THE FUTURE OF MEDICINE:
OPTIMIZING THE PATIENT EXPERIENCE WITH PDURS

Healthcare faces numerous challenges. Managing chronic health conditions, from diabetes to insomnia, require comprehensive and ongoing care that often exceeds the capacity of current healthcare systems.

What happens when we get a diagnosis of diabetes, or obesity, or cancer? The associated risks and comorbidities can develop quickly, demanding fast lifestyle changes. If we're diagnosed with cancer, our risk of suicide increases by 26%1. Over 50% of people with diabetes will develop diabetic retinopathy, which left untreated leads to blindness. If detected and treated early, the risk of severe vision loss is reduced by 95%.2 Men with a BMI over 40 are 52% more likely to die from cancer than men with a healthy BMI. Women with a BMI over 40 are 62% more likely to die from cancer than women with a healthy BMI.3

And we are certainly in trouble if we are diagnosed with insomnia. About 10% of Americans have insomnia, around 30 million people. Medical guidelines state that patients should start their treatment with Cognitive Behavioral Therapy4, not the drugs that have significant side effects. So let's find a doctor. There were 659 behavioral sleep medicine providers in the US in 2021. One more time, that's 659. For 30 million people! So what do patients get first? Drugs that have a whole host of side effects including addiction, depression, decreased memory function, and dementia, instead of DTx5.

In an era where brief doctor visits and limited access to specialized treatments often fall short, patients and providers need ongoing support and personalized treatment for holistic care.

While managing the full patient odyssey is always going to be difficult, the answer is right in front of us: digital therapeutics(DTx), digital diagnostics, remote monitoring, VR and AR, wearables, connected devices, and smart devices. You will hear it referred to as AI, aging in place, food as medicine, music as medicine, tech enabled care, virtual care, medication management, and now, PDURS.

PDURS: AN OVERVIEW

“Prescription Drug Use Related Software,” or PDURS, is a term coined by the US FDA in 2023 to address a growing need for guidance around the mixed use of drugs and software.

Note 1: it is pronounced Puh-durs, not putters, or P-Doors. It sounds like how you’d say PDUFA.

Note 2: it has become normal vernacular to actually call the software product enhancing a drug, the “PDURS”, so when I say that and it sounds weird, it is.

Note 3: I’m putting this together from 100s of conversations that I have had with various stakeholders over the last 6 months. This will continue to evolve for decades, so please reach out if you disagree with anything or want to add anything to this piece.

We are all familiar with the concept of drug-device combo products, and you have probably heard of “companion apps” that offer little to no clinical benefit. With the rise of clinically validated software making medical claims, there are an increasing number of pharmaceutical companies that are pairing their drugs with a software that supports the patient on their journey with that drug.. Let’s rewind to 2017 with Propellor attaching to inhalers, Proteus surrounding a pill with a sensor, Welldoc demonstrating a strong benefit in chronic care management, Akili treating ADHD, and software interventions like Freespira that include a hardware component. Fast forward 7 years, and the FDA’s foresight must be applauded, because the evolution of Software as a Medical Device (SaMD) has coincided perfectly with the release of the FDA’s draft guidance on PDURS, which should be finalized in 2025. Now we have a much clearer way to build software to provide additional benefits to drugs, with a whole host of positive health outcome potential for patients.

ISO defines DTx as “health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient’s health”. You could sit in a room for hours and still not complete a list of all the potential use cases for

DTx. But the complexities of the current healthcare systems, the entrenched insurance landscape, the slowness of policy change, and the costs associated with innovation in healthcare, has stifled our ability to demonstrate digital health's true potential. Germany has over 60 stand alone prescription digital therapeutics (PDTs) covered by insurance, France is following suit, as are South Korea and Japan. In the US, coverage for stand-alone DTx is still not clear. We have supply codes for remote therapeutic monitoring (RTM) and we should see new G-codes in the 2025 Physician Fee Schedule to cover digital mental health treatment devices. While we still see great potential for standalone DTx, there is nearer term potential for DTx, and SaMD in general, used alongside drugs under the proposed PDURS regulatory pathway.

