

Erin Allmann Updyke

"From the moment of birth, you begin to age. The changes are almost entirely internal and imperceptible. But by your 20s the sun has probably left its first telltale marks on your most prominent feature, your face. You start to get tiny lines or wrinkles. Or as dermatologists put it, you experience photo aging. Usually by your early 30s and with each passing year, those first fine furrows begin to deepen and multiply. To some, the lines are signs of character or a merry disposition to be neither fretted over nor fought against. To many others though they are scars, reminders of the disappearance of youth.

Not surprisingly then, eliminating wrinkles is a roughly \$3 billion business in youth conscious America. In the past 15 months however we have been told that much of this energy and enterprise may have been rendered obsolete by a drug that purports to improve skin tone and erase wrinkles. Its scientific name is all-trans retinoic acid but most of us know it by its brand name Retin-A. Once a popular acne cream marketed by Ortho Pharmaceutical, a \$600 million a year subsidiary of \$9 billion Johnson & Johnson, Retin-A has been hailed by doctors and the press as the first drug, as opposed to a cosmetic, that shows promise not only in treating the symptoms of aging but also in actually reversing part of the process itself."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

Do you like my dramatic rendition there?

Erin Welsh

I loved the dramatic rendition. I do want to know how big the industry is today.

Erin Allmann Updyke

Oh I can't wait to tell you.

Erin Welsh

Because that's from the same Money Magazine, right? Okay, 1988.

Erin Allmann Updyke

Cannot wait.

Erin Welsh

\$3 billion in 1988. Wow.

Erin Allmann Updyke

Yeah. So that quote was excerpted from the article that you quoted, Erin, thank you for sending me this, last episode, which was 'The Selling of Retin-A' by Leslie Vreeland in CNN Money Magazine published April 1, 1989.

Erin Welsh

1989. Got it. Ugh. I'm so excited for this episode.

Erin Allmann Updyke

It's going to be a good one.

Erin Welsh

Hi, I'm Erin Welsh.

Erin Allmann Updyke

And I'm Erin Allmann Updyke.

Erin Welsh

And this is This Podcast Will Kill You.

Erin Allmann Updyke

So last week, if you haven't listened to last week's episode, I recommend it. Must you before today? Not necessarily but it's a good primer.

Erin Welsh

Yeah.

Erin Allmann Updyke

No makeup term intended. Get it?

Erin Welsh: Good one.

Erin Allmann Updyke: Because last week we focused all about how Retin-A came to be and really the horrific backstory of the person, Albert Kligman, who was very much at the forefront of the development of Retin-A and all of the horribly unethical experiments that went down in order to create this product that now is so ubiquitous. And today we are going to talk about what Retin-A even is, what are all of the other retinoids that are out there, and what do they do and do they actually work and how and why.

Erin Welsh: How and why? Love it. I'm so excited because that's definitely something I didn't come across in any bit of my research. I was like I don't know if retinol works for anti-aging or whatever.

Erin Allmann Updyke: Yeah.

Erin Welsh: And I know that I have my biases in terms of disbelieving any claim that any skincare products makes in general. But yeah.

Erin Allmann Updyke: Yeah. Yeah. It's going to be fun. We're going to get all into it. But first-

Erin Welsh: But first.

Erin Allmann Updyke: We're drinking the same thing as last week.

Erin Welsh: We are. Quarantini is Skin Deep and it has carrot juice, again vitamin A, blah, blah, blah, beta-carotene.

Erin Allmann Updyke: Blah, blah, blah.

Erin Welsh: I remember that. Beta-carotene to vitamin A to tretinoin.

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh: That's the pathway. So we got carrot juice in there, we got ginger, lemon, vodka. It's a hit.

Erin Allmann Updyke: It's a hit. And the full recipe is up on our website thispodcastwillkillyou.com and our social media channels. If you're not following us, you should be. And we've always got a non alcoholic placeborita version as well.

Erin Welsh: On our website you can find great things. You can find transcripts, you can find the sources for each and every one of our episodes, you can find a contact us form if you want to hear a certain topic or you just want to say hi or if you say hey, come say hi to us, come to my organization and give a talk. We've got a submit your firsthand account form, we've got links to merch, to Patreon, to music by Bloodmobile, to our bookshop.org affiliate account, our Goodreads list. Wow. I think I got most of it. Yeah.

Erin Allmann Updyke: So many things on that one little website, who could believe it? Also rate, review, and subscribe. Okay. Shall we get into... This is going to be a big one.

Erin Welsh: Yeah.

Erin Allmann Updyke

So let's just take a break and get started.

Erin Welsh

That sounds great.

TPWKY

(transition theme)

Erin Allmann Updyke

Retinoids.

Erin Welsh

Retinoids.

Erin Allmann Updyke

So how I'm going to try and break down or organize this episode is we'll first talk about what the heck is a retinoid and what is vitamin A. And again, not a ton of detail because we're really going to focus on the uses of vitamin A or retinoids in skin and skincare and then how and what the evidence is to actually support that. And then finally we'll get into how that evidence has perhaps been extrapolated by the cosmetic industry to sell us all anti-aging products and whether or not there's any data to support such extrapolations.

Erin Welsh

Love it. Oh my gosh, I'm so excited.

Erin Allmann Updyke

It's going to be really, really fun. I'm excited about it. So the term 'retinoid' encompasses a pretty wide range of chemicals. Retinoids as a large group are essentially all either vitamin A derivatives or they function like vitamin A in our bodies or in our skin. So whatever their chemical structure may be, because especially with the development of more synthetic retinoids, they don't look the same as vitamin A looks. Whatever their chemical structure, the things that we classify as retinoids are binding to specific receptors, retinoid receptors, and acting in a similar way to vitamin A. And vitamin A's other name is retinol or all-trans retinol. And again there are a bunch of different types or a bunch of different forms. And you might be familiar with some of these names. Retinol, retinol esters, retinaldehyde, tretinoin, isotretinoin, adapalene. There is a whole range of these chemicals and they all again function at these retinoid receptors. And we're going to lump them for the purposes of this episode into two major buckets, prescription retinoids and over the counter retinoids. Cool?

Erin Welsh

Cool.

Erin Allmann Updyke

So what the heck do any of these retinoids actually do? Vitamin A, which vitamin A is just call it like equivalent to all of these for the purposes of this, okay? Just we're lumping it all.

