelin)
Antiandrogens (flutamide, biclutamide)
Tests
Physical exam and blood tests every 3 months
Survival
Progression
Quality of life

Randomization explanation

500 cancer patients
who had not been in a trial

Control

Cancer patients are offered the opportunity to receive treatment as part of a randomized clinical study.

In a randomized cancer clinical study, patients are put into groups and each group is given a different treatment plan. This helps doctors find out if one treatment plan is better than another. In order to make sure the clinical study is fair, doctors cannot choose which group the patient joins. Patients are assigned (or randomized) to their group by chance (not doctor or patient choice).

Randomization explanation

500 cancer patients
who had not been in a trial

It is helpful for some patients to think about randomization as being like the flip of a coin. Just as

It is helpful for some patients to think about randomization as being like the sex of a baby. Just as a pregnant woman has an equal chance of giving birth to a male or female baby, a patient has an equal chance of being in any of the groups being compared in the clinical study.

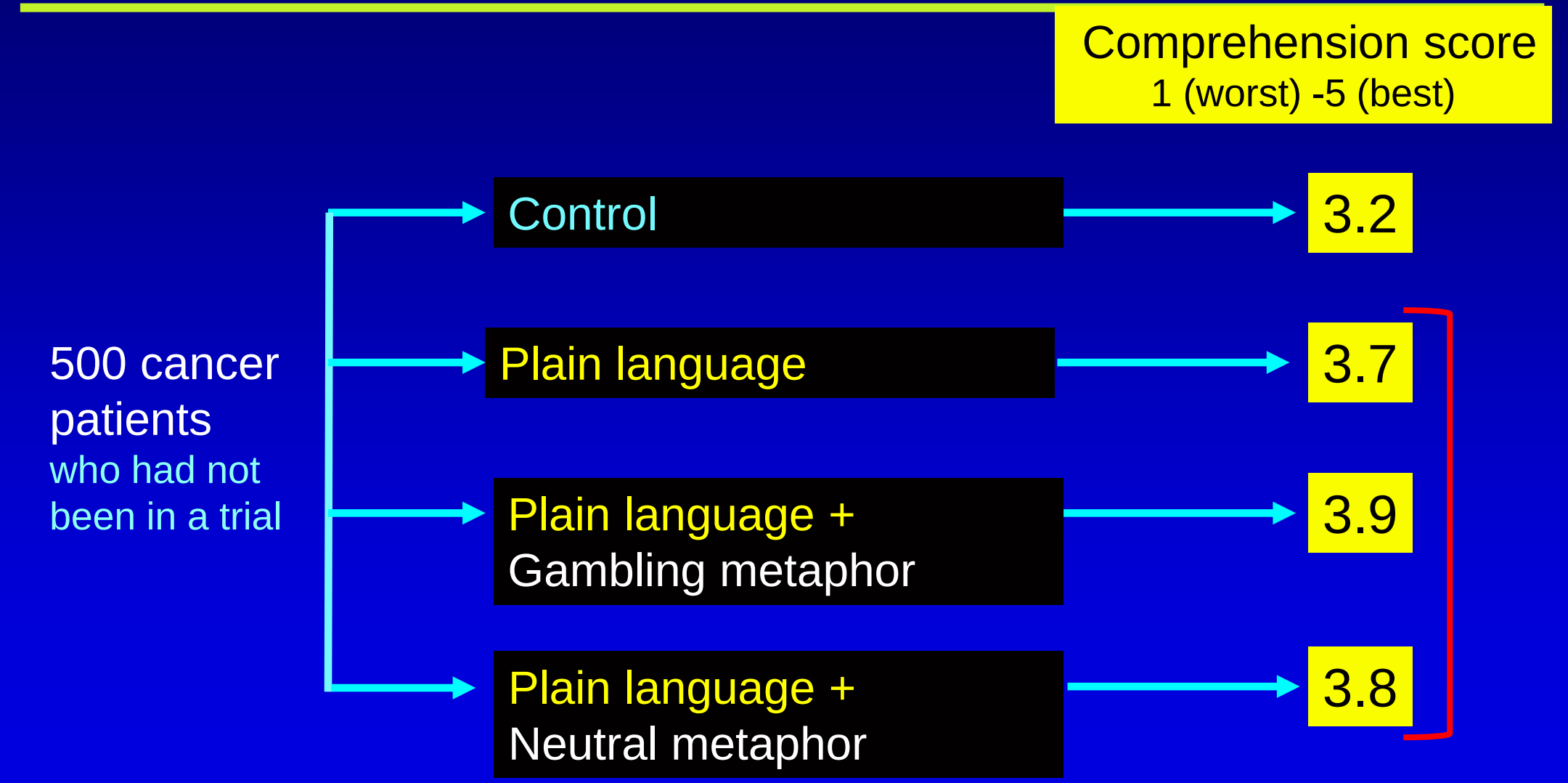
Plain language +
Neutral metaphor

Krieger, et. al, J Natl Cancer Inst 2017

Best understood

Lowest health literacy: Neutral metaphor

Highest health literacy: Gambling metaphor



Krieger, et. al, J Natl Cancer Inst 2017

Suggestions for effective information

Key information should include:

What is the science behind the study Mention prior work that justifies study, acknowledge concerns, and highlight answer is unknown.

What are the tradeoffs for you?

Summarize reasons a patient might want – or not want - to participate

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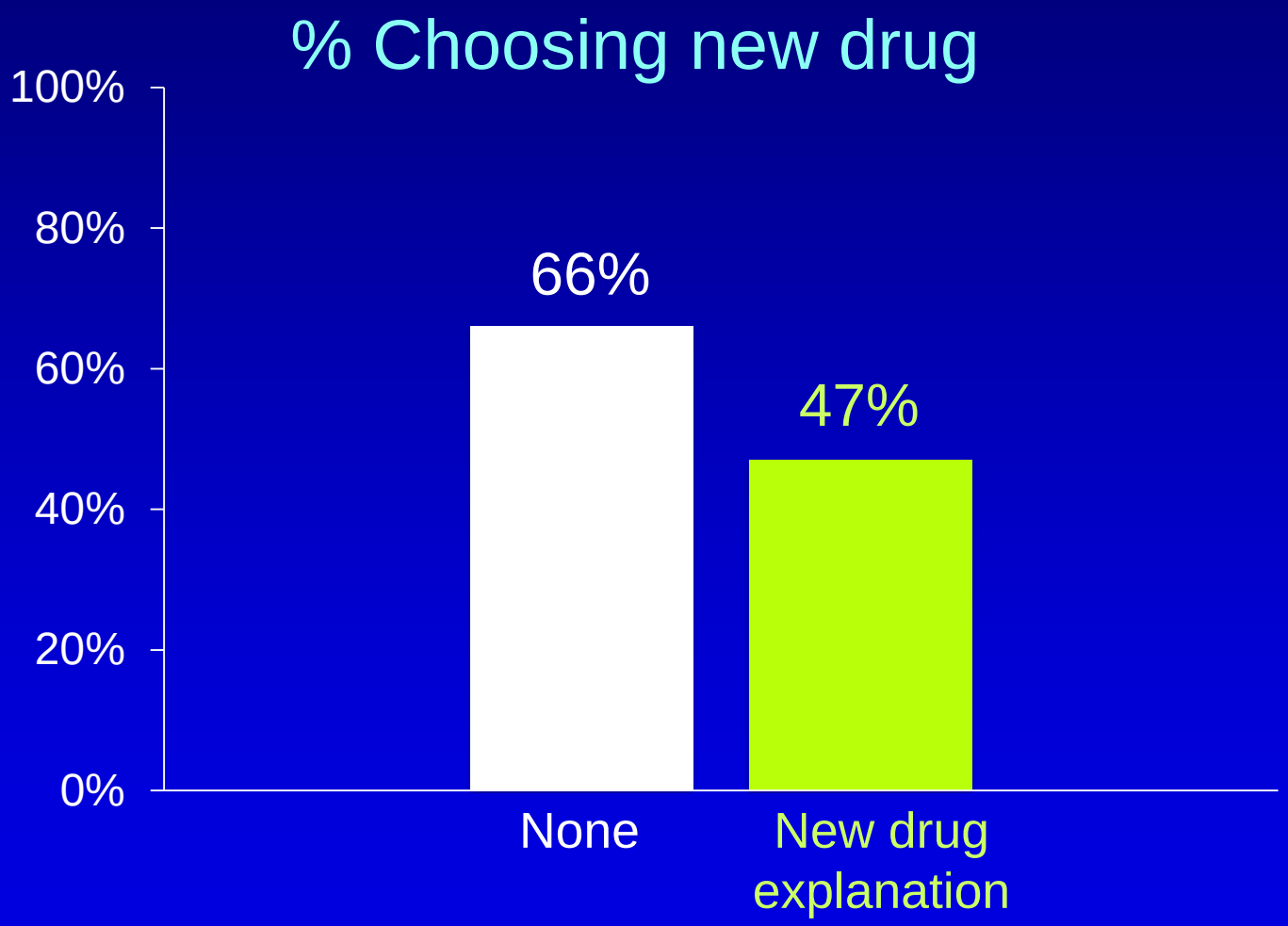
New = better misconception

