Prescription Digital Therapeutics

- Clinical Policy Bulletins
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Number: 0999

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses prescription digital therapeutics.

1. **Medical Necessity**

   Aetna considers FDA approved or cleared mobile apps for contraception based on fertility awareness (e.g., Natural Cycles) to be medically necessary per federal preventive care mandates, when prescribed by a treating provider.

   Note: Natural Cycles is currently the only FDA-cleared fertility app. One annual subscription to Natural Cycles is covered per benefit period; no additional supplies or services are covered.

2. **Experimental, Investigational, or Unproven**

   The following prescription digital therapeutics (PDTs) are considered experimental, investigational, or unproven because there is insufficient evidence in the published peer-reviewed literature of the the effectiveness of these PDTs:

   1. BlueStar Rx
   2. Canvas Dx
   3. DaylightRx
   4. d-Nav Insulin Management Program
   5. Drowzle Pro
   6. Endeavor Rx
   7. Freespira
   8. Halo AF Detection System
   9. Insulia
   10. Leva Pelvic Health System
   11. Luminopia One (Digital Dinocular Therapy)
   12. MindMotion GO
   13. My Dose Coach
   14. myVisionTrack (Home Vision Monitor [HVM])
   15. Nerivio
   16. NightWare
   17. Parallel
   18. Regulora
   19. RelieVRx
   20. reSET
   21. reSET-O
   22. SleepioRx
   23. Somryst.

3. **Related Policies**

- CPB 0070 - Diabetes Tests, Programs and Supplies

CPT Codes / HCPCS Codes / ICD-10 Codes

HCPCS codes covered if selection criteria are met:

Code	Code Description
***FDA approved or cleared mobile apps for contraception based on fertility awareness*-no specific codes**	
A9293	Fertility cycle (contraception & conception) tracking software application, fda cleared, per month, includes accessories (e.g., thermometer)

HCPCS codes not covered for indications listed in the CPB:

***Drowzle Pro, MindMotion GO, My Dose Coach, myVisionTrack (Home Vision Monitor [HVM]), Parallel, Regulora, RelieVRx, DaylightRx and SleepioRx* - no specific codes**	
A9291	Prescription digital behavioral therapy, fda cleared, per course of treatment
A9292	Prescription digital visual therapy, software-only, fda cleared, per course of treatment
E1905	Virtual reality cognitive behavioral therapy device (cbt), including pre-programmed therapy software
G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
S9002	Intra-vaginal motion sensor system, provides biofeedback for pelvic floor muscle rehabilitation device

Other HCPCS codes related to the CPB:

T1505	Electronic medication compliance management device, includes all components and accessories, not otherwise classified

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Background

With the rapid advancement of technology in healthcare, there has been an increase in the growth of software technologies created for the purpose of improving healthcare delivery. The U.S. Food and Drug Administration (FDA) refers to these as “device software functions,” a category of software that also includes mobile medical applications (MMAs), which may be deployed on various platforms (e.g., mobile platforms, other general-purpose computing platforms, or in the operation or control of a hardware device), and are designed to enable consumers to better manage their health and well-being, assist healthcare providers to improve and facilitate patient care, diagnose a condition, or trigger a command necessitating patient action. Some examples of the previously mentioned MMA functionalities include the Radiation Emergency Medical Management (REMM) app and the National Institute of Health's LactMed (FDA, 2021b).

Although the FDA encourages the development of MMAs with the intention to improve healthcare and to provide consumers and healthcare practitioners useful information, the FDA recognizes its public health responsibility in the provision of oversight to ensure the safety and effectiveness of such device software functions. To provide guidance and a framework in the evaluation and review of the clinical evidence, safety, and efficacy of device software functions and MMAs, the International Medical Device Regulators Forum (IMDRF), directed by the FDA, states that medical purpose software consists of

1. software in a medical device and
2. software as a medical device (SaMD) (IMDRF, 2021).

Additionally, the Center for Devices and Radiological Health, which functions within the FDA, takes a customized, risk-based approach with a priority on the subset of software functions that qualify under the regulatory definition of "device" and ensure those that have a potentially greater risk must require FDA review (FDA, 2021f). Furthermore, software functions that the FDA specifies as device software functions requiring regulatory oversight include:

- "Software functions that are an extension of one or more medical devices by connecting to such a device(s) for purposes of controlling the device(s) or analyzing medical device data"; or
- "Software functions (typically, mobile apps) that transform the mobile platform into a regulated medical device by using attachments, display screens, or sensors or by including functionalities similar to those of currently regulated medical devices. Software functions that use attachments, display screens, sensors or other such similar components to transform a mobile platform into a regulated medical device are required to comply with the device classification associated with the transformed platform"; or
- "Software functions that become a regulated medical device by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations. These types of functions are similar to or perform the same function as those types of software devices that have been previously cleared or approved".

The FDA will not require manufacturers to submit premarket review applications or registration their software with the FDA for software functions that qualify under the regulatory definition of a "device" when such software functions pose a minimal risk to patients and consumers. Software functions that belong to this FDA discretionary approach include functions that are as follows (FDA, 2021f):

- "Help patients (i.e., users) self-manage their disease or conditions without providing specific treatment or treatment suggestions"; or
- "Automate simple tasks for healthcare providers".

More recently, a novel therapeutic class referred to as prescription digital therapeutics (PDTs) have entered into the digital healthcare space. This therapeutic class is different from other traditional health and wellness apps in that it possesses the following unique characteristics (Digital Therapeutics Alliance, 2021):

- PDTs deliver evidence-based and high quality software-driven therapeutic interventions that diagnose, prevent, manage, or treat a medical disorder or disease independently or in combination with medications, devices, or other treatments to optimize patient care and health outcomes; and
- PDTs are authorized by the FDA (i.e., cleared or approved) with approved directions for use; and
- PDTs undergo rigorous evaluation for safety and effectiveness in clinical trials with clinically-meaningful results published in peer-reviewed journals; and
- PDTs are prescribed and initiated by a qualified and licensed healthcare practitioner.

In order to provide regulatory oversight for software-based medical devices that is both streamlined and efficient, the FDA launched the Pre-Cert Pilot Program test phase in 2019. "In the Pre-Cert program, the FDA is proposing that software products from pre-certified companies would continue to meet the same safety and effectiveness standard that the agency expects for products that have followed the traditional path to market." A proposed aim is to focus on the software developer or digital health technology developer, rather than mainly on the product. Additionally, "the FDA's Total Product Lifecyle (TPLC) approach enables the evaluation and monitoring of a software product from its premarket development to post-market performance, along with continued demonstration of the organization's excellence." Proposed key components of the FDA's TPLC methodology include the following (FDA, 2021d):

- "Excellence Appraisal: Identifying the objective criteria and methodology that the FDA will use to pre-certify a company and decide whether a company can keep its precertification status."
- "Review Determination: Developing a risk-based framework so a pre-certified company can determine the premarket review pathway for their products. Potentially pre-certified companies could market their lower-risk devices without the FDA's premarket review or only a streamlined premarket review based on the company's precertification level and International Medical Device Regulators Forum (IMDRF) risk categorization."
- "Streamlined Review: Identifying the type of information that a pre-certified company would include in its premarket submission for the FDA to review software products for safety and effectiveness before patients access them."
- "Real-world Performance: Identifying the type of information that may be available to or accessibly by a pre-certified company about how its software product is performing with patients to support the regulatory status of the product and new and evolving product functions."

In September 2017, the following 9 companies out of over 100 candidates were chosen by the FDA to participate in the development of the Software Pre-Cert Pilot Program: Apple, Fitbit, Johnson & Johnson, Pear Therapeutics, Phosphorous, Roche, Samsung, Tidepool, and Verily (FDA, 2021d).

Other professional organizations such as the American Medical Association, American Psychiatric Association, and the Academy of Managed Care Pharmacy are also beginning to develop a framework and provide guidance to healthcare practitioners as they begin to integrate mobile health technologies, mobile apps, and digital therapeutics as a component in the delivery of patient care.

BlueStar Rx

WellDoc (Columbia, MD) developed the BlueStar Rx System which is indicated for use by healthcare providers and their patients who are 18 years of age and older to aid in their self-management of type 1 or type 2 diabetes. The BlueStar Rx System is an FDA-cleared software app that is complimentary to the patient's current therapies (e.g., pharmacologic, diet, exercise, and counseling). Patients can use the mobile app or the web version of BlueStar. The software app includes an always-on, fully-automated software coach that sends a report to the patient's healthcare provider team via facsimile, email, or electronic medical record and a patient portal is managed by an administrator who can manage, review, report, survey and communicate with the patient. In addition to reporting blood glucose results and supporting medication adherence, the BlueStar Rx System delivers coaching messages based on current time blood glucose results and trends. A prescription is required by a licensed healthcare professional for the BlueStar Rx system which also includes an insulin dose calculator that enables patients to use their prescribed regimen to determine insulin dosage based on a given amount of carbohydrates and/or blood glucose values. WellDoc states on their website that "The BlueStar Rx System is not intended to replace the care provided by a licensed healthcare professional, including prescriptions, diagnosis, or treatment" (Digital Therapeutics Alliance, 2021b; WellDoc, 2021).

Quinn and colleagues (2011) conducted the Mobile Diabetes Intervention Study, a cluster-randomized clinical trial to assess whether the addition of mobile application coaching and patient/provider web portals to community primary care compared to standard diabetes management would decrease glycosylated hemoglobin levels in patients with type 2 diabetes. This study randomly assigned 26 primary care practices consisting of 163 participants to one of three stepped treatment groups or a control group (usual care). The primary outcome was a change in glycated hemoglobin levels over a 1-year treatment duration and secondary outcomes included changes in patient-reported diabetes symptoms, diabetes distress, depression, and other clinical (blood pressure) and laboratory (lipid) values. Maximal treatment included a mobile- and web-based self-management patient coaching system and provider decision support. Automated, real-time educational and behavioral messaging were sent to patients via mobile phone in response to individually analyzed blood glucose results, diabetes medications, and lifestyle behaviors. Quarterly summary reports regarding patient’s glycemic control, diabetes medication management, lifestyle behaviors, and evidence-based treatment options were sent out to providers. Results included 1.9% mean declines in glycated hemoglobin in the maximal treatment group and 0.7% in the usual care group, a difference of 1.2% ($p<0.001$) over 12 months. Significant differences were not noticeable between groups for patient-reported diabetes distress, depression, diabetes symptoms, or blood pressure and lipid levels (all $p>0.05$). The investigators concluded that the combination of behavioral mobile coaching with blood glucose data, lifestyle behaviors, and patient self-management data individually evaluated and presented with evidence-based guidelines to providers significantly decreased glycosylated hemoglobin levels over 1 year.

Agarwal and colleagues (2019) evaluated BlueStar mobile app, an FDA-approved mobile prescription therapy, to determine if app usage results in improved hemoglobin A_{1c} (HbA_{1c}) for diverse participants in real-life clinical contexts. The study involved of a multicenter pragmatic randomized controlled trial consisting of 110 participants randomized to the immediate treatment group (ITG) receiving the intervention for 6 months, and 113 participants randomized to the wait-list control (WLC) group receiving usual care for the first 3 months and then receiving the intervention for 3 months. The primary outcome was glucose control measured by HbA_{1c} levels at 3 months and secondary outcomes determined intervention impact on patient self-management, experience of care, and self-reported health utilization using validated scales (i.e., the Problem areas in Diabetes, the Summary of Diabetes Self-Care Activities, and the EuroQo1-5D). The BlueStar mobile app captured the intervention usage data. The results did not show evidence of intervention impact on HbA_{1c} levels at 3 months (mean difference [ITG-WLC] -0.42, 95% Confidence Interval [CI] -1.05 to 0.21; $p=0.19$). Additionally, no intervention effect on secondary outcomes measuring diabetes self-efficacy, quality of life, and healthcare utilization behaviors were observed. Significant variation in app usage by site was noted such that participants from one site logged in to the app a median of 36 days over 14 weeks (interquartile range [IQR] 10.5-124), whereas participants at another site showed a notable decrease in app usage (median 9; IQR 6-51). The investigators concluded that there was no difference between intervention and control arms for the primary outcome of glycemic control measured by HbA_{1c} levels and the low usage of the app among participants warrants further study of patient and site-specific factors that increase app usage.

Canvas Dx

Cognoa (Palo Alto, CA) developed Canvas Dx which is an FDA-cleared software medical device that is indicated for use by healthcare providers as an aid in the diagnosis of Autism Spectrum Disorder (ASD) for patients ages 18 months through 72 months who are at risk for developmental delay based on concerns of a parent, caregiver, or healthcare provider. Canvas Dx utilizes a clinically validated artificial intelligence (AI) technology that integrates three separate user-friendly inputs. The inputs include a parent/caregiver questionnaire regarding the child's behavior and development collected via a parent/caregiver facing app, a questionnaire completed by a video analyst who reviews parent/caregiver recorded videos of the child, and a healthcare provider questionnaire completed by a physician during child and parent/caregiver interaction via a healthcare provider portal. A device output is then generated after an algorithm evaluates all of these inputs which will be used by the physician in addition to their clinical judgement. The device is by prescription only and Cognoa states on the www.canvasdx.com website "The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process" (Canvas Dx, 2021; Cognoa, 2021).

Abbas and colleagues (2017) applied machine learning (ML) to gold standard clinical data captured across thousands of children at-risk for autism spectrum disorder to develop a low-cost, quick, and easy to use autism screening tool. Two algorithms to identify autism, included one based on short, structured parent-reported questionnaires and short, semi-structured home videos of children identifying key behaviors which are then combined in an algorithm to yield a single assessment of higher accuracy. The performance of these algorithms and their combination was assessed in a multicenter clinical study comprised of 162 children. While significant accuracy improvement compared to standard screening tools in measurements of AUC, sensitivity, and specificity was demonstrated, the authors discuss a myriad of confounding factors in the clinical analysis and also note the results are statistically limited. Additional clinical studies are warranted to firmly support the findings of this study that a mobile, machine learning process can be a reliable method for detection of autism outside of clinical settings.

Abbas and associates (2020) evaluated a multi-modular, machine learning-based assessment of autism via a mobile app in a blinded, multi-site clinical study comprised of 375 children who were 18 to 72 months of age. The machine learning-based assessment of autism consisted of three complimentary modules for a unified outcome of diagnostic-grade reliability. The complimentary modules (i.e., Cognoa assessment modules) included a 4-min, parent-report questionnaire presented via a mobile app, a list of key behaviors identified from 2-minute, semi-structured home videos of children, and a 2-minute questionnaire presented to the clinician at the time of clinical assessment. The results demonstrated that the machine learning-based assessment outperformed baseline autism screening assessments (i.e., the Child Behavior Checklist [CBCL], the Modified Checklist for Autism in Toddlers, Revised [M-CHAT-R], and the Social Responsiveness Scale – Second Edition [SRS]) administered to children by 0.35 (90% Confidence Interval [CI]: 0.58 to 0.81) in specificity when operating at 90% sensitivity. Additionally, in children less than 48 months of age, the investigators' machine learning-based assessment outperformed the most accurate baseline screening assessment by 0.18 (90% CI: 0.08 to 0.29 at 90%) in AUC and 0.30 (90% CI: 0.11 to 0.50) in specificity when operating at 90% sensitivity. The investigators discuss the limitations of the study, including that the children preselected have a high risk of autism, and that there is a need to validate this new machine learning-based assessment in the primary care clinic setting.

Megerian et al (2022) stated that ASD can be reliably diagnosed at 18 months, yet significant diagnostic delays persist in the U.S. In a prospective, double-blinded, multi-center study, these investigators examined the accuracy of an AI-based software as a medical device designed to aid primary care healthcare providers (HCPs) in diagnosing ASD. The Device combines behavioral features from 3 distinct inputs (a caregiver questionnaire, analysis of 2 short home videos, and an HCP questionnaire) in a gradient boosted decision-tree ML algorithm to produce either an ASD-positive, ASD-negative, or indeterminate output. This study compared the Device's outputs to diagnostic agreement by 2 or more independent specialists in a cohort of 18- to 72-month-olds with developmental delay concerns (425 study completers, 36 % female, 29 % ASD prevalence). Device output positive predictive value (PPV) for all study completers was 80.8 % (95 % CI: 70.3 % to 88.8 %) and negative predictive value (NPV) was 98.3 % (90.6 % to 100 %). For the 31.8 % of participants who received a determinate output (ASD-positive or ASD-negative) Device sensitivity was 98.4 % (91.6 % to 100 %) and specificity was 78.9 % (67.6 % to 87.7 %). The Device's indeterminate output acted as a risk control measure when inputs were insufficiently granular to make a determinate recommendation with confidence. If this risk control measure were removed, the sensitivity for all study completers would fall to 51.6 % (63/122) (95 % CI: 42.4 % to 60.8 %), and specificity would fall to 18.5 % (56/303) (95 % CI: 14.3 % to 23.3 %). Among participants for whom the Device abstained from providing a result, specialists identified that 91 % had 1 or more complex neurodevelopmental disorders. No significant differences in Device performance were found across participants' sex, race/ethnicity, income, or education level. For nearly 1/3 of this primary care sample, the Device enabled timely diagnostic evaluation with a high degree of accuracy. The authors concluded that while future investigation is needed, the Device shows promise to significantly increase the number of children being able to be diagnosed with ASD in a primary care setting; thus, potentially facilitating earlier intervention and more efficient use of specialist resources.

