

Fulfilling the Promise of Medications

Supporting Optimal Use with Aids and Devices

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Optimal medication use is multi-faceted in its dependencies on regimens, prescribing physicians, clinical oversight by pharmacists and behavior of individuals; and suboptimal medication use is broad and far-reaching in clinical, quality of life and economic consequences. Suboptimal use of medications is not only prevalent and consequential, but also represents a significant portion of the aggregate risk for poor events in a population that can be reduced through intervention and proper application of patient supports. This is an environmental scan of the existing aids and devices along with synchronization strategies intended to support optimal medication use.

To date, multiple but disparate approaches to influence and achieve optimal medication use have been deployed. They lack unifying modalities and interventions that can be applied broadly. We have used this analysis to bring forth a roadmap for a best in class solution that connects healthcare to the home, with access that extends into the daily lives of patients, creating a passive omnipresence and connectedness with healthcare team members and family caregivers.

Achieving Optimal Medication Use

Optimal medication use is a function of two connected, but distinctly different components: optimal regimens and optimal consumption. Optimal regimens (drug use plans) consist of optimal combinations of active ingredients, in the optimal strengths, in the optimal forms, scheduled at the optimal administration times throughout a person's course of therapy (oftentimes lifelong). Optimal consumption is the ability to adhere to the optimized regimen (which may be dynamic and ever-changing) without varying from it.

Though seemingly straightforward, achieving optimal medication use often requires highly coordinated, well trained, continuously and completely informed prescribers and care team members to create an optimal drug use plan, as well as a patient with the capacity and willingness to follow that plan. For patients such as elderly Medicare recipients, who see 13 different prescribers in one year and fill 50 unique medications in that year achieving optimal medication use is anything but straightforward and the trend of increasing numbers of patients with growing complexity of medication use continues to rise. The number of elderly patients on five or more medications is up more than 5% over a five-

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year periodⁱ and polypharmacy that leads to drug therapy problems such as interactions and duplications increased 18% while the use of dietary supplements increased by more than 20% over a five year span.ⁱⁱ

Adequate supports are essential to serving these populations. Patients with multiple prescribers who receive care from multiple locations traverse a system of care without continuity with respect to their medication regimens. Without adequate supports for many of the patients in our healthcare system, the promise of medications to produce health and increased quality of life is not achieved.

The Clinical and Economic Consequences of Suboptimal Use of Medications

The Medicare recipient described above is 100 times more likely to have a preventable hospitalization, oftentimes resulting from suboptimal use of medications, leading to poor clinical and economic outcomes.ⁱⁱⁱ

This highlights the essential role (and presence) of modifiable risk in subsets of the population with special medication use needs. Suboptimal use of medications is not only prevalent and

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consequential, but also represents a significant portion of the aggregate risk for poor events in a population that can be reduced through intervention and proper application of patient supports.

Clinical Consequences of Suboptimal Regimen

Suboptimal regimens are commonplace. Whether under or non-treatment for conditions resulting from lack of access to prescribers for refills or poly-pharmacy from multiple prescribers, “regimen drift” is almost certain to occur over time for patients with multiple chronic and/or recurring illnesses owed to multiple incomplete, misinformed, under-informed or otherwise inadequate reconciliations of prior drug use plans to updated drug use plans when moving from one setting of care to the next, to the next, and prescriber to prescriber, and pharmacy to pharmacy. Even for patients with one chronic condition such as hypothyroidism, the lack of an updated lab result or repeat visit to their prescriber, could result in poor outcomes from suboptimal or even harmful dosing.

Without well-founded, continually updated and re-optimized regimens, patients have little chance of achieving the full benefit of medication use. And in many instances, patients could be harmed. One study demonstrated that polypharmacy resulted in a significantly higher hospitalization risk in elderly patients, nearly 1.7 fold higher than those not taking potentially inappropriate medications.^{iv}

Economic Consequences of Suboptimal Regimen

It's estimated that the cost of increased morbidity and mortality resulting from drug therapy problems such as therapeutic duplications, suboptimal dosing, drug interactions, and others is more than \$200 billion (in 2016 terms).^v While recent attention has (rightly so) been given to adherence and the clinical and economic consequences of nonadherence (an aspect of suboptimal consumption), suboptimal regimens remain a very insidious, under-recognized and costly problem in our healthcare system.