Prescription drugs have long been searching for a revitalization. Many blockbuster drugs are now generics, biologics have quickly become biosimilars, new molecules are focused on rare diseases and are designed to take care of very complex patients, and of course we are seeing completely game changing drugs like GLP-1s. The need to focus on patient safety, dose optimization, side effect management, behavior change, and improved therapeutic outcome is imperative. And that can all be managed through PDURS. So let's take a look at the various benefit potentials of pairing software with a drug and why this topic is gaining so much attention as a game-changer in health care:

PDURS FOR PATIENT SAFETY

We start with why we absolutely need PDURS: Patient safety. Often when a pill is prescribed, the doctor does not know what the patient is doing until their next visit. During that period, patients may experience minor side effects, potentially harmful reactions, or incorrect dosing. These are all concerns as negative side effects could be avoided with the right intervention.

Comorbidity Management: Consider a scenario where someone is diagnosed with cancer. Patients often experience depression and anxiety. Throat cancer is so painful, that people can't swallow, and unfortunately that can cause people to have suicidal ideation, or worse. A PDURS can help patients manage these types of comorbidities to ensure that they have the best mental health possible throughout their treatment. Across all cancer patients hypertension, COPD, diabetes, cardiovascular diseases, congestive heart failure and peripheral vascular disease were among the most commonly recorded comorbid conditions6.

Imagine struggling with any disease or disorder during cancer treatment. Patients simply aren't in a mental state to manage hypertension effectively if we're worried about going through chemotherapy. Many of these comorbidities can be managed, in a clinically meaningful way, with a PDURS. There is a clear value to the patient to understand the full spectrum of their diagnoses and be able to manage all of the issues that come along with it. Additionally, that data can be shared with your provider to further ensure your safety.

Side Effect Management: Similar to comorbidities, there are a wide range of side effects from pharmacologic interventions that can impact patient safety. We discussed anxiety and depression associated with cancer diagnosis as a comorbidity, but what about the actual side effects of drugs in areas like bipolar disorder and depression that have increased suicidality as a potential risk? GLP-1s can cause GI issues. Other drugs can cause insomnia, or even weight gain. A PDURS can be used to manage many of these side effects, especially when starting on a new drug or adjusting your dose up or down.

Dose Optimization: Historically, and currently, dose optimization is done by starting a patient on a low dose, testing the outcome a few months later, making adjustments… let's call it trial and error. And as you increase the amount of drug you put in your body, you can also increase the side effects. Through remote monitoring, progress tracking, and other remote interventions, patients can get on the right dose for them faster and with less risk through PDURS.

Adherence and Patient Engagement: Products that ensure patients take their medication correctly and on time are essential for achieving positive outcomes and managing side effects. While general medication adherence apps may not typically qualify as PDURS, addressing challenges with complex medications and incorporating behavioral components would certainly fit within this category.

PDURS FOR PATIENT OUTCOMES

And now that we've upgraded medications to manage patient safety, let's look at how we can improve patient outcomes. There's a lot of crossover here between outcomes and safety. The DTA will work on taxonomy and definitions over time to provide more clarity.

Enhanced Clinical Benefit: In some cases, we see that the clinical benefit of a drug alone isn't as strong as we'd like, or only works in a certain patient population. For example, taking buprenorphine alone is generally not enough to end an opioid dependency. I bring this example up because substance use disorder products could be PDURS or a standalone DTx used with a drug. Either way, it is improving the patient journey, but this is a scenario where the lines are blurred. Consider a product that is helping but not fully alleviating symptoms, for example in postpartum depression. designed for a very specific use case like postpartum depression. This is where PDURS can step in, offering additional support to optimize treatment, address unmet needs, and provide continuous monitoring and interventions that enhance the effectiveness of the medication.

Precision Medicine: Precision medicine is a medical approach that considers a patient's unique genes, environment, and lifestyle to help prevent, diagnose, or treat disease. The last two can really only be managed well through technology. I have read 3rd party reports that make negative statements such as: "this diabetes solution only works well for people with really bad A1C". I disagree with that being negative. PDURS can be targeted to specific people with "really bad A1C". We can use the PDURS to help define that patient cohort and help those patients manage their lifestyle with their insulin and regain control over their disease.