Erin Welsh

Perfect. That's fine.

Erin Allmann Updyke

Vitamin A is an essential nutrient. It's a fat soluble vitamin so it dissolves in fat and we can store it in our fat. And like all vitamins, this is something that we need in our diets, we don't make it ourselves, and it is essential for life and survival. We need vitamin A from the very earliest stages of embryonic development all the way until our death. Vitamin A is essential in the formation of our nervous system and the way that our bodies are built and patterned as an embryo, like the way that an embryo is literally built. And it's also essential for vision and its role in vision is really well established and again worthy of its whole own episode. But that's not today.

Erin Welsh

That's not today.

Erin Allmann Updyke

We get vitamin A in our diet in the form of carotenoids like beta-carotene in our carrots and then also from eating/ingesting preformed vitamin A in our foods. Like if you're eating meat, it probably has some vitamin A in it as well.

Erin Welsh

Okay.

Erin Allmann Updyke

But today we're going to focus on how we use retinoids specifically in our skin because they have become such a seemingly ubiquitous and essential part of skincare. So to understand how these retinoids work in our skin, let us first understand our skin a little bit better.

Erin Welsh

Love it.

Erin Allmann Updyke

So our skin is composed of three major layers. Starting from the bottom, AKA the inside of our bodies and going towards the outside, we have this subcutaneous tissue, it's also called the hypodermis and that's mostly just like fat and stuff. It's like your fluff, right.

Erin Welsh

Okay.

Erin Allmann Updyke

And then you have your dermis, which is like the bottom layer of what is really like skin skin. And your dermis is made up of stuff like collagen and elastins which are made by these cells that are called fibroblasts. Your dermis is also where all of the blood supply is to your skin. And your dermis is the really strong part that really holds us together quite literally. And then on top of your dermis is your epidermis. And your epidermis is very, very thin. It ranges on the soles of your feet and the palms of your hands it's the thickest, maybe the width of two credit cards stacked together.

Erin Welsh

All right.

Erin Allmann Updyke

If you can imagine that. I don't know, whenever I see those I'm like I don't know, is it the fancy credit cards now or old school credit cards? I don't know. It's pretty thin.

Erin Welsh

I know. One of mine is metal and very thick but I'll just say it's one of... It's that.

Erin Allmann Updyke

It's like that thick, I don't know.

TPWKY

(transition theme)

Erin Allmann Updyke

And then in other places, like the skin on your eyelids is incredibly thin, like the width of maybe a sheet of paper thick.

Erin Welsh

Okay.

Erin Allmann Updyke

And our epidermis specifically, this teeny tiny little layer is the number one protection that we have from the outside world. And despite how relatively thin it is just like in general and also compared to the other layers, the dermis and our subcutaneous tissue, it still also has a whole bunch of layers within it. And we talked a little bit about the different layers of skin in our skin cancer episode. But I almost imagine it like one of those really, really fancy cakes that they make on Great British Bake Off where you have a bunch of different layers that are like different compartments but all together they're delicious cake.

Erin Welsh

Okay. Like the really thin layers? Like how many layers are we talking?

Erin Allmann Updyke

So let's get into it.

Erin Welsh

Yeah.

Erin Allmann Updyke

There's the basal cell layer which is the bottom of our epidermis. This sits on top of a basement membrane that touches our dermis. And our basal cell layer is the cells that proliferate. So these are like stem cells. They proliferate, they replicate. And as they replicate they also migrate upwards towards the outside world, towards the top of your epidermis. And as they migrate they also differentiate. And the major cell that we have in our epidermis are called keratinocytes. And they're called this because they make keratin which is the protein that we make in our skin and our hair and our nails, etc. And so this basal cell layer is the first, like the bottom layer. And then you have a bunch of these keratinocytes. And then as they migrate upwards and continue to differentiate, they form from these fat, chunky, juicy, I don't know, like a mousse layer of cake.

Erin Welsh

Okay. Yum.

Erin Allmann Updyke

Into something more flat and squat like say, I don't know, like a meringue layer. Something a little bit more firm.

Erin Welsh

Meringue is like fluffy, right?

Erin Allmann Updyke

Yeah but not like a cooked meringue, somewhere between super jelly and more firm. I'm losing it on the baking references here.

Erin Welsh

I'm trying, my baking knowledge is much more limited than yours. So like a pudding layer?

Erin Allmann Updyke

No, not a pudding layer. Anyways, we're just going to ignore the baking-

Erin Welsh

Like a frosting layer? Okay.

Erin Allmann Updyke

It'll make sense again at the top. So then they get to be more squat and flat and stuck really close together. And then at the very top of our skin, the very first layer like when you're touching right here, that layer is super keratinized. Basically those cells no longer even really look like cells, they just look like layers of keratin because they're so smooshed and stuck together. They no longer have a nucleus. Those are kind of like fondant that you put on top of the cake. Okay?

Erin Welsh

Okay.

Erin Allmann Updyke

All right. We're trying. That very important outermost layer, the fondant, is called the stratum corneum. And the stratum corneum is a really important part of our whole epidermis. It holds our water in like fondant holds the rest of this jello cake together. It protects us against UV damage and oxidative stress, it protects against infections and other environmental toxins. Just below the stratum corneum, all those other cells, they're still very keratinized like the next layer down but they have a little bit more room between them, there's a little bit more kind of like mortar holding the bricks together, more fatty stuff. And then you have just the rest of your kind of cell layers down to that basal layer. Throughout this we also have other cells, right. We have melanocytes which are our pigment-producing cells. We also have hair follicles, sebaceous glands that produce sebum, we have nerves, we have other immune cells. But most of your skin are these keratinocytes.

So being our largest organ by surface area, a lot of different things can go wrong in our skin, especially as it is constantly being insulted from everything in our environment. And as it turns out, retinoids are used medically by prescription to treat a pretty wide variety of skin conditions. So let's get into some of this. Focusing mostly on prescription retinoids here, we'll talk more about over the counter versions later. Prescription retinoids are often used to treat acne which is again what you talked a lot about, Erin, in last week's episode. One of the main first things that we figured out that retinoids can do. So acne is what happens when pores and your hair follicles, which pores are kind of like hair follicles that no longer have a follicle in them, they're just little channels down to the lower layers of your skin.

Erin Welsh

Okay.