Patients' nonadherence to medications results in equally profound economic consequences, representing between \$100 and \$300 billion dollars to the US Healthcare System.

Clinical Consequences of Suboptimal Consumption

Patient nonadherence is arguably the most well-recognized of all the barriers to optimal medication use. Patient

nonadherence to medications remains quite prevalent, with roughly a third of all prescribed medications not being filled,^{vi} and more than a third of those that did reach their first fill not persisting for more than a year.^{vii} The clinical consequences are profound. Numerous studies have found a connection between lack of patients'

Medication administration errors have been found to account for \$21 billion dollars in healthcare spending resulting in nearly 7,000 preventable deaths

adherence and poor or worsening clinical outcomes. Nonadherence to diabetic therapies resulted in a 20% increase in hypoglycemic events.^{viii} Approximately 18% of patients newly diagnosed to oral diabetes medications and taking them for 2.5 years developed microvascular and macrovascular complications as a result of nonadherence.^{ix} Another study observed the impact of nonadherence to antidepressants in major depressive disorder. Results demonstrated that patients who were adherent to certain antidepressants were 14% less likely to be hospitalized and 20% less likely for ED visits.^x

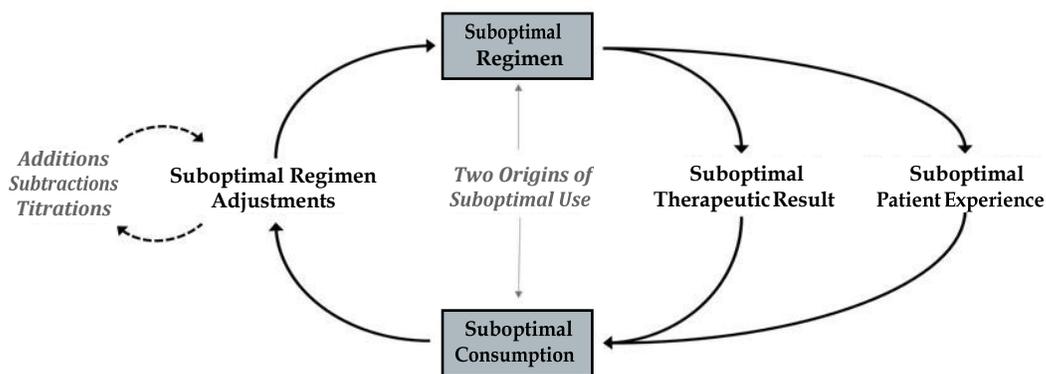
We often forget, though, that lack of proper administration contributes to poor clinical outcomes. This type of suboptimal use can emanate directly from patients through poor (or completely erroneous) administration technique such as in the improper inhalation of corticosteroids for asthma or COPD treatment, or it can be the result of a caregiver or care team such as a nurse, administering

the wrong medication or injecting or applying improperly such as putting medication patches on top of other medication patches for cardiac treatments or pain management. Improper administration of medications can often lead to death, hospitalization, or emergency department use.^{xi}

Economic Consequences of Suboptimal Consumption

Patients' nonadherence to medications results in equally profound economic consequences, representing between \$100 and \$300 billion dollars to the US Healthcare System.^{xii} Nonadherence to diabetic therapies resulted in a \$2,432 increase in total medical costs.^{viii} Optimal consumption of medications goes beyond a patient's adherence to following a drug use schedule; medication administration errors have been found to account for \$21 billion dollars in healthcare spending resulting in nearly 7,000 preventable deaths.^{xii}

Figure x: Cycle of Suboptimal Medication Use



Failing to Achieve Optimal Medication Use: The Evidence is Overwhelming

Whether through suboptimal regimens or suboptimal consumption, evidence continues to mount that suboptimal use of medications is endemic, with a multi-faceted set of underlying drivers and environmental influencers.

