Communicating uncertainty about benefits and harms of pharmaceutical products

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Tysabri

Unique risk communication challenges

Promising new drug quickly withdrawn after 2 cases of an unexpected, often fatal harm: PML

Reintroduced after risk factors for PML identified

But then new cases of PML seen in low risk group

Common uncertainties at drug approval

Standard uncertainty All new drugs

Extra uncertainty Preliminary evidence of benefit only

Extra uncertainty Worrisome harm signal ➔post-marketing study

Standard uncertainty All new drugs

Short track record at time of approval

- Studies relatively short – median duration 14 weeks long
- Limited number of patients – median number ~ 450 patients
- Studies

New = More uncertainty

Consequences

- Unknown how benefits or safety will hold up over time
- Unforeseen, serious side effects often emerge after large numbers of people have used the drug.

Downing, teal, JAMA, 2013

misconception

Standard ~~uncertainty~~ All new drugs

New = Better

The first and only NON-ESTROGEN ORAL treatment for moderate to severe dyspareunia, due to menopause

- REVERSES key physiological signs of vulvar and vaginal atrophy (VVA), which include increasing superficial cells, decreasing parabasal cells, and decreasing vaginal pH
- Significantly IMPROVED the most bothersome symptom (MBS)* of VVA, which was moderate to severe dyspareunia
- Available in a 60-mg ORAL tablet taken once daily with food
- Most common adverse reactions include hot flush, vaginal discharge, muscle spasms, hyperhidrosis, and genital discharge

FIRST AND ONLY

The FIRST FDA-approved estrogen agonist/antagonist for moderate to severe dyspareunia, due to menopause.

BIG NEWS!

RAISE YOUR TESTOSTERONE WITH LESS GEL

Talk to your doctor today about AndroGel 1.62% so you can use less gel compared to AndroGel 1%. You could pay as little as $10 a month. Visit AndroGelOffer.com or call 1-855-AGEL-162.

AndroGel® (testosterone gel) 1.62% CIII

1.62%

LESS GEL*

Pay as little as $10

AndroGel® (testosterone gel) 1.62% CIII


AXIRON
A different application method
Th first and only estosterone thera
ap rarm


Samsca (tolvaptan) tablets
PROMOTING FREE WATER CLEARANCE
First-in-class r the treatment of clinically important,
-hypovolemic hyponatremia
The first and only oral selective vasopressin V2-receptor antagonist


NOW AVAILABLE
A NEW estosterone
replacement gel for low-T


Introducing
TUDORZA™ GENUAIR™
A new LAMA in COPD[1]*
Imagine the possibilities
TUDORZA GENUAIR demonstrated a statistically significant improvement
in lung function (morning pre-dose [trough] FEV1) at 24 weeks vs. placebo
(TUDORZA 400 mcg BID, 55 mL vs. placebo, -73 mL, p<0.0001)[21]


NEW
FORTESTA™
(testosterone) Gel

New=better misconception is common

National survey of US adults

Many (~ 40%) mistakenly believe FDA only approves—and only permits advertising of—extremely effective drugs or drugs without serious side effects.

Drug approval means FDA believes benefit outweighs harm.

It does NOT mean benefits are large or important, or drug is very safe or even that all serious side effects are known.