Wall et al (2023) noted that a growing number of AI-based medical devices are receiving clearance from the FDA. Debate has arisen regarding best practices for the regulation and safe oversight of such devices whose capabilities, if "unlocked", include iterative learning and adaptation with exposure to new data. One regulatory mechanism proposed by the FDA is the pre-determined change control plan (PCCP). These investigators provided what they believed would be the 1st example of how a PCCP has been leveraged to improve the performance of a de-novo autism diagnostic device in practice. Following the PCCP's model update procedures included in the marketing authorization of the 1st generation of the device ("algorithm V1"), they carried out an algorithmic threshold optimization procedure to improve the device's ability to detect or rule out autism in children ages 18 to 72 months without changing the accuracy or intended use of the device. Decision threshold optimization was attained using a repeated train/test validation procedure on a dataset of 722 children with concern for developmental delay, aged 18 to 72 months (28 % autism, 22 % neurotypical, 50 % other developmental delay, mean age of 3.6 years, 39 % female). In 1,000 repeats, 70 % of samples were selected for threshold optimization and 30 % for evaluation, ensuring that no training data appeared in the test set. Out-of-sample performance was estimated by examining the selected threshold pair on the test set and comparing the performance metrics of the new pair to the corresponding V1 metrics on the same test set. The device, with optimized decision thresholds, produced a determinate output for 66.5 % (95 % CI: 62.5 % to 71.0 %) of children. Positive predictive value (PPV) and negative predictive value (PPV) were 87.5 % (95 % CI: 82.5 % to 96.7 %) and 95.6 % (95 % CI: 93.7 % to 97.9 %) respectively. The authors concluded that threshold optimization improved the device's ability to accurately detect or rule out autism in a greater proportion of children. These researchers stated that given the current wait-list crisis for autism evaluations in the U.S., the potential increase in coverage offered by the optimized thresholds is promising and emphasizes the value of regulatory mechanisms that allow software as medical devices to adapt safely and appropriately given real world data. Moreover, these researchers stated that additional real-world data will aid in clarifying the extent to which autism prevalence, and

other assumptions built into this model, are reflective of the real-world usage population. They noted that planned and ongoing real-world evidence studies may also shed light on how the device can be integrated into primary care practice settings, and how its use may impact time to diagnosis and treatment initiation.

DaylightRx

According to a news release from Big Health (San Francisco, CA), a developer of digital treatments, on September 4, 2024, the U.S. Food and Drug Administration (FDA) granted clearance for its digital therapeutic, DaylightRx. DaylightRx is a prescription device delivering cognitive behavioral therapy that is available for use on the order of a licensed healthcare professional. The device is intended as an adjunct to usual care for the treatment of patients 22 years of age and older with generalized anxiety disorder (GAD).

DaylightRx is designed to improve a patient's GAD symptoms through cognitive behavioral therapy that teaches evidence-based techniques to change the thoughts and behaviors that sustain chronic worry and anxiety. The following features are included in DaylightRx: interactive lessons on applied relaxation to reduce tension, stimulus control to decrease worry frequency, cognitive restructuring to break the swirl of anxious thoughts, and exposure to reduce intensity of worry. Additionally, guided practice exercises are included to support patients in integrating these techniques into their daily lives. DaylightRx is for a 90-days treatment course.

d-Nav Insulin Management Program

Hygieia offers the d-Nav Insulin Management Program, a digital therapeutic which is indicated for adult patients with type 2 diabetes who manage their condition with insulin injections. The d-Nav Insulin Management Program combines an FDA-cleared software mobile app enabled by AI technology, and virtual clinical support to make autonomous (algorithm-based) adjustments to insulin doses based on the patient's glucose levels. Hygieia embeds the d-Nav application onto a blood glucose monitor and the technology is activated when there is a prescription. The d-Nav program relies on use of a handled device such as a smartphone or a device provided by Hygieia. Patients use the d-Nav technology before every insulin injection by entering their most recent glucose reading, and then receive a personalized dose recommendation on their handheld device. Data is sent to the cloud where it is monitored by d-Nav Care Specialists who are available for support.

Bergenstal and colleagues (2012) hypothesized that the Diabetes Insulin Guidance System (DIGS™) (Hygieia, Inc., Ann Arbor, MI) software, which automatically advises patients on adjustment of insulin dosage, would provide safe and effective weekly insulin dosage adjustments. The authors conducted a 16-week feasibility study (designed as a prospective, open-label, uncontrolled, single-arm, single-center study with intention-to-treat) in which they enrolled patients (n=46) with type 1 (n=20) and type 2 diabetes (n=26) treated with a variety of insulin regimens and having suboptimal glycemic control. Thirty-eight patients completed the study. The 12-week intervention period followed a 4-week baseline run-in period. During the intervention, DIGS processed patients' glucose readings and provided insulin dosage adjustments on a weekly basis. If approved by the study team, the adjusted insulin dosage was communicated to the patients. Insulin formulations were not changed during the study. The primary outcome was the fraction of DIGS dosage adjustments approved by the study team, and the secondary outcome was improved glycemic control. The authors found that during a cumulative period of 8.9 patient-years, the DIGS software recommended 1,734 insulin dosage adjustments, of which 1,731 (99.83%) were approved. During the run-in period the weekly average glucose was stable at 174.2±36.7 mg/dL (9.7±2.0 mmol/L). During the following 12 weeks, DIGS dosage adjustments resulted in progressive improvement in average glucose to 163.3±35.1 mg/dL (9.1±1.9 mmol/L) ($p<0.03$). Mean glycosylated hemoglobin decreased from 8.4±0.8% to 7.9±0.9% ($p<0.05$). Concomitantly, the frequency of hypoglycemia decreased by 25.2%. The authors concluded that the DIGS software provided patients with safe and effective weekly insulin dosage adjustments. Widespread implementation of DIGS may improve the outcome and reduce the cost of implementing effective insulin therapy. The authors acknowledge that their study was limited by lack of a control group. Thus, they could not have unequivocally excluded the possibility that improved glycemia resulted from participation in the study. Furthermore, the study duration was relatively short; therefore, it is possible that different HbA1c levels would have been recorded during a longer follow-up. Because weekly mean glucose levels were stable during the run-in period and improved particularly toward the middle of the active phase, it is the authors' belief that HbA1c would have further improved. Randomized controlled trials are warranted, as well as additional studies to focus on improved glycemic balance among the minority of patients who experience frequent hypoglycemia.

Bashan and Hodish (2012) hypothesize that frequent insulin dosage adjustments based on glucose readings alone are sufficient for a safe and effective therapy. The authors conducted a 3-month open-label prospective pilot study recruiting 14 subjects with suboptimal controlled insulin-treated Type-2 and Type-1 diabetes (n = 11 with Type-2 diabetes, n = 3 with Type-1; n = 12 completed the study follow-up). Subjects were treated with basal-bolus insulin therapy that was titrated weekly for 12 weeks. Dosage adjustments were made by the study Endocrinologist by reviewing subjects' glucose readings, exclusively based on log sheets and contingent upon the approval of the on-site study team. To corroborate that the glucose readings were sufficient for making dosage adjustments, the authors used software to process only glucose readings and recommend insulin dosage adjustments. The recommendations made by the software were retrospectively compared to the ones made by the study Endocrinologist. The authors found that all 568 recommendations were approved by the study team and in 99.3% of the cases the recommendations were clinically similar to the ones made by the software. No hazardous disagreements were found. The mean A1C improved from 9.8% (± 2.0) to 7.9% (± 1.3) ($p=0.001$) in 12 weeks and the weekly mean glucose progressively

improved from 220.3 mg/dl (± 51.9) to 151.5 mg/dl (± 19.2) (p<0.0001). The frequency of minor hypoglycemia was 22.7 per patient-year in subjects with Type-2 diabetes and 42.7 in the subjects with Type-1 diabetes. No severe hypoglycemic events occurred. The authors concluded that glucose readings are sufficient to adjust insulin therapy in a safe and effective manner, when adjustments are made on a weekly basis. Thus, dedicated software may help adjust insulin dosage between clinic visits. The authors acknowledge that the main weakness of this pilot study was its relatively small subject number and short follow-up (3.25 patient year); however, since the investigated parameter was the process of insulin dosage adjustments, the actual "n" value was considerable (n = 568).

Donnelly et al (2015) carried out a service evaluation of the effectiveness of using d-Nav (a hand-held device that automates the process of insulin dosage titration using the Diabetes Insulin Guidance System [DIGS] software) in achieving glycemic control in patients with type 2 diabetes (T2D). The study comprised an exploratory, single-center, pilot study on the use of d-Nav in patients with T2D aged 21 years or older with a hemoglobin A1c (HbA1c) level of greater than or equal to 53 mmol/mol (greater than or equal to 7.0 %) who were receiving insulin therapy for at least 1 year. Patients were asked to use d-Nav to monitor their blood glucose level before every insulin injection and, when they suspected the occurrence of hypoglycemia, to allow d-Nav to adjust their insulin dosage. At scheduled 3-monthly clinic visits, HbA1c was measured and information on episodes of hypoglycemia collected from d-Nav and by patient reporting. Patients were followed for a minimum of 6 months. A total of 94 patients completed the evaluation as active users. The mean (± standard deviation) HbA1c for active users decreased from 77 ± 15 mmol/mol (9.2 ± 1.4 %) at baseline to 62 ± 13 mmol/mol (7.8 ± 1.2 %) at the 3- to 5-month clinic visit and to 59 ± 13mmol/mol (7.5 ± 1.2 %) at the 6- to 12-month clinic visit. In patients for whom paired data were available, the decreases were statistically significant at both post-baseline visits (both p < 0.001). The frequency of minor hypoglycemia (blood glucose of less than or equal to 3.6 mmol/L) was low and well within the tolerated range. The authors concluded that d-Nav is shown to be a safe and effective solution for blood glucose management in insulin users with T2D.

The authors stated that this study was a pilot exploratory service evaluation in patients registered at a busy diabetes clinic and was not intended to be a clinical trial. Accordingly, it was limited in terms of the lack of a control group and modest patient numbers. However, the findings from this study indicated that further investigation into the use of the-Nav service is needed; and further studies are planned. Moreover, these researchers stated that in addition to evaluating patient satisfaction with the d-Nav solution, there is a need to conduct a large-scale, health economic evaluation of the service.

Schneider et al (2018) noted that studies have shown that improvements in glycemic control are associated with avoidance or delayed onset of diabetes complications, improvements in health-related quality of life (HR-QOL), and reductions in diabetes-related healthcare costs. Clinical practice guidelines recommend maintaining a HbA1c level of less than 7 %, but among T2D patients using insulin, 2/3 have HbA1c above 7 % and 1/3 have HbA1c above 9 %. These researchers examined the use of insulin management services to enable patients to optimize insulin dosing to achieve HbA1c targets and subsequently reduce healthcare costs. Cost savings may be achieved via reduced complications and hospitalizations, as well as reduced outpatient, physician, and clinic costs. This study quantified the reduction in pharmaceutical expenses related to the use of an enhanced insulin management service to improve glycemic control. A total of 217 insulin-reliant patients were enrolled in the d-Nav Insulin Guidance Service via a participating insurance group. A prospective cost-analysis was carried out using data from enrolled patients who completed the first 90 days of follow-up. Of the 192 patients who completed the 90-day study period, 54 (28.13 %) were prescribed 1or more expensive medications at baseline, but 45 (83.33 %) of those patients were eligible for medication discontinuation after 90 days. At baseline, the annual cost of expensive medications per patient was $7,564 (CI: $5,191 to $9,938) and $1,483 (CI: −$1,463 to $4,429) at 90 days (p < 0.001). Direct savings from medication elimination was estimated to be $145 per patient per month (PPPM) or $1,736 per patient per year (PPPY) for all patients and $514 PPPM/$6172 PPPY for the target group. Patients who completed the 90-day period significantly reduced HbA1c levels from 9.37 % (CI: 7.72 % to 11.03 %) at baseline to 7.71 % (CI: 6.70 % to 8.73 %) (p < 0.001). A total of 170 (88.54 %) patients had improved HbA1c at 90 days. The authors concluded that the use of the insulin guidance service achieved improved glycemic control by optimizing insulin dosing, which enabled most patients using the service to reduce or eliminate the use of expensive diabetes medications. Moreover, these researchers stated that further investigation is needed to examine the impact of optimized insulin dosing on other diabetes-related healthcare costs in a usual practice setting.

The authors stated that this study had 2 main drawbacks. First, because this study entailed the use of a medical device, patient adherence or lack thereof may impact HbA1c levels and overall study outcomes. Second, direct cost savings may also vary depending on cost of medication in different markets. These investigators stated that further follow-up research is recommended to better understand the long-term impact of the insulin guidance service on healthcare cost.

Howard-Thompson et al (2018) stated that in patients with T2D, insulin may be used to augment therapy with oral glycemic medications or as insulin replacement therapy. The American Diabetes Association (ADA) suggested the use of long-acting (basal) insulin to augment therapy with 1 or 2 oral agents or 1 oral agent plus a glucagon-like peptide 1 receptor agonist when the A1C level is 9 % or more, especially if the patient has symptoms of hyperglycemia or catabolism. Insulin regimens should be adjusted every 3 or 4 days until targets of self-monitored blood glucose levels are reached. A fasting and pre-meal blood glucose goal of 80 to 130 mg/dL and a 2-hour post-prandial goal of less than 180 mg/dL are recommended. Insulin use is associated with hypoglycemia and weight gain. Insulin analogs are as effective as human insulin at lowering A1C levels with lower risk of hypoglycemia; however, they have significantly higher cost. Patients with 1 or more episodes of severe hypoglycemia (i.e., requiring assistance from others for treatment) may benefit from a short-term relaxation of glycemic targets. Several new insulin formulations have been approved recently that are associated with less risk of hypoglycemia compared with

older formulations. The objectives of therapy should be individualized based on many factors, including age, life expectancy, co-morbid conditions, duration of diabetes, risk of hypoglycemia, cost, patient motivation, and QOL.

Bergenstal et al (2019) conducted a multicenter, randomized controlled trial to determine whether the combination of the d-Nav device and health-care professional support is superior to health-care professional support alone. The investigators recruited patients (n=181) from three diabetes centers in the USA that were aged 21-70 years, diagnosed with type 2 diabetes with a glycated hemoglobin (HbA1c) concentration of 7.5 percent or higher and 11 percent or lower, and had been using the same insulin regimen for the previous 3 months. Exclusion criteria included body-mass index (BMI) of 45 kg/m2 or higher; severe cardiac, hepatic, or renal impairment; and more than two severe hypoglycemic events in the past year. Eligible participants were randomly assigned (1:1), with randomization blocked within each site, to either d-Nav and health-care professional support (intervention group, n=93) or health-care professional support alone (control group, n=88). Both groups were contacted seven times (three face-to-face and four phone visits) during 6 months of follow-up. The primary objective was to compare average change in HbA1c from baseline to 6 months. Safety was assessed by the frequency of hypoglycemic events. The primary objective and safety were assessed in the intention-to-treat population. The investigators used Student's t test to assess the primary outcome for statistical significance. At baseline, mean HbA1c was 8.7 percent (SD 0.8; 72 mmol/mol [SD 8.8]) in the intervention group and 8.5 percent (SD 0.8; 69 mmol/mol [SD 8.8]) in the control group. The mean decrease in HbA1c from baseline to 6 months was 1.0 percent (SD 1.0; 11 mmol/mol [SD 11]) in the intervention group, and 0.3 percent (SD 0.9; 3.3 mmol/mol [9.9]) in the control group (p<0.0001). The investigators found that the frequency of hypoglycemic events per month was similar between the groups (0.29 events per month [SD 0.48] in the intervention group vs 0.29 [SD 1.12] in the control group; p=0.96). The investigators concluded that the combination of automated insulin titration guidance with support from health-care professionals offers superior glycemic control compared with support from health-care professionals alone. Such a solution facilitated safe and effective insulin titration in a large group of patients with type 2 diabetes, and now needs to be evaluated across large health-care systems to confirm these findings and study cost-effectiveness.

Garg (2019) reviewed the Bergenstal et al (2019) study and reported doubts about its reproducibility in clinical practice. The author provided correspondence to The Lancet which states that “The control group seems to have received negligible clinical care from their health-care providers. The insulin dose in the control group was almost the same at the end of 6 months as at the baseline. I do not know any diabetes centre where providers will not make insulin dose adjustments in a patient with poor glycemic control over a period of 6 months, despite seven patient contacts. Therefore, at best, it seems that the d-Nav Insulin Guidance System helps providers with clinical inertia overcome their clinical inertia. The premise that d-Nav will help in saving time for health-care providers is not proven by the results of this study”.

Harper et al (2023) stated that for patients using basal-bolus insulin therapy, it is widespread clinical practice to aim for a 50-50 ratio between basal and total daily bolus. However, this practice was based on a small study of individuals without diabetes. To examine the rule in real-world practice, these investigators retrospectively analyzed patients on basal-bolus therapy that was adjusted at least weekly by an artificial intelligence (AI)-driven titration within the d-Nav Insulin Management Technology. They obtained de-identified data from the Diabetes Centre of Ulster Hospital for patients with 4 inclusion criteria: T2D, on d-Nav for more than 6 months, on basal-bolus insulin therapy for greater than 80 % of the time (based on insulin analogs), and no gap in data for more than 3 months. These researchers included a cohort of 306 patients, followed by the d-Nav service for 3.4 ± 1.8 years (mean ± SD), corresponding to about 180 autonomous insulin dose titrations and about 5,000 autonomous individual dose recommendations per patient. After an initial run-in period, mean HbA1c values in the cohort were maintained close to 7 %. Surprisingly, in just over 75 % of the cohort, the average basal insulin fraction was less than 50 %; in 50 % of the cohort average basal insulin fraction of less than 41.2 %; and in 25 % the basal insulin fraction was less than 33.6 %. In addition, the basal insulin fraction did not remain static over time. In 50 % of the patients, the basal insulin fraction varied by greater than or equal to 1.9×; and, in 25 % of the patients, greater than or equal to 2.5×. The authors concluded that these findings showed that a 50-50 ratio of basal-to-bolus insulin did not generally apply to patients with T2D who successfully maintain stable glycemia; thus, the 50-50 ratio should not serve as an ongoing treatment guide. Moreover, these findings emphasized the importance of at least weekly insulin titrations.