Under treatment

Under treatment is arguably the least recognized, and most pernicious drivers of suboptimal medication use and poor outcomes. Under treatment has been found to be the most prevalent of drug therapy problems discovered during comprehensive medication reviews and is more pronounced when the interventionist has access to clinical findings and laboratory results. Sub-therapeutic and suboptimal dosing of medication has even been found to result in clinical trial failure and effect size retardation owed to under dosing.^{xiii}

Over treatment

Over treatment can occur when too many medications are included in the medication use plan or the dose of one or more of those treatments is too high.^{xiv,xv} Over treatment was the motivating factor for Drug Regimen Reviews and the focus of quality Surveys in long term care settings beginning in the 70s and 80s to prevent the overuse of psychoactive medications.^{xvi} Commonplace also in pain management and behavioral health, overtreatment can be the result of both inadvertent as well as overt actions.

Conflicting Treatment

Drug-Drug interactions and Drug-Condition mismatches also contribute to suboptimal medication use and occur frequently even though numerous computerized order entry decision support systems and drug utilization review programs exist to prevent it. Despite these medication use systems, adverse drug reactions still occur in a variety of clinical settings. An estimated 350,000 adverse drug reactions occur in U.S. nursing homes that a portion of these reactions could come from drug-drug interactions and drug-condition interactions.^{xvii}

Patient Nonadherence

Nonadherence rates, in the US, currently range from 25% to 50%.^{xi} Widespread and problematic patient nonadherence is not unique to the US Healthcare Ecosystem, but is a global phenomenon. In a review of nearly 100 studies on patient persistence to therapy, fully one-third of patients initiated on a medication never procure the medication initiated, and a third to half of those that do procure their first supply, do not persist with continued procurement by the end of the first year of therapy for many medications used to treat chronic illness.^{vii} Even in the clinical trials process, where protocols are tightly controlled and patient supports are many, evidence of nonadherence to medications being studied is beginning to emerge.^{xiii}

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Improper Administration

Even when the optimal regimen is put in place alongside a patient centered medication use plan and a willing patient and/or care team to administer medications according to that plan, improper administration can occur, rendering all of the efforts to optimize drug use meaningless, or worse – causing harm. It is important that proper medication use education is provided to patients to ensure that they are receiving the optimal benefits from their drug therapy. In one study, parents and children were interviewed to determine how they use inhalers. Nearly 70% of the patients interviewed were using the inhalers incorrectly, possibly resulting in suboptimal therapy.^{xviii}

Reasons for Failure to Achieve Optimal Medication Use

Lack of Patient Access

Willing and able patients are not able to follow a medication use plan (or even achieve an appropriate medication use plan without access to prescribers to prescribe the medication and/or receive refills. Once a prescription is written, the patient must also be able to pay for the medication (or portion thereof) to procure it. Even when the prescription is written and the patient has the means by which to pay for it (or co-payment is reduced or non-existent) the patient may not be able to travel to the pharmacy to pick it up, or to the clinic to get it prescribed.

Lack of Care Coordination

Once the prescription is written, it must work in concert with and harmoniously with the other prescriptions written and (sometimes) filled at the pharmacy. With 13 different prescribers in one year, the Medicare recipient with multiple chronic illnesses needs a regimen

review after every visit to ensure that new meds, dropped medications and titrated medications work with all of the other medications and a new medication use plan must be enacted. Otherwise drug misadventures and suboptimal regimens ensue.

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Lack of Actionable Feedback Loops

Once a medication use plan is set, it cannot go without regular check-ins. As patients age, diseases progress, body weight changes, behavioral circumstances oscillate, metabolism and pharmacokinetics change, medication clearance wanes, patient motivation(s) evolve, intentions and patient goals change, and a host of other dynamic circumstances are at play. Medication use plans rely on actionable feedback to be effective.

Patient Feedback

The value of obtaining actionable feedback from the patient is woefully underappreciated. We often forget as providers of care that, ultimately, we work for the sake of meeting

patient goals, which can change over time. We also forget that patients are often the experts in judging their own health, their own wellness and the effectiveness of the treatments they have been prescribed. Patients are experts in their own livelihoods and expectations of their medications. And they are likely the first to pick up on suboptimal or stale medication use plans that need to be re-engineered owed to side effects, lack of symptom resolution or failure to otherwise meet the needs of the patient. Precious little feedback is received from patients in the creation of regimens and medication use plans, and even less is provided after the prescription is written or the regimen is set. One of the best examples of the lack of patient feedback being sought or provided in our system lies in dose titrations and inter-class changes in therapies owned to "treatment failure", when in actuality, the patient isn't consuming the medication properly either by act of omission or improper administration. This can be both active and inadvertent, but

rarely does the prescriber seek feedback before pulling the trigger on escalating therapy to a higher dose or to second line therapy.