Many (~40%) U.S. adults mistakenly believe the FDA only approves “extremely effective” drugs and one-quarter mistakenly believe only drugs without serious side effects are approved.

Schwartz, Woloshin, Arch Intern Med 2011
Donoghue, et. al, J Health Comm 2016

Drug approval means FDA believes benefit outweighs harm for this indication - NOT that benefits are important or drug is very safe.

PAXCID was approved by the FDA in 2009. As with all new drugs, rare but serious drug side effects may emerge after the drug is on the market – when larger numbers of people have used the drug.



Schwartz, Woloshin ,Arch Intern Med, 2011

Address misconception with track record

What is the treatment's track record?

FDA-approved drug

- When was it approved?
- Is it approved for this indication? If so, when?
- Mention if accelerated approval

Drug in development

- How many people have taken it – and for how long?

experience is particularly limited.

Suggestions for effective information

Key information should include:

What is the science behind the study Mention prior work that justifies study, acknowledge concerns, and highlight answer is unknown.

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More efficient use of study design figure to explain:

What will happen? Include eligibility criteria, randomization (consider metaphors), burden of testing and treatment and outcome measures.

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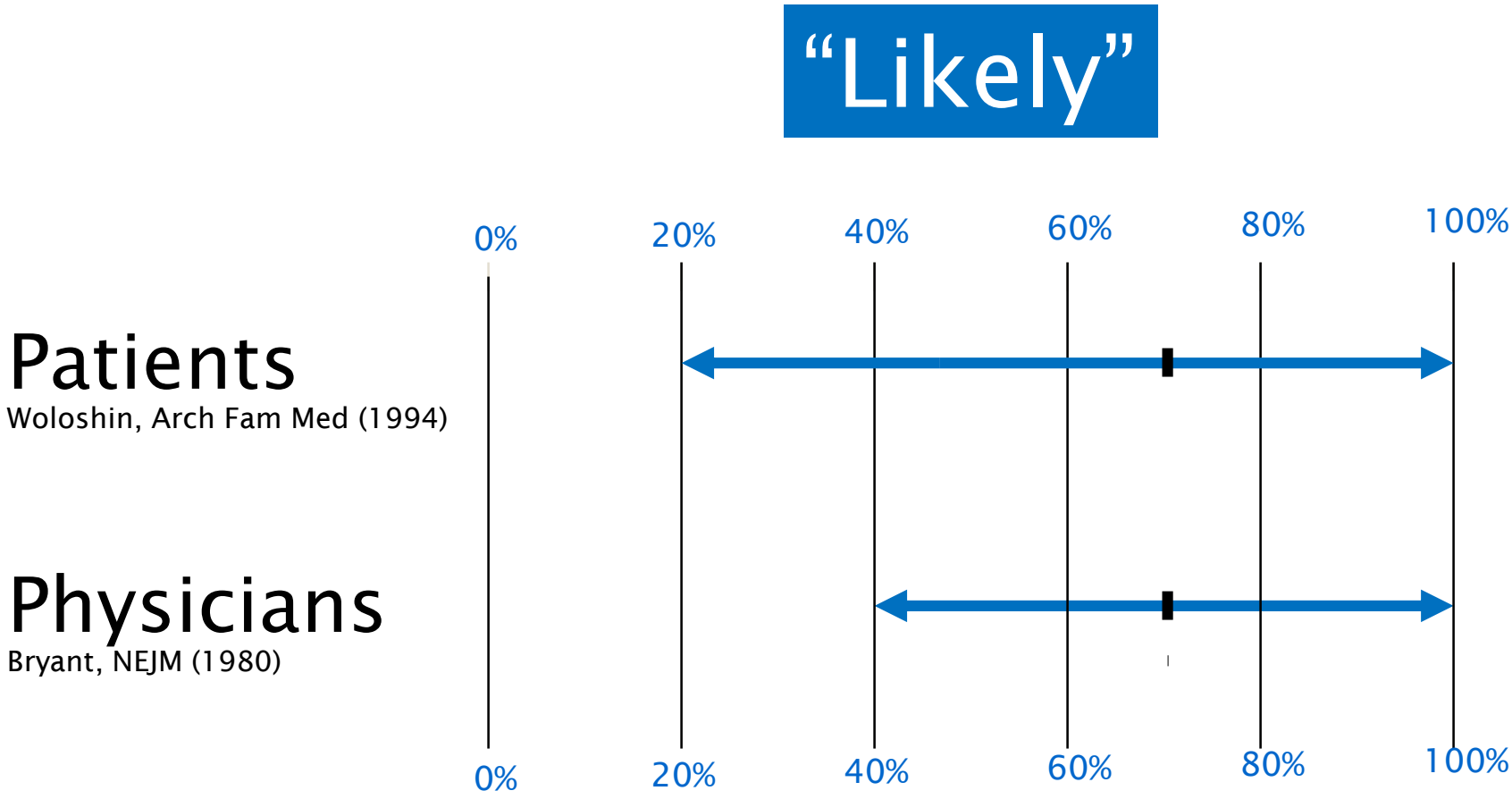
Likely