The authors stated that this study's drawbacks included its observational design, limited ethnic diversity, lack of information on additional anti-diabetes medications, possible dietary changes, physical activity and the lack of a negative control group. On the other hand, the 50-50 rule that has been used by providers for years was based on a 1988 study of a few patients without diabetes, about whom these investigators did not have additional background data, nor did the previous study show the mechanisms behind the findings.

Nayak et al (2023) noted that optimizing insulin therapy for patients with type 2 diabetes mellitus (T2DM) could be challenging given the need for frequent dose adjustments. Most patients received sub-optimal doses and did not attain glycemic control. In a randomized study, these researchers examined if a voice-based conversational AI (VBAI) application could aid T2DM patients titrate basal insulin at home to achieve rapid glycemic control. This trial was carried out at 4 primary care clinics at an academic medical center from March 1, 2021, to December 31, 2022. A total of 32 adults with T2DM requiring initiation or adjustment of once-daily basal insulin were followed-up for 8 weeks. Statistical analysis was carried out from January to February 2023. Subjects were randomized in a 1:1 ratio to receive basal insulin management with a VBAI application or standard of care (SOC). Primary outcomes were time to optimal insulin dose (number of days needed to achieve glycemic control), insulin adherence, and change in composite survey scores measuring diabetes-related emotional distress as well as attitudes toward health technology and medication adherence. Secondary outcomes were glycemic control and glycemic improvement. Analysis was conducted on an ITT basis. The study population included 32 patients (mean [SD] age, 55.1 [12.7] years; 19 women [59.4 %]).

Subjects in the VBAI group more quickly achieved optimal insulin dosing compared with the SOC group (median of 15 days (IQR, 6 to 27 days) versus longer than 56 days (IQR, longer than 29.5 to longer than 56 days); a significant difference in time-to-event curves; p = 0.006) and had better insulin adherence (mean [SD] of, 82.9 % [20.6 %] versus 50.2 % [43.0 %]; difference, 32.7 % [95 % CI: 8.0 % to 57.4 %]; p = 0.01). Subjects in the VBAI group were also more likely than those in the SOC group to achieve glycemic control (13 of 16 [81.3 %; 95 % CI: 53.7 % to 95.0 %] versus 4 of 16 [25.0 %; 95 % CI: 8.3 % to 52.6 %]; difference, 56.3 % [95 % CI: 21.4 % to 91.1 %]; p = 0.005) and glycemic improvement, as measured by change in mean (SD) fasting blood glucose (FBG) level (-45.9 [45.9] mg/dL [95 % CI: -70.4 to -21.5 mg/dL] versus 23.0 [54.7] mg/dL [95 % CI: -8.6 to 54.6 mg/dL]; difference, -68.9 mg/dL [95 % CI: -107.1 to -30.7 mg/dL]; p = 0.001). There was a significant difference between the VBAI group and the SOC group in change in composite survey scores measuring diabetes-related emotional distress (-1.9 points versus 1.7 points; difference, -3.6 points [95 % CI: -6.8 to -0.4 points]; p = 0.03). The authors concluded that in this randomized clinical trial of a VBAI application that provided autonomous basal insulin management for adults with T2DM, subjects in the AI group had significantly improved time to optimal insulin dose, insulin adherence, glycemic control, and diabetes-related emotional distress compared with those in the SOC group. These researchers stated that these findings suggested that voice-based digital health solutions can be useful for medication titration. Moreover, these investigators stated that further work is needed to validate this technology in larger, more diverse populations.

The authors stated that this study had several drawbacks. First, because subjects were followed-up for 8 weeks, glycemic control was measured by mean FBG level, rather than HbA1c level. Second, it was not possible to determine whether incomplete insulin logs in the SOC group reflected non-adherence to insulin or non-adherence to the log; however, this limitation was also present in VBAI group, given that insulin adherence was similarly based on self-reported data. Third, incomplete FBG logs for some SOC group subjects necessitated review of medical records to determine whether glycemic control had been achieved at 8 weeks. Fourth, except for data collected during review of the medical record, all data collected in this study were self-reported. Fifth, this study did not compare VBAI with other apps using similar insulin titration software to specifically evaluate the attribution of a voice-based interface. Sixth, mean FBG levels worsened in the SOC group, which could have resulted in an over-estimation of the effect size of the intervention. Seventh, this study randomized only 39 English-speaking subjects.

Mayya et al (2024) stated that DM is an important chronic disease globally. Different countries and diverse cultures employ varying approaches in addressing this chronic condition. furthermore, with the advancement of computation and automated decision-making, many tools and technologies are now available to patients afflicted by this disease. These investigators analyzed approaches taken towards management of this DM in India and the U.S. They reviewed available evidence to examine the use of AI in the management of patients with DM. These researchers provided insights to comparison of DM management in terms of the nature of the healthcare system, availability, electronic health records (EHRs), cultural factors, data privacy, affordability, as well as other important variables. Interestingly, variables such as quality of EHRs, and cultural factors are key impediments in implementing an efficiency-driven management system for dealing with DM. The authors provided key observations associated with DM management in India and the U.S. They presented 2 main contributions: a discussion comparing management approaches for this disease in India and the U.S., and key observations regarding AI techniques applicable to DM management. These researchers stated that a key improvement in the management of DM by means of AI has been illustrated in the article. Moreover, they stated that further exploration of these AI techniques is needed to improve healthcare outcomes for processes associated with DM management.

Drowzle Pro

Resonea (Scottsdale, AZ) developed the Drowzle Pro which is an FDA-cleared mobile application digital home sleep test. Drowzle Pro functions via a digital platform utilizing a smartphone for in-home screening of obstructive sleep apnea (OSA) in adults. The mobile software is used to gather symptom data for sleep apnea risk, including severity of daytime sleepiness and personal chronic disease risk factors. Drowzle Pro also records sleep breathing patterns and transmits the sound files to secure servers in the cloud. By being a stand-alone software medical device, The mobile application then analyzes and interprets the sleep breathing results, along with profile data provided by the patient, to measure and monitor sleep-related health risks over time. The mobile application’s deployment via the patient's own phone, enables it to be an option when polysomnography in the lab or conventional home sleep testing may not be feasible. The results assist the healthcare professional in determining the need for further diagnosis and evaluation. Furthermore, Drowzle Pro is not intended as a substitute for full polysomnography when additional parameters such as sleep stages, limb movements, or electroencephalogram (EEG) activity is required. Drowzle Pro is only available by prescription for adults 21 years of age and older (FDA, 2022a; Resonea, 2022).

EndeavorRx

Akili Interactive Labs, Inc. (Boston, MA) developed EndeavorRx which is an FDA-authorized digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8 to12 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. This digital treatment is delivered through an action video game experience and is designed to challenge a child’s attention span during gameplay with the necessary focus and flexibility to perform multiple tasks at the same moment. EndeavorRx should be considered for use as part of a therapeutic program that may consist of clinician-directed therapy, medication, and/or educational programs, which target symptoms of the disorder. Specifically, EndeavorRx is a prescription only medical device where one prescription will provide 3 months of access to this

treatment. The duration of EndeavorRx daily treatments last approximately 25 minutes and should be completed by the patient without interruption (Akili Interactive Labs, 2021; Digital Therapeutics Alliance, 2021d).

In the Software Treatment for Actively Reducing Severity of ADHD (STARS-ADHD) study, Kollins and colleagues (2020) evaluated an investigational digital therapeutic, AKL-T01, for improved attentional performance in pediatric patients with attention-deficit hyperactivity disorder (ADHD). AKL-T01 (Akili Interactive Labs, Boston, MA) targets attention and cognitive control delivered through a video game-like interface through at-home play for 25 minutes per day, 5 days per week for 4 weeks. The STARS-ADHD study consisted of a randomized, double blind, parallel group, controlled trial of 348 pediatric patients aged 8 to 12 years with confirmed ADHD and Test of Variables of Attention (TOVA) Attention Performance Index (API) scores of -1.8 and below performed by 20 research institutions in the USA. Study participants were randomly assigned 1:1 to AKL-T01 or a digital control intervention which was in the form of a challenging and engaging word game. The study's primary outcome was a mean change in TOVA API from pre-intervention to post-intervention. Additionally, participant safety, tolerability, and compliance were also evaluated. Study participants who received AKL-T01 (n=180 [52%]; mean [SD] age, 9.7 [1.3] years) or control (n=168 [48%]; mean [SD] age, 9.6 [1.3] years), the non-parametric estimate of the population median change from baseline TOVA API was 0.88 (95% Confidence Interval [CI] 0.24-1.49; p=0.0060). The mean SD change from baseline on the TOVA API was 0.93 (3.15) in the AKL-T01 group and 0.03 (3.16) in the control group. No serious adverse events or discontinuation occurred. Participant compliance was a mean of 83 (83%) of 100 expected sessions played (SD, 29.2 sessions). The investigators concluded based on the evidence, AKL-T01 might be used to improve objectively measured inattention in pediatric patients with ADHD with minimal adverse events.

Freespira

Freespira, Inc. (Kirkland, WA) developed Freespira which is an FDA-cleared digital therapeutic that utilizes a proprietary sensor, physiologic feedback display, and coaching to instruct patients over 28-days to normalize the respiratory irregularities underlying a key physiological mediator of anxiety attacks and post-traumatic stress disorder (PTSD) symptoms (carbon dioxide hypersensitivity). Freespira is an adjunctive digital treatment for symptoms of panic disorder (PD) and PTSD used under the supervision of a healthcare professional, in combination with other pharmacological and/or non-pharmacological interventions. Specifically, Freespira consists of a small, portable case with a commercial-grade portable sensor that is capable of measuring real-time carbon dioxide (CO_2) and respiratory rate with wireless connectivity to a tablet computer that comes with a pre-installed app to guide treatment. Training is provided from a clinically supervising coach via telehealth in the form of guidance and support on appropriate use and best practices over the 28 day duration. The functionality of Freespira is based on breath sample delivery via a nasal canula connected to the Freespira sensor and by teaching patients to breath in synch and at different rates with rising and falling audio tones. Additionally, visual graphs of respiratory rate and exhaled CO_2serve as a prompt to adjust breathing volume in order to achieve normal CO_2targets. The coach is able to see the patient's uploaded physiologic data from the app and provide patient-tailored and specific coaching to further augment engagement, adherence, and symptom reductions over time. Freespira is used for 17 minutes twice daily for 28 days at home and although a prescription is not required from a physician, this digital therapeutic must be authorized by a licensed healthcare provider (Digital Therapeutics Alliance, 2021e).

Tolin and colleagues (2017) evaluated Freespira (Palo Alto Health Sciences, Inc., Danville, CA) in a multicenter, single arm trial consisting of 69 adult participants with panic disorder (PD). Study participants received 4 weeks capnometry guided respiratory intervention (CGRI) using Freespira, which provided feedback of end-tidal CO_2($PETCO_2$) and respiration rate (RR) transmitted by a sensor device. The intervention was delivered via home use after initial training by a clinician and provided remote monitoring of participant adherence and progress by the clinician. Outcomes assessment occurred post-treatment at 2- and 12-month follow-up. CGRI was associated with a response rate of 83% and remission rate of 54%. Additionally, large decreases in panic severity were noted as well as similar decreases in functional impairment and in global illness severity. The investigators noted that gains were largely sustained at follow-up and $PETCO_2$moved from the slightly hypocapnic range to the normocapnic range. This study served as a benchmarking analyses against a prior published controlled trial and confirmed prior clinical results and further supported the viability of CGRI in the treatment of PD.

Halo AF Detection System

LIVMOR, Inc. (Frisco, TX) developed the Halo AF Detection System which is an FDA-cleared digital technology that is delivered on a Samsung wearable smartwatch device and provides continuous monitoring of pulse rhythms for the detection of atrial fibrillation (AF), on demand during the day and automatically overnight. A prescription is required from a physician for patients to use the Halo AF Detection System (LIVMOR, 2020).

Currently, there is a lack of published peer-reviewed evidence available.

Insulia

Voluntis (Cambridge, MA) developed the Insulia app which is an FDA-cleared software medical device that is indicated for use by healthcare professionals (HCPs) and their type 2 adult diabetes patients who are receiving treatment with a long-acting insulin analog. Insulia facilitates insulin titration for patients using any brand of basal insulin including Lantus, Levemr, Toujeo, Tresiba, and Basaglar. This app is complimentary to basal insulin therapy and may be used on a compatible smartphone or

computer. The Insulia app's functionality includes the secure capture, storage, and transmission of the patient's diabetes related data via a web portal. Additionally, the visual reports and graphs supported by this app enables the HCP to review, analyze, and evaluate patient data to better manage the patient's diabetes. The app also comes with an accompanying coaching feature to ensure continual patient support. A prescription is required from a qualified healthcare provider for the patient to use the Insulia app (Digital Therapeutics Alliance, 2021f; Voluntis, 2021).

In the TeleDiab-2 study, Franc and colleagues (2019) evaluated the efficacy and safety of two telemonitoring systems to optimize basal insulin (BI) in participants with inadequately controlled type 2 diabetes. The study was a 13-month randomized controlled trial consisting of 191 individuals (mean age 58.7 years, mean hemoglobin A_{1c} [HbA_{1c}] 8.9%). Study participants were randomized into three groups including group 1 (standard care, n = 63), group 2 (interactive voice response system, n = 64), and group 3 (Diabeo-BI app software, n = 64). At 4 months follow-up, HbA_{1c} reduction was significantly higher in the telemonitoring groups (group 2: -1.44% and group 3: -1.48% vs group 1: -0.92%; p < 0.002). Furthermore, target fasting blood glucose was achieved by twice as many patients in the telemonitoring groups as in the control group, and insulin doses were also titrated to greater levels. The absence of severe hypoglycemia was noted in the telemonitoring groups. Mild hypoglycemia frequency was similar in all groups. The investigators concluded both telemonitoring systems improved glycemic control to a similar extent without an increase in hypoglycemic episodes.

Leva Pelvic Health System

Renovia Inc. (Boston, MA) developed the Leva Pelvic Health System which is an FDA-cleared medical device and consists of an intravaginal wand with motion sensors and app-based software program. This medical device is indicated for urinary incontinence in women with the aim of strengthening pelvic floor muscles and rehabilitating and training weak pelvic floor muscles in order to manage stress, mixed and mild to moderate urgency urinary incontinence, including over-active bladder. Under the guidance of the leva app, the patient performs 2 and a half minute exercise sessions twice a day for 8 to 12 weeks or until patient satisfaction with results. The patient performs the exercise while standing with the leva wand placed intravaginally for the exercise duration followed by immediate removal after use. Exercise data is transmitted from the wand to the software program on the patient's smartphone and the healthcare provider receives a monthly summary and individual patient reports. This securely captured and transmitted data highlights therapy adherence, symptoms, perceived improvement, and material remarks from leva's care management team which can then be used for short- and long-term follow up care. The Leva Pelvic Health System requires a prescription from a qualified healthcare provider for patients to use this medical device as first-line therapy either alone or in combination with other therapies (Digital Therapeutics Alliance, 2021g; Renovia, 2021).

Rosenblatt and colleagues (2019) evaluated the effectiveness and patient satisfaction of the leva Pelvic Digital Health System (leva), a pelvic floor muscle training (PFMT) with an accelerometer-based system for the treatment of female urinary incontinence (UI). This prospective, single-center, open label study consisted of 23 female participants who were premenopausal with mild to moderate stress or mixed UI for 6 weeks duration with supervision. The study results were as follows: the Urogenital Distress Inventory (UDI) score decreased from 36.7 ± 4.7 to 1.45 ± 0.8 at 6 weeks (p<0.0001), the Patient's Global Impression of Severity score decreased from 1.5 ± 0.1 to 0.2 ± 0.1 (p<0.0001) at study endpoint, the pelvic floor muscle (PFM) contraction duration increased from 13 ± 2.6 at baseline to 187 ± 9.6 seconds (p<0.0001), repeated contractions in 15 seconds increased from 5.9 ± 0.4 at enrollment to 9.6 ± 0.5 at 6 weeks (p< 0.0001), and maximum pelvic floor angle (a measure of lift) increased from 65.1 ± 2.0˚ to 81.1 ± 1.8˚ (p<0.0001). Additionally, increasing PFM contraction duration and maximum pelvic floor angle correlated with decreasing UDI-6 scores, r = -0.87, p=0.01; r = -0.97, p=0.0003, respectively. Device-related adverse events were absent.

Weinstein and colleagues (2022) evaluated whether the use of an intravaginal motion-based digital therapeutic device for pelvic floor muscle training (PFMT) was superior to PFMT alone in women with stress-predominant urinary incontinence (SUI). This study was a multicenter, randomized-controlled trial consisting of 61 female participants with SUI or SUI-predominant mixed urinary incontinence. The intervention group (n=29) was treated with PFMT using the device and the control group (n=32) received treatment with PFMT alone. Primary outcomes were measured at 8 weeks and included change in Urinary Distress Inventory, short-version and improvement in the Patient Global Impression of Improvement. In addition, participants completed Pelvic Organ Prolapse and Colorectal-anal Distress Inventories, Pelvic-Floor-Impact Questionnaire and a 3-day bladder diary. Study results were as follows: no statistical difference was noted in Urinary Distress Inventory, short-version scores between the intervention (-13.7 ± 18.7) and the control group (-8.7 ± 21.8; p=0.85), or in Patient Global Impression of Improvement (interventions 51.7% and control group 40.6%; p=0.47). Furthermore, Pelvic Organ Prolapse and Colorectal-anal Distress Inventories and Pelvic-Floor-Impact Questionnaire scores improved significantly more in the intervention group than the control group (all p<0.05) and median number of SUI episodes decreased from baseline to 8 weeks by -1.7 per day [(-3)-0] in the intervention group and -0.7[(-1)-0] in the control group, (p=0.047). Notably, this study was prematurely stopped due to device technical considerations.