Caregiver Feedback

With many of the traits of patient feedback, caregivers are often a crucial source of information about suboptimal regimens as well as consumption. They are both sentinels as well as coaches. Often family members, but sometimes neighbors or patient advocates, they are a member of the team and without them care team members and prescribers often operate in a vacuum of information. Caregivers at current are disconnected from care team members and prescribers in most instances.

Care Team Member Feedback

Since prescribers often only have 1-3 interactions at 8-15 minutes at a time with patients, care team members such as pharmacists, home health nurses, aides, behavioral health coordinators, care managers, social workers, patient navigators as well as prescribers and other care team members should endeavor to provide actionable feedback to prescribers, caregivers and patients. They often act as conduit between patients and caregivers and the multitude of prescribers involved in one's care over time.

Prescriber Feedback

Even prescribers fail to provide feedback to other prescribers. Referrals are rarely accompanied with medication lists and annotations therein that provide a narrative of how a patient arrived at a particular medication use plan and why it may need to be changed.

Lack of Individualized, Patient Centered Medication Use Plan

Each patient's conditions, combinations of conditions, disease trajectory, life trajectory, wants, needs and desires are different. Two persons living across the street from each other may be have the same age, gender, race, set of conditions, and medications and have completely

different experiences with their medications, beliefs about their medications, use patterns with their medications, metabolism of their medications, and manner in which they chose to administer their medications. Individualized, patient centered medication use plans are needed for every patient and need to be updated frequently to fully realize the promise of medications.

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Lack of Integration of Medication Use Plan with Daily Life

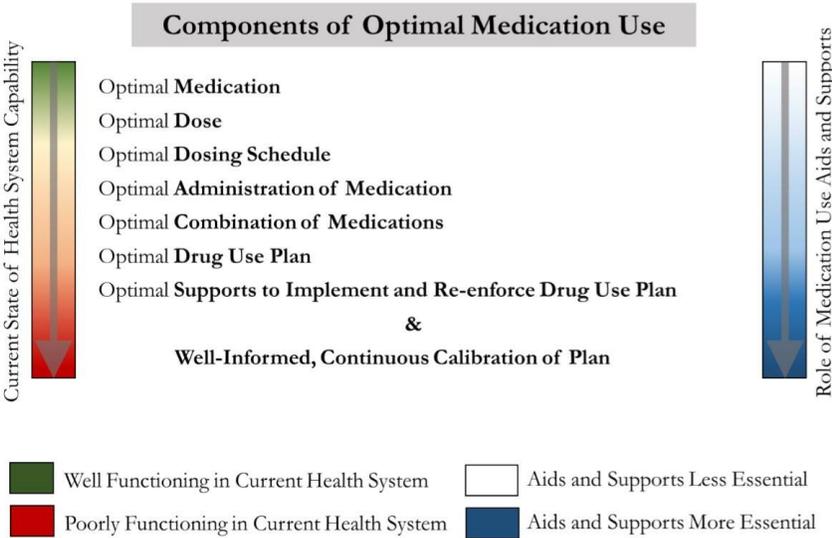
The burden of taking medications is also underappreciated. Imagine having to take five, 10, even 15 or more medications a day, many taken multiple times a day; some with food, some without; some in the morning, some at night; some injected, some mixed with fluids, some large pills and some small. It can seem like a full-time job just to follow a medication use plan unless it flows with daily life.

Supporting Optimal Medication Use through the Use of Aids, Devices and Synchronization

Medication use aids, devices and synchronization strategies play a very important role in supporting optimal medication use. Whether the modalities themselves, or the care team member interventions that go with them, a wide body of evidence suggests that multiple strategies can be deployed successfully to optimize medication use. In a review of 218 reports of care team member interventions using a variety of modalities and strategies, authors consistently found

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Packaging and Pill Boxes

Adherence packaging and pill boxes in one form or another have been in the marketplace for a number of decades.

A meta-analysis of 52 studies found that overall, packaging-based interventions increased fill rates by an average of eight percentage points.^{xx} These are the most widely accessible ancillary aides with the longest history of use.