Schwartz, Woolskin, JAMA Int Med 2011

Europe's "Black Triangle" for new drugs

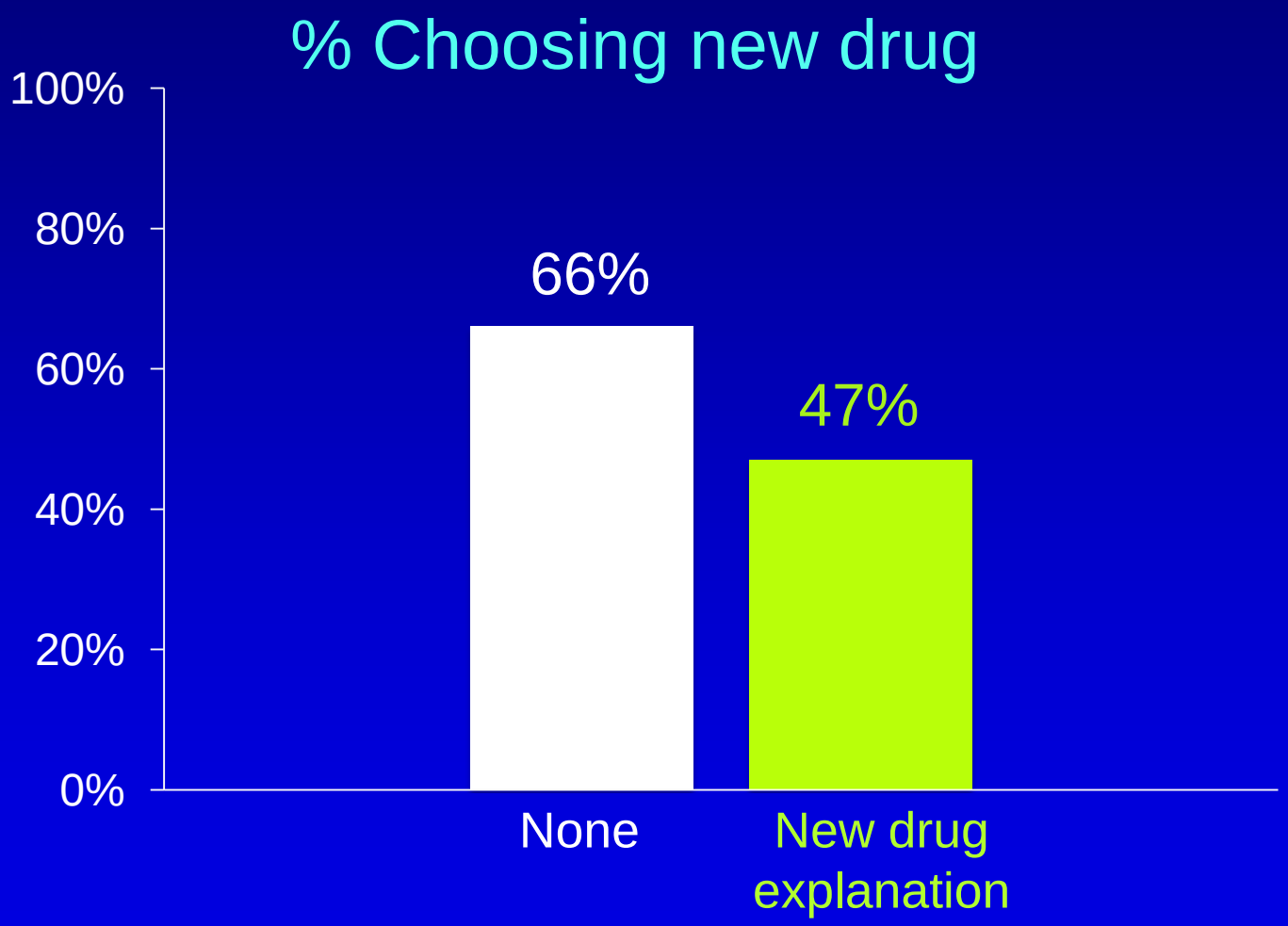
UK drug regulator - and now European Union - require black triangle warning for prescribing and consumer information.

Acknowledge that despite rigorous approval process, much will be learned after marketing (and encourages adverse effect reporting).

NEW DRUG

In 2006, IOM called for implementation in US
(and 2-year moratorium on DTC ads for new drugs)

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 , JAMA Int Med , 2011

Routinely highlight uncertainty

Flag new drugs for first few years on market *Use a graphic or text to communicate that the limited experience with new drugs means greater uncertainty.*

Common uncertainties at drug approval

Standard uncertainty All new drugs

Extra uncertainty Preliminary evidence of benefit only

Extra uncertainty Worrisome harm signal ➔post-marketing study

Extra uncertainty Preliminary evidence of benefit only

Accelerated approval (~ 10% of new drug approvals)

Conditional approval of drugs for serious diseases with limited treatment options based on preliminary evidence

Shorter study duration than FDA standard

e.g. Tysabri

- 1 year of data (standard for MS drugs is 2 years)
- Conditional on results holding up at 2 years

Downing, et,al, JAMA 2013

Tysabri

Prescribing information at accelerated approval

	TYSABRI® plus AVONEX® n=589	Placebo plus AVONEX® n=582
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	1.0
Percentage of patients with:		
0 lesions	67%	40%
1 lesion	26%	29%
2 lesions	4%	10%
3 or more lesions	3%	21%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with:		
0 lesions	96%	76%
1 lesion	3%	12%
2 or more lesions	1%	12%

All analyses were intent-to-treat. For each endpoint, $p<0.001$. Determination of p-values: relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and MRI endpoints by ordinal logistic regression adjusting for baseline lesion number.

INDICATIONS AND USAGE

TYSABRI® is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. This indication is based on results achieved after approximately one year of treatment in ongoing controlled trials of two years in duration. The safety and efficacy of TYSABRI® beyond one year are unknown.

Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

CONTRAINDICATIONS

TYSABRI® should not be administered to patients with known hypersensitivity to TYSABRI® or any of its components.

WARNINGS

Hypersensitivity

TYSABRI® has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. These reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to TYSABRI®.

Tysabri

Prescribing information at accelerated approval

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Poisson regression
by logistic regression
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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?		
Percent of people with no relapses (23% more had no relapses)	76%	53%
Change in disability	Unknown	

Bottom line

- **Accelerated approval based on the 1-year results of a planned 2-year trial**
  Because other multiple sclerosis drugs were all approved based on 2 year results, Tysabri's approval is conditional on the results holding up at 2 years.