In a remote, virtually executed, 8-week, prospective, randomized controlled superiority trial, Weinstein et al (2022) examined if pelvic floor muscle training (PFMT) using a motion-based digital intra-vaginal device is more effective than home pelvic floor muscle training for treatment of stress or stress-predominant mixed urinary incontinence (UI). This trial included women with stress or stress-predominant mixed UI; they were randomized to PFMT using a motion-based digital therapeutic device or a home training program using written and narrated instructions. Primary outcomes were change in UDI-6 (Urogenital Distress Inventory, Short Form) score and stress urinary incontinence (SUI) episodes on a 3-day bladder diary. A sample size of 139 per

group (n = 278) was planned to meet the power analysis requirements for the UDI-6 score (n = 278) and the bladder diary (n = 78). Pre-specified secondary outcomes included quality-of-life (QOL) surveys and adherence reporting. From September 2020 to March 2021, a total of 5,353 participants were screened, and 363 were randomized: 182 in the intervention and 181 in the control group. There were no baseline clinic-demographic differences between the 2 groups. The mean change in UDI-6 score was significantly greater for the intervention group compared with the control group (18.8 versus 14.7, p = 0.01). The median (inter-quartile range [IQR]) number of SUI episodes on the 3-day bladder diary was significantly reduced from 5 (3 to 8) and 5 (3 to 8) episodes to 1 (0 to 3) and 2 (1 to 4) (p = 0.005) in the intervention group compared with control group, respectively. A significantly greater number of participants in the intervention group than in the control group reported they were "much improved" or "very much improved" on the PGI-I (Patient Global Impression of Improvement) (63/143 [44.1 % versus 45/156 [28.8 %], odds ratio [OR] 1.94, 95 % CI: 1.21 to 3.15). There were no device-related severe adverse events (AEs). The authors concluded that in this all-remote, virtually conducted trial, PFMT guided by a motion-based digital therapeutic device resulted in significantly improved UI symptoms and reduction of UI episodes compared with a home training program. Moreover, these researchers stated that longer-term follow-up is underway to better understand the durability of the treatment regimen and examine the need for maintenance exercises to maintain the benefits of therapy.

The authors stated that a drawback of this study was the inability to carry out a physical examination before enrollment. For example, pelvic organ prolapse beyond the introitus was an exclusion criterion, and subjects were asked about “seeing or feeling a bulge”, a question that has been used in other epidemiologic studies. Baseline pelvic floor muscle strength assessment may have added value to a study of 1st-line UI treatment, although research and expert consensus supported digital health in the remote context, including initiation of PFMT in the absence of a physical examination. These researchers noted that this study employed a conservative version of the device available for use incorporating motion-based biofeedback and remote monitoring. Components, including audio-visual evidence-based education, remote coaching, and monthly patient progress reports to prescribing health care professionals, of the commercial version of the device were removed from the system used in the trial. Further investigation will examine these additional components and potential added benefits to PFMT alone.

In a retrospective, cohort study, Keyser et al (2023) examined the effectiveness of a prescription digital therapeutic (pDTx) in reducing UI symptoms in real-world users. This trial entailed data from users of a pDTx designed to guide PFMT between July 1, 2020 and December 31, 2021. The primary outcome was UI symptom change as reported via in-app Urogenital Distress Inventory (UDI-6). Included subjects were female, 18 years of age or older with a diagnosis of stress, urgency, or mixed UI who completed the UDI-6 at baseline and 8 weeks. Demographic, symptom, and adherence data were summarized. Paired t-test and Wilcoxon signed rank test were used to analyze change in outcomes from baseline to 8 weeks across adherence and UI diagnosis groups. Of 532 women with UI, 265 (50 %) met criteria and were included in the analysis. Mean age was 51.2 ± 11.5 years (range of 22 to 84, n = 265). Mean body mass index (BMI) was 27.3 ± 6.2 kg/m2 (range of 15.2 to 46.9, n = 147). Most participants had stress UI (59 %) followed by mixed UI (22 %), urgency UI/OAB (11 %), and unspecified UI (8 %). UDI-6 scores improved by 13.90 ± 15.53 ($p \leq 0.001$); 62 % met or exceeded MCID. Device-reported PFMT adherence was 72 % at 4 weeks and 66 % at 8 weeks (100 % = 14 uses/week). Participants in each diagnosis category reported significant improvement on UDI-6 score from baseline to 8 weeks. No association between UDI-6 score improvement and adherence category, age, BMI, or UI subtype was identified. The authors concluded that this study showed effectiveness of a pDTx in reducing UI symptoms in a real-world setting. Users achieved statistically and clinically significant symptom improvement over an 8-week period. These researchers stated that enhanced data collection of relevant demographic and clinical information will further add to the value and applicability of the data. These results may inform additional research and development, including efforts to improve in-app data collection and promote adherence. Given the opportunity of pDTx, additional work designed to present larger patient cohorts is planned, including application of machine learning to expanded data sets. Clinically validated pDTx designed to treat UI in women may help to scale treatment and management of this significant, yet under-treated health condition.

The authors stated that study drawbacks included the challenges of real-world survey data. Among participants with UI, this in-app survey response rate of 50 % was greater than other real-world, incontinence-related published response rates ranging from 11 % to 34 %. Completion of the in-app UDI-6 survey was not required to use the pDTx, and users who completed the survey may differ from those who did not. Therefore, selection bias may have limited interpretation and generalizability of results. Furthermore, lower response rates to clinico-demographics such as parity, mode of delivery, and past or current UI interventions limited the analysis of these parameters and their relationship to symptom improvement. It was possible that concurrent UI treatments, such as medications (e.g., anti-cholinergics, hormonal therapies) or pessaries also influenced outcomes. As with most apps, continuous improvement and updates may result in improved data reporting, which is largely dependent upon patient motivation and engagement, as compared to the financial compensation or direct over-sight common in randomized trials. Expansion of the onboarding, educational, and motivational content could further enhance patient engagement and provide more complete data sets moving forward.

Weinstein et al (2023) examined the long-term effectiveness of an 8-week regimen of PFMY guided by a motion-based DTx device compared with a standard home program in the treatment of SUI and stress-predominant mixed urinary incontinence (MUI). The primary virtual trial was carried out from October 2020 to March 2021; a total of 363 women with SUI or stress-predominant MUI were randomized to complete PFMT using the device (intervention group) or a standard home pelvic floor muscle training program (control group) for 8 weeks. Primary outcomes included change in UDI-6 score and SUI episodes on a 3-day bladder diary. The PGI-I was also assessed, with "much better" and "very much better" responses considered as improvement. In this planned secondary analysis, symptom and adherence data were collected in follow-up at 6 and 12 months. A modified intention-to-treat (ITT) analysis was conducted using Student's t-tests and $\chi 2$ tests as appropriate. Of 299

participants analyzed at 8 weeks, 286 (95.7 %) returned 6- and 12-month data (151 in the control group, 135 in the intervention group). Mean age was 51.9 ± 12.8 years, and mean BMI was 31.8 ± 7.4; 84.6 % of participants were parous, and 54.9 % were post-menopausal. Mean change in UDI-6 score from baseline to 6 and 12 months was significantly greater in the intervention group than in the control group (20.2 ± 20.9 versus 14.8 ± 19.5, p = 0.03 and 22.7 ± 23.3 versus 15.9 ± 20.3, p = 0.01, respectively). Participants in the intervention group had more than twice the odds of reporting improvement on the PGI-I compared with participants in the control group (OR 2.45, 95 % CI: 1.49 to 4.00). The authors concluded that PFMT guided by a motion-based digital therapeutic device yielded significantly greater UI symptom improvement compared with a standard home pelvic floor muscle training program at 6 and 12 months, although continued improvement waned over time. These researchers stated that this technology may facilitate PFMT access and adherence for women with SUI and stress-predominant MUI and represents an effective modality for scaling 1st-line care.

The authors stated that drawbacks of this study included the lack of physical examination and other objective measures of pelvic floor muscle performance at baseline and follow-up. Furthermore, bladder diaries were not collected at 6 or 12 months to enable comparison of number of UI episodes reported during the active study period. In addition, although these researchers were able to collect information regarding continued use for participants in the intervention group due to reporting from the device, they were unable to collect parallel information for participants in the control group. Although this limited the ability to understand the presence or absence of continued pelvic floor muscle training in the control group, it is inherent in the design of the control group and typical for the use of home PFMT.

Luminopia One (Digital Binocular Therapy)

Luminopia, Inc. (Cambridge, MA) developed Luminopia One which received FDA approval via the De Novo Pathway and is a software-only digital therapeutic for use with commercially available Head-Mounted Displays (HMDs) which are compatible with the software application. The FDA classifies Luminopia One as a Class II medical device. Luminopia One is indicated for improvement in visual acuity in amblyopia patients, aged 4-7, associated with anisometropia and/or with mild strabismus, having received treatment instructions (frequency and duration) as prescribed by a trained eye-care professional. Luminopia One is intended for both previously treated and untreated patients; however, patients with more than 12 months of prior treatment (other than refractive correction) have not been studied. Luminopia One is intended to be used as an adjunct to full-time refractive correction, such as glasses, which should also be worn under the HMD during Luminopia One therapy. Luminopia One is intended for prescription use only, in an at-home environment (FDA, 2023). The safety and effectiveness Luminopia One beyond 12 weeks is unknown. Patients with an interpupillary distance of less than 52 mm should not use Luminopia One (Luminopia, 2023).

Xiao and colleagues (2021) evaluated the efficacy and adherence of Luminopia One, a dichoptic treatment that applies therapeutic modifications to streaming content selected by the patient. The investigators conducted a single-arm, multicenter prospective pilot study enrolling children from 4 to 12 years of age with anisometropic, strabismic, or mixed amblyopia at 10 pediatric ophthalmic and optometric practices across the United States. Luminopia one was prescribed for 1 hour/day, 6 days/week for 12 weeks of at-home use. The primary endpoint was best-corrected visual acuity (BCVA) at the 12-week follow-up visit. Ninety participants (mean age, 6.7 ± 2.0 years), in all, were enrolled, and 73/90 participants (81%) had prior treatment beyond refractive correction. For those who completed the 12-week visit, mean amblyopic eye BCVA improved from 0.50 logMAR to 0.35 logMAR (1.5 logMAR lines; 95% confidence interval [CI], 1.2-1.8 lines; p < 0.0001). Mean stereo-acuity improved by 0.28 log arcsec (95% CI, 0.14-0.42 log arcsec; p < 0.0001). Median adherence was 86% (interquartile range, 70% to 97%). The study cohort showed a high adherence over the 12-week study period with participants demonstrating clinically and statistically significant improvements in visual acuity and stereo-acuity.

In a randomized, double-masked, clinical trial, Elhusseiny et al (2021) examined the BCVA and stereo-acuity (SA) gains in children aged less than 7 years, and adults with unilateral amblyopia treated with a prototype virtual reality (VR)-based binocular amblyopia therapy. Patients at Boston Children's Hospital with unilateral anisometropic and/or strabismic amblyopia and history of prior amblyopia treatment failure were randomized to either a full-treatment group (8 weeks of binocular treatment using therapeutic software application in VR head-set) or a sham-crossover group (4 weeks of sham treatment followed by 4 weeks of binocular treatment). Amblyopic eye VA and SA were evaluated at 4, 8, and 16 weeks' follow-up. The study cohort included 20 participants (10 females), with a median age of 9 years (range of 7 to 38 years). In the full-treatment group (11 patients), the mean amblyopic eye logMAR VA at 16 weeks was 0.49 ± 0.26, compared with 0.47 ± 0.20 at baseline. In the sham cross-over group, it was 0.51 ± 0.18 at 16 weeks, compared with 0.53 ± 0.21 at baseline. Stereo-acuity (log arcsec) was significantly improved, from 7.3 ± 2 at baseline to 6.6 ± 2.3 at 8 weeks (p < 0.001) and 6.7 ± 2.6 at 16 weeks (p < 0.001). No significant AEs (diplopia, asthenopia, or worsening strabismus) were noted in either group. The authors concluded that although the VR-based prototype for binocular amblyopia therapy did not significantly improve VA in the amblyopic eyes of older children and adults, SA did significantly improve compared with baseline; improvements were clinically minute. Moreover, these researchers stated that larger studies are needed to confirm these findings.

The authors stated that this trial was limited by its small sample size (n = 20) and modest follow-up (16 weeks). These investigators did not achieve the target sample size due to participant attrition. The observed improvements in stereopsis, while statistically significant, were clinically minute; whether or not the observed benefits would be reproducible in a larger study is uncertain.

Xiao and colleagues (2022) conducted a phase 3 randomized controlled trial evaluating the safety and efficacy of Luminopia One, a dichoptic digital therapeutic for amblyopia. The study consisted of 105 children aged 4 to 7 years with amblyopia who were enrolled at 21 academic and community sites in the U.S. Randomization was 1:1 to the treatment or comparison group, stratified by site. Participants in the treatment group (n = 51) used Luminopia One at home for 1 hour per day, 6 days per week and wore glasses full-time while participants in the comparison group (n = 54) continued wearing glasses full-time alone. The primary efficacy outcome was change in amblyopic eye visual acuity (VA) from baseline at 12 weeks, and VA was measured by masked examiners. Safety evaluation was based on the frequency and severity of stud-related adverse events. Primary analyses were conducted using the intention-to-treat population. At 12 weeks, amblyopic eye VA improved by 1.8 lines (95% confidence interval [CI], 1.4-2.3 lines; n = 45) in the treatment group and by 0.8 lines (95% CI, 0.4-1.3 lines; n = 45) in the comparison group. At the planned interim analysis (adjusted α = 0.0193), the difference between groups was significant (1.0 lines; p = 0.0011; 96.14% CI, 0.33-1.63 lines) and the study was stopped early for success, according to the protocol. No serious adverse events were reported. Although the investigators concluded that the value of Luminopia One as an effective treatment in clinical practice, future studies are warranted for comparison with other methods and in additional patient populations.

Tailor et al (2022) stated that current treatments for amblyopia, typically patching or pharmacological blurring, have limited success. Less than 2/3 of children achieve good VA of 0.20 logMAR in the amblyopic eye, with limited improvement of stereopsis, and poor adherence to treatment. A new approach, based on presentation of movies or computer games separately to each eye, may yield better results and improve adherence. These treatments aim to balance the input of visual information from each eye to the brain. In a Cochrane review, these investigators examined if binocular treatments in children, aged 3 to 8 years, with unilateral amblyopia would result in better visual outcomes than conventional patching or pharmacological blurring treatment. They identified 1 eligible RCT of conventional patching treatment versus novel binocular treatment, and analyzed a subset of 68 children who met the age criterion of this review. These researchers obtained data for the mean change in amblyopic eye VA, AEs (diplopia), and adherence to prescribed treatment at 8- and 16-week follow-up intervals, although no data were available for change in BCVA after 52 weeks. Risk of bias for the included study was considered to be low. The certainty of evidence for the VA outcomes at 8 and 16 weeks of treatment and adherence to the study intervention was rated moderate using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, down-grading by 1 level due to imprecision. The certainty of evidence was down-graded by 2 levels and rated low for the proportion of participants reporting AEs due to the sample size. Acuity improved in the amblyopic eye in both the binocular and patching groups following 16 weeks of treatment (improvement of -0.21 logMAR in the binocular group and -0.24 logMAR in the patching group, mean difference (MD) 0.03 logMAR (95 % CI: -0.10 to 0.04; 63 children). This difference was non-significant and the improvements in both the binocular and patching groups were also considered clinically similar. Following 8 weeks of treatment, acuity improved in both the binocular and patching groups (improvement of -0.18 logMAR in the patching group compared to -0.16 logMAR improvement in the binocular-treatment group) (MD 0.02, 95 % CI: -0.04 to 0.08). Again this difference was statistically non-significant, and the differences observed between the patching and binocular groups were also clinically non-significant. No AE of permanent diplopia was reported. Adherence was higher in the patching group (47 % of participants in the iPad group achieved over 75 % compliance compared with 90 % of the patching group). Data were not available for changes in stereopsis nor for contrast sensitivity following treatment.

The authors concluded that there was only 1 RCT that offered evidence of the safety and effectiveness of binocular treatment. These investigators were moderately confident that after 16 weeks of treatment, the gain in amblyopic eye acuity with binocular treatment was likely comparable to that of conventional patching treatment. However, due to the limited sample size and lack of long-term (52 week) follow-up data, it was not yet possible to draw robust conclusions regarding the overall safety and sustained effectiveness of binocular treatment. They stated that further research, using acknowledged methods of VA and SA assessment with known reproducibility, is needed to inform decisions regarding the implementation of binocular treatments for amblyopia in clinical practice, and should incorporate longer term follow-up to establish the effectiveness of binocular treatment. These researchers stated that RCTs should also include outcomes reported by users, adherence to prescribed treatment, as well as recurrence of amblyopia following cessation of treatment.