- PATIENT SELF-ADMINISTERED**
Pill Boxes that are manually filled by the patient come in many varieties, but for the most part is designed as plastic receptacles that are generically calendared to represent days and times of days for administration. Pill Boxes have been shown in some studies to achieve clinical endpoints such as decreased blood pressure, with increased rates of procuring the medication, even in the absence of a care team member intervention.^{xxi} In combination with care team members supports such as pharmacist encounters, Pill Boxes have shown to optimize anti-coagulant use by nearly doubling the time spend in the appropriate INR range.^{xxii}
- PHARMACY ADMINISTERED**
Blister Packaging that is akin to unit dose packaging with calendaring, in combination with pharmacist intervention has been shown to increase adherence rather dramatically (61.2% to 96.9%) and lead to significant reductions in blood pressure and LDL levels.^{xxviii}
- MANUFACTURER/RE-PACKAGER ADMINISTERED**
Re-packaged medications that allow for calendared, “single pill per push” dispensing was shown to increase PDC but not MPR,^{xxiv} suggesting that patients using vials bank up medications for later use, perhaps leading to even more irregular or out of range adherence to the prescribed regimen and schedule. Reminder packaging that includes both data and time of administration has shown to improve both blood pressure as well as hemoglobin A1c endpoints.^{xxv}

Reminder/Alerting Systems

- TELEPHONIC AND TEXT-BASED**
Text messaging was found to be more effective at engagement of patients, with a greater than fifty percent higher rate of engagement, with a 77% success rate at improving adherence to medication regimen, care plan and clinical outcomes.^{xxvi} Text messaging can come in many forms, from letting a customer know that their refill

is ready for pickup to interactive texting schema(s) that have skip patterns that detect when outreach is needed and provide tailored messaging.

- WEB-BASED AND MOBILE APPLICATIONS**
Web-based and mobile applications related to medication use have grown exponentially with the advent of the smart phone. Over 4,000 apps now exist to support patients in some way related to their medications. One study found improvements in Morisky Scale (MMAS-4) by patient report^{xxvii} from ePatient engagement with apps. To date the most challenging aspect of app use to monitor patient medication taking and coaching towards following the medication use plan, is actually syncing the app sufficiently with the patients actual medication use plan medications and schedule, and keeping it synced in a dynamic, ever changing plan without placing the burden of manual entry and re-entry into the app by the patient or caregiver.
- IN-HOME DEVICE**
Electronically monitored dosing systems that provide a feedback loop to patients is a promising strategy.^{xxviii} Though historically difficult to systematize and integrate with conventional dispensing systems, in-home devices provide an opportunity to incorporate the physical features of pill boxes, and adherence packaging, with the ability to also maintain software and connectivity to the internet. To date, in-home dispensing systems have also been limited in their ability to engage patients in medication taking and can inadvertently cause additional medication taking burden, not less, with special caps on bottles or other means by which to track patient medication taking in order to provide valuable feedback to patients, caregivers, care team members and prescribers.

Supporting Optimal Use through Behavior Change Supports

- ONE-WAY EDUCATIONAL MATERIALS**
Educational materials have existed for many decades that endeavor to support patients in their medication use taking. From the (and often complex and difficult to read) handouts you receive at the pharmacy with every new prescription to the additional patient education material leaflets provided for high risk medications to the direct to consumer advertising that permeates our broadcast and cable outlets, one-way educational materials are a plenty. Their effectiveness has not been well established

despite their widespread use however, with patients deriving little incremental knowledge, and even less actionable understandings of their medications from one-way flows of information.^{xxxix}