Remote Monitoring: Tracking patients' progress through remote monitoring and remote diagnostic tools is very important. You don't need to go to the doctor's office to take a PHQ-9 for example. If your mental health is in decline, and you don't have your next checkup for 6 months, the doctor won't know, and technology is the only solution here. A PDURS can markedly help that patient. And as discussed already, it is vital to track decline in vision associated with diabetes.

Behavioral Change: Last, but certainly not least, nearly all diagnoses require some level of change to a patient's lifestyle - whether it be the food they eat, the sleep they require, or the amount of exercise that they need. In an ideal world, there is a PDURS that can deliver cognitive behavioral therapy or help with behavioral change to ensure the best outcome of a drug.

THIS HAS PIQUED PHARMA'S INTEREST:

Hopefully after reading the last section, you can see the multitude of reasons that PDURS is beneficial for the patient. Pharma sees all of the points above as a way to evolve solutions to decades old problems with pills. Collecting real world evidence with drugs is particularly difficult when adherence is measured through de-identified claims data that shows whether or not a patient refills their scripts once a month, and even then, the pharma company doesn't know if the patient is taking their drugs, taking them on time, using them properly, etc.

SOME KEY POINTS FOR PHARMA:

Adherence: We know that patients don't take their drugs every day. We know that patients stop taking drugs even when they need them. Improved adherence can have an improved impact on health, reducing risks of complications and improving long-term outcomes, which should lead to an increase in patients refills.

Real World Experience and Adverse Events: One of the key benefits of PDURS is its ability to help patients monitor and manage side effects. By providing real-time feedback and guidance, PDURS can help patients recognize when they may need to adjust their dosage or consult with their healthcare provider, ultimately leading to a more tailored and effective treatment plan. But this goes a step further for pharma because they can truly understand how their product works in the real world with PDURS. Today, adverse events are only reported if the patient feels like it or reports it to someone trained to tell the manufacturer. With a higher touch patient experience, we can start to truly understand and improve the way that humans interact with their medication.

Brand Differentiation: There is a shortage of healthcare providers, and many are overworked and dealing with burnout. If a doctor knows that your product will help manage side effects better, or ensure that a patient is taking the proper dose, or that it will have a better clinical benefit, then there is a logical argument that the doctor will prescribe the drug/PDURS combo product over a competitor or a generic.

Considering all of this, there is a very compelling reason why pharma is interested in PDURS: data. Pharma doesn't have much access to patient behavior outside of knowing whether or not a patient refilled their script. Sure you can purchase claims

data from one of the claims aggregators, but that doesn't let you understand real world / real time feedback about a patient's interaction with a drug and how they manage their disease.

Of course you could make the argument that people don't want to share their data with big pharma, or with anyone. But population health only improves when we have data - and when pharma has data, they truly have some of the smartest people who can turn those insights into impactful solutions. For example, if a patient starts on 5 mg of a blood pressure medication and their dosage is gradually increased to 25 mg, their daily blood pressure can be monitored in real time. If, at 15 mg, the patient's blood pressure drops significantly, this crucial information (data that would otherwise be difficult to capture) can guide adjustments to their treatment plan, ensuring safety and improving care outcomes. This is a real world scenario where data that would otherwise go unnoticed becomes accessible.
This data could be used to understand the patient journey, patient behavior, how to best manage the disease, how to better manage side effects, etc.

We could talk about data scenarios and potential for a very long time…let's move on.

STAND ALONE VS. PDURS

I am often asked when something should be a PDURS vs. a stand alone DTx. To the point where people wonder if there is a need for standalone DTx. I think the answer is clear - if the SaMD product must be used with a certain drug, then it should be a PDURS, and if it can be used across multiple drugs or without a drug, then it should probably be a stand alone intervention. However, there are a multitude of reasons why you would potentially make what could be stand alone a PDURS.

There are products for depression associated with diabetes for example. These products can work to treat patients, on any medication, with diabetes. Do we truly need a PDURS version of this product for every diabetes drug? No, we don't. But if there is a diabetes drug that very clearly shows an increase in depression severity in patients, then you would want a PDURS product.

> *I believe that every pharma company will have a PDURS center of excellence where they make a PDURS decision on every drug that they manufacture. That's 20,000 drugs in the US that need a PDURS determination.*

HOW WILL THESE GET PAID FOR?