In a prospective, randomized, masked, controlled, multi-center, non-inferiority study, Wygnanski-Jaffe et al (2023) compared visual outcomes following the use of a novel binocular eye-tracking-based home treatment (CureSight; NovaSight, Ltd) with patching. A total of 103 children aged 4 to less than 9 years with anisometropic, small-angle strabismic or mixed-mechanism amblyopia were randomized 1:1 to either CureSight treatment or patching. The CureSight treatment uses combined anaglyph glasses and an eye tracker to induce real-time blur around the fellow eye fovea in dichoptic streamed video content. Participants used the device for 90 mins/day, 5 days/week for 16 weeks (120 hours). The patching group received 2 hours of patching 7 days/week (224 hours). The pre-specified non-inferiority margin was 1 line. The primary outcome was the improvement in the amblyopic eye visual acuity (VA), modeled with a repeated measures analysis of co-variance. Secondary outcomes included stereo-acuity, binocular VA, and treatment adherence rates, analyzed by a 1-sample Wilcoxon test within each group and a 2-sample Wilcoxon test comparing groups. Safety outcomes included the frequency and severity of study-related adverse events (AEs). The CureSight group VA improvement was found to be non-inferior to patching group improvement (0.28 ± 0.13 logarithm of the minimum angle of resolution [logMAR] [p < 0.0001] and 0.23 ± 0.14 logMAR [p < 0.0001], respectively; 90 % confidence interval [CI] of difference, -0.008 to 0.076). Stereo-acuity improvement of 0.40 log arcseconds (p < 0.0001) and improved binocular VA (0.13 logMAR; p < 0.0001) were observed in the binocular treatment group, with similar improvements in the patching group in stereo-acuity (0.40 log arcseconds; p < 0.0001) and binocular VA (0.09 logMAR; p < 0.0001), with no significant difference between improvements in the 2 groups in either stereo-acuity (difference, 0; 95 % CI: -0.27 to -0.27; p = 0.76) or binocular VA (difference, 0.041; 95 % CI: -0.002 to 0.085; p = 0.07). The binocular treatment group had a significantly

higher adherence than the patching group (91 % versus 83 %; 95 % CI: -4.0 % to 21 %; p = 0.011). No serious AEs were observed. The authors concluded that binocular treatment was well-tolerated and non-inferior to patching in amblyopic children aged 4 to less than 9 years; and high adherence may provide an alternative therapeutic option for amblyopia. Moreover, these researchers stated that whether this binocular treatment can apply for other forms of amblyopia and to older children and adults is yet to be examined.

The authors stated that this trial had several drawbacks. First, most patients had anisometropic amblyopia (90 % of the patients in this study versus 50 % to 60 % in comparable RCTs. Although the amblyopia-type subgroup analysis showed no significant difference in the groups, further generalizability confirmation to strabismic and mixed amblyopia populations should be explored. Moreover, future studies are needed to examine the impact of dosing on the rapidity of visual improvement and its durability and the effect of subgroups on treatment effectiveness compared with other binocular treatments. Tropia was limited to no more than 5 prism diopters. Second, using a subjective self-logging compliance diary by the guardians of the patching group was a drawback because evidence is ample for over-estimating compliance in this type of patching monitoring. Third, these investigators used a non-inferiority margin of 1 line (0.1 logMAR), which is more than that used in the other non-inferiority studies, with more conservative limits of either 0.05 or 0.075 logMAR. If these researchers had carried out the statistical comparison using either of the more conservative non-inferiority margins, the study conclusions would have been the same. Nevertheless, in retrospect, these investigators believed that a more conservative non-inferiority limit should have been considered, and they intend to use such margins when planning future studies.

In a prospective, pilot study, Zhu et al (2023) examined VA and SA improvements in children with amblyopia treated with either binocular dichoptic treatment or patching treatment. A total of 34 participants between 4 and 9 years of age with unilateral anisometropic amblyopia and without history of prior amblyopia treatment were enrolled into 3 groups. Full treatment group (FTG; n = 12): participants were prescribed the binocular dichoptic treatment to watch for 90 mins/day, 5 days/week. Part-time treatment group (PTTG; n = 8): participants were prescribed the same binocular treatment as FTG, 90 mins/day, 3 days/week. Patching treatment group (PTG; n = 14): participants wore an adhesive patch over the dominant eye for 2 hours/day, 7 days/week. Amblyopic-eye distance VA (DVA), near VA (NVA) and SA were evaluated at baseline, 4, 8, and 12 weeks. At 12 weeks, mean amblyopic-eye DVA improved 1.8 lines (95 % CI: 1.1 to 2.5) in FTG, 1.5 lines (95 % CI: 0.4 to 2.7) in PTTG, and 3.0 lines (95 % CI: 2.0 to 4.0) in PTG. The amblyopic-eye NVA improved 2.9 lines (95 % CI: 2.4 to 3.5) in FTG, 1.7 lines (95 % CI: 0.5 to 3.0) in PTTG, and 2.8 lines (95 % CI: 1.8 to 3.9) in PTG. The SA improved 0.38 log-arcseconds (95 % CI: 0.24 to 0.53) in FTG, 0.59 log-arcseconds (95 % CI: 0.36 to 0.82) in PTTG, and 0.40 log-arcseconds (95 % CI: 0.13 to 0.67) in PTG. No significant differences were found in DVA, NVA or SA improvement between FTG and PTG at 12 weeks. The authors concluded that VA and SA after binocular dichoptic treatment produced a similar therapeutic outcome to patching, suggesting a potential value for binocular therapy when treating anisometropic moderate degree of children's amblyopia.

Wiecek et al (2024) stated that individuals with amblyopia experience central vision deficits, including loss of VA, binocular vision, and stereopsis. In a prospective, cohort study, these researchers examined the differences in peripheral binocular imbalance in children with anisometropic amblyopia, strabismic amblyopia, and typical binocular vision to examine if there are systematic patterns of deficits across the visual field. This trial recruited 12 participants with anisometropic amblyopia, 10 with strabismic amblyopia, and 10 typically sighted controls (age range of 5 to 18 years). Binocular imbalance was tested at 0°, 4°, and 8° eccentricities (4 angular locations each) using band-pass filtered Auckland optotypes (5 cycles per optotype) dichoptically presented with differing contrast to each eye. The inter-ocular contrast ratio was adjusted until the participant reported each optotype with equal frequency. Participants with anisometropic and strabismic amblyopia had a more balanced contrast ratio, or decreased binocular imbalance, at 4° and 8° eccentricities as compared with central vision. Participants with strabismic amblyopia had significantly more binocular imbalance in the periphery as compared with individuals with anisometropic amblyopia or controls. A linear mixed effects model showed a main effect for strabismic amblyopia and eccentricity on binocular imbalance across the visual field. The authors concluded that there was evidence of decreased binocularity deficits, or inter-ocular suppression, in the periphery in anisometropic and strabismic amblyopia as compared with controls. Notably, those with strabismic amblyopia exhibited more significant peripheral binocular imbalance. These variations in binocularity across the visual field among different amblyopia subtypes may necessitate tailored approaches for dichoptic treatment.

The authors stated that a drawback of this trial was that the locations of testing were not randomized, although the conditions were interleaved to minimize learning effects. This was carried out intentionally to make the task easier for the pediatric participants. Testing was completed sequentially so the central location was tested once, and then in a clockwise fashion and 4° and 8° (once per location), and the process repeated. These investigators did not observe any effect of quadrant, and it was unlikely that the eccentricity effect reported across cohorts would differentially affect subtypes of amblyopia. In addition, the task was limited to 8° eccentricity testing for peripheral vision and 4-degree para-foveal vision. These investigators stated that future studies that examine binocular balance in both the mid and far periphery would be informative for mapping the full extent of binocular imbalance across the visual field. Furthermore, although these researchers found that participants with strabismic amblyopia had more peripheral suppression compared with individuals with anisometropic amblyopia, this difference may be attributed partly to a difference in testing. These investigators did not align stimuli on corresponding retinal points in individuals with strabismic amblyopia, although it was presumed that dichoptic stimuli in the periphery of anisometropic participants would have been overlapping. The authors made this decision to better evaluate what peripheral vision would be like under real-world viewing conditions, rather than in a simulated environment. These researchers were also limited on the ability to subjectively align dichoptic stimuli in the periphery in children, because this task would require reliable subjective feedback from pediatric participants as well as the presence of suppression in amblyopic participants. Also, these investigators noted that participants

with amblyopia showed significantly greater binocular imbalance compared with typically sighted participants; however, it was important to note that the control group still exhibited a variety of binocular imbalances across all retinal locations. This finding was in alignment with previous reports on normally sighted adults that showed sensory eye dominancy varied across the binocular visual field in sign and magnitude. Similar to that study, these researchers found that foveal binocular imbalance predicted peripheral binocular imbalance. The authors stated that this study used contrast to dichoptically balance the signal between the amblyopic and fellow eye; however, little is known regarding monocular contrast perception in the peripheral vision of individuals with amblyopia. These researchers stated that future investigations that quantifies sensitivity to contrast across different spatial frequencies at more eccentric retinal locations will aid in informing the nature of binocular combination in an amblyopic visual system. This knowledge, in combination with binocular balance measures described in this study, will aid in developing customized therapies that target the most impacted locations of the visual field. Finally, with the emergence of new dichoptic binocular therapies, the integration of binocular perception across the visual field in the pediatric population is of the utmost importance. Specifically, therapies differ in the region of treatment/binocular combination; some therapies implement anti-suppression therapy only in central vision, whereas others require the participant to integrate binocular information across the entire visual field. In the context of these findings, it may be more important to dichoptically balance binocular information in central vision, whereas unaltering peripheral eccentric visual stimuli for individuals with anisometropic amblyopia. This strategy would have the advantage of treating the retinotopic location most impacted in anisometropic amblyopia while promoting binocular fusion with peripheral stimuli. Alternatively, individuals with strabismic amblyopia may benefit from stimuli that require binocular balancing across the entire visual field.

An UpToDate review on “Amblyopia in children: Management and outcome” (Coats and Paysse, 2024) states that “Strategies to encourage compliance include allowing the child to play a favorite video game or watch television only when the patch is worn. Digital applications for smartphones, tablets, and other devices have been developed that can provide binocular training as a complement or alternative to patching. Data are limited on the efficacy of these devices. In addition, the games available on these platforms may not hold the child's attention for a sufficient amount of time. Other strategies to improve compliance have been explored (e.g., supervised inpatient occlusion treatment and suturing or gluing the occluder in place), but these are generally impractical”.

The AAO’s Preferred Practice Pattern on “Binocular (Dichoptic) Digital Therapy,” (AAO, 2024) stated that “Research with this technology is ongoing, which will be used to delineate use of binocular therapy for treatment of amblyopia”.

MindMotion GO

MindMaze (Lausanne, Switzerland) developed MindMotion GO which is an FDA-cleared medical device software used in combination with the Microsoft Kinect v2 and Leap Motion controller that supports the physical rehabilitation of adults in the acute inpatient settings, outpatient clinics, and at home. The software employs game-based digital therapies which includes rehabilitation exercises for the upper extremity, trunk, and lower extremity; audio-visual feedback and graphic movement representations for individuals; and individual performance metrics for the healthcare professional. Prior to use of MindMotion GO, individual assessment, exercise guidance, and approval by the healthcare professional is required (FDA, 2022c; MindMaze, 2022).

My Dose Coach

Sanofi (Cambridge, MA) developed My Dose Coach which is an FDA-cleared basal titration app for adult patients with type 2 diabetes who have been prescribed a once-daily long-acting basal insulin. This app is intended to function as aid to the patient by providing dose suggestions based upon the healthcare provider's independent professional judgement. Prior to My Dose Coach use, the healthcare provider sets up the dose instructions for the specific patient and initiates the app using specific patient instructions. My Dose Coach utilizes dose plan instructions given by the patient's healthcare provider to give dose suggestions of once-daily long-acting basal insulin (i.e., basal insulin titration) that are based on the patient's fasting blood glucose as well as hypoglycemia occurrence. It is available by prescription only and is not intended to replace the care or advice of a healthcare provider (FDA, 2022d).

myVisionTrack (Home Vision Monitor [HVM])

Visual Art and Science, LLC (Richardson, TX) developed myVisionTrack which is an FDA-cleared mobile app designed as a vision function test. It is intended for the detection and characterization of central 3 degrees metamorphopsia (visual distortion) in individuals with maculopathy, including age-related macular degeneration and diabetic retinopathy, and aids in monitoring progression of disease factors causing metamorphopsia. The myVisionTrack app allows patients to regularly perform a simple self-test at home who have this capability. It is not intended to diagnose and a prescription is required for use (FDA, 2022e).

Natural Cycles App

The Natural Cycles (NC) is an FDA-cleared birth control app, which is powered by a proprietary algorithm that determines a woman’s fertility status based on her basal body temperature (BBT). Users measure their BBT with the NC thermometer, enter it

into the app, and the proprietary algorithm will use temperature, period, and cycle data to determine the user's fertility status. Users can use their daily fertility status to plan or prevent pregnancy.

Pearson et al (2021a) noted that digital fertility awareness-based methods of birth control are an attractive alternative to hormonal or invasive birth control for modern women. They are also popular among women who may be planning a pregnancy over the coming years and wish to learn about their individual menstrual cycle. In a prospective, real-world cohort study, these researchers examined the effectiveness of the NC app at preventing pregnancy for a cohort of women from the U.S. and described the key demographics of current users of the app in such a cohort. This trial included users who purchased an annual subscription to prevent pregnancy. Demographics were assessed via answers to in-app questionnaires. Birth control effectiveness estimates for the entire cohort were calculated using 1-year pearl index (PI) and 13-cycle cumulative pregnancy probability (Kaplan-Meier life table analysis). The study included 5,879 women who contributed an average of 10.5 months of data for a total of 5,125 woman-years of exposure. The average user was 30 years old with a body mass index (BMI) of 24 and reported being in a stable relationship. With typical use, the app had a 13-cycle cumulative pregnancy probability of 7.2 % and a 1-year typical use PI of 6.2. When the app was used under perfect use, the PI was 2.0. The authors concluded that the data presented in this study provided insights into the cohort of women using the NC app in the U.S. and gave country-specific effectiveness estimates. The contraceptive effectiveness of the app was in line with previously published figures from NC (PI of 7 for typical use and 2 for perfect use). Digital fertility awareness-based methods (FABMs) are a reality for a growing number of women of reproductive age and it is important that country-specific scientific evidence describing the effectiveness of such methods is encouraged.

Pearson et al (2021b) stated that digital FABM offers an alternative choice for women who do not wish to use hormonal or invasive methods for birth control. In a prospective, observational real-world study, these investigators examined the key demographics of current users of the NC app and evaluated the contraceptive outcomes of women preventing pregnancy in a U.K. cohort of women. The typical-use effectiveness of the method was calculated using both 13-cycle cumulative probability of pregnancy (life table analysis) and PI for the entire study cohort. Perfect-use PI was calculated using data from cycles where sexual intercourse during the fertile window was marked as protected and no unprotected sex was recorded on fertile days. A total of 12,247 women were included in the study and contributed an average of 9.9 months of data for a total of 10,066 woman-years of exposure. The mean age of the cohort was 30, mean BMI was 23.4, the majority were in a stable relationship (83.2 %) and had a university degree or higher (83 %). The 1-year typical use, PI was 6.1 (95 % CI: 5.6 to 6.6) and with perfect-use was 2.0 (95 % CI: 1.3 to 2.8); 13-cycle pregnancy probability was 7.1 %. The authors concluded that this was the 1st study that described the use of a digital contraceptive by women in the U.K. It provided the demographics of users and how they correlated with the apps effectiveness at preventing pregnancy.

A National Institute for Health and Clinical Excellence's Medtech Innovation Briefing on "Natural Cycles for monitoring fertility" (NICE, 2021) noted that the innovative aspects are that NC is the 1st fertility-awareness app that comes with a basal thermometer and has been CE-marked as a medical device. The intended place in therapy is as a fertility-awareness contraception method. It would be used as a strategy to monitor ovulation, predict fertility, and may be used alongside abstinence or a barrier contraceptive method. The main points from the evidence were from 3 studies (2 retrospective analyses and 1 prospective observational study). These included 70,113 people using the app at home with typical follow-up of 6 to 9 months. They showed that NC can be used as a fertility-awareness contraception method. No evidence was identified on using the app to help plan a pregnancy.

Manhart and Duane (2022) noted that the NC app uses daily BBT to define the fertile window via a proprietary algorithm and is clinically established effective in preventing pregnancy. These researchers compared the app-defined fertile window of NC to that of CycleProGo, an app that uses BBT and cervical mucus to define the fertile window; and compared the app-defined fertile windows to the estimated physiologic fertile window. Daily BBT were entered into NC from 20 randomly selected regularly cycling women with at least 12 complete cycles from the CycleProGo database. The proportion of cycles with equivalent (± 1 cycle day) fertile-window starts and fertile-window ends was determined. The app-defined fertile windows were then compared to the estimated physiologic fertile window using Peak mucus to estimate ovulation. A total of 57 % of cycles (136/238) had equivalent fertile-window starts and 36 % (72/181) had equivalent fertile-window end days. The mean overall fertile-window length from the NC app was 12.8 days compared to 15.1 days for CycleProGo ($p < 0.001$). The NC algorithm declared 12 % to 30 % of cycles with a fertile-window start and 13 % to 38 % of cycles with a fertile-window end within the estimated physiologic fertile window. The CycleProGo algorithm declared 4 % to 14 % of cycles with a fertile-window start and no cycles with a fertile-window end within the estimated physiologic fertile window. The authors concluded that the NC app designated a higher proportion of cycles days as infertile within the estimated physiologic fertile window than CycleProGo.