- **INTERACTIVE APPLICATIONS**
Unlike one-way applications that rely broadcast or generically delivered and applied approaches with little configuration or patient preference expressed, interactive applications allow for configurable or patient-specific interactions.
- **SOCIAL MEDIA**
Social media has become a powerful tool in influencing behavior and motivation. By sharing experiences with medications and/or receiving easy to consume information about medication taking, patients are more likely to engage and maintain that engagement with mediums and channels that align with their everyday information consumption habits and not via healthcare specific information channels. Oftentimes, social media also presents information in a more consumable format, allowing for text and embedded videos and vignettes and expresses of similar patients' experiences and medication burdens.
- **ONLINE PEER SUPPORT (AFFINITY) GROUPS**
An extension of the social media concept is peer support or affinity groups. Patients and caregivers who are experiencing disease state, care delivery, and medication taking burdens (as well as many other types of burdens) can now engage in support groups without respect to geographic location and time, which allows for not only self-directed disease state matching with patients and caregivers, but also cultural and social preference considerations as patients and caregivers join these groups via formal web-page, application, and/or discussion group or web-log.
- **GAMIFICATION**
Gamification represents the addition of behavioral science and economics to the support of the patient and caregiver in following a care plan. Loss incentives have been found to stimulate a 50% increase in physical activity and provide some insight into adherence gamification applications.^{xxx} For medication use plans, gamification has shown promising results^{xxxi} in influencing patient behavior.^{xxxii} Gamification allows for two way communication, activity tracking and represents a powerful means by which to engage the patient.

Supporting Optimal Use through Continuous Monitoring of Clinical and Patient Reported Outcomes

- **IN-HOME CLINICAL MEASUREMENT**
It is easy to overlook the role of durable medical equipment and its role in continuous feedback through provision of clinical measurement feedback to both patient and care team members. Blood pressure readings where essential to the near halving of a population with low adherence receiving intervention to reduce blood pressure through close monitoring of adherence to medication regimens and coaching for understanding of blood pressure goals and consequences of high blood pressure.^{xxxiii}
- **PATIENT REPORTED OUTCOMES APPLICATIONS**
There is some evidence that patient reported measures are helpful in stimulating a more context-based dialogue and increases the likelihood of detect unknown, advancing, or ill-managed conditions.^{xxxiv} There is also evidence that patient reported outcomes can be utilized to determine a need for medication use aids and supports and that a common understanding of goals and expectations^{xxxv} leads to higher levels of adherence to the prescribed drug use plan.^{xxxvi}

Supporting Optimal Use through Care Team Connectivity

Connectivity to caretakers, family, peer groups, prescribers and care team members aides in the ability to implement strategies to optimize medication use. Technologies that successfully connect the patient to the rest of the healthcare ecosystem and the patient's social circles holds great promise. However, many elderly, disabled and/or otherwise complex patients don't have reliable internet connectivity through wi-fi connections^{xxxvii} or find it difficult to access or use connection points, or do so in a consistent manner.^{xxxviii}

- **CONNECTED COMPLIANCE AND PERSISTENCY PROGRAMING**
Whether apps, or even now with in-home devices, one key to supporting optimal medication use is tracking past medication taking and being able to act or intervene when patients' deviate from a pre-ordained medication use plan. Cloud-based tracking allows for others who are not in the home to more efficiently and effectively monitor and intervene.

- **CONNECTED CARETAKER, FAMILY AND PEER SUPPORTS**
When a connected solution is extended to caretakers, family members and other peer supports, either as one-to-one or in groups similar to now popularized exercise online exercise groupings and achievement and burden sharing modalities, a more patient centered, distributed and crowd-sourced support solution emerges.
- **CONNECTED CARE TEAM AND PRESCRIBERS**
When a connected solution that includes patients as well as their family, caretaker and peer supports are included, a more complete narrative of patient needs emerges. Additionally, care team members and prescribers now have more than just the patient to rely on when providing directives to optimize use or consumption of medications.

Supporting Optimal Use through Synchronization

- **SYNCHRONIZATION**
Medication synchronization is the process by which dispensing pharmacies can align a patient's medications to be filled on the same day of each month, thereby allowing for fewer trips to the pharmacy. In addition to the benefit of reducing the burden of time and travel to the pharmacy, synchronization also allows (uniquely) for pharmacy workflow that makes assessments of drug regimens at the patient level instead of the drug product

level. This allows for medication use plans to be tailored to each patient who subscribes to medication synchronization and represents a seminal workflow process change to allow for more clinically oriented activities to occur. Emerging evidence suggests synchronization leads to better adherence to medication use plans as well as downstream clinical and economic outcomes. Substantial improvements in PDC have been linked to synchronization of medications (up to 30 percentage points)^{xxix}. Adherence rates have been shown to increase to approximately 65-75% within one year of being enrolled in a synchronization program.^{xi}

- **APPOINTMENT BASED MODEL**
Because medication synchronization operates at the patient level and provides for a pre-determined date of execution, it lays the groundwork for an appointment-based model. Foreign to pharmacies is the notion of a predetermined time in which to schedule and see a patient. Unlike the rest of the healthcare system, pharmacies emanated from a retail and mercantile upbringing, modeling itself on consumer convenience and patient whim. Showing up at the pharmacy without prior acknowledgement of the specific time of arrival has been a historical impediment to clinical encounters in the community pharmacy setting. The appointment-based model solves for this historical limitation.