Erin Allmann Updyke

When these get stuffed with dead skin cells and bacteria that end up proliferating, they can eventually come to the surface and burst forth. And when that happens you get a lot of inflammation, you get a lot of pain, and potentially a lot of scarring. We use retinoids very often to treat acne, especially to treat acne that can cause that kind of scarring because not all acne does. Retinoids are also used to treat some kinds of psoriasis. And psoriasis is something that can result in what are called hyperkeratotic, meaning there's a lot of thick disorganized keratin production and it forms these plaques. And so retinoids can be used to help treat that.

Erin Welsh

How do those plaques form?

Erin Allmann Updyke

Oh my gosh, psoriasis is its whole own episode.

Erin Welsh

Okay, I know. Is there like a TL;DR?

Erin Allmann Updyke

TL;DR is its like disorganization of keratinization and the sloughing of your skin. And it's an autoimmune disorder-

Erin Welsh

Okay.

Erin Allmann Updyke

So there's a lot more detail to it.

Erin Welsh

Did not read the instruction manual and we're just going to throw keratin everywhere?

Erin Allmann Updyke

Right, right, right, right.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah, it's like a lot more detailed than that, especially for psoriasis because it's like autoimmune.

Erin Welsh

Right.

Erin Allmann Updyke

So there's like your immune system in general not reading the manual. So yeah, in general not reading manuals is accurate.

Erin Welsh

Okay, okay.

Erin Allmann Updyke

Retinoids are also sometimes used to treat certain types of skin cancers including Kaposi's sarcoma and also other more rare forms of things that tend to be under this umbrella of abnormal keratinization or what's called desquamation, which is basically when your cells are not adherent to each other in your skin the way that they should be, right. Because they should be pretty well brick and mortared together.

Erin Welsh

Okay.

Erin Allmann Updyke

Like enclosed by this fondant is like one tight nug, right?

Erin Welsh

Yeah.

Erin Allmann Updyke

But desquamation means that things are not well connected so then you get a lot of flaking, a lot of itching. So these are things like ichthyosis or Darier's disease. There's a lot of different things that can potentially benefit from retinoid treatment. And of course the big elephant, the wrinkly elephant in the room, retinoids are used for photo aging. Now let's take a minute here, shall we? Aging of course is a completely natural process. And I don't mean "natural" in quote unquote the way that Goop says the word natural. I mean that aging is not a disease state but it is characterized by visible changes in the architecture of our skin. Aging skin is characterized by things like a loss of hydration and like an inability to regulate hydration as well because of damage to that kind of outer layer of skin. It's also characterized by reduced collagen production, a loss of elasticity, and a delay in recovery after injury to the skin. And there's probably more.

UV damage, like exposure to the sun, speeds up and exacerbates this aging process in a way. And that is the process that people are talking about when they say photo aging. And so photo aging looks like all of the things that, I'm not going to say any brand names, but certain brand of skincare product commercials might tell you that you must avoid at all cost, right. It manifests on your skin as things like fine lines, wrinkles, depigmentation, things called solar lentigines which are those spots, sun spots, loss of elasticity, blah, blah, blah, blah, blah. Histologically we see a thinning of your epidermis, so those cake layers altogether are thinner.

Erin Welsh

Okay.

Erin Allmann Updyke

And disorganization of some of the connective tissue. So it's not like laid down in really nice sheets the way that it is in non photo damaged skin.

Erin Welsh

Looks like a cake that I would make then.

Erin Allmann Updyke

I think you can make a great cake, Erin, don't sell yourself short.

Erin Welsh

Thank you but I beg to differ.

Erin Allmann Updyke

Yes. A homemade cake, okay?

Erin Welsh

Yes, okay.

Erin Allmann Updyke

And so all of these changes are going to vary not just with the amount of UV exposure that someone's exposed to but also with things like the amount of melanin in your skin. Because melanin, which is the pigment produced by our melanocytes, is protective against UV damage. And it's just going to vary based on straight up genetics in ways that we don't fully understand. But there's a lot of genetics involved in both aging and photoaging. So how do retinoids then fit into these drugs? I said that we use them for these things. How exactly? Like what are they doing? Okay.

Erin Welsh

Right. And how are they doing all of these different things? Because it sounds like the mechanisms of aging or the mechanisms of a condition like psoriasis, like acne, are different. So what is the unifying thing that is... Yeah.

Erin Allmann Updyke

Excellent question, let's get into it.

Erin Welsh

Okay.

Erin Allmann Updyke

So retinoids I already said are this group of a variety of different chemicals with different chemical structures that act on this common ground of these retinoid receptors. We have a bunch of these throughout our body, like six different kinds of retinoid receptors. There's a few of them, like three or four at least that are present in pretty good numbers in our epidermis and our dermis. What retinoids do is they bind to these specific receptors which are on our DNA. And what they do then is they modulate the expression of other genes. So what does that mean? They are changing the way that our skin cells are interacting with our environment. So our skin again is the major barrier between us and our outside world.

So we might think of it as just a thing that just sits there but it's not, it's an organ and it's a very dynamic organ. It's constantly responding to changes, changes in light, in temperature, humidity, responding to pathogens, trying to fix all of the damage that UV rays are imposing on it. So topical retinoids especially bind to these retinoid receptors, they turn some genes on and turn other genes off. And what it seems like they do is they turn on genes that produce things like growth factors and they turn off genes that do stuff like chop up collagen into tiny little bits. And they also can turn on genes that help to induce that skin cell, those keratinocytes, to differentiate from that basal cell layer and just increase turnover overall of cells.

Erin Welsh

Okay.

Erin Allmann Updyke

So that's a lot of different functions, right.

Erin Welsh

Yeah. And this is both topical and oral retinoids.

Erin Allmann Updyke

So yeah, all of them are going to work in the same way. Topical retinoids and oral retinoids, they're going to bind to the same receptors, they're binding to the same things. The oral ones are going to be much stronger and they're going to be binding to additional receptors that are not only present in your skin but other places as well and reaching deeper down into your dermis that topical preparations are not going to reach as well. Because your dermis is where the blood flow is and it's actually really hard to get things that you apply topically all the way down deep.

Erin Welsh

Right, too many layers of defense in there.