Karasneh et al (2020) stated that the use of mobile applications (apps) for health and well-being has grown exponentially in the past 10 years, as such apps were reported to be ideal platforms for behavioral change and symptoms monitoring and management. These investigators systematically review period-tracking apps available at Google Play and Apple App Stores and determined the presence, features, and quality of these Smartphone apps. Furthermore, behavioral changes associated with the top 5 rated apps were assessed. This study used the Systematic Search Criteria through Google Play Store and iTunes Apple Store, using terms related to period-tracking. Apps were scanned for matching the inclusion criteria and the included apps were assessed by 2 reviewers using the Mobile Application Rating Scale (MARS), a tool that was developed for classifying and assessing the quality of mHealth apps. A total of 49 apps met the inclusion criteria. Most of the apps enabled setting user goals, motivations, and interactivity, tracking multiple symptoms or mood changes, allowed notifications, and used graphs to illustrate the tracking result over a specific period of time. The majority of features and functions within these apps were offered for free,

while some apps included limited in-app purchases or needed Internet connection to function. Certain apps were reported by participants to promote behavioral change and increase knowledge and awareness regarding monthly periods. Moreover, the risk of bias is also present when apps are assessed by founders or funding bodies, as is the case with the app Natural Cycles, which was evaluated in 3 different studies. The authors concluded that period-tracking apps were easy to use and navigate and can hence be readily adopted into routine tracking and management of periods; however, most apps were not based on significant evidence and may need further development to support period-related symptom management.

Pearson et al (2021a) noted that digital fertility awareness-based methods of birth control are an attractive alternative to hormonal or invasive birth control for modern women. They are also popular among women who may be planning a pregnancy over the coming years and wish to learn about their individual menstrual cycle. In a prospective, real-world cohort study, these researchers examined the effectiveness of the Natural Cycles app at preventing pregnancy for a cohort of women from the U.S. and described the key demographics of current users of the app in such a cohort. This trial included users who purchased an annual subscription to prevent pregnancy. Demographics were assessed via answers to in-app questionnaires. Birth control effectiveness estimates for the entire cohort were calculated using 1-year pearl index (PI) and 13-cycle cumulative pregnancy probability (Kaplan-Meier life table analysis). The study included 5,879 women who contributed an average of 10.5 months of data for a total of 5,125 woman-years of exposure. The average user was 30 years old with a body mass index (BMI) of 24 and reported being in a stable relationship. With typical use, the app had a 13-cycle cumulative pregnancy probability of 7.2 % and a 1-year typical use PI of 6.2. When the app was used under perfect use, the PI was 2.0. The authors concluded that the data presented in this study provided insights into the cohort of women using this app in the U.S. and gave country-specific effectiveness estimates. The contraceptive effectiveness of the app was in line with previously published figures from Natural Cycles (PI of 7 for typical use and 2 for perfect use). Moreover, these researchers stated that further investigation is needed to examine the real-world effectiveness of the method in diverse populations of women. Digital fertility awareness-based methods (FABMs) are a reality for a growing number of women of reproductive age and it is important that country-specific scientific evidence describing the effectiveness of such methods is encouraged. In addition, contraceptive effectiveness in the wider population in relationship to demographics, education, and a host of other variables should be examined to aid in personalized patient counseling depending on individual needs.

The authors stated that this study had several drawbacks. First, it is not generalizable to the U.S. population as this is a convenient sample cohort, the majority of which are highly educated and financially comfortable. However, it provided the 1st evidence of a cohort study in the U.S. with the only approved app for contraception. Second, all data were self-reported and were not verified as it would be in a traditional clinical study setting; thus, these investigators could not be sure of the motivation of the users, which may partially explain the higher pregnancy probability in the 29 to 34 years age group in this analysis. Neither the responses to in-app questions nor sexual intercourse logging was mandatory for study inclusion, so only a subset of cycles (18 %) contained information regarding user behavior during the fertile window. Those who discontinued using the app during the study period were contacted for follow-up information to assess potential pregnancy status. Third, due to the nature of the product, a proportion or subjects declined to reply and were lost to follow-up.

Pearson et al (2021b) stated that digital fertility awareness-based contraception offers an alternative choice for women who do not wish to use hormonal or invasive methods. In a prospective, observational real-world study, these investigators examined the key demographics of current users of the Natural Cycles app and evaluated the contraceptive outcomes of women preventing pregnancy in a U.K. cohort of women. The typical-use effectiveness of the method was calculated using both 13-cycle cumulative probability of pregnancy (life table analysis) and PI for the entire study cohort. Perfect-use PI was calculated using data from cycles where sexual intercourse during the fertile window was marked as protected and no unprotected sex was recorded on fertile days. A total of 12,247 women were included in the study and contributed an average of 9.9 months of data for a total of 10,066-woman years of exposure. The mean age of the cohort was 30, mean BMI was 23.4, the majority were in a stable relationship (83.2 %) and had a university degree or higher (83 %). The 1-year typical use, PI was 6.1 (95 % CI: 5.6 to 6.6) and with perfect-use was 2.0 (95 % CI: 1.3 to 2.8); 13-cycle pregnancy probability was 7.1 %. The authors concluded that this was the 1st study that described the use of a digital contraceptive by women in the U.K. It provided the demographics of users and how they correlated with the apps effectiveness at preventing pregnancy.

The authors stated that 1 drawback of this trial was that all data were self-reported and was not verified as it would be in a traditional clinical study setting; thus, these researchers could not be sure of the motivation of the users that may partially explain the higher pregnancy probability in the 29 to 34 years age group in this analysis. Neither the responses to in-app questions nor sexual intercourse logging was mandatory for study inclusion, so only a subset of cycles (18 %) contained information regarding user behavior during the fertile window. Those who discontinued using the app during the study period were contacted for follow-up information to evaluate potential pregnancy status. However, due to the nature of the product, a proportion declined to reply and were lost to follow-up. In addition, users that had recently discontinued hormonal contraceptives, had diagnosed infertility or were breast-feeding were also included in the analysis. These groups of users, although a small proportion, would have reduced fertility potentially affecting the effectiveness of the app as a contraceptive. These researchers noted that cycle tracking apps have come under scrutiny regarding the data supporting their use in fertility monitoring. The assumption of pregnancy in users lost to follow-up, during the fertile window or luteal phase, is recognized as generating a conservative pregnancy rate estimate, and was used in this study. Furthermore, the inclusion criteria (of this study) required that the user is in “Prevent a Pregnancy” mode and that she has entered 20 daily data points. These investigators chose not to limit the inclusion criteria by cycle length or regularity as this was a real-world observational design and designed to examine the effectiveness of the app in a cohort similar to the user population as a whole. In order to have a more complete data set, and to reduce loss to follow-up, prospective clinical

studies are planned that will evaluate multiple factors and user traits in a more structured clinical environment. It remains to be seen whether clinical “prescribing” of the app would lead to higher user retention rates.

The National Institute for Health and Clinical Excellence (NICE)’s MedTech innovation briefing on “Natural Cycles for monitoring fertility” (2021) stated that “The main points from the evidence summarized in this briefing are from 3 studies (2 retrospective analyses and 1 prospective observational study). These included 70,113 people using the app at home with typical follow-up of 6 to 9 months. They show that Natural Cycles can be used as a fertility-awareness contraception method. No evidence was identified on using the app to help plan a pregnancy … Key uncertainties around the evidence or technology are that Natural Cycles has not been directly compared with any other contraception”.

Manhart and Duane (2022) noted that the Natural Cycles app uses daily basal body temperature (BBT) to define the fertile window via a proprietary algorithm and is clinically established effective in preventing pregnancy. These researchers compared the app-defined fertile window of Natural Cycles to that of CycleProGo, an app that uses BBT and cervical mucus to define the fertile window; and compared the app-defined fertile windows to the estimated physiologic fertile window. Daily BBT were entered into Natural Cycles from 20 randomly selected regularly cycling women with at least 12 complete cycles from the CycleProGo database. The proportion of cycles with equivalent (± 1 cycle day) fertile-window starts and fertile-window ends was determined. The app-defined fertile windows were then compared to the estimated physiologic fertile window using Peak mucus to estimate ovulation. A total of 57 % of cycles (136/238) had equivalent fertile-window starts and 36 % (72/181) had equivalent fertile-window end days. The mean overall fertile-window length from Natural Cycles was 12.8 days compared to 15.1 days for CycleProGo ($p < 0.001$). The Natural Cycles algorithm declared 12 % to 30 % of cycles with a fertile-window start and 13 % to 38 % of cycles with a fertile-window end within the estimated physiologic fertile window. The CycleProGo algorithm declared 4 % to 14 % of cycles with a fertile-window start and no cycles with a fertile-window end within the estimated physiologic fertile window. The authors concluded that Natural Cycles designated a higher proportion of cycles days as infertile within the estimated physiologic fertile window than CycleProGo. Moreover, these researchers stated that the use of cervical mucus in addition to BBT may improve the accuracy of identifying the fertile window; further studies with other markers of ovulation and the fertile window would give additional insight into the clinical implications of app-defined fertile window differences.

Nerivio

Theranica Bio-Electronics Ltd. (Montclair, NJ) developed Nerivio which is a wireless wearable neuromodulation device that is operated by a smartphone software application. Nerivio device is FDA-cleared via the De Novo Pathway and is indicated for the acute treatment of migraine with or without aura in patients 12 years of age or older. Nerivio can serve as a replacement for current migraine therapy or work in combination with existing therapy. The functionality of the Nerivio device is based on it being applied to the patient’s upper arm at the onset of migraine with self-administered treatment that is adjusted at an intensity that is not painful for a duration of 45 minutes. Notably, patients with congestive heart failure, severe cardiac disease, cerebrovascular disease, or uncontrolled epilepsy are not candidates for Nerivio treatment. Additionally, patients with active implantable medical devices, such as a pacemaker or hearing aid implant, should not use Nerivio. A prescription from a qualified healthcare provider is required for patients to use Nerivio (Digital Therapeutics Alliance, 2021h).

Grosberg and colleagues (2021) evaluated the efficacy and safety of remote electrical neuromodulation (REN) in patients with chronic migraine. This was an open-label, single-arm study consisting of 91 participants with chronic migraine and whose headaches were treated with the REN device (Nerivio, Theranica Bio-Electronics Ltd, Israel) for 4 weeks. In addition, participants used an electronic diary to record their symptoms at treatment initiation, 2 hours after treatment, and 24 hours after treatment. The primary outcome was the percentage of participants who achieved pain relief at 2 hours post-treatment. Secondary outcomes included pain freedom and improvement of associated symptoms and functional disability. Study results were as follows: pain relief and pain disappearance at 2 hours were achieved by 59.3% (54/91) and 20.9% (19/91) of participants, respectively, and sustained pain relief at 24 hours was observed in 64.4% (29/45) of those who achieved pain relief at 2 hours. REN had a favorable effect on nausea, photophobia, and phonophobia and improved functional ability. A device-related adverse event was observed.

Hershey and colleagues (2021) conducted a post-hoc analysis from a clinical study consisting of 35 adolescent participants which compared the efficacy of remote electrical neuromodulation (REN) to that of standard-care medications (triptans or over-the-counter medications) for the acute treatment of migraine. Specifically, efficacy was compared between a run-in phase in which attacks were treated with standard-care medications, and an intervention phase in which attacks were treated with REN. Efficacy was compared using the McNemar’s test at four endpoints (two hours post-treatment); single-treatment pain freedom and pain relief, and consistency of pain freedom and pain relief (defined as response in at least 50% of the available first four treatments). Post-hoc analysis results were noted as follows: at two hours post-treatment, pain freedom was achieved by 37.1% of participants with REN, vs. 8.6% of participants with medications ($p=0.004$), pain relief was achieved by 71.4% with REN, vs. 57.1% with medications ($p=0.225$), consistency of pain freedom was achieved by 40% with REN, vs.8.6% with medications ($p<0.001$), and consistency of pain relief was achieved by 80.0% with REN, vs. 57.2% with medications ($p=0.033$). The investigators concluded that REN may have a higher efficacy than certain standard-care medications for the acute treatment of migraine in adolescents.

Montieth et al (2023) stated that migraine is a chronic neurological disease manifesting as attacks of disabling head pain and associated symptoms; REN is a non-pharmacological, prescribed, wearable device (Nerivio). This device has been cleared by

the FDA for the acute and/or preventive treatment of migraine with or without aura in patients 12 years of age or older. It is affixed to the user's arm during 45-min treatment sessions and is operated using a smart-phone app. In a post-marketing, surveillance study, these researchers examined if frequent use of REN for the acute treatment of migraine in adolescents resulted in a reduction in monthly migraine treatment days (MMTD), as previously reported in adults through a dedicated prevention clinical trial. The study included prospective, real-world data from adolescent patients who used REN on at least 10 days every 28-day month, following the REN migraine prevention guideline of an every-other-day pattern. Additional requirements were at least 3 REN treatment days in each of the 2 subsequent months. The number of MMTD was used as a proxy measure for the number of monthly migraine days (MMD). The change in MMTD from the 1st month, taken as a "baseline" to each of the following months was used to evaluate the presence and size of potential migraine preventive benefits of REN in adolescents. A total of 83 adolescents were eligible for analysis. The users were 15.9 ± 1.3 years of age (mean ± SD), and 89 % of them were female. The results showed a substantial month-to-month reduction in the mean (± SD) number of REN treatment days from 12.6 (± 3.2) MMTD in the 1st month to 9.0 (± 4.8) MMTD in the 2nd month ($p < 0.001$), and a further decrease to 7.4 (± 4.2) MMTD in the 3rd month ($p < 0.001$). This indicated an accumulative reduction of 5.2 (± 4.8) mean REN MMTD from the 1st month to the 3rd month of consecutive REN treatment. The users also reported consistent 2-hour acute pain responses in at least 50 % of their treated attacks, with 61.9 % of the users reported experiencing pain relief, 24.5 % reported pain freedom, 67.4 % indicated relief in functional disability, and 41.3 % reported complete freedom from functional disability. The authors concluded that the frequent use of REN among adolescents as an acute treatment for migraine attacks resulted in a decrease in the mean number of monthly treatment days in the subsequent months, suggesting that REN may have potential preventive benefits for migraine in this subpopulation. Moreover, these researchers stated that further investigations are needed to evaluate the long-term impact on migraine-related disability and QOL of adolescents using REN for migraine prevention.

The authors stated that this study had several drawbacks. First, the number of MMD was not measured directly but derived from the number of abortive MMTD, and preventive effects were extrapolated from using the device for acute treatment and not directly for migraine prevention. However, given that the exact same stimulation was used for both abortive and preventive treatment and that the frequency of treatments fulfilled the usage pattern in the prevention pivotal trial in adults, deriving MMD from MMTD was clinically meaningful. Second, as a post-marketing surveillance study, the cohort was selected from the users treated with the REN device, presumably reflecting that those who found it useful were likely to use it more. To directly examine preventive benefits from treating with the REN wearable device in adolescents, further research is needed with a pre-planned clinical trial including those who require migraine prevention treatment and will report their migraine attacks in a daily migraine diary (migraine days), which is available in the Nerivio application. A dedicated study will further allow the collection of patient-centered outcomes, such as treatment satisfaction and QOL. Third, frequency swings in the number of monthly migraine attacks are quite common, especially in patients with chronic migraine; therefore, using a single month for migraine baseline assessment may be short. However, 1 month is the most common baseline period used in migraine studies, including previous REN studies. Furthermore, the reduction in number of MMTD between the 1st and 3rd months was larger than the overall standard deviation of MMTD over all users during the 3 study months, indicating a larger effect of MMTD reduction over that of frequency swings; thus, suggesting that the reduction of MMTD due to an effective REN treatment overcame the natural fluctuations in migraine frequency. An extended study, tracking adolescents for more treatment months, will shed more light on the long-term effectiveness of REN for migraine prevention in adolescents. Fourth, the patients in the present study had a high attack frequency, which is a known risk factor for migraine chronification, and is associated with the sensitization of migraine-related structures . As mentioned earlier, the wearable REN device activates an endogenous pain mechanism, the CPM, to abort attacks and preventive migraine days. However, there is a need for investigations designed to elucidate the underlying central mechanisms that drive the observed therapeutic clinical effects of migraine prevention with REN, and specifically the potential of brain re-organization and neuroplasticity.

Werner et al (2024) noted that migraine is a prevalent neurological disorder severely impacting children and adolescents, yet only 1 pharmacotherapy is approved for ages 6 to 12 years. Remote electrical neuromodulation (REN) is a non-pharmacological, prescribed, wearable device cleared by the FDA for acute and/or preventive treatment of migraine with or without aura in patients 12 years and older. In a prospective study, these researchers examined the safety and effectiveness of REN in children aged 6 to 11 years. Acute treatment of migraine data were collected via the REN device (Nerivio) smart-phone app. Endpoints were device safety (primary); consistent treatment effectiveness (headache pain, functional disability, associated migraine symptoms), and REN-medication combinations 2 hours post-treatment. Children (n = 293), median age of 11 years (IQR = 9 to 11), 73.7 % girls, conducted 5,493 REN treatments; no AEs were reported. Effectiveness in at least 50 % of REN treatments was calculated from all patients who voluntarily reported pain levels, symptoms, and/or disability at treatment onset and at 2 hours post-treatment, with 72.2 % (13/18) of patients reporting pain relief, 36.0 % (9/25) pain freedom, 83.3 % (15/18) functional disability relief, and 38.9 % (7/18) functional disability freedom. Migraine-associated symptoms disappeared in at least 50 % of REN treatments in 70.0 % (7/10) of patients for nausea/vomiting, 50.0 % (4/8) phonophobia, and 22.2 % (2/9) photophobia; 63.6 % (7/11) reported freedom from at least 1 associated symptom. REN was used as a stand-alone treatment, with over-the-counter medications, and with prescribed headache medications in 45.4 %, 34.4 %, and 20.9 % of treatments, respectively. The authors concluded that REN may serve as a safe and effective acute treatment of migraine for children.