The Need for a Simplified, Accessible and Unified Set of Medication Use Supports

Limitations of Currently Accessible Aids and Supports

Some experts believe that the variety of available aids and supports are important to maintain since patients' needs are represented by a diverse and disparate set of factors that lead to suboptimal medication use and therefore each patient should be assessed individually for the selection of aid and/or support.^{xii} Yet, it can be operationally or financially challenging for a clinic, hospital, pharmacy, care management entity or other sponsor or entity that provides medication use supports to make available the plethora of options in the marketplace. Some options may not achieve the desired effect size versus others, other options may be cost prohibitive for the patient, and others may be difficult for patients to participate fully in, whether owed to lack of reliable internet connectivity. For electronic devices, web-based applications and mobile application, homogenous adoption across an entire population of interest has been elusive.^{xiii} Improved clinical outcomes have also been

elusive for multi-device deployment for heart failure supports including scale, blood pressure, and heart rate remotely with nurse-based coaching^{xliii} perhaps owed to lack of medication use intervention and elegant, patient friendly use of the devices. That finding was specifically tested in another study of web linked application integrated with a smartphone to monitor BP, glucose and ECG monitors with no significant findings^{xliv} without active care team involvement in the intervention.

The Need for a High-Fidelity Monitoring and Early Experiences

High fidelity monitoring of medication consumption has revealed incongruity between prescription purchasing and procurement findings and actual patient consumption. In order for widely adopted proxies of medication consumption such as Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) to be relevant, assumptions of patient consumption must be made by interpolating medication procurement and associated days of supply. A number of high-fidelity medication consumption studies are beginning to emerge that make a strong case that even when a patient appears to be adherent to a drug regimen based on procurement data emanating from pharmacy fill, billing and claims systems, suboptimal consumption can be present.^{vii} Precise and accurate data regarding administration of medications by patients is essential to the achievement of optimal medication use. From the prescriber's perspective, lack of precise and accurate consumption data leads to drug misadventures and suboptimal regimen development. From the care team member perspective, it leads to an inability to provide targeted and actionable coaching and reinforcement. From the patient's perspective, it prevents continuous feedback that helps them gauge their performance. From the Pharmaceutical Manufacturer's perspective, it prevents needed separation of results owed to the activity of the moiety of interest and results owed to patient behavior (adherence to regimen and administration).

The Prescriber Perspective

The phrase "you don't know what you don't know" may well describe the current circumstance describing the lack of understanding (or even acknowledgement) that patients most oftentimes don't come anywhere near following the medication use plan that has been put together across numerous prescribers (if a medication use plan that brings all of the medications together even exists). Many studies have now found a large difference between what prescribers believe to be conventional rates of adherence for their patients and the actual rates of adherence, with the actual rates being much lower. What's worse, for many drugs,

a PDC can over-represent adherence with patients filling, but not taking the medications or taking medications in bursts of waxing and waning, even if consistently filling medications over time. A "medication-taking EKG" that illustrates in granular, administration by administration relief, provides a sort of play by play view (see figure below).^{vii} This type of graphical representation of medication taking would be quite illuminating for many prescribers who have very little appreciation for the level of deviation from instructions for medication use and medication use plans that takes place every day in their panel of patients.

The Care Team Member Perspective

High fidelity representations of medication use plan adherence can be great tools for care team members such as pharmacists and care managers, who often play the role of coach, advocate and coordinator. Having access to potentially real time, high information, situationally specific dashboards enable care team members to tailor their messaging, responses and (re)calibrate interventions with much greater specificity and patient centeredness.