"The clinical meaningfulness of a decrease in the relapse rate through only one year is uncertain…The effect at 1 year can be considered as a surrogate for an effect at 2 years. The usual limitations of a surrogate must be borne in mind, in particular the difficulty in reliably predicting the magnitude of natalizumab's effect at 2 years." FDA Medical Reviewer

Extra uncertainty Preliminary evidence of benefit only

Accelerated approval (~ 10% of new drug approvals)

- Shorter study duration than FDA standard

Surrogate primary outcome

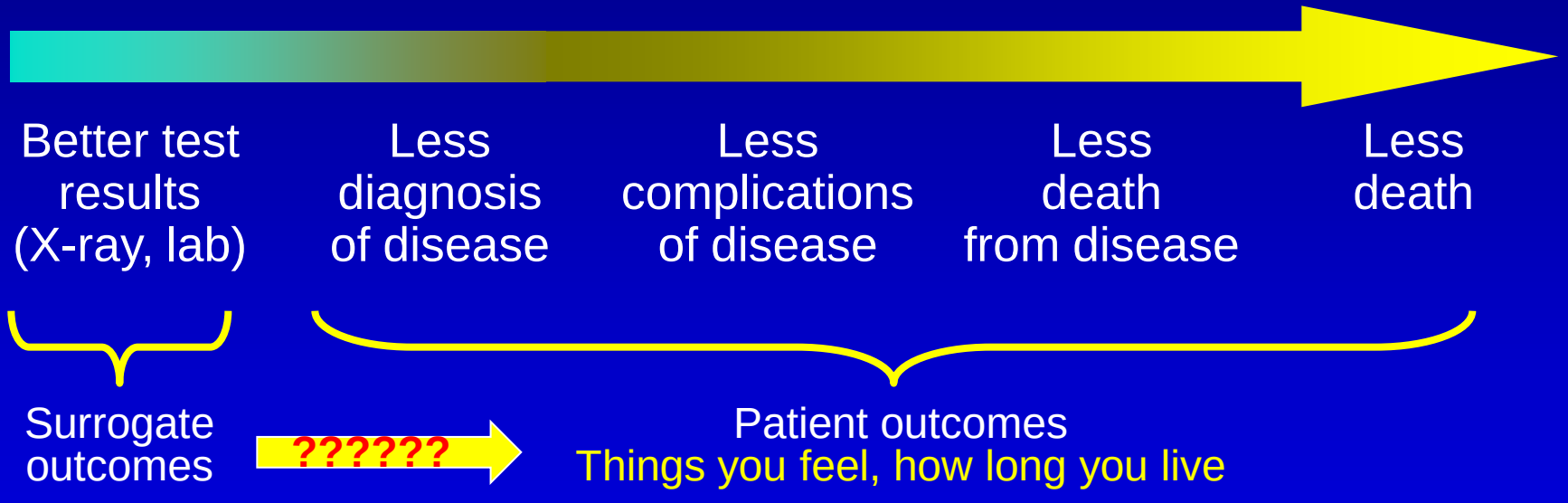
- Almost half of new drugs approved on surrogate only.