Erin Allmann Updyke

Exactly, we've got such great skin. So all of this variety of functions, what does it end up doing? What do we see with retinoid application? We see a thickening of that epidermal layer. So the whole entire, from the basal layer to the top, we see a thickening of that, especially the mouse section in the middle, those healthy growing keratinocytes in the middle. We also see an increase in collagen and elastin production. And so this is sometimes called a regeneration of the extracellular matrix. This is the stuff that holds our skin together. And because retinoids are turning off genes that are chopping up collagen, we see more collagen and elastin being made. And because it's also increasing cell turnover, what that means is that you're sloughing off skin, it's pushing from that basal layer up and up and up to that stratum corneum and being kicked off of our bodies-

Erin Welsh

Okay.

Erin Allmann Updyke

Into my carpet more rapidly.

Erin Welsh

Okay.

Erin Allmann Updyke

So that is one of the ways that it helps in acne because by pushing out cells more rapidly, you're also reducing the amount of sebum that's produced and sitting around which helps to reduce the formation of those areas where you've got nuggets of dead skin cells that are being able to sit there which means that you have less of a conducive environment for bacteria to grow and thrive.

Erin Welsh

Yep.

Erin Allmann Updyke

It's also why you often see if someone has acne or even doesn't have that much acne and starts using a retinoid, you can often see this... There's a lot of different terms for it, like purging is not a very medical term but you can see a worsening of your acne when you initially start using it. And that's because it takes time for that epidermal turnover to push all of what's already deep in your skin out to the surface.

Erin Welsh

Okay.

Erin Allmann Updyke

And I'm not done, there's more. The reason that this then ends up helping in things like pigmentation changes, like say sunspots, is because in increasing that cell turnover you're reducing how much time the keratinocytes, those skin cells, are in contact with the melanocytes. Which is a fancy way of saying you just have less pigment that's getting built up in random little cells. And in doing all of this, retinoids also seem to help protect against further UV damage. And I find this point especially interesting because retinoids can actually make people much more sensitive to the sun.

Erin Welsh

Right.

Erin Allmann Updyke

They can heighten photosensitivity, they can make you have rashes or have more easy sunburns. But on a large scale, part of what they are doing is turning on and off genes that are also getting turned on and off in the opposite direction from UV damage, if that makes sense. So they're kind of counteracting what ultraviolet light is doing to our skin.

Erin Welsh

Right, okay. So if ultraviolet light flips the switch to off, retinoids are flipping that that on.

Erin Allmann Updyke

Exactly.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. So that is all of what we know. And again there's a lot more detail, I've got a bajillion papers if you want the real deep deets. But that is what we know about how these retinoids are working and why it is that they are used medically for the indications that they are often used for. Now all of this data that we have is almost entirely exclusively from tretinoin, AKA retinoic acid, AKA the stuff you can only get with a prescription.

Erin Welsh

So prescription only, is that... I want to know more about this and maybe this is a bigger question. But is that because strength? Is that because application? Like why is that prescription only?

Erin Allmann Updyke

Ooh Erin, we will get there.

Erin Welsh

Okay.

Erin Allmann Updyke

Okay.

Erin Welsh

Okay, okay, okay.

Erin Allmann Updyke

But that is kind of like the big picture of retinoids in general.

Erin Welsh

Okay.

Erin Allmann Updyke

Do you have any questions? I'm shocked.

Erin Welsh

I mean I do but I know that you're going to get into a lot of it.

Erin Allmann Updyke

Yeah. Okay.

Erin Welsh

And so I want to be like but how does that this?

Erin Allmann Updyke

Yeah, yeah.

Erin Welsh

And how? What is it? Increase cell proliferation, is that a thing all the time? Like is that something that we should aim for or does that have potential consequences? Like are there consequences to retinoid use?

Erin Allmann Updyke

I mean absolutely, yes. So there are definitely major side effects. The biggest side effects for topical preparations of any type of retinoid but especially the prescription retinoid, so tretinoin and other similar retinoids, because there are other ones as well. The biggest side effect tends to be skin irritation and that's because it is doing all of the things that we said that it's doing, right. So it's increasing your cell turnover. It's like forcing your skin to be making a whole bunch more of what it's doing. And so especially depending on your skin type, depending on what you've been using before, depending on your sun exposure, some people have really strong negative reactions to various retinoids and really can't tolerate them. The other big thing to know about retinoids is that they are also teratogenic. So teratogenic means potentially incredibly harmful to a developing fetus. Now this is very true for isotretinoin which is the form of retinoid that is used orally in the US.

Erin Allmann Updyke

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Erin Welsh

Okay.

Erin Allmann Updyke

There are other forms of retinoids that are used orally in other places. So this is true for oral forms of vitamin A. While vitamin A is an absolutely necessary part of human embryonic development, like you can't make a brain or an embryo without vitamin A, it's concentration dependent. So if you have too much of it, you also are at risk for pretty severe developmental problems in a developing embryo. So with oral retinoids we see very high rates of congenital defects which can include anything from congenital heart malformations, neurologic malformations, so problems with your heart, problems with the nerves, problems with the way that the face is formed, and a whole range of really, really wide ranging developmental problems because it tends to affect really early stages of embryonic development. As well as a very high rate of spontaneous abortion when people are on oral retinoids and get pregnant.

Erin Welsh

Okay. I have a couple of questions.

Erin Allmann Updyke

Give it to me.

Erin Welsh

Why would you go on oral retinoids vs topical? Is it just to have more of these systemic or like deeper dermal effects?

Erin Allmann Updyke

Great question. So the main indication medically for oral isotretinoin is severe acne that has been unresponsive to everything else.

Erin Welsh

Okay. And then question two, you said that high doses of vitamin A can lead to congenital defects. Is that something that you would encounter outside of oral tretinoin? Like eating a lot of carrots? You know what I mean?

Erin Allmann Updyke

Yeah.

Erin Welsh

Does our body have a way of excreting excess vitamin A that is taken like through dietary forms?

Erin Allmann Updyke

Excellent question. It's not, it's a fat soluble vitamin so we're not excreting it.

Erin Welsh

Okay.

Erin Allmann Updyke

So it absolutely can build up in our tissues. It would be very difficult to get vitamin A toxicity just from eating something like carrots. Because again, those are precursor vitamins that you're getting in the form of carotenoids and things like that. So in that way it's not impossible but very difficult. Certainly if you're taking a bunch of supplements that aren't isotretinoin but are other vitamin A supplements, then yes, you definitely could see similar effects.