The Patient and Caregiver Perspective

There is an unknown demand for continuous, configurable, actionable, and patient centered feedback. Rare are medication or health related modalities that successfully weave themselves into the background of our lives. Patients yearn for feedback and providing them with high fidelity findings,

perhaps with gamification and care-team member interjections may be quite an effective way to execute successfully on medication use plans.

The Manufacturer Perspective

The need for high-fidelity dosing and consumption data during clinical trials suggests that up to half of the variability in pharmacokinetics studies of drug distribution and disposition in the body is the result of nonadherence to the administration protocol prescribed during the study.^{xliii} For some therapeutic categories, lack of high fidelity data may be leading to suboptimal dosing strategies during the FDA approval process when moving from Phase 1 and Phase 2 trials and into Phase 3 trials where patient consumption has historically not been monitored with high fidelity consumption data outputs.^{xliii}

Connected, In-Home Medication Dispensing Devices

To date, disparate approaches to influence and achieve optimal medication use have been deployed, owed both to a broad failure on the part of practitioners and policymakers alike to appreciate the depth and pervasiveness of suboptimal medication use, but also because of a lack of unifying modalities and interventions that can be applied broadly, with some level of ubiquity and common workflow framework, while still allowing for patient centeredness.

Building Medication Optimization Supports into Workflow

Pharmacies have the distinct advantage of frequent touch points with the patient. Patients may visit a pharmacy 5-10 times per year more often than other types of providers. But with this accessibility comes a cost. Historically,

patients have not scheduled times to pick up their medications at the pharmacy, even for chronically ill patients that pick up many of the same medications on the same refill cycles every month. The consequence of this accessibility is unscheduled and unpredictable interactions with patients. As a result, adding effective and properly engineered clinical and medication use support functions have been historically elusive for dispensing pharmacies since patients with special medication use needs are not differentiated in

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workflow process from other patients in line at the cash register to pick up their medications. The appointment-based model (built on medication synchronization solutioning) solves for this problem by allowing for predictable interactions with patients. It also forces the pharmacy to operate at the patient-level and not the prescription fill level.

Accessibility Extending into the Daily Lives of Patients-Medications, unlike most interventions deployed by the health system are mostly dependent on the patient for

proper execution and effect. To achieve optimization, the prescribing-to-filling-to-consuming-to-providing bio- feedback and patient voice for re-prescribing cycle must follow the patient wherever they go and in a manner that is congruent with the everyday goings on of that patient-consumer. Therein lies both the challenge and the opportunity with medication use supports. On the one hand, optimal medication use supports require the healthcare system to receive continuous feedback and monitoring and afford workflow compatible intervention. On the other, if this state of continuous feedback and adjustment can be achieved, the opportunity to improve patient care goes well beyond medication use.

Passive Omnipresence

Much like our phones act as passive data collectors for traffic patterns by interacting with cell towers as we travel down the highway, in-home dispensing devices that have absolute capture of medication taking provide for passive omnipresence- the ability to engage in continuous and in-context consumption of data streams that allow for in-context interjections based on predictive models, algorithms or human judgement based on those data streams. The use of passive omnipresence in geo-mapping devices allows for the passive sharing of data (no requirement to be activity engaged in an application) that informs traffic patterns in-context so that if your route to a particular location experiences a sudden increase and slowdown in traffic. Add the proper intelligence to those passive-capture data streams

and the application then maintains the ability to interject when the consumer finds it beneficial and helpful instead of annoying and out of context (like alerting somebody to traffic on a highway you don't need to use in the next 30 min). Similarly, in-home medication devices can provide for very effective passive-omnipresence. If the patient has a medication regimen schedule and they are scheduled to take a medication at 8AM tomorrow morning, and the in-home dispensing device determines that at 9AM no medication has been dispensed, it becomes a valid, important and meaningful data point. In this way, the medication regimen is like the driving directions on the mapping application.

It provides the intended context against which passive data collection (without the requirement of active user interface engagement) can be compared to provide for passive omnipresence.

Bringing It All Together

Building medication optimization supports into dispensing pharmacy workflow, with an in-home or everyday presence, through data streams that allow for passive omnipresence with in-context interjections by applications, care team members, or caretakers are the trifecta of solving for the previously impossible task of large scale, population-level medication optimization supports and interventions that allow for mass customization and patient centeredness.

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