Downing, et,al, JAMA 2013

Surrogate outcomes should translate into patient outcomes

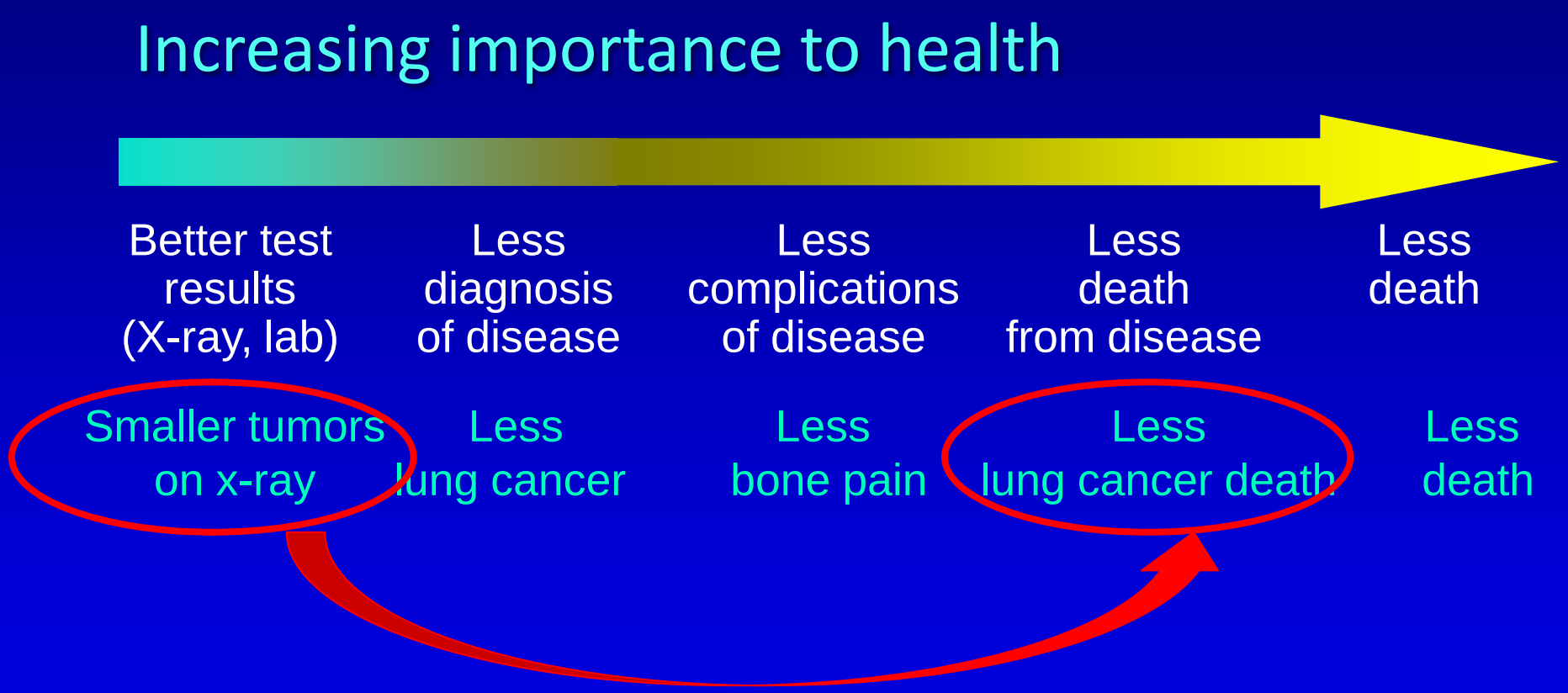
Spectrum of outcomes

But they don't always…



Surrogate outcomes should translate into patient outcomes

But they don't always….. **IRESSA for lung cancer**



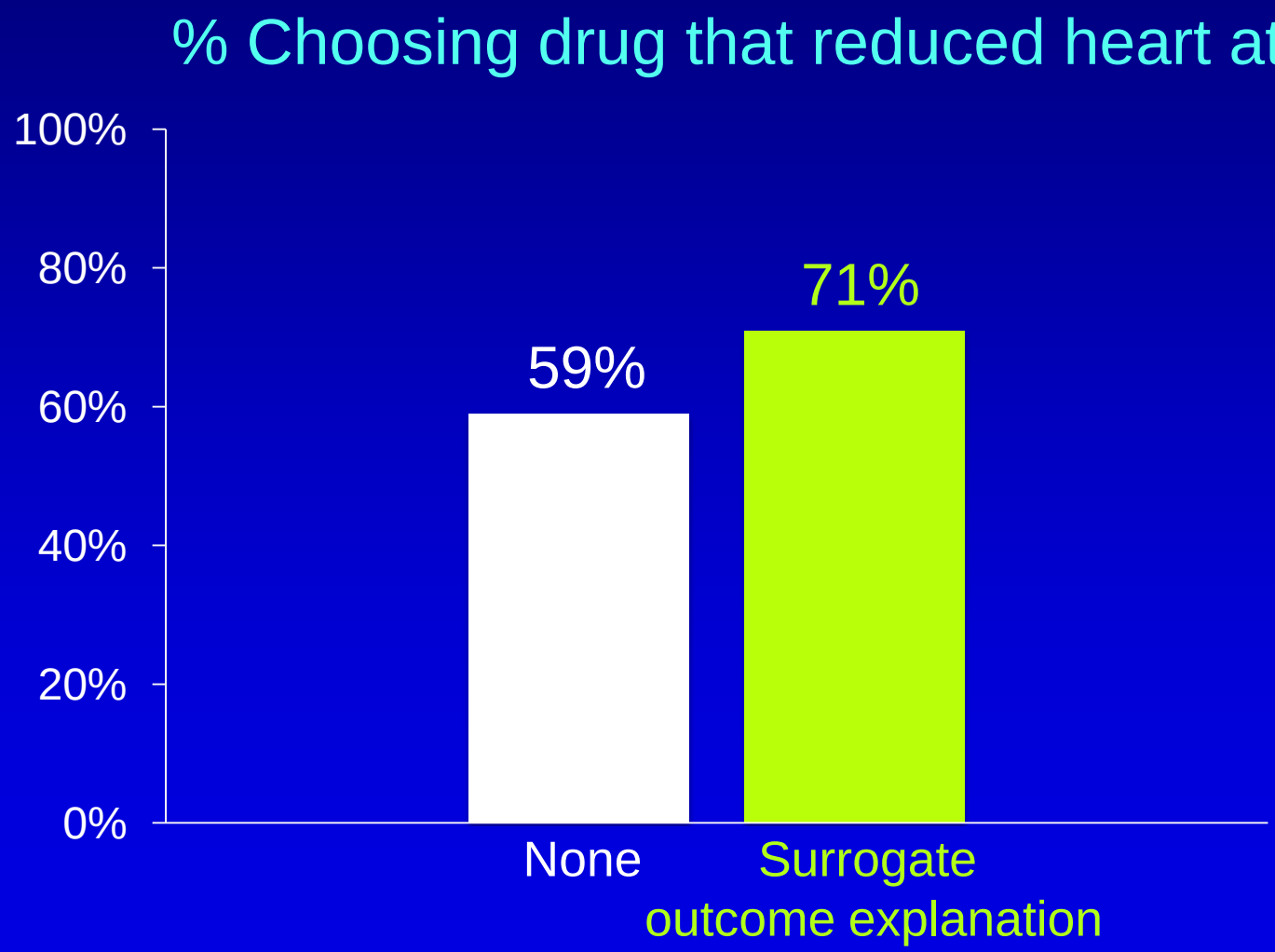
Effect of surrogate outcome explanation

Imagine you had vascular disease. You could take a drug that lowered cholesterol and reduced heart attacks.

Or you could take a drug that has only been shown to lower cholesterol. Both drugs have the same side effects.

If both drugs were free, which would you rather take?

CHOLESTAT has only been shown to lower cholesterol levels.
It is not known whether it will help patients feel better or live longer.



Liptruzet™
(ezetimibe and atorvastatin) tablets
10/10, 10/20, 10/40, 10/80 mg

LIPTRUZET treats **2 SOURCES** of LDL (bad) cholesterol

Zetia

Atorvastatin

FOOD **&** **FAMILY HISTORY**

Liptruzet™
(ezetimibe and atorvastatin) tablets
10/10, 10/20, 10/40, 10/80 mg

LIPTRUZET treats **2 SOURCES** of LDL (bad) cholesterol

FOOD & **FAMILY HISTORY**

Did you know that bad cholesterol comes from 2 sources? We all know there is cholesterol in the food we eat, but your body also makes cholesterol naturally, based on family history.

LIPTRUZET treats 2 sources by helping block the absorption of cholesterol that comes from food and reducing the cholesterol

LIPTRUZET has not been shown to reduce heart attacks or strokes more than atorvastatin alone

Unexplained muscle pain or weakness could be a rare but serious side effect and should be reported to your doctor right away. Talk to your doctor about all the medicines you take. This may help avoid muscle problems or other side effects. Also tell your doctor if you have muscle problems that do not go away even after your doctor has advised you to stop taking LIPTRUZET.