Erin Welsh

Okay.

Erin Allmann Updyke

So what I want to mention because I do think that this is an important part of the story is that because of the risk of birth defects and spontaneous abortion, but mostly because of the risk of birth defects, when someone is on something like isotretinoin or Accutane is one of the brand names for it, there are very extensive restrictions on the prescribing of this medication in the US and in most other countries. In a lot of places it's only dermatologists or other specialists that can prescribe it at all. And almost universally, anyone with a uterus who is considered of childbearing age has to read through a really extensive document that outlines the risks and guidelines of use, they have to sign a pledge committing to using two forms of contraceptive therapy starting one month prior to the medication and continuing for at least 1-3 months after they're done using isotretinoin. And in some cases they have to take monthly pregnancy tests before they can get each prescription which also means you can only get your prescriptions 30 days at a time. And despite all of this rigmarole, from what I have read there is no real evidence that this has actually decreased the risk of fetal exposure to isotretinoin.

Erin Welsh

Wait, why though?

Erin Allmann Updyke

Because I mean I think because there are so many layers to this, right. Like A) not all birth control is perfect, B) signing a pledge is not the same thing as doing it.

Erin Welsh

Sure.

Erin Allmann Updyke

C) how much are these risks actually being explained vs oh just sign here and do this and then you'll get your medicine.

Erin Welsh

Yeah.

Erin Allmann Updyke

Right? Like there's a lot, a lot, a lot of different layers to it.

Erin Welsh

Okay.

Erin Allmann Updyke

There's also a registry in the US that you have to sign up for and every person involved has to sign, the prescribing provider, the pharmacist who's dispensing it, the patient. And so it's all on a registry in the US which is a country that has restrictions on access to birth control and is banning abortions and criminalizing pregnancy. Okay, anyways.

Erin Welsh

Yeah. Yeah. Yep, yep, yep.

Erin Allmann Updyke

Yep. So it's important to know, it can be a very effective medication for severe scarring like cystic acne that hasn't responded to things like topical preparations. It has the potential for serious side effects like birth defects. It also has some other side effects. It can increase your liver enzymes, it can increase your cholesterol. Most of those are transient and so they tend to get better as soon as somebody stops the medication. And in some cases this medicine also can make people feel really bad, like cause things like depression to worsen, anxiety, and things like that. And we don't really understand the mechanisms of any of that.

Erin Welsh

Okay.

Erin Allmann Updyke

But it's not a medication that is easily prescribed, just like bloop. But anyways, let's get back to wrinkles.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

Shall we?

TPWKY

(transition theme)

Erin Allmann Updyke

All right. So I told you everything about what we know about something like Retin-A.

Erin Welsh

Yeah.

Erin Allmann Updyke

Or even adapalene which I will say is now over the counter, you can get adapalene. It's Differin is one of the brand names in the US. And that used to be only available with a prescription but now some concentrations of it are available without a prescription.

Erin Welsh

Just real quick because I feel like maybe you'll go down this road but the different formations of this, do they have just like different effects or they target different genes or what's the deal? Yeah.

Erin Allmann Updyke

I'm so glad you asked, Erin. So the prescription strength retinoids are all either retinoic acid which is tretinoin, Retin-A, or they are synthetic versions of a retinoid that are active when you put them on.

Erin Welsh

Okay.

Erin Allmann Updyke

That is the biggest difference between over the counter retinols that you can buy at CVS or wherever, Target, Costco, anywhere. Sak's if you want to buy expensive versions, right. All of those types which have names like retinol, retinaldehyde, and a whole bunch of these retinol esters; all of those types of retinols are not the active form. Retinoic acid, tretinoin, Retin-A is the active form of a retinoid. That's what's binding to your receptors. That's what's doing the thing.

Erin Welsh

Okay.

Erin Allmann Updyke

The other ones that are available through a prescription adapalene, there's also like I mentioned already isotretinoin. There's a newer one called tazarotene. There's a whole variety of these. These are synthetic versions. They look different than retinoic acid but they are binding to the receptors themselves. So they again, they work when you put them on. Everything that you can buy over the counter has to be converted. It is a derivative and isn't the thing that is binding to the receptor.

Erin Welsh

Okay.

Erin Allmann Updyke

So if you put on an over the counter retinol, it says retinol on the bottle, it has to be converted through a two step process before it becomes retinoic acid and is doing a thing to your skin.

Erin Welsh

Okay. So like what then is that process? Or like how is it... Yeah.

Erin Allmann Updyke

It's oxidation by enzymes in your skin. Basically your skin has to see it and be like oh I know what this thing is, it's like a vitamin A, I'm going to use it. Boop, boop, boop. Then it converts it and then it uses it.

Erin Welsh

But like ultimately then how is it... Is it just like the strength, the power? Like the concentration? Okay, okay.

Erin Allmann Updyke

Yeah. So here's the bottom line. Because I feel like one of the big questions that I had in doing this episode is like there's these prescription strength versions and there's these over the counter versions. We use the prescription strength for a lot of stuff. We have good data for tretinoin that it's doing most of the things that we're prescribing it for. There's less data for the photo aging effects of the other ones.

Erin Welsh

Okay.

Erin Allmann Updyke

Because they don't need to do that study. We'll get there.

Erin Welsh

Yeah, yeah. I'm excited for that.

Erin Allmann Updyke

But what about all of these other ones, right? Because you can get so many else. And the bottom line is that while we have evidence that some of these might work, we don't have the type of evidence that you would expect from a drug and we will probably never have that kind of evidence. So what it ends up being is that all of the over the counter retinoids are substantially less potent than tretinoin. So it's often, like the number that's cited is that retinol, which is one of the most common over the counter versions, is about 10x less potent than tretinoin, the prescription strength.

Erin Welsh

Okay.

Erin Allmann Updyke

So they put it in your bottle in theory at 10x higher concentration, right. Okay.

Erin Welsh

I feel like they tell me that it's not right.