The authors stated that this study had several drawbacks. First, it was not a controlled trial, and it entailed a cohort of patients using the Nerivio device; thus, it might be more difficult to interpret the placebo contribution. Nevertheless, the observed findings aligned with findings in previous REN controlled clinical trials as well as in other REN real-world evidence studies. Second, while effectiveness rates were high, not all children provided data for effectiveness calculations. REN effectiveness was calculated

from voluntarily in-app reports of symptoms and use/avoidance of rescue medications at both treatment onset and at 2 hours post-treatment. Therefore, because baseline and post-treatment reports were voluntary, the fact that the data were collected from real-world treatments (as opposed to a structured clinical trial), and that many children at this young age of 6 to 11 years did not have their own smart-phones and used their parents' smart-phones to administer the REN treatment; therefore, it was not surprising that the children went about their day once they achieved pain freedom or relief from their migraine attacks and did not bother to provide reports. Moreover, the fact that most patients (76.1 %) continued treating 4 or more treatments even without providing symptom reports by itself represented satisfaction. This further highlighted the importance of guiding patients to use the REN device -- the same as with other acute treatments of migraine -- a few times before their parents or care-givers decide whether their child should continue using it. Third, this cohort included all children under the age of 12 years who were treated with REN until the time of data analysis. The age among the cohort of children was not uniformly distributed, with more children in the older subgroup than the very younger subgroup of 6 to 7 years of age. This was not surprising, given that the incidence of migraine increases with age. These researchers stated that more data are continuously collected from all children treating with REN; thus, larger cohorts of young children are expected to be available for future studies. These researchers stated that a future study examining REN for migraine prevention in this age group is recommended.

NightWare

NightWare, Inc. (Hopkins, MN) developed NightWare which is an FDA-cleared medical device with a Breakthrough Device designation and is indicated for the reduction of sleep disturbance associated with nightmares in adult patients 22 years of age or older who suffer from nightmare disorder or have nightmares from post-traumatic stress disorder (PTSD). The functionality of this medical device is based on artificial intelligence (AI) and smart technology on the Apple Watch. NightWare is driven by the Apple Watch heart rate monitor sensor and other biometric sensors to continually evaluate the patient’s level of sleep disturbance (i.e., stress index) during sleep by tracking heart rate and body movements to determine nightmare occurrence. Once a nightmare is detected, the NightWare system quickly sends vibrations to interrupt nightmares without waking the patient. Through AI algorithms, both intensity and frequency of vibrations are based on an individual’s specific needs at that moment. As the NightWare system captures more data, it adapts to the patient’s sleep patterns. A prescription from a physician is required for NightWare to be used by patients (NightWare, 2021).

Currently, there is a lack of published peer-reviewed evidence available.

Parallel

Mahana Therapeutics, Inc.'s (San Francisco, CA) Parallel (formerly known as ReguI8) is an FDA-cleared digital therapeutic mobile application designed to deliver cognitive behavioral therapy for patients 22 years of age and older who have been diagnosed with irritable bowel syndrome (IBS). The mobile application uses the patient's mobile phone or tablet to deliver therapy on demand as a complement to the provider's care. It is available by prescription only as a 3-month treatment for patients with IBS and is intended to reduce the severity of symptoms when used as an adjunct with other IBS treatments (FDA, 2022a; Mahana Therapeutics, 2020).

Regulora

metaMe Health Inc. (Chicago, IL) developed Regulora which is an FDA-cleared prescription-only digital therapeutic software indicated for use in the treatment of abdominal pain due to irritable bowel syndrome (IBS). It is considered as a software as a medical device housed on and is accessed through the user's mobile device which can be performed at home. Regulora is intended to provide behavioral therapy through gut-directed hypnotherapy for patients 22 years of age and older who have been diagnosed with irritable bowel syndrome. It is indicated as a 3-month treatment for patients with abdominal pain due to IBS and is intended to be used in combination with other IBS treatments (FDA, 2022f).

RelieVRx

AppliedVR, Inc. (Van Nuys, CA) developed RelieVRx (formerly EaseVRx) is an FDA-authorized prescription-use immersive virtual reality system designed to provide adjunctive treatment based on cognitive behavioral therapy skills and other evidence-based principles for patients 18 years of age or older with a diagnosis of chronic lower back pain. The device is designed for in-home use for the reduction of pain and pain interference associated with chronic lower back pain. Therapy is provided via a virtual reality display using a software program containing the behavioral therapy content. The patient's pain centers are engaged through mindful escapes, pain education, diaphragmatic breathing, and relaxation/interoception. The virtual reality treatment is self-administered over 8 weeks with an average daily session of 7 minutes duration (Applied VR, 2022; FDA, 2022g).

reSET

Pear Therapeutics, Inc. (Boston, MA) developed reSET which is an FDA-cleared software application that provides cognitive behavioral therapy for substance abuse disorder as an adjunct to a contingency management system for patients 18 years of age and older who are enrolled in outpatient treatment under the supervision of a healthcare provider. Specifically, reSET

delivers therapy established on the community reinforcement approach (CRA), an intensive form of validated neurobehavioral therapy for substance abuse disorder in addition to contingency management and reinforcement of concept mastery to augment learning. reSET consists of 62 interactive modules (32 core modules and 30 supplemental modules). The core modules involve CRA concepts, skill building to reinforce behavior change and prevent relapse. The supplemental modules focus on specific topics (e.g., relationship skills, living with hepatitis C). Modules may typically take 10 to 20 minutes to complete. The reSET app is supported on a mobile operating system (e.g., smartphone or tablet). A prescription is required from a licensed healthcare provider for a patient to use reSET which provides a 12 week duration of therapy (Digital Therapeutic Alliance, 2021i; Pear Therapeutics, 2021a).

Campbell and colleagues (2014) evaluated the effectiveness of the Therapeutic Education System (TES), an internet-delivered behavioral intervention inclusive of motivational incentives, as a clinician-extender in the treatment of substance abuse disorder. The multisite randomized controlled trial consisted of adult men and women (n=507) entering 10 outpatient addiction treatment programs who were randomly assigned to receive 12 weeks of either treatment as usual (n=252) or treatment as usual plus TES, with the intervention replacing about 2 hours of standard care per week (n=255). TES involved 62 computerized interactive modules covering skills for achieving and maintaining abstinence, plus prize-based motivational incentives contingent on abstinence and treatment adherence. Treatment as usual involved individual and group counseling at the participating programs. The primary endpoint measures were abstinence from drugs and heavy drinking (measured by twice-weekly urine drug screens and self-report) and time to dropout from treatment. The study results were as follows: participants in the TES group had a lower dropout rate (hazard ratio=0.72, 95% Confidence Interval [CI] = 0.57, 0.92) and a greater abstinence rate (odds ratio=1.62, 95% CI=1.12, 2.35). This effect was more dramatic among participants who had a positive urine drug or breath alcohol screen at study entry (n=228) (odds ratio=2.18, 95% CI=1.3, 3.68). The investigators noted that additional investigation is needed to assess effectiveness in non-specialty clinical settings and to distinguish the effects of the community reinforcement approach and contingency management facets of TES.

Luderer and colleagues (2022) performed an exploratory analysis of data from a study to determine how patient engagement with a digital therapeutic for substance abuse disorder (SUD) in the clinic setting was associated with abstinence outcomes. The investigators evaluated engagement for 206 participants enrolled in a treatment program for SUDs related to cocaine, alcohol, cannabis, or other stimulants with randomization to receive treatment as usual (TAU) or reduced TAU plus the digital Therapeutic Education System (TES) for 12 weeks. Participant eligibility for contingency management incentives for module completion (Community Reinforcement Approach topic areas were covered) and negative urine drug screens were noted. The association of module completion with end-of-treatment abstinence was analyzed. Participants completed a mean of 38.8 (range 0-72) TES modules over 12 weeks of treatment. Study completers (n = 157) completed a mean of 45.5 (range 9-72) TES modules, whereas study non-completers (n = 49) completed a mean of 17.4 (range 0-45) TES modules. A strong positive correlation between TES engagement (i.e., total number of modules completed) and the probability of abstinence during weeks 9-12 of treatment among 157 study completers (OR = 1.11; 95% Confidence Interval [CI] 1.08-1.14) was observed. Each module completed increased the odds of abstinence during weeks 9-12 by approximately 11% for study completers and 9% for the full sample. Additionally, a similar, but weaker, association between engagement and abstinence among 49 patients who did not complete the study (OR = 1.02; 95% CI 0.98-1.07) was observed. The investigators concluded that a greater engagement with a digital therapeutic for patients with SUD (i.e., number of modules completed over time) showed strong association with probability of abstinence in the last four weeks of treatment among those who completed the recommended 12-week treatment.

Maricich and colleagues (2022) performed a secondary analysis of patients with substance use disorders related to alcohol, cannabis, cocaine, or other stimulants (n = 399, patients with opioid use disorder [OUD] excluded) from a previously-published randomized controlled trial. Patients received 12-weeks of outpatient treatment-as-usual (TAU; n = 193) or TAU with reduced counseling plus a digital therapeutic (DT) (n = 206) providing computerized cognitive behavioral therapy and contingency management. Primary outcomes were abstinence in weeks 9-12 and retention in treatment. The 399 patients in this analysis (206 in the DT group and 193 in the TAU group) reported substance use disorders related to alcohol, cannabis, cocaine, or other stimulants (e.g., methamphetamines). Demographic and baseline characteristics such as age, sex, race, education, and reported primary substance use disorder were balanced between treatment groups. Abstinence was significantly higher in the DT group compared to TAU (40.3 vs. 17.6%; $p < 0.001$) as was retention in therapy (76.2 vs. 63.2%, $p = 0.004$). Intergroup adverse event rates were not significantly different ($p = 0.68$). The investigators concluded that the use of a DT safely increased abstinence (reduced substance use) and retention in treatment among patients with substance use disorders related to alcohol, cannabis, cocaine, or other stimulants (including methamphetamines).

reSET-O

Pear Therapeutics, Inc. (Boston, MA) developed reSET-O which is an FDA-cleared software application that provides cognitive behavioral therapy for opioid use disorder as an adjunct to outpatient treatment that includes trans-mucosal buprenorphine and contingency management outpatient treatment for patients 18 years of age or older who are under the supervision of a healthcare provider. Specifically, reSET-O delivers behavioral therapy based on the community reinforcement approach (CRA), a type of cognitive therapy targeting opioid use disorder. In addition, reSET-O combines CRA with reinforcement of concept mastery which should be initiated concurrently with contingency management and buprenorphine treatment to aid patient retention with opioid use disorder in outpatient treatment. reSET-O is supported on a mobile operating system (e.g., smartphone or tablet) and is a 12-week software application that requires a prescription from a licensed healthcare provider for patient use (Digital Therapeutics Alliance, 2021j; Pear Therapeutics, 2021a).

Christensen and colleagues (2014) examined the benefit of adding an internet-delivered behavior therapy to a buprenorphine medication program and voucher-based motivational incentives. This was a block-randomized, unblinded, parallel, 12-week treatment study consisting of 170 opioid-dependent adult participants (mean age = 34.3 years; 54.1% male; 95.3% white). Study participants received either an internet-based community reinforcement approach intervention plus contingency management (CRA+) and buprenorphine or contingency management alone (CM-alone) plus buprenorphine. The primary endpoints, measured over the course of treatment, were longest continuous abstinence, total abstinence, and days retained in treatment. Study results were as follows: in comparison to CM-alone participants, CRA+ participants displayed, on average, 9.7 total days more of abstinence (95 % CI: 2.3 to 17.2), and had a reduced hazard of dropping out of treatment (hazard ratio = 0.47; 95 % CI: 0.26 to 0.85). Previous treatment for opioid dependence significantly mediated the additional improvement of CRA+ for longest continuous days of abstinence. The investigators concluded that an internet-based CRA+ treatment has efficacy and adds clinical benefits to a contingency management/medication based program for opioid dependence.

Maracich and colleagues (2021) evaluated the safety and efficacy of a digital therapeutic in treatment-seeking individuals with opioid use disorder (OUD) in an analysis of randomized clinical data (RCT) data. This secondary analysis of a RCT consisted of 170 adult participants meeting DSM-IV criteria for OUD. Participant randomization to 12 weeks of treatment-as-usual (TAU) or TAU plus a digital therapeutic occurred. TAU consisted of buprenorphine maintenance therapy, 30 mins bi-weekly clinician interaction, and abstinence-based contingency management. The digital therapeutic consisted of 67 digital, interactive educational modules based on the Community Reinforcement Approach. The primary outcomes were treatment retention and abstinence (negative urine drug screen) during weeks 9 to 12 of treatment. Adverse events monitoring served as the safety parameter. The study results were as follows: recipients of TAU plus a digital therapeutic had significantly greater odds of opioid abstinence during weeks 9 to 12 compared to TAU: 77.3 % versus 62.1 %, respectively (p = 0.02), or 2.08, 95 % CI: 1.10 to 3.95, and the risk of participants leaving treatment was significantly lower in the digital therapeutic group (hazard ratio [HR] 0.49, 95 % CI: 0.26 to 0.92). The difference in observed rate of adverse events between groups was not significant (p = 0.42). The investigators concluded that TAU plus a digital therapeutic improves clinically significant patient outcomes including abstinence from illicit opioids and retention in treatment compared with TAU.

Maricich and colleagues (2021) conducted a study to evaluate real-world digital therapeutic (PDT) use and associated clinical outcomes among patients with opioid use disorder (OUD). Specifically, this study involved a real-world evaluation of patients who filled either a 12- or 24-week (refill) prescription for the reSET-O® PDT, a PDT consisting of 67 interactive lessons that unlock in sequence during use with an opportunity to earn rewards for progress and/or negative urine screens. The investigators collected engagement/retention data (ongoing engagement in weeks 9-12, or 21-24) via the PDT and performed analysis with descriptive data. Evaluation of substance use was from a composite of patient self-reports and urine drug screens (UDS). Missing UDS data were assumed to be positive. A regression analyses of hospital encounters for 12- versus 24-week prescriptions controlling for covariates was conducted. In a cohort of 3,817 individuals with OUD who completed a 12-week PDT prescription, a cohort of 643 was prescribed a second 12-week 'refill' prescription, for a total treatment time of 24 weeks. Mean age of the 24-week cohort was 39 years, 56.7% female. At 24 weeks of total treatment: abstinence in the last 4 weeks of treatment was 86% in an analysis in which patients with no data were assumed to be positive for illicit opioids. Over 91% of patients were retained in treatment. An analysis of matched insurance claims showed that those treated for 24 weeks had a 27% decrease in unique hospital encounters compared to those who got the first 12-week prescription only. In summary, 93% of this cohort completed 8 or more core lesson modules in the second prescription period, 85% completed at least half of core modules, and 64% completed all 32 core modules. Patients used the PDT outside of clinic hours about 40% of the time. 94.4% of patients had 80% or greater negative reports of opioid use across the second 12 weeks of treatment. A 27% decrease in unique hospital encounters was observed in patients who completed a second prescription vs. patients who completed only one prescription. The data demonstrated that a second prescription (24 weeks) of a PDT for OUD is associated with improved outcomes, high levels of retention, and fewer hospital encounters compared to a single prescription for a PTD. Patients showed durable and high levels of engagement with the PDT, reduced substance use, and improved treatment retention through 24 weeks of treatment.

A Veteran's Administration and Department of Defense Clinical Practice Guideline on substance abuse disorders (VA/DoD, 2021) stated that "there are currently FDA-cleared apps in clinical use for the treatment of SUD (e.g., ReSET and ReSET-O), but literature leading to clearance did not meet the inclusion criteria for this CPG’s systematic evidence review."

Luderer et al (2023) stated that home-based (unsupervised) buprenorphine initiation is considered safe and effective; however, many patients report barriers to successful treatment initiation. PDTs are software-based disease treatments regulated by the FDA. The reSET-O PDT was authorized by the FDA in 2018 and delivers behavioral treatment for individuals receiving buprenorphine for OUD. A prototype PDT (PEAR-002b) designed for use with reSET-O was developed to assist in unsupervised buprenorphine initiation. The primary objective of this pilot study is to examine the acceptability of PEAR-002b in individuals with OUD who use it to support buprenorphine initiation, their unsupervised buprenorphine initiation success rate, and their medication adherence.

A total of 10 adults with OUD will be recruited for acceptability and feasibility testing. Outcomes will be evaluated using week-1 visit attendance, participant interviews and satisfaction surveys, as well as UDS. A total of 3 tools will be used in the study: PEAR-002b, reSET-O, and EmbracePlus. PEAR-002b includes a new set of features designed for use with reSET-O. The mechanism of action for the combined PEAR-002b and reSET-O treatment is a program of medication dosing support during week 1 of the initiation phase, cognitive behavioral therapy (CBT), and contingency management. During the medication initiation phase, subjects are guided via a process to support proper medication use. PEAR-002b advises them when to take their buprenorphine based on provider inputs (e.g., starting dose), self-reported substance use, and self-reported withdrawal

symptoms. This study also administers the EmbracePlus device, a medical-grade smartwatch, to pilot methods for collecting physiologic data (e.g., heart rate and skin conductance) and assess the device's potential for use along with PDTs that are designed to improve OUD treatment initiation. Home buprenorphine initiation success will be summarized as the proportion of subjects attending the post-buprenorphine initiation visit (week 1) and the proportion of subjects who experience buprenorphine initiation-related adverse events (AEs) (e.g., precipitated withdrawal). Acceptability of PEAR-002b will be evaluated based on individual participants' ratings of ease of use, satisfaction, perceived helpfulness, and likelihood of recommending PEAR-002b. Medication adherence will be examined by participant self-report data and confirmed by UDS. UDS data will be summarized as the mean of individual participants' proportion of total urine samples testing positive for buprenorphine or norbuprenorphine over the 4-week study. As of September 2022, participant enrollment is ongoing. The authors concluded that, to their knowledge, this is the 1st study to develop a PDT that assists with unsupervised buprenorphine initiation with the intent to better support patients and prescribers during this early phase of treatment. This pilot study will examine the acceptability and utility of a DT to help individuals with OUD with unsupervised buprenorphine initiation.