Your doctor should do simple blood tests to check your liver before treatment with LIPTRUZET and if you have symptoms of liver problems during treatment. Tell your doctor right away if you feel tired or weak, or have a loss of appetite, upper belly pain, dark urine, or yellowing of your skin or the whites of your eyes.

Talk to your doctor about all your medical conditions before taking LIPTRUZET. Side effects of LIPTRUZET included muscle and body pain and changes in liver function tests.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please read the Patient Information on the adjacent page for more information.

For more information, including special offers, please call **1-855-4LIPTRU** or visit **liptruzet.com.**

MERCK

Merck Helps™ Having trouble paying for your Merck medicine? Merck may be able to help. www.merck.com/merckhelps

Routinely highlight uncertainty

Flag new drugs for first few years on market *Use a graphic or text to communicate that the limited experience with new drugs means greater uncertainty.*

Warn when evidence of benefit is especially weak *Be clear about the extra uncertainty inherent with study duration shorter than FDA standard, weak study uncontrolled studies or surrogate outcomes.*

Common uncertainties at drug approval

Standard uncertainty All new drugs

Extra uncertainty Preliminary evidence of benefit only

Extra uncertainty Worrisome harm signal ➔post-marketing study

Many drugs aggressively promoted in no uncertain terms

INTRODUCING **BELVIQ®**

What is BELVIQ?

BELVIQ is an FDA-approved prescription weight-loss medication that, when used with diet and exercise, can help some overweight* adults with a weight-related medical problem, or obese adults, lose weight and keep it off. It is not known if BELVIQ when taken with other prescription, over-the-counter, or herbal weight-loss products is safe and effective. It is not known if BELVIQ changes your risk of heart problems, stroke, or death due to heart problems or stroke.

*Overweight (body mass index [BMI] of 27 kg/m^2 or greater) with at least one weight-related medical condition, such as high blood pressure, high cholesterol, or type 2 diabetes; Obese (BMI of 30 kg/m^2 or greater)