There are, of course, a variety of PDURS business models. The first one presented to me was a scenario where the PDURS product was included on the drug label to help manage side effects, and would be no additional cost to the drug. It would be designed to provide additional care management to the patient and to help with data collection to understand the patient journey. Therefore, insurance would cover the drug on formulary under the pharmacy benefit like it always does, and the PDURS product would be dispensed at the doctors discretion. Whether or not the standalone drug has a different NDC than the drug + PDURS has yet to be seen. There are certainly analogs in the drug + device combo space that mirror this. In the case where the clinical claim is tied to both the drug and PDURS, then the PDURS must be dispensed with the drug, and again we'd most likely be looking at the NDC / formulary route on the pharmacy benefit.

If the products are "cross-labeled" (ie. distributed separately) and billed separately then you would be combining pharmacy and medical benefit. In the long term, we will see a lot of this, but I suspect we're going to see much of this fall under the NDC paradigm because that is, justifiably so, Pharma's expertise.

I'd love to be able to say that we aren't reinventing the wheel here. The pathways for drug-device combos have been explored for decades. But I can't find a clean analog where a drug-device combo could directly require the use of CPT codes for a physician service like Remote Patient Monitoring (CPAP machines do offer RTM possibilities but there isn't a drug included). With the new codes for mental health treatment devices proposed in the 2025 physician fee schedule, we could easily see mental health PDURS products billed separately as a G-Code or CPT supply code in the future. And as we continue to work with CMS on how they pay for SaMD under new and existing benefit categories, then we will continue to see this space evolve.

And we could certainly start seeing PDURS fall under value based care arrangements (I think that's pretty far off though).

Please share your thoughts on reimbursement as well so I can continue to gather information as we work with government and commercial payors and purchasers.

WHAT IS THE DIGITAL THERAPEUTICS ALLIANCE DOING FOR PDURS?

DTA has formed a dedicated PDURS Task Group. This task group, comprised of manufacturers, pharma, law firms, and subject matter experts, is identifying PDURS opportunities and potential hurdles and crafting strategies to navigate them. We're actively collaborating with the FDA, OIG,ONC, and CMS to address regulatory, compliance, and reimbursement challenges.

When developing and commercializing PDURS, having the right tools and resources is essential. DTA offers a suite of valuable resources that can serve as a foundation for PDURS projects, including the Commercial Launch Playbook, the Value Assessment and Integration Guide, and insights into Global Regulatory & Reimbursement Pathways. These tools provide a strategic starting point, offering guidance on market entry, value demonstration, and navigating complex regulatory landscapes. Additionally, DTA's PDURS Task Group is dedicated to addressing gaps specific to PDURS guidance, offering expert insights to help drive successful development and commercialization efforts.

ARE WE SOLVING CHALLENGES?

PDURS truly has the potential to get us closer to providing seamless, integrated, healthcare to patients. As I go through the list of current gaps, PDURS might be the only solution for many of them. And we do require frameworks and guidance in healthcare to build appropriate guardrails that allow us to develop consistent products and services for patients.

We aren't there yet: Why is Germany reimbursing for standalone DTx, but in the US we don't? Forcing DTx into Remote Patient Monitoring only makes sense in certain scenarios. The codes for digital mental health treatment devices will only cover a small number of products as a physician service. And because much of our healthcare is defined around time based reimbursement, we stifle innovation by saying that efficiencies cost much less than old, arduous solutions. And we really stifle innovation by not knowing how to pay for software as a medical device (in 2024!)

DIGITAL THERAPEUTICS ALLIANCE

> *If I could reinvent healthcare from scratch, and design it for the 21st century, it would combine all education, drugs, devices, services, providers, care management, and digital interventions into an individual care plan and bundled service that spans across multiple therapeutic areas. I'm not sure we'll get there in my lifetime - But I'm really excited to see PDURS as a step in the right direction.*

If you feel like you now have more questions than answers, great! We're exploring uncharted waters here. Feel free to sit in the bleachers and watch the game. Or, get involved and make a difference. Reach out to info@dtxalliance.org to learn more.

1https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2800688 2https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/diabetic-retinopathy#:~:text=Anyone%20with%20any%20kind%20of,diabetes%20will%20develop%20diabetic%20retinopathy
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