- Nausea, vomiting or diarrhea
- Lowered white blood cell count (may make you more likely to get an infection)
- Lowered platelets (may make you more likely to bruise or bleed)
- Lowered red blood cell count (may make you feel tired or weak)
- Numbness and pain of the hands and feet
- Hair loss
- Muscle weakness/muscle and joint aches
- Mild to severe allergic reaction at the time the infusion is given
- Nail changes - drying and lines
- Fluid in arms and/or legs
- Changes in liver enzymes
- Fever
- Skin rash or dry skin
- Loss of appetite
- Taste changes
- Fatigue (feeling tired)

Less Likely

- Shortness of breath
- Sores in the mouth or throat
- Itching
- Headaches
- Fluid around the heart or the lungs
- Changes in kidney function tests which may lead to stopping docetaxel
- Low blood pressure
- Irregular heart beat (arrhythmias) or heart failure
- Skin irritation, redness, heat, swelling and pain at the site of injection of the medication
- Redness or irritation of the skin at a prior site of radiation therapy

Variable interpretation of words



Likely

3%

67%

- Nausea, vomiting or diarrhea
- Lowered white blood cell count (may make you more likely to get an infection)
- Lowered platelets (may make you more likely to bruise or bleed)
- Lowered red blood cell count (may make you feel tired or weak)
- Numbness and pain of the hands and feet
- Hair loss
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- Nail changes - drying and lines
- Fluid in arms and/or legs
- Changes in liver enzymes
- Fever

NCI Consent Form Template

Common 21% - 100%
Occasional 4% - 20%
Rare ≤ 3%

- Low blood pressure
- Irregular heart beat (arrhythmias) or heart failure
- Skin irritation, redness, heat, swelling and pain at the site of injection of the medication
- Redness or irritation of the skin at a prior site of radiation therapy

Annals of Internal Medicine | ORIGINAL RESEARCH

Communicating Data About the Benefits and Harms of Treatment

A Randomized Trial

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

ELSEVIER

CrossMark

Replication

Journal of Clinical Epidemiology

Journal of Clinical Epidemiology 74 (2016) 7–18

GRADE SERIES

Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format

Docetaxel (Taxotere)

Likely

- Nausea, vomiting or diarrhea
- Lowered white blood cell count (may make you more likely to get an infection)
- Lowered platelets (may make you more likely to bruise or bleed)
- Lowered red blood cell count (may make you feel tired or weak)
- Numbness and pain of the hands and feet
- Hair loss

It's more than just frequency

Sort by frequency and seriousness

- Fatigue (feeling tired)

Less Likely

- Shortness of breath
- Sores in the mouth or throat
- Itching
- Headaches
- Fluid around the heart or the lungs
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Equally bad?

