Carlo simulation. Potential drug-drug, gene-drug, or gene-drug-drug interaction risk was characterized as minor, moderate, or major.
Results. Based on prescription data only, the probability of a DDI of any impact (mild, moderate, or major) was 26% [95% CI: 0.248-0.272] in the population. This probability increased to 49.6% [95% CI: 0.484-0.507] when simulated genetic polymorphisms were additionally assessed. When assessing only major impact interactions, there was a 7.8% [95% CI: 0.070-0.085] probability of drug-drug interactions and 10.1% [95% CI: 0.095-0.108] probability with the addition of genetic contributions. The probability of drug-drug-gene interactions of any impact was correlated with the number of prescribed medications, with an approximate probability of 77%, 85%, and 94% in patients prescribed 5, 6, or 7+ medications, respectively. When stratified by specific drug class, antidepressants (19.5%), antiemetics (21.4%), analgesics (16%), antipsychotics (15.6%), and antiparasitics (49.7%) had the highest probability of major drug-drug-gene interaction.
Conclusions. In a community-based population of outpatients, the probability of drug-drug interaction risk increases when genetic polymorphisms are attributed to the population. These data suggest that pharmacogenetic testing may be useful in predicting drug interactions, drug-gene interactions, and severity of interactions when proactively evaluating patient medication profiles.
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Comparative Effectiveness of an FDA-Authorized Digital Therapeutic to Medications and Cognitive Behavioral Therapy Treating Chronic Insomnia in Adults

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Abstract

Introduction. Chronic insomnia affects the physical and mental health, quality of life, and productivity of 6 to 10% of the adult population (15-25 million U.S. adults). Available treatments include guideline-recommended first-line cognitive behavioral therapy for insomnia (CBT-I) and medications. However, limitations such as patient access to CBT-I and limited efficacy, the presence of significant side effects, as well as safety concerns about medications limit favorable outcomes. Somryst is an FDA-authorized prescription digital therapeutic for the treatment of chronic insomnia in adults. The purpose of this analysis is to compare the effectiveness of the digital therapeutic vs CBT-I and medications for primary insomnia.
Methods. Chronic insomnia trials focused on digital therapeutic, CBT-I, or medication were identified in a systematic literature review. Studies using a comparator arm that cannot be considered clinically equivalent to other treatments in the network were excluded (eg, meaningfully different definition of placebo arm). A Bayesian network meta-analysis was performed in R on the mean change from baseline and the proportion of remitters using the insomnia severity index (ISI) endpoint with follow-up timepoints between 6 and 12 weeks. Mean change in ISI score from baseline was analyzed as a continuous endpoint while comparisons of the proportion of remitters were performed using odds ratios. The analysis used a random-effects model for the base case analysis. A surface under the cumulative ranking curve (SUCRA) analysis was performed to rank the treatments on each endpoint.
Results. In total, 13 studies reported ISI mean change from baseline data. Only the digital therapeutic and CBT-I were significantly different than placebo. The digital therapeutic had the greatest mean change from baseline in ISI from placebo (−5.77 points, 95% Credible Interval (CrI) [−8.53, −3.07]), followed by CBT-I (−4.3 points, 95% CrI [−6.32, −2.39]). In the SUCRA analysis, the digital therapeutic had the highest probability (56%) of being the most effective treatment based on ISI mean change from baseline. Only 8 studies reported the proportion of ISI remitters. Only the digital therapeutic showed a statistically significant difference in remission vs placebo and had the highest odds ratio for remission vs placebo (12.33 95% CrI [2.28, 155.91]). The odds ratio for remission vs placebo in CBT-I was not statistically significant (4.08 95% CrI [0.45, 45.58]). The digital therapeutic had the highest probability (64%) of being the most efficacious for inducing remission per ISI.
Conclusions. Somryst was projected to be the most effective therapy on both mean change in ISI and ISI remission within 6 to 12 weeks of treatment start vs either CBT-I or medications. Further investigation should be performed to demonstrate the long-term effectiveness of all chronic insomnia treatments.
Funding. Pear Therapeutics

Outcomes from Engagement and Use of a Prescription Digital Therapeutic to Treat Opioid Use Disorder: A Real-World Pilot Study

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Abstract

Introduction. The opioid epidemic in the United States is getting worse: in 2020 opioid overdose deaths hit an all-time high of 92,183. This underscored the need for more effective and readily available treatments for patients with opioid use disorder (OUD).

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Prescription digital therapeutics (PDTs) are FDA-authorized treatments delivered via mobile devices (eg, smartphones). A real-world pilot study was conducted in an outpatient addiction treatment program to evaluate patient engagement and use of a PDT for patients with OUD. The objective was to assess the ability of the PDT to improve engagement and care for patients receiving buprenorphine medication for opioid use disorder (MOUD).