Important Safety Information

- **Pregnancy:** Do not take BELVIQ if you are pregnant or planning to become pregnant, as weight loss offers no potential benefit during pregnancy and BELVIQ may harm your unborn baby.
- **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions:** Before using BELVIQ, tell your doctor about all the medicines you take, especially medicines that treat depression, migraines, mental problems, or the common cold. These medicines may cause serious or life-threatening side effects if taken with BELVIQ. Call your doctor right away if you experience agitation, hallucinations, confusion, or other changes in mental status; coordination problems; uncontrolled muscle spasms; muscle twitching; restlessness; racing or fast heartbeat; high or low blood pressure; sweating; fever; nausea; vomiting; diarrhea; or stiff muscles.
- **Valvular heart disease:** Some people taking medicines like BELVIQ have had heart valve problems. Call your doctor right away if you experience trouble breathing; swelling of the arms, legs, ankles, or feet; dizziness, fatigue, or weakness that will not go away; or fast or irregular heartbeat. Before taking BELVIQ, tell your doctor if you have or have had heart problems.
- **Changes in attention or memory:** BELVIQ may slow your thinking. You should not drive a car or operate heavy equipment until you know how BELVIQ affects you.
- **Mental problems:** Taking too much BELVIQ may cause hallucinations, a feeling of being high or in a very good mood, or feelings of standing outside your body.
- **Depression or thoughts of suicide:** Call your doctor right away if you notice any mental changes, especially sudden changes in your mood, behaviors, thoughts, or feelings, or if you have depression or thoughts of suicide.
- **Low blood sugar:** Weight loss can cause low blood sugar in people taking medicines for type 2 diabetes, such as insulin or sulfonylureas. Blood sugar levels should be checked before and while taking BELVIQ. Changes to diabetes medication may be needed if low blood sugar develops.
- **Painful erections:** If you have an erection lasting more than 4 hours while on BELVIQ, stop taking BELVIQ and call your doctor or go to the nearest emergency room right away.
- **Slow heartbeat:** BELVIQ may cause your heart to beat slower.
- **Decreases in blood cell count:** BELVIQ may cause your red and white blood cell counts to decrease.
- **Increase in prolactin:** BELVIQ may increase the amount of a hormone called prolactin. Tell your doctor if your breasts begin to make milk or a milky fluid, or if you are a male and your breasts increase in size.
- **Most common side effects in patients without diabetes:** Headache, dizziness, fatigue, nausea, dry mouth, and constipation.
- **Most common side effects in patients with diabetes:** Low blood sugar, headache, back pain, cough, and fatigue.
- **Nursing:** BELVIQ should not be taken while breastfeeding.
- **Drug interactions:** Before taking BELVIQ, tell your doctor if you take medicines for depression, migraines, or other medical conditions, such as: triptans; medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, or antipsychotics; cabergoline; linezolid (an antibiotic); tramadol; dextromethorphan (an over-the-counter (OTC) common cold/cough medicine); OTC supplements such as tryptophan or St. John's Wort; or erectile dysfunction medicines.
- BELVIQ is a federally controlled substance (CIV) because it may be abused or lead to drug dependence.

For more information about BELVIQ, talk to your doctor and see the Patient Information on the reverse side.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

BELV0922

You could be carrying more than just extra weight.

In FDA clinical trials, people who added BELVIQ to diet and exercise were able to **lose weight as well as improve certain health risk factors†**, such as high blood pressure, high blood sugar, and high cholesterol levels.

FDA-APPROVED FOR WEIGHT LOSS

BELVIQ® (lorcaserin HCl) CV

Power Over Portion™

VISIT StartBELVIQFree.com

OR CALL 1-855-BELVIQ1 TO GET A

15-DAY FREE‡ TRIAL

†BELVIQ was evaluated in three clinical studies involving overweight adults (with at least one weight-related medical condition) and obese adults. All three studies compared people taking BELVIQ plus diet and exercise to people using diet and exercise alone (placebo). The results of the first two studies (involving 7,190 people without diabetes) showed that 47.1% of people taking BELVIQ lost 5% or more of their body weight, compared with 22.6% of the placebo group. People taking BELVIQ also had significant improvements in their blood pressure and cholesterol levels. A third clinical study (involving 604 overweight people with type 2 diabetes) showed that 37.5% of people taking BELVIQ lost 5% or more of their body weight, compared with 16.1% of the placebo group. People taking BELVIQ also had significant improvements in their blood sugar levels. Nearly half of all participants completed the first two studies; nearly two-thirds of the participants completed the third study.

‡Restrictions apply.

Extra uncertainty
Worrisome harm signal ➔post-marketing study

Harms with similar weight loss drugs Pulled from market because they caused cardiovascular events or valve disease.

Signal with Belviq Increase in heart valve problems not statistically significant but a 20% increase still possible.

European regulator Belviq's benefits did not outweigh its possible harms; company withdrew its marketing application.

FDA Dangers of obesity greater than possible harms of drug. Approved the drug with post-marketing trial for cardiovascular harm.

FDA press release

The drug's manufacturer will be required to conduct six postmarketing studies, including a long-term cardiovascular outcomes trial to assess the effect of Belviq on the risk for major adverse cardiac events such as heart attack and stroke.

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The most common side effects of Belviq in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation, and in diabetic patients are low blood sugar (hypoglycemia), headache, back pain, cough, and fatigue.

Belviq is manufactured by Arena Pharmaceuticals GmbH of Zofingen, Switzerland, and distributed by Eisai Inc. of Woodcliff Lake, N.J.