Most dangerous side effects	**Life-threatening allergic reaction during infusion** (especially with first or second infusion)	Uncertain how often	
	Liver damage or failure (higher chance if you have liver problems already)		
	Severe fluid retention in legs or around lungs or heart		
Serious side effects		Any	Severe
Common	**Low red blood cell count (anemia)** (makes you more likely to feel tired or weak)	67%	5%
	Low white blood cell count (neutropenia) (makes you more likely to get infection)	41%	32%
	Nerve problems including numbness, tingling or burning in hands or feet	30%	2%
Less common	**Low platelets** (makes you more likely to bruise or bleed)	3%	1%
Rare	**Severe skin reactions including redness and swelling of arms and legs with peeling of skin**	Uncertain how often	
	Blurred vision or loss of vision		
Symptom side effects			
Common	**Hair loss**	65%	-
	Fatigue (feeling tired)	53%	5%
	Nausea or vomiting	41%	3%
	Diarrhea	32%	2%
	Nail changes – drying and lines	30%	0%
	Swelling of hands, face or feet	24%	8%
Less common	**Mouth or lip sores**	20%	1%
	Taste changes	18%	0%
	Loss of appetite	17%	1%
	Shortness of breath	15%	3%
	Muscle or joint pain	15%	0%
	Excess tearing or eye redness	10%	1%
	Rash	6%	0%

NCI Cancer Therapy Evaluation Program Informed Consent

Lay language for side effects

HIGHLIGHTS OF PRESCRIBING INFORMATION

Boxed Warning

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, AND FLUID RETENTION

See full prescribing information for complete boxed warning

- **Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m^2 (5.1)**
- **Should not be given if bilirubin > ULN, or if AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. LFT elevations increase risk of severe or life-threatening complications. Obtain LFTs before each treatment cyc (8.6)**
- **Should not be given if neutrophil counts are < 1500 cells/mm^3. Obt frequent blood counts to monitor for neutropenia (4)**
- **Severe hypersensitivity, including very rare fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of Docetaxel Injection and administration of appropriate therapy (5.4)**
- **Contraindicated if history of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80 (4)**
- **Severe fluid retention may occur despite dexamethasone (5.5)**

Docetax

- **B** ...tic BC af ...namide as
- **N** ... with ... NSCLC (1.2)
- **Hormone Refractory Prostate Cancer (HRPC):** with prednisone in androgen independent (hormone refractory) metastatic prostate cancer (1.3)
- **Gastric Adenocarcinoma (GC):** with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (1.4)
- **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN):** with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (1.5)

Most dangerous side effects

DOSAGE AND ADMINISTRATION

Administer in a facility equipped to manage possible complications (e.g., anaphylaxis). Administer intravenously (IV) over 1 hr every 3 weeks. PVC equipment is not recommended. **Use only a 21 gauge needle to withdraw Docetaxel Injection from the vial.**

- BC locally advanced or metastatic: 60 mg/m^2 to 100 mg/m^2 single agent (2.1)
- BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (2.1)
- SCCHN: 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles (2.5)
- SCCHN: 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1-4); for 3 cycles (2.5)

For all patients:

- Premedicate with oral corticosteroids (2.6)
- Adjust dose as needed (2.7)

DOSAGE FORMS AND STRENGTHS

- 20 mg/2 mL single use vial (3)
- 80 mg/8 mL multi-use vial (3)
- 160 mg/16 mL multi-use vial (3)

Warnings and Precautions

WARNINGS AND PRECAUTIONS

- Acute myeloid leukemia: In patients who received docetaxel doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia (5.6)
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment (5.7)
- Neurologic reactions: Reactions including paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent (5.8)
- Eye disorders: Cystoid macular edema (CME) has been reported and requires treatment discontinuation (5.9)
- Asthenia: Severe asthenia may occur and may require treatment discontinuation (5.10)
- Pregnancy: Fetal harm can occur when administered to a pregnant ...