Methods. Patients with OUD treated at an ambulatory addiction treatment clinic were invited to participate in the pilot. The reSET-O PDT is comprised of 31 core therapy lessons plus 36 supplementary lessons, plus contingency management rewards. Patients were asked to complete at least 4 lessons per week, for 12-weeks. Engagement and use data were collected via the PDT and rates of emergency room data were obtained from patient medical records. Data were compared to a similar group of 158 OUD patients treated at the same clinic who did not use the PDT. Abstinence data were obtained from deidentified medical records.

Results. Pilot participants (N = 40) completed a median of 24 lessons: 73.2% completed at least 8 lessons and 42.5% completed all 31 core lessons. Pilot participants had significantly higher rates of abstinence from opioids in the 30 days prior to discharge from the program than the comparison group: 77.5% vs 51.9% ($P < .01$). Clinician-reported treatment retention for pilot participants vs the comparison group was 100% vs 70.9% 30 days after treatment initiation ($P < .01$), 87.5% vs 55.1% at 90 days post-initiation ($P < .01$), and 45.0% vs 38.6% at 180 days post-initiation ($P = .46$). Emergency room visits within 90 days of discharge from the addiction program were significantly reduced in pilot participants compared to the comparison group (17.3% vs 31.7%, $P < .01$).

Conclusions. These results demonstrate substantial engagement with a PDT in a real-world population of patients with OUD being treated with buprenorphine. Abstinence and retention outcomes were high compared to patients not using the PDT. These results demonstrate the potential value of PDTs to improve outcomes among patients with OUD, a population for which a significant need for improved treatments exists.

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A Model-Informed Drug Development Approach Supporting the Approval of a New Valbenazine Dose for Tardive Dyskinesia

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Abstract

Introduction. Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with dopamine receptor blocking agents (eg, antipsychotics). Valbenazine is a highly selective vesicular monoamine transporter 2 inhibitor with several safe and effective dosing options now approved for once-daily (QD) treatment of TD in adults. Valbenazine 80 mg QD is the recommended dose for TD; however, 40 or 60 mg QD (newly approved dose) may be considered depending on response and tolerability. The recent approval of valbenazine 60 mg was based on results from an analysis that used the FDA's model-informed drug development (MIDD) approach and leveraged existing data from the 6-week, phase 3 registration trial of valbenazine (KINECT 3).

Methods. A population pharmacokinetic (popPK) model was developed to describe plasma concentration-time profiles for valbenazine and its primary active metabolite, [+]-α-dihydrotetrabenazine ([+]-α-HTBZ). An exposure-response (E-R) model was developed using the area under the concentration-time curve (AUC) of [+]-α-HTBZ (exposure) and change from baseline in the Abnormal Involuntary Movement Scale total score (AIMS-CFB) (response). Stepwise E-R model development evaluated various linear and nonlinear models to describe AIMS-CFB vs [+]-α-HTBZ AUC and time. E-R relationships established with the 40 and 80 mg data were used to predict AIMS-CFB for a 60 mg dose up to week 6, accounting for study-to-study, inter-individual, and residual variabilities.

Results. Steady-state valbenazine and [+]-α-HTBZ concentrations were well described by a joint parent-metabolite popPK model. An Emax model with asymptotic exponential delay in the maximal valbenazine effect adequately characterized the E-R relationship between AIMS-CFB and [+]-α-HTBZ AUC. The simulated confidence intervals of response were consistent with the observed KINECT 3 results, demonstrating the utility of the model to predict efficacy results. The established E-R model was subsequently used to predict AIMS-CFB for valbenazine 60 mg QD at week 6. Mean AIMS scores decreased (improved) in a dose-dependent manner, with 60 mg QD predicted to result in least-squares mean (SEM) AIMS-CFB of −2.7 0.4, which is between the reported AIMS-CFB for 40 mg (−1.9 ± 0.4) and 80 mg (−3.2 ± 0.4). All simulated trials demonstrated valbenazine 60 mg to be significantly superior to placebo in AIMS-CFB after 6 weeks of treatment.

Conclusions. This analysis integrated and leveraged data from two previously approved valbenazine doses (40 and 80 mg QD) using an MIDD approach. The results provided key evidence that an intermediate dose (newly approved 60 mg QD) could be considered therapeutically beneficial without the need for an additional clinical trial. The availability of a valbenazine 60 mg dose to complement the previously approved doses fills an existing medical need for patients with TD who could benefit from this third effective dose.

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