For more information:

exercise counseling. Compared with placebo, treatment with Belviq for up to one year was associated with average weight loss ranging from 3 percent to 3.7 percent.

About 47 percent of patients without type 2 diabetes lost at least 5 percent of their body weight compared with about 23 percent of patients treated with placebo. In people with type 2 diabetes, about 38 percent of patients treated with Belviq and 16 percent treated with placebo lost at least 5 percent of their body weight. Belviq treatment was associated with favorable changes in glycemic control in those with type 2 diabetes. The approved labeling for Belviq recommends that the drug be discontinued in patients who fail to lose 5 percent of their body weight after 12 weeks of treatment, as these patients are unlikely to achieve clinically meaningful weight loss with continued treatment.

Belviq should not be used during pregnancy. Treatment with Belviq may cause serious side effects, including serotonin syndrome, particularly when taken with certain medicines that increase serotonin levels or activate serotonin receptors. These include, but are not limited to, drugs commonly used to treat depression and migraine. Belviq may also cause disturbances in attention or memory.

In 1997, the weight-loss drugs fenfluramine and dexfenfluramine were withdrawn from the market after evidence emerged that they caused heart valve damage. This effect is assumed to be related to activation of the serotonin 2B receptor on heart tissue. When used at the approved dose of 10 milligrams twice a day, Belviq does not appear to activate the serotonin 2B receptor.

Heart valve function was assessed by echocardiography in nearly 8,000 patients in the Belviq development program. There was no statistically significant difference in the development of FDA-defined valve abnormalities between Belviq and placebo-treated patients. Because preliminary data suggest that the number of serotonin 2B receptors may be increased in patients with congestive heart failure, Belviq should be used with caution in patients with this condition. Belviq has not been studied in patients with serious valvular heart disease.

Strength – and direction - of uncertainty lost in label

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BELVIQ safely and effectively. See full prescribing information for BELVIQ.

BELVIQ (lorcaserin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

BELVIQ is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) (1) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension,

- Cognitive Impairment: May cause disturbances in attention or memory. Caution with use of hazardous machinery when starting BELVIQ treatment (5.3)
- Psychiatric Disorders, including euphoria and dissociation: Do not exceed recommended dose of 10 mg twice daily (5.4)
- Monitor for depression or suicidal thoughts. Discontinue if symptoms develop. (5.4)
- Use of Antidiabetic Medications: weight loss may cause hypoglycemia. Monitor blood glucose. BELVIQ has not been studied in patients taking insulin. (5.5)
- Priapism: Patients should seek emergency treatment if an erection lasts >4 hours. Use BELVIQ with caution in patients predisposed to priapism. (5.6)

ADVERSE REACTIONS

The effect of BELVIQ on cardiovascular morbidity and mortality has not been established.

- One tablet of 10 mg twice daily (2)

Because of concerns that BELVIQ might increase cardiovascular morbidity and mortality, FDA has required a long-term randomized trial to be completed by 2017.

established. Manage with immediate BELVIQ discontinuation and provide supportive treatment. (5.1)

- Valvular heart disease: If signs or symptoms develop consider BELVIQ discontinuation and evaluate the patient for possible valvulopathy. (5.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2012

Direct-to-consumer ad

What is BELVIQ?

BELVIQ is an FDA-approved prescription weight-loss medication that, when used with diet and exercise, can help some overweight* adults with a weight-related medical problem, or obese adults, lose weight and keep it off. It is not known if BELVIQ when taken with other prescription, over-the-counter, or herbal weight-loss products is safe and effective. It is not known if BELVIQ changes your risk of heart problems, stroke, or death due to heart problems or stroke.

You could be carrying more just extra weight.

In FDA clinical trials, people who added BELVIQ to diet and exercise were able to **lose weight as well as improve certain health risk factors†,** such as high blood pressure, high blood sugar, and high cholesterol levels.

Because of concerns that BELVIQ might increase cardiovascular morbidity and mortality, FDA has required a long-term randomized trial to be completed by 2017.

†BELVIQ was evaluated in three clinical studies involving overweight adults (with at least one weight-related medical condition) and obese adults. All three studies compared people taking BELVIQ plus diet and exercise to people using diet and exercise alone (placebo). The results of the first two studies (involving 7,190 people without diabetes) showed that 47.1% of people taking BELVIQ lost 5% or more of their body weight, compared with 22.6% of the placebo group. People taking BELVIQ also had significant improvements in their blood pressure and cholesterol levels. A third clinical study (involving 604 overweight people with type 2 diabetes) showed that 37.5% of people taking BELVIQ lost 5% or more of their body weight, compared with 16.1% of the placebo group. People taking BELVIQ also had significant improvements in their blood sugar levels. Nearly half of all participants completed

New drug warning

Direct-to-professional ad

BELVIQ® (lorcaserin HCl) IV

Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults who are overweight (BMI ≥27 kg/m²) with at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes) or who are obese (BMI ≥30 kg/m²)

Limitations of Use

The effect of BELVIQ on cardiovascular morbidity and mortality has not been established.