Erin Allmann Updyke

Well... Erin, when I tell you how many papers I read for this to try and really get a sense of all of these other types of retinoids. Do they work or do they not? I still don't have a clear answer. All of the data that exists for these over the counter versions of retinoids are subject to major industry bias because nearly every study is funded by industry. Most of them are pretty small studies. None of them are really great studies. But there is a really big amount of data out there that is a conglomeration of data on histologic samples. So you cut skin, you apply stuff, you look at it under a microscope. Animal studies, so you put it on a mouse and see what happens to their cute little wrinkles. And human studies, which some of them are well designed and some of them are really not well designed. But they're human studies on face skin, on arm skin, on butt skin, on a whole bunch of different kinds of skin. And overall the conclusion that I come to is that there is a preponderance of evidence that some of these retinols work in a similar way to tretinoin. Mostly retinaldehyde there's maybe stronger evidence for and this is a type of retinol that only has to be converted one time in your skin before it's active.

Erin Welsh

Okay.

Erin Allmann Updyke

And to a lesser extent retinol which is one of the more common kinds and has to be converted twice. At certain concentrations these seem to be effective for treating photo aging which is the only thing that people are studying them for. So that's what they're studying them for.

Erin Welsh

Okay. Effective meaning what?

Erin Allmann Updyke

Effective meaning when you test them they reduce the appearance... I'm putting all of this in air quotes. They reduce the appearance of fine lines, they reduce the appearance of sunspots, solar lentigines, and in some cases might improve things like skin roughness or brightness or evenness or things like that. Again, these are not well designed studies. And I want to now remind ourselves of a really important part because what I said is that there is evidence for some of these types of retinoids that at certain concentrations they may be similarly effective to tretinoin. So let's remind ourselves of our supplements episode. If you haven't listened, please do, it's one of my favorites.

So cosmetics or cosmeceuticals which is when a cosmetic product is actually supposed to be doing something to your skin, anything that you're buying over the counter are regulated entirely differently than drugs that you get from the pharmacy. And much like supplements which are also not regulated, cosmeceuticals are not regulated essentially at all. Which means that just like for supplements, skincare companies can make a huge variety of claims about what their products can or can't do but they do not have to do any research to prove these claims. They do not have to get any kind of approval from the FDA and they don't have to even tell the FDA what's in any of their bottles of anything before it comes to market.

Erin Welsh

Really? Like there's no even ingredient quantity list because it's like proprietary?

Erin Allmann Updyke

You have to have ingredients on your bottle.

Erin Welsh

Yeah.

Erin Allmann Updyke

You don't have to tell the FDA anything about what it is before you sell it to consumers. Yep. Which also means that these companies have absolutely no reason to waste their money doing how much work it would take and spending how much money it would require to do good, well researched, well designed, side by side, randomized controlled trials where you're actually testing things the way that you need to-

Erin Welsh

Right.

Erin Allmann Updyke

To get something approved as a drug.

Erin Welsh

Rather than in ensure... Like an actual double blind or like instead of just ensuring that the data will fall the way you want it to fall.

Erin Allmann Updyke

Exactly.

Erin Welsh

Because just going back to all the different measures that you said, reduce the appearance of wrinkles, reduce the appearance of solar lentigines, increase skin elasticity. I know that you said some of the was histologic changes but I feel like two things are important to remember. One is that some of those observations seem to be just that, like subjective, does it look less wrinkly? Like how do you measure that quantitatively? But then number two, even if you do measure it quantitatively in some capacity, you could say 'reduce the appearance' even if it's the most minor reduction. And so is there actually meaning in that reduction?

Erin Allmann Updyke

Oh my gosh, Erin, I mean that's even like a whole other level because drugs don't even necessarily have to show that, right.

Erin Welsh

Right.

Erin Allmann Updyke

Like if you have statistical significance, that's not the same as clinical significance. That's something that's true in all of medicine and definitely not just skincare products but especially in skincare products. And I mean yeah, bottom line is not at any single cream or anything prescription or otherwise that you rub on your face is going to make you look like, I don't know, who doesn't have any wrinkles?

Erin Welsh

A baby?

Erin Allmann Updyke

A baby. Yeah, a baby. There you go. I was going to try and say a famous person, I can't think of any. But yeah, so 100%, that is definitely true. I will say there are ways to quantify things like hyperpigmentation or the depth of wrinkles and things like that. And some studies do that. But a lot of studies don't. And that's the point. I have so many sources that you guys can go and read through and some of these studies are fine. Some of these studies are halfway decent. But a lot of them aren't. And so it's really like you have to look at all of the evidence, right. And there isn't an incentive to do better studies.

Erin Welsh

Right.

Erin Allmann Updyke

And so here's the other thing that becomes so problematic with the way that these cosmetics and cosmeceuticals are regulated. There is no good way as a consumer to sort through these thousands of products that are available. And because labeling laws are essentially nonexistent, you have no idea what it is that you're actually getting, much less what percentage of these various retinols that you're getting.

Erin Welsh

Right.

Erin Allmann Updyke

So as an example, I did a Google search, I googled 'best over the counter retinoid'. That's what I googled. I found a bunch of these top 10 lists, like US World News is like best ones and health.com, click on my affiliate link, Allure. I looked at all of these. I went through every single one of these top 10. By the way they're all different which tells you something.

Erin Welsh

Yeah, it does.

Erin Allmann Updyke

I read through the ingredients on every single one of these bottles that they recommended as top 10. Most of them had absolutely no concentration listed, most of these use retinol which again has some data to support its use. A lot of them used retinyl palmitate which is a type of retinol ester that actually has data that shows it doesn't work, it doesn't do anything in fact. Very few of them use retinaldehyde which again is another one that has some data. And I will say it's the one that people are the most hyped up about.

Erin Welsh

Okay.

Erin Allmann Updyke

Which you just again have to take with grains of salt.

Erin Welsh

This is the newest iteration or like...?

Erin Allmann Updyke

Exactly.

Erin Welsh

Yeah, okay.

Erin Allmann Updyke

And all of these products that you're buying are also chock full of things like a bunch of other B vitamins, hyaluronic acids, all of these other things that skincare companies are claiming are also going to help your skin whether or not it's true, whether or not they have any data to show for it. And by putting all of these products in combination, you have no idea if any effect that you're seeing is from the retinoid that's in there or from anything else in that formulation, right. And... And I just keep going, Erin, because it's ridiculous. The formulation really matters for retinoids because retinoids are not stable. In light and in oxygen they break down very easily. So if you don't know how long your bottle has been sitting on the shelf, you don't know if it's still active.