Adverse reactions

Serious side effects

thrombocytopenia, neuropathy, dysgeusia, dysphea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia (6)

Symptom side effects

DRUG INTERACTIONS

- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter ...

A consistent, structured format

Lunesta

What this drug is for:
To make it easier to fall or to stay asleep

Who might consider taking it:
Adults age 18 and older with insomnia for at least 1 month

Recommended monitoring:
No blood tests, watch out for abnormal behavior

Other things to consider:
Reduce caffeine intake (especially at night), increase exercise, establish a regular bedtime, avoid daytime naps

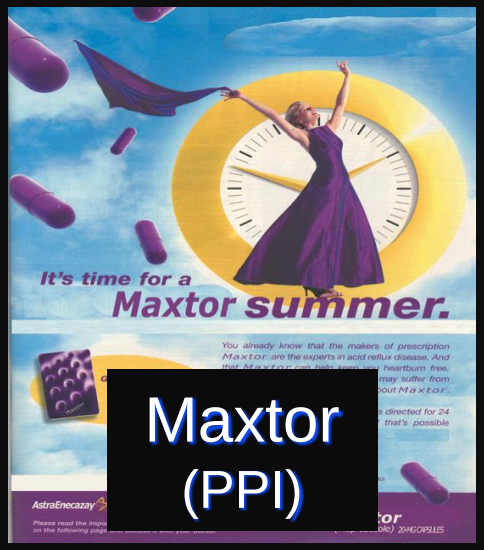
How long has the drug been in use?
Lunesta was approved by FDA in 2005. As with all new drugs we simply don't know how its safety record will hold up over time. In general, if there are unforeseen, serious drug side effects, they emerge after the drug is on the market (when a large enough number of people have used the drug).

Lunesta Study Findings

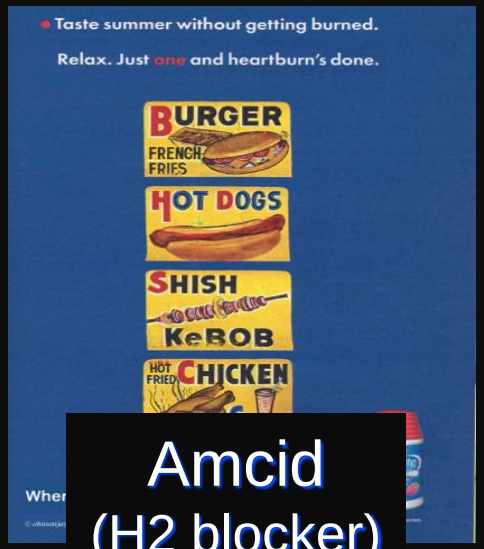
788 healthy adults with insomnia for at least 1 month – sleeping less than 6.5 hours per night and/or taking more than 30 minutes to fall asleep – were given LUNESTA or a sugar pill nightly for 6 months. Here's what happened:

What difference did LUNESTA make?	People given a sugar pill	People given LUNESTA (3 mg each night)
Did Lunesta help?		
LUNESTA users fell asleep faster (15 minutes faster due to drug)	45 minutes to fall asleep	30 minutes to fall asleep
LUNESTA users slept longer (37 minutes longer due to drug)	5 hours 45 minutes	6 hours 22 minutes
Did Lunesta have side effects?		
Life threatening side effects:		
No difference between LUNESTA and a sugar pill	None observed	None observed
Symptom side effects:		
More had unpleasant taste in their mouth (additional 20% due to drug)	6%	26%
More had dizziness (additional 7% due to drug)	3%	10%
More had drowsiness (additional 6% due to drug)	3%	9%
More had dry mouth (additional 5% due to drug)	2%	7%
More had nausea (additional 5% due to drug)	6%	11%

Drug Box: National Randomized Trial



Maxtor
(PPI)



Amcid
(H2 blocker)

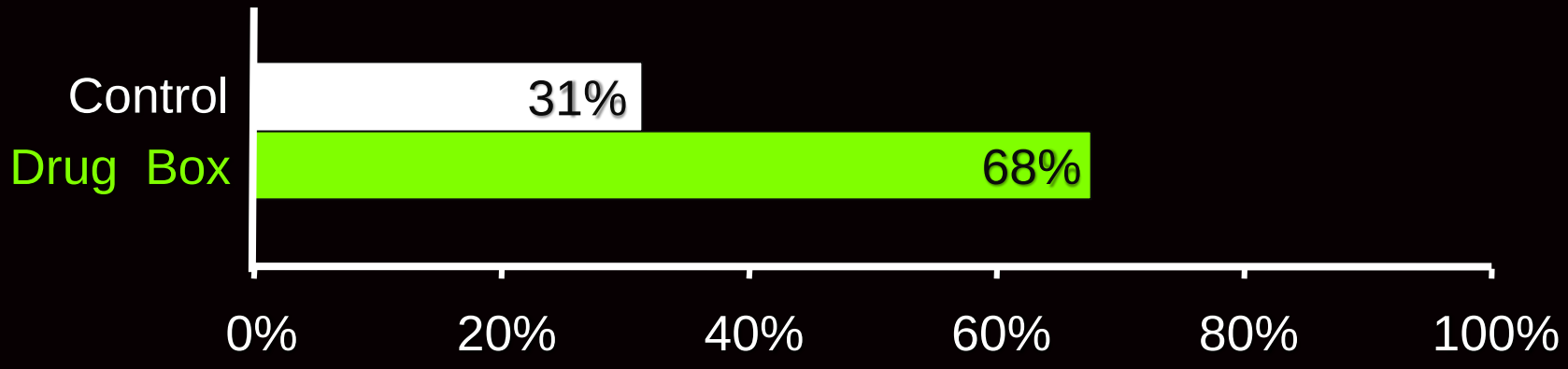
Study Features (n=231)

Real world challenge: Show people ads for 2 drugs treating the same condition.

The drugs have similar side effects but one is substantially more effective.

Can people choose the objectively *better* drug?

If you could take either drug for free, which drug would you rather take?



% correctly choosing the better drug

Ann Intern Med 2009

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Reprioritize side effects to better answer

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FDA "breakthrough drug" designation

Colloquial meaning: important, definitive advance

FDA meaning: potentially promising during early research

"Treats a serious or life threatening condition…may demonstrate a substantial improvement…over available therapies"

Based only on preliminary evidence (e.g. uncontrolled studies, surrogate outcomes)

Breakthrough breakthrough: Words matter

Online survey on 597 U.S. adults (Amazon's mechanical Turk)

If you had a potentially deadly medical condition and could choose between 2 drugs recently approved by FDA, which would you choose?

92% ☑ Axabex, called a "breakthrough" drug by FDA

8% ☑ Hypapax, a drug that has shown some early promise in trials but which has not been shown to improve survival or disease related symptoms.

Krishnamurti, Woloshin, Schwartz, Fischhoff, JAMA Intern Med, 2015

Undermine informed consent to participate in research?

The Washington Post
Democracy Dies in Darkness

Health & Science

Ecstasy could be 'breakthrough'

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies

Home > Search Results > Study Record Detail

Open Label Multi-Site Study of Safety and Effects of MDMA-assisted Psychotherapy for Treatment of PTSD

ClinicalTrials.gov Identifier: NCT03282123

Status: RECRUITING

Some are miracles, but….

"…no evidence that these drugs provide improvements in safety or novelty; nor was there a statistically significant efficacy advantage when compared with non-breakthrough-designated drugs".

Hwang, J Clin Oncol, 2018

Cancer center advertising

Promoting trials for treatment

Cancer center advertising
Promoting trials for treatment

Misleading marketing tactics

Patient testimonials about successful treatment emphasize anecdote over evidence.

Implies patients in trials get access to great treatments since every great new treatment was first offered in a trial.

Mention benefits but not harms

Most new drugs not better than standard care – some are more toxic: FDA approves ≤ 10% of new drug in early trials

London, Kimmelman.JAMA Oncol 2018

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Limit generation of unrealistic expectations that undermine consent

Rename FDA breakthrough designation (e.g. potentially promising)

Enforce regulation of cancer center trial advertising