Package Size	NDC
Bottle of 60	62856-529-60

Storage

- Store at 25° C (77° F); excursions permitted to 15° C to 30° C (59° F to 86° F).

Bottle and tablets shown not actual size.

Abbreviation: BMI, body mass index, calculated by dividing weight (in kg) by height (in meters) squared.

IMPORTANT SAFETY INFORMATION

Contraindications

- BELVIQ should not be taken during pregnancy or by women who are planning to become pregnant.

Warnings and Precautions

- BELVIQ is a serotonergic drug. The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors, tricyclic antidepressants, bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists, particularly when used in combination. Patients should be monitored for the emergence of serotonin syndrome symptoms or NMS-like reactions, including agitation, hallucinations, coma, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, incoordination, nausea, vomiting, diarrhea, and muscle rigidity. Treatment with BELVIQ and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.

But uncertainty alone isn't enough

Uncertainties need to be in context of benefit and harm

Prescription Drug Facts Box

- Body of research: consumers value and understand box
- FDA Risk Communication Advisory Committee unanimous endorsement
-Section 3507, Affordable Care Act

BELVIQ (lorcaserin) for weight loss in overweight (with weight-related problems) or obese adults

What is this drug for?

To help people lose weight, when combined with exercise and a reduced-calorie diet. If you don't lose at least 5% of your bod weight after 3 months, stop taking the drug, because it is unlikely to work.

Who might consider taking it?

Adults who are overweight (BMI 27 to 29.9) with a weight-related health problem (high blood pressure, high cholesterol, heart disease, type 2 diabetes, or sleep apnea) or people who are obese (BMI 30 or higher).

What other choices are there?

Diet or exercise, other approved weight loss medications, or weight loss surgery if severe obesity (BMI 40 or higher)

STUDY FINDINGS (Combined results of the 2 identical trials that were the basis of FDA approval)

6,136 non-diabetic adults - overweight with related health problems or obese - age 18-65, mostly women, average weight 221 pounds . **All counseled to do 30 minutes of moderate exercise and eat 600 fewer calories a day.** People were randomized to either BELVIQ or PLACEBO **for 1 year**. Here's what happened:

	BELVIQ (10 mg twice a day)	PLACEBO (No drug)
How did BELVIQ help?		
% of weight lost at 1 year		
BELVIQ caused 3% more weight loss (about 6 pounds)	Lost 6% of weight	Lost 3% of weight
Percent of people who lost various amounts of weight		
Lost 5%-9% of their weight	25%	14%
Lost 10%-19% of their weight	18%	8%
Lost 20% or more of their weight	4%	1%
What were BELVIQ 's side effects?		
Serious side effects		
More people had **leaky aortic or mitral valves** (0.4% more)	2.4%	2%
More had **memory or attention problems** (1.4%more)	1.9%	0.5%
Symptom side effects		
More people had **headache** (7% more)	17%	10%
More had **dizziness** (5% more)	9%	4%
More had **nausea** (3% more)	8%	5%
More had **fatigue** (3% more)	7%	4%
More had **dry mouth** (3% more)	5%	2%
More had **constipation** (2% more)	6%	4%

BOTTOM LINE

- **Limited benefit** "The efficacy of lorcaserin [BELVIQ] is not impressive but also is not out of line with other weight loss drugs…a small proportion of patients may achieve impressive and probably quite important weight loss. Unfortunately, this will not be the experience of the majority of users" -- Director, FDA Office of Drug Evaluation

  The nearly identical weight loss in the trials above make the benefit numbers more believable. But the only long-term (2-year) study showed that people on the drug gained some weight back after the first year.

- **Concern about serious side efffects** The FDA is requiring the company to conduct a large trial to learn if the drug causes heart attacks, strokes and heart valve problems.

  Don't take BELVIQ with other drugs - like some antidepressants, headache medicines and cough medicines with dextromethorphan - which raise serotonin levels and can cause a dangerous overdose:

- **Shorter track record means unexpected new, unexpected side effects are possible** As with all new drugs, important side effects may emerge after the drug is on the market when larger numbers of people—some with other conditions and on other medications—use the new drug. Since this is the first drug of its kind to receive FDA approval, experience is particularly limited.

Consumer Reports
July 2013

Routinely highlight uncertainty

Flag new drugs for first few years on market *Use a graphic or text to communicate that the limited experience with new drugs means greater uncertainty.*

Warn when evidence of benefit is especially weak *Be clear about the extra uncertainty inherent with study duration shorter than FDA standard, weak study uncontrolled studies or surrogate outcomes.*

Point out post-marketing trials required for signals of harm *Specify what post-marketing trials were required, why, and when results will be available –in the Highlights of the label (in either "Limitations of use" or "Warnings & Precautions" sections)*

Prominently acknowledge uncertainty at approval *Explain uncertainties about benefit or harm in FDA press releases, the professional label, and consumer information.*