Drugs, pharmaceuticals are tested in their entirety, right. Drugs are tested by the entirety of the formulation. So no matter what brand, whether it's generic, whether it's brand name Retin-A, if you are getting something that says it's 0.1% tretinoin then you are getting a formulation that has been tested to at least be noninferior to every other version of tretinoin that's available with a prescription. There is robust studies at least now because they've been forced to do it after that lawsuit apparently. And there's safety data to back all of this up. With cosmetics, sure, they can do a bunch of tinkering and add a bunch of stuff in that makes it go on smooth, makes it feel nice, right. But that doesn't mean that it's doing anything.

Erin Welsh

Yeah.

Erin Allmann Updyke

And just like with supplements, when independent organizations have gone through and actually tested off the shelf a whole bunch of different retinoids, that's exactly what they found is that they either don't contain what they claim they do or they don't contain it at the concentrations they claim or at like ridiculous concentrations that were nothing like the randomized control trials that the company funded to do anyways.

Erin Welsh

Right.

Erin Allmann Updyke

Or when they put them on their shelves, they degrade far more rapidly than they should. Therefore they're not effective by the time your bottle is gone. So would robust randomized control trials be really helpful? Yeah, they would. Where's the incentive? It doesn't exist.

Erin Welsh

Right.

Erin Allmann Updyke

You asked, Erin, what is the anti-aging market? Let me tell you.

Erin Welsh

Yeah.

Erin Allmann Updyke

In 2021 it was estimated to be valued at \$63 billion.

Erin Welsh

Did the article from 1989 say \$3 billion?

Erin Allmann Updyke

\$3 billion in 1989. \$63 billion in 2021.

Erin Welsh

Stop.

Erin Allmann Updyke

And most numbers that I saw, and this was from a number of different websites because this information is not like conglomerated into studies yet, most numbers said between \$68-72 billion today. And it is rapidly growing, like it just keeps growing. Who needs research? You've got marketing!

Erin Welsh: I mean okay. Just like here's the little devil's advocate here where I'm thinking okay well if the pharmaceutical companies aren't going to do this research, then who would do the research? Universities, researchers, research organizations. Is that the best use of funding?

Erin Allmann Updyke: No, it absolutely isn't, right.

Erin Welsh: So it's never gonna get done.

Erin Allmann Updyke: Because we're talking about wrinkles on your skin.

Erin Welsh: Yeah, right.

Erin Allmann Updyke: Now I will say acne is a totally different thing.

Erin Welsh: Totally different thing.

Erin Allmann Updyke: And that part of why... We should do a whole episode.

Erin Welsh: Yeah.

Erin Allmann Updyke: But that is part of why the FDA agreed to make adapalene, or what is Differin Gel is the brand name in the US, over the counter in the US in 2016 is because it was so restrictive to be able to get and it really works. And acne can be very problematic, it can cause a lot of scarring, it can cause a lot of psychosocial distress. It can cause like... It's painful. Acne is a very big deal. But we're talking about our wrinkles on your skin.

Erin Welsh: Wrinkles. Photo aging. Yeah.

Erin Allmann Updyke: Photo aging. Like I'm sorry, it's not the same thing. So no, it's not. And here's the other thing, it's not that this research is not being done, right. These companies invest heavily in R&D. But they are absolutely not going to be incentivized to publish that and let everyone else get their formulations. Why would they, right?

Erin Welsh: Right.

Erin Allmann Updyke: They're going to keep it in house. I mean of course it's capitalism.

Erin Welsh: It's capitalism.

Erin Allmann Updyke: I mean come on.

Erin Welsh: I mean so the answer to the question 'does it work for anti-aging?' is so layered, right. You could say yes.

Erin Allmann Updyke: You could say yes.

Erin Welsh: And you could say this study indicates that this, but you have to consider the effect size. How much does it actually reduce the appearance of wrinkles?

Erin Allmann Updyke: Yeah.

Erin Welsh: You could consider how well this study showed it but it did a different test. You could show that yes, it was statistically significant but the sample size was 10 individuals. There are so many different challenges in getting to an answer that is not with a million different layers of qualifiers.

Erin Allmann Updyke: 100%. I will say looking at all of the evidence from all of the things-

Erin Welsh: Sure.

Erin Allmann Updyke: Tretinoin has evidence, has good evidence overall that it can reduce some signs of photoaging. But yes, the question of what does that mean to one person vs another?

Erin Welsh: Right.

Erin Allmann Updyke: Does it matter to you? Does it not?

Erin Welsh: Well and then a follow up question that I would have to tretinoin and yes, okay, if there is evidence that is in support of reducing the signs of photoaging, how long do those effects last? If you use tretinoin, like how long does it take for tretinoin to have that impact? And then if you stop using tretinoin, do the effects go away?

Erin Allmann Updyke: It's a good question. Most of the evidence I saw is that it takes at least weeks. Like there are some... You also mentioned something about the FDA put a-

Erin Welsh: Yeah. Caveat?

Erin Allmann Updyke: Caveat on there that there's no histological changes. So it is interesting. The histologic changes that we see with tretinoin max out at a certain number of weeks and then seem to go back to being less histologic changes. But the visible changes when they do, I forget the names of the fancy photographs and things where they take things and measure things, those changes, like the visible changes remain and continue to improve. But the histologic changes seem to be more transient. So people are still trying to figure out what does that mean? Does that mean that the histology is not necessarily what is driving the visible changes? Anyways that's a little bit too detailed. But what was your question?

Erin Welsh: How long do the effects last?

Erin Allmann Updyke: Oh yeah. So they take weeks to months to see an effect but they do seem to last pretty long and you are also going to continue to age for your entire life. So like if you stop using them, you will go back to photo aging after a few months to a year, it seems like they last for at least a little bit of time.

Erin Welsh: But if you use them forever, you are also still going to photo age.

Erin Allmann Updyke: To some extent.

Erin Welsh: Yeah.

Erin Allmann Updyke: But significantly less than if you had never used them.

Erin Welsh: How significant?

Erin Allmann Updyke: Well statistically significant, Erin.

Erin Welsh: I know but what does that mean?

Erin Allmann Updyke: Clinically significant. Depends on the person. I mean it is because all of this is for cosmetics.

Erin Welsh: Right.

Erin Allmann Updyke: It's for how you look, how you appear.

Erin Welsh: Yeah.

Erin Allmann Updyke: Now especially as women, is that something that we are judged on constantly? Absolutely. I have a lot of feelings. And I think that's why I have so many resources and sources for this episode-

Erin Welsh: Yeah.

Erin Allmann Updyke: Is because I have a lot of feelings about this. But I'm trying to not dive into my feelings and just talk about the data.

Erin Welsh: Erin, conceal don't feel.

Erin Allmann Updyke: Thank you. Awesome.

Erin Welsh: Just kidding, never take that advice. That was the villain song.

Erin Allmann Updyke: It is, it is, it's true. But yeah. So I mean it is a really, really interesting, frustrating area and it's also, it is very, very hard to get good data. There are so many people out there who are trying to break it down in ways that are understandable for people which I appreciate but almost always at the end of it they are also being paid by skincare companies.

Erin Welsh: Yeah.

Erin Allmann Updyke: And so it's very difficult to then take all of that information as nonbiased, right.

Erin Welsh: Right. And we all have our biases.

Erin Allmann Updyke: We do.

Erin Welsh: In general. But it is different when there's monetary support for those biases I think.

Erin Allmann Updyke: Yeah, yeah. So I'm not gonna tell you any brands. I mean I did mention the brand names of some things just so people know what I'm talking about.

Erin Welsh: Yeah.

Erin Allmann Updyke: You can get generic. But do you use retinoids, Erin?

Erin Welsh: No because it made me break out. Yeah, I had a little thing of retinol and I don't know what happened but I started to use it and it made me break out. And I was like you know what? I'm not doing this.

Erin Allmann Updyke: Probably because it made you purge.

Erin Welsh: Yeah, probably. And I just don't really...

Erin Allmann Updyke: That's fair. I have two different bottles. I just bought a new one.

Erin Welsh: During the episode? Like prep?

Erin Allmann Updyke: During researching for this episode. I was like I'm going to try it.

Erin Welsh: That's hilarious.

Erin Allmann Updyke: I still have never used prescription strength which I think is especially funny because I could have had a friend call in a prescription for me at any point. I mean I still could but I've never used the prescription which is the one that has the most evidence. It's all just... I don't know, Erin.

Erin Welsh: I know. It's complicated. And I think I struggle a lot to articulate how I feel about aging and wrinkles and the freckles on my face and the fine lines and this and that and I don't know. I don't know.

Erin Allmann Updyke: I will say all of the studies that I read, and I read a lot, they all look at these areas near your eyes and near your mouth.

Erin Welsh: Laugh lines.

Erin Allmann Updyke: And I'm like I don't even care about those wrinkles, what about this one? There's nothing. There is nothing that will touch this between my eyebrows except Botox.

Erin Welsh: Botox.

Erin Allmann Updyke: We already did that episode. But yeah, Erin, I don't know what my conclusion is. There's some evidence for some things but it is almost impossible to know if any of the things that you can buy over the counter are going to work. And so there are a lot of people whose stance is absolutely don't waste your money, they're a complete waste of money. And I think that that might be a slightly unfair stance because for some people they might work because again there is some evidence that they work in some cases. But it's also not okay to say oh these totally work because there's such a huge range.

Erin Welsh: Right.

Erin Allmann Updyke: And it's just so difficult as a consumer. Like nobody is looking out for us to help us sort through this essentially. So once again, the consumer just has to waste our money. Or not.

Erin Welsh: It is supplements redux.

Erin Allmann Updyke: It is, 100%.

Erin Welsh: We're doing the same thing where it's like what's the harm? Well you're spending your money on stuff that may or may not do anything.

Erin Allmann Updyke: Yeah. And you might get a really bad reaction to it.

Erin Welsh: Yeah.

Erin Allmann Updyke: Because even though over the counter retinols, because they're less potent, tend to have less side effects of the peeling and the irritation, the redness, they're not without side effect.

Erin Welsh: Right. Yeah. Yeah. I don't know.

Erin Allmann Updyke: It's a lot, Erin.

Erin Welsh: Anyways. It's a lot.

Erin Allmann Updyke: It is a lot. If you want to read more, I have, I don't know, 2.5 entire pages of citations. So let me tell you about some of my favorite ones. Couple textbooks that I read, cosmetic dermatology textbooks if you want some more detail on the skin and just like big picture stuff. My two favorite review papers that looked at the overall evidence for these over the counter vs prescription strength retinols were one by Levin et al from 2010 that was titled 'How Much Do We Really Know About Our Favorite Cosmeceutical Ingredients?' I liked that one. I also really liked one by Tetali et al from 2020 that was titled 'Popular Over the Counter Cosmeceutical Ingredients and Their Clinical Efficacy'. I thought those were pretty well balanced reviews. But I also have a whole bunch of actual data papers if you want to get real deep dive in. I've got some on the evidence just for tretinoin and then also some on the teratogenicity of retinols.

So one thing I should mention that I did not mention earlier is that when I was talking about the increased risk of birth defects and spontaneous abortion with the use of retinoids, that applies to oral retinoids. Recommendations from every single medical society are to not use any kind of retinoid including over the counter, including topical just for your skin products at any time while you're pregnant, no matter what. All of the data that we have on the risks of birth defects is for oral medications of retinoids. We don't have strong data that shows that topical retinoids that you put on your skin increase the risk of birth defects. But out of an abundance of caution, the recommendation still stands to not use any kind of retinoid product. So just to clarify, if anyone was wondering why. So I got all those sources and there's a whole bunch more and we'll post the list of all of them on our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh: We will thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke: Thank you to Tom Breyfogle and Lianna Squillace for the audio mixing.

Erin Welsh: Thank you to everyone at Exactly Right.

Erin Allmann Updyke: And thank you to you, listeners. I hope you enjoyed this two part deep dive.

Erin Welsh

Yeah.

Erin Allmann Updyke

Do you use retinols? Do you use prescription retinols? Do you not use any retinols? Do you use over the counter retinols? I really want to know.

Erin Welsh

Do you have feelings about retinols?

Erin Allmann Updyke

Do you have feelings? I have a lot of feelings.

Erin Welsh

Yeah.

Erin Allmann Updyke

Should we do a whole episode about wrinkles?

Erin Welsh

Oh yeah. I thought you were going to say should we do a whole episode about feelings. Yes. Yes, yes. And a big thank you of course to our wonderful, lovely, generous, fantastic patrons. We appreciate your support. It means the world to us.

Erin Allmann Updyke

It really does. Thank you so, so much.

Erin Welsh

Well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.