SleepioRx

According to a news release from Big Health (San Francisco, CA), a developer of digital treatments, on August 8, 2024, the U.S. Food and Drug Administration (FDA) granted clearance for its digital therapeutic, SleepioRx. SleepioRx is intended as an adjunct to usual medical care for the treatment of patients aged 18 years of age and older with chronic insomnia/insomnia disorder. SleepioRx delivers evidence-based techniques aimed at the cognitive and behavioral factors that sustain insomnia and chronic sleep problems. The user experience is customized based on symptoms and daily sleep tracking with real time therapeutic content to aid in falling asleep during the 90-day treatment. The Sleepio prescription device is available for use on the order of a licensed healthcare professional. The device delivers cognitive behavioral therapy for insomnia (CBT-I).

Espie et al. (2012) conducted a randomized, placebo-controlled trial to determine the effectiveness of a novel web-based cognitive behavioral therapy (CBT) course delivered by an automated virtual therapist compared with a credible approach. The investigators noted the requirement of a comparator approach because web products may be intrinsically engaging and susceptible to placebo response.

One hundred and sixty-four adult patients were randomized to one of 3 arms: CBT (n = 55), image relief therapy placebo (IRT placebo; n = 55), or treatment as usual (TAU; n = 54). CBT and IRT each consisting of 6 online sessions delivered by an animated personal therapist, with automated web and email support. The researchers provided participants with access to a video library/back catalogue of session content and Wikipedia style articles. Online CBT users were provided access to a moderated social network/ community of users. TAU consisted of no restrictions on usual care and access to an online sleep diary.

The authors performed major assessments at baseline, post-treatment, and at follow-up 8-weeks post-treatment with outcomes appraised by online sleep diaries and clinical status. Regarding the primary endpoint of sleep efficiency (SE; total time asleep expressed as a percentage of the total time spent in bed), online CBT was associated with sustained improvement at post-treatment (+20%) relative to both TAU (+6%; d = 0.95) and IRT (+6%: d = 1.06), and at 8 weeks (+20%) relative to IRT (+7%: d = 1.00) and TAU (+9%: d = 0.69). These findings were reflected across a range of sleep diary measures. Clinical benefits of CPB were seen by modest superiority over placebo on daytime outcomes (d = 0.23-0.37) and by substantial improved sleep-wake functioning on the Sleep Condition Indicator (range of d = 0.77-1.20). Three-quarters of CBT participants (76% [CBT] vs. 29% [IRT] and 18% [TAU]) completed treatment with SE > 80%, more than half (55% [CBT] vs. 17% [IRT] and 8% [TAU]) with SE > 85%, and over one-third (38% [CBT] vs. 6% [IRT] and 0% [TAU]) with SE > 90%; these improvements were largely maintained during follow-up.

The investigators concluded that CBT delivery through a media-rich web application with automated support and a community forum is effective for the sleep improvement and related daytime functioning of adults with insomnia disorder.

Felder et al. (2020) conducted a randomized clinical trial to test the efficacy of a digital cognitive behavioral therapy for insomnia (CBT-I) compared with standard treatment among pregnant women with insomnia symptoms. Of the 2,258 women evaluated for trial eligibility through use of an online self-report questionnaire, 208 were randomized to receive digital CBT-I (n = 105) or standard treatment (n = 103) for insomnia. The study included pregnant women up to 28 weeks gestation who either had elevated insomnia symptom severity or met the criteria for insomnia caseness based on self-reported questionnaires. Individuals completed outcome measures at 10 weeks (postintervention) and 18 weeks (follow-up) after randomization. All study visits were completed remotely, and the intervention was delivered digitally.

Digital CBT-I comprised of 6 weekly sessions of about 20 minutes each. Standard treatment mirrored standard care. Women receiving standard treatment had no restraints placed on the receipt of nonstudy treatments, including medication and psychotherapy.

All outcomes assessment were performed remotely through self-report questionnaires administered by online survey. The primary outcome was the change in insomnia symptom severity (measured by the Insomnia Severity Index) from baseline to postintervention. Secondary outcomes were sleep efficiency and nightly sleep duration (defined by sleep diary), global sleep quality (measured by the Pittsburgh Sleep Quality Index), depressive symptom severity (measured by the Edinburgh Postnatal

Depression Scale), and anxiety symptom severity (measured by the Generalized Anxiety Disorder Scale-7). The investigators examined the change from baseline to follow-up for each outcome.

The 208 individuals had a mean (SD) age of 33.6 (3.7) years and a mean (SD) gestational age of 17.6 (6.3) weeks at baseline. Individuals randomized to receive digital CBT-I experienced statistically significantly greater improvements in insomnia symptom severity from baseline to postintervention compared with women randomized to receive standard treatment (time-by-group interaction, difference = -0.36; 95% Confidence Interval [CI], -0.48 to -0.23; $\chi 2 = 29.8$; $p < 0.001$; $d = -1.03$). Improvements from baseline to postintervention for all secondary outcomes, except for sleep duration, were statistically significant. A similar pattern of outcomes was evident for change from baseline to follow-up.

The researchers concluded that digital CBT was an effective, scalable, safe, and acceptable intervention for improving insomnia symptoms during pregnancy.

Fleming et al. (2024) conducted a parallel group randomised controlled trial remotely in individual's homes/online to assess the efficacy of digital cognitive behavioural therapy for insomnia to improve sleep after stroke.

Randomisation was online with minimisation of between-group differences in age and baseline Sleep Condition Indicator-8 score. In all, 86 community-dwelling stroke survivors consented, of whom 84 completed baseline assessments (39 female, mean 5.5 years post-stroke, mean 59 years old), and were randomised to digital cognitive behavioural therapy or control (sleep hygiene information). Follow-up was at post-intervention (mean 75 days after baseline) and 8 weeks later. The main outcome measure was self-reported insomnia symptoms, as per the Sleep Condition Indicator-8 (range 0-32, lower numbers indicate more severe insomnia, reliable change 7 points) at post-intervention.

The investigators noted significant improvements in Sleep Condition Indicator-8 for digital cognitive behavioural therapy compared with control (intention-to-treat, digital cognitive behavioural therapy n = 48, control n = 36, 5 imputed datasets, effect of group $p \leq 0.02$, $\eta 2p = 0.07$-0.12 [medium size effect], pooled mean difference = -3.35). Furthermore, secondary outcomes demonstrated shorter self-reported sleep-onset latencies and better mood for the digital cognitive behavioural therapy group, but no significant differences for self-efficacy, quality of life or actigraphy-derived sleep parameters.

Cost-effectiveness analysis showed that digital cognitive behavioural therapy dominates over control (non-significant cost savings and higher quality-adjusted life years). The individuals did not report any related serous adverse events.

The authors concluded that digital cognitive behavioural therapy for insomnia effectively improves sleep after stroke. However, additional research is necessary to assess earlier stages post-stroke, with a longer follow-up period to establish digital cognitive behavioural therapy as a part of routine post-stroke care.

Somryst

Pear Therapeutics, Inc. (Boston, MA) developed Somryst which is an FDA-cleared software app that provides digital cognitive behavioral therapy for insomnia (CBT-I) for chronic insomnia in patients who are 22 years of age and older. With the aim of improving a patient's insomnia symptoms, Somryst is accessible on a mobile device (e.g., smartphone or tablet) and consists of 6 treatment cores focused on CBT-I concepts (e.g., sleep restriction and consolidation, stimulus control and cognitive restructuring). Patients should complete one core every 7 days and complete their daily sleep diary and follow the sleep restriction window recommendation provided by this software app. Somryst uses sleep restriction and consolidation and, therefore, is not to be used in individuals with any disorder worsened by sleep restriction (e.g., bipolar disorder, schizophrenia, other psychotic spectrum disorders), untreated obstructive sleep apnea, parasomnias, epilepsy, high risk of falls, pregnancy, and unstable or degenerative illness considered to be exacerbated by sleep restriction delivered as a part of CBT-I. Somryst is a 9-week therapy duration that is complimentary to current therapy. Additionally, a prescription from a licensed healthcare provider is required for a patient to use this software app (Digital Therapeutics Alliance, 2021k; Pear Therapeutics, 2021b).

Ritterband and colleagues (2022) conducted a retrospective investigation to evaluate outcome and patient engagement data of Sleep Health Using the Internet (SHUTi), a digital therapeutic delivering Cognitive Behavioral Therapy for insomnia (CBT-I) in a large real-world dataset of adults with insomnia. This real-world analysis is based on a dataset of consecutive users of SHUTi, the precursor program to the first FDA-authorized prescription digital therapeutic (PDT) Somryst (equivalent clinical content and enhanced features). SHUTi is a fully automated, interactive digital CBT-I intervention accessible via an internet-connected browser on mobile devices and computers. It delivers six sequential treatment modules (called Cores) based on key elements of CBT-I, which include an overview of insomnia, sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relapse prevention. This real-world dataset analysis included 7216 adults who purchased access to SHUTi between December 2015 and February 2019. The Insomnia Severity Index (ISI) was given at the start of each of six treatment Cores of the intervention. Users recorded sleep diaries between Cores to track changes in sleep over time and obtain tailored sleep recommendations. Program usage was determined from the number of Cores completed and sleep diaries recorded. Users demonstrated a reduction in mean ISI scores and a corresponding increase in effect size at the start of each subsequent Core (compared to Core 1) (range: $d = 0.3$-1.9). Effect sizes at the last Core relative to the first were moderate-to-large for diary-derived sleep onset latency and wake after sleep onset. A reduction in number of medicated nights was also noted, with those with severe insomnia displaying the largest reduction from last-to-first week of treatment ($d = 0.3$). At the last Core, 61% met

criteria for meaningful treatment response (reduction of >7 points on ISI) and 40% met criteria for remission (ISI<8). Engagement was comparable to SHUTi research trials. The investigators concluded that real-world data suggest that digital therapeutics can result in relatively high levels of engagement and clinically meaningful sleep improvements.

Christensen and colleagues (2016) evaluated whether an online self-help insomnia program could reduce depression symptoms. This was a randomized controlled study consisted of 1149 participants (aged 18-64 years) with insomnia and depression symptoms, but who did not meet criteria for major depressive disorder. Study participants were randomly assigned (1:1) to receive SHUTi (a 6 week, modular online insomnia program based on cognitive behavioral therapy for insomnia) or HealthWatch (an interactive, attention-matched, internet-based placebo control program). The primary endpoint was depression symptoms at 6 months, as measured with the Patient Health Questionnaire (PHQ-9). Results were based on 581 (51%) participants completing the study program assessments at 6 weeks and 504 (44%) participants completing 6 months follow up. SHUTi recipients had significantly lower depression symptoms on the PHQ-9 at 6 weeks and 6 months compared with HealthWatch (F[degrees of freedom 2,640.1] = 37.2, p<0.0001). Major depressive disorder was diagnosed in 22 (4%) participants at 6 months (n=9 in the SHUTi group and n=13 in the HealthWatch group), with no superior effect of SHUTi vs. HealthWatch (Fisher's exact test=0.52; p=0.32). No adverse events were noted. The investigators concluded that online cognitive behavior therapy for insomnia treatment is a pragmatic and effective method to reduce depression symptoms and may have the capability to reduce depression at the population level.

Ritterband and colleagues (2017) evaluated a web-based, automated cognitive behavior therapy for insomnia (CBT-I) to improve insomnia in 9 weeks (short-term) and 1 year (long-term). This was a randomized clinical study consisting of 303 participants with chronic insomnia. Participant randomization occurred 1:1 where participants either received the internet CBT-I (Sleep Healthy Using the Internet [SHUTi]) or the online patient education program. SHUTi was a 6-week fully automated, interactive, and tailored web-based program incorporating the primary tenets of face-to-face CBT-I, whereas the online patient education program consisted of nontailored and fixed online information about insomnia. The primary sleep outcomes consisted of self-reporting online ratings of insomnia severity (Insomnia Severity Index) and online sleep diary-based values for sleep-onset latency and wake after sleep onset, collected prospectively for 10 days at each assessment period. The secondary sleep outcomes were comprised by sleep efficiency, number of awakenings, sleep quality, and total sleep time. The results of the three primary sleep outcomes revealed that the overall group x time interaction was significant for all variables, favoring SHUTi recipients (Insomnia Severity Index [F3, 1063 = 20.65, p<0.001), sleep-onset latency [F3, 1042 = 12. 68, p<0.001]). With-in group effect sizes exhibited improvements from baseline to post-assessment for the SHUTi recipients (range, Cohen d=0.79 [95% CI, 0.55-1.04] to d=1.90 [95% CI, 1.62-2.18]). Treatment effects were sustained at the 1 -year follow-up (SHUTi Insomnia Severity Index d=2.32 [95% CI, 2.01-2.63], sleep-onset latency d=1.41 [95% CI, 1.15-1.68], and wake after sleep onset d=0.95 [95% CI, 0.70-1.21]), with 56.6% (69 of 122) reaching remission status and 69.7% (85 of 122) deemed treatment responders at 1 year based on Insomnia Severity Index data. Secondary sleep outcomes, with the exception of total sleep time, showed significant overall group x time interactions, favoring the SHUTi group. The investigators concluded that internet-delivered CBT-I may have a pivotal role in the communication of effective behavioral treatments.

In a network meta-analysis (NMA), Forma et al (2022) compared the effectiveness of the only FDA-authorized PDT, Somryst, versus face-to-face CBT-I, or FDA-approved prescription medications for insomnia. These investigators carried out a systematic literature review to identify relevant studies. A Bayesian NMA was performed to examine mean change in ISI; proportional change in ISI remitters; mean change in wake after sleep onset (WASO); and mean change in sleep onset latency (SOL). A total of 20 studies provided data on the PDT, CBT-I, CBT-I in combination with self-help (SH), or 2 prescription medications (eszopiclone and zolpidem). The PDT was associated with significant mean change in ISI (-5.77, 95 % CI: - 8.53 to -3.07) and ISI remitters (OR 12.33; 95 % CI: 2.28 to 155.91) compared to placebo; and had the highest probability of being the most effective treatment overall for ISI mean change (56 %), and ISI remitters (64 %). All evaluated interventions significantly outperformed placebo for WASO but no significant differences were observed for SOL (5 interventions). Sensitivity analyses excluding medications and meta-regression (assessing type, duration, delivery method for CBT-I) did not affect NMA results. The authors concluded that this NMA showed that a PDT delivering CBT-I had the highest probability of being most effective compared to face-to-face CBT-I, prescription sleep medications, or placebo, as measured by reductions in mean ISI score from baseline and ISI-determined remittance. These researchers stated PDT has the potential to improve accessibility to guideline-recommended CBT-I treatment for adults who have access to and are able to appropriately use digital treatments for chronic insomnia. Moreover, they stated that further investigations with longer follow-up time including broader treatment types and additional outcome metrics, are needed to further delineate the most effective and cost-effective treatments for chronic insomnia.

The authors stated that this NMA had several drawbacks. First, although there was significant heterogeneity in the placebo arm between studies (e.g., waitlist, treatment as usual, care as usual, image relief therapy, minimal psycho-education, patient education, and sleep hygiene), the placebo arms were assumed to be similar to allow comparability in the network. This assumption could bias the comparisons performed. Second, these investigators focused their analysis on patients with chronic or primary insomnia; and excluded studies that specifically examined patients with co-morbid insomnia. These researchers did this to minimize potential heterogeneity in the patient population examined. Third, this analysis focused on a comparison of relatively short-term outcomes (6 to 12 weeks). The comparative effectiveness of pharmacologic and behavioral treatment strategies on longer-term outcomes is also important; however, this t analysis was limited by the lack of comparable time-points between studies. Although direct comparisons were not possible, longer-term data were available from randomized trials showing sustained benefits for DTs over time. Fourth, while there were other DT products currently available, the PDT included within this analysis remains the only FDA-authorized PDT indicated for the treatment of patients with chronic insomnia. Fifth, in

some studies included in the network for the PDT, patients could be taking concomitant prescription sleep medication, which may have confounded comparisons against prescription sleep medications. Notably though, in this study, patients receiving PDT treatment had a greater probability of becoming ISI remitters alongside improvements in other endpoints, despite the fact that a lower proportion of patients were receiving concomitant prescription sleep medication at the end of study. Sixth, this analysis focused on 4 important metrics for chronic insomnia (ISI, percentage of ISI remitters, WASO and SOL), which are patient-reported endpoints that may be subject to reporting bias or recall bias. However, the ISI is a reliable and well-validated metric to quantify the perceived severity of insomnia for patients, often used alongside WASO and SOL as well-established outcome measures in the field of chronic insomnia. Furthermore, this analysis was limited by the definition of ISI remittance, which varied slightly across the included studies. Seventh, this analysis was also limited by the small number of studies and patients included, suggesting the need for ongoing research to confirm the findings of this study. Nevertheless, these were studies that included the important outcomes of ISI, WASO, and SOL that allowed for a comparison of remission rates and change in sleep outcomes across medications, CBT-I, and the PDT.

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Policy History

- Last Review 05/13/2025

  Effective: 01/07/2022

  Next Review: 10/09/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes