Promoting benzodiazepine cessation through an electronically-delivered patient self-management intervention (EMPOWER-ED): Randomized controlled trial protocol

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ABSTRACT

Background: Long-term benzodiazepine dependence carries significant health risks which might be reduced with low-cost patient self-management interventions. A booklet version of one such intervention (Eliminating Medications Through Patient Ownership of End Results; EMPOWER) proved effective in a Canadian clinical trial with older adults. Digitizing such an intervention for electronic delivery and tailoring it to different populations could expand its reach. Accordingly, this article describes the protocol for a randomized controlled trial to test the effectiveness of an electronically-delivered, direct-to-patient benzodiazepine cessation intervention tailored to U.S. military veterans.

Methods: Design: Two-arm individually randomized controlled trial.
Setting: US Veterans Health Administration primary care clinics.
Participants: Primary care patients taking benzodiazepines for three or more months and having access to a smartphone, tablet or desktop computer.
Intervention and comparator: Participants will be randomized to receive either the electronically-delivered EMPOWER (EMPOWER-ED) protocol or asked to continue to follow provider recommendations regarding their benzodiazepine use (treatment-as-usual).
Measurements: The primary outcomes are complete benzodiazepine cessation and 25% dose reduction, assessed using administrative and self-report data, between baseline and six-month follow-up. Secondary outcomes are self-reported anxiety symptoms, sleep quality, and overall health and quality of life, measured at baseline and 6-month follow-up, and benzodiazepine cessation at 12-month follow-up.
Comments: This randomized controlled trial will evaluate whether the accessibility and effectiveness of a promising intervention for benzodiazepine cessation can be improved through digitization and population tailoring.

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1. Introduction

Long-term dependence on prescribed benzodiazepines is a public health concern that has been subject to significant concern in multiple countries, including Israel, the United Kingdom, and the United States [1–4]. Although useful as short-term medications for some patients such as those experiencing transitory sleep difficulties, long-term use of benzodiazepines can convey significant risk for many patient populations including older adults, persons with sleep problems or post traumatic stress disorder or those taking opioids [5–7]. The range of adverse outcomes associated with longer-term benzodiazepine use can include cognitive decline, falls, motor vehicle accidents, opioid-benzodiazepine overdose and benzodiazepine dependence and/or use disorder [8,9]. And although in the short-term benzodiazepines can improve symptoms for some of their most common indications such as sleep disturbance, in the long-term they can exacerbate them [10]. Therefore, effective strategies are needed to help people discontinue long-term benzodiazepine use.

Although therapist-delivered cognitive-behavioral psychological interventions can reduce benzodiazepine use [11], limits on patient willingness and health care system resources make providing individual psychotherapy to every patient with long-term benzodiazepine usage very challenging. A less costly, more scalable, approach is to use the Internet to directly provide patients with structured materials that impart risk information and encourage them to reduce or cease benzodiazepine consumption, either on their own or in consultation with their prescribing physician. In addition to requiring less professional staff time, interventions that do not require patients to travel and that can be accessed at any time and from virtually any place have the added advantage of being attractive to individuals who might not access clinic-based psychotherapy.

Interventions that operate on smartphones and desktop computers are increasingly being studied as a low-cost, highly accessible method for changing substance use behavior [12,13]. To our knowledge, there are no studies evaluating a digitized intervention for promoting benzodiazepine cessation or reduction. That said, computer-delivered interventions have been shown effective at reducing hazardous drinking [14–16]. For example, Cunningham and colleagues [14,15] have demonstrated that heavy drinkers reduce alcohol consumption in response to a computer-delivered, self-administered assessment of alcohol consumption coupled with personalized feedback on risks and on variance from normative population consumption. Further, electronically-delivered interventions are inexpensive to disseminate and increasingly preferred by patients [16,17], increasing their likelihood of broad adoption in healthcare systems [18].

A promising model for such an intervention comes from a Canadian clinical trial of self-management materials, delivered in printed booklet form, that provide information about the risks of long-term benzodiazepine use and suggest strategies for tapering down. The Eliminating Medications Through Patient Ownership of End Results (EMPOWER) study demonstrated that older long-term benzodiazepine users who were mailed a booklet of the EMPOWER materials were eight times more likely to discontinue use of benzodiazepines than were controls [19]. If EMPOWER was found to be effective in electronic form, it would greatly expand its potential reach.

One national health care system in which such an intervention could be particularly valuable is the US Veterans Health Administration (VHA). The VHA is a government-financed health care system which offers comprehensive care to over nine million individuals with prior service in the U.S. military. In the VHA, 355,298 Veterans were prescribed benzodiazepines in the fiscal year 2016, almost two-thirds (63.6%) of whom took them for three months or more [20]. Further, the VHA population includes many older adults and many who take prescribed opioids, further increasing the health risks of long-term benzodiazepine use.

To tailor EMPOWER to the veteran population, our research team worked with VHA patients, prescribing providers and administrators; we then worked with software developers to convert the intervention to a computer-delivered format we call EMPOWER-ED (ED, Electronically Delivered) [21]. This protocol describes how the effectiveness of EMPOWER-ED will be evaluated in a randomized controlled trial enrolling a markedly different population and format than in the initial Canadian study. The primary hypotheses of the RCT are that long-term users of benzodiazepines who are assigned to receive EMPOWER-ED will be significantly more likely than controls to cease taking benzodiazepines entirely or reduce their benzodiazepine dose by at least 25% at 6-month follow-up. The secondary hypotheses are that, relative to controls, participants receiving EMPOWER-ED will experience reduced anxiety symptoms, better sleep quality, and higher overall health-quality of life at six-month follow-up. Because these functional outcomes were not measured in the original EMPOWER study, assessing whether they change is a unique contribution of the present trial. In addition to being important in themselves, these three functional outcomes may moderate or mediate participants’ response to EMPOWER-ED. For example, participants who experience better sleep or reduced anxiety upon initial benzodiazepine tapering may be more likely to continue to full cessation. In contrast, if functional outcomes deteriorate, patients (or the physicians who advise them) may be inclined to abandon EMPOWER-ED; if this were a common result it would likely reduce the adoption of EMPOWER-ED within VHA. Finally, our secondary analysis will also examine whether any effects of EMPOWER-ED observed on our primary outcomes at six-month follow-up are maintained at 12-month follow-up.

2. Methods

2.1. Study design and setting

This study will be an RCT conducted at the Central Arkansas Veterans Healthcare System (CAVHS). Patients with at least one primary care appointment in the last year will be screened for eligibility. Primary care is provided at the CAVHS medical facility, as well as eight affiliated community-based outpatient clinics. We obtained human participants approval from the VA Central Arkansas Veterans Health Care System Research and Development Committee and Institutional Review Board. The study is registered at clinicaltrials.gov (NCT04572750).

2.2. Participants

We will generate a list of potentially eligible participants using VHA’s centralized patient database. Enrollment eligibility criteria are having a designated primary care provider at CAVHS or its affiliated sites, having an active benzodiazepine prescription dispensed for three months or longer [19], and having access to the Internet and a desktop computer, tablet or smartphone. Individuals will not be eligible for enrollment if they are receiving palliative care or have a current diagnosis of dementia, schizophrenia, seizure disorder and/or spinal cord injury. Study staff will contact and screen individuals on the list for other exclusion criteria that cannot be determined through the centralized patient database, namely acute suicidality, lack of access to a smartphone or tablet and inability to speak and understand English. Because tapering down often requires pill-splitting, patients taking capsule form medication will be excluded.

2.3. Recruitment

Recruitment is set to run from April 2022 to March 2023. Potentially eligible persons will be asked to respond to a study invitation letter, sent via mail, inviting them to participate in the study. Individuals meeting study eligibility criteria will receive a description of the study over the telephone including what is requested in terms of participation, including the possibility of receiving EMPOWER-ED, and, that
participants in both conditions will be re-contacted in six-months (Fig. 1). A research assistant will obtain consent from those who are interested in participating. Participants will receive US$30 for completing the baseline interview and US$30 for completing the six-month follow-up interview.

2.4. Sample size

The original EMPOWER study reported an eight-fold difference in benzodiazepine cessation and reduction rates, which converts to a Cohen’s d greater than 0.8 [19]. However, we powered the present study using a more conservative estimate of the intervention effect based on a recent meta-analysis of 17 clinical trials [22] showing that computer-delivered interventions demonstrate an effect size on drug use somewhat lower than medium (0.36).

To attain 80% power with .05 type I error rate to detect a medium effect size of 0.35 with intra-class coefficient of 0.008 (based on the original EMPOWER study [19]) for the primary outcomes of benzodiazepine cessation and reduction, 66 patients per group will be needed. Assuming an 80% six-month follow-up rate, this will require enrollment at baseline of 170 participants (i.e., 85 per group).

2.5. Randomization

Simple randomization of participants will be conducted using SAS by the study biostatistician. Because existing research has not identified variables consistently likely to moderate the impact of the intervention on outcomes, the sample will not be stratified prior to randomization.

![Flowchart of procedure](image)
To facilitate randomization, research assistants, guided by a biostatistician, will generate and store a randomized list on an encrypted electronic file and will be the only study staff with access to this information. Study principal investigators (KH and MAC) will also be blinded to participant allocation. Once consented, participants will be asked to complete a baseline assessment conducted by telephone prior to being randomized to condition-EMPOWER-ED or treatment-as-usual. Thus, research assistants will be blinded to participant condition for the baseline interview. At six-month follow-up, each interviewer will be given an envelope with the participant’s study ID, to be opened after completion of the interview and while they are still on the phone with the participant. This will allow interviewers to remain blinded to condition while assessing main outcomes and allow for subsequent questions about participants’ use of the EMPOWER website.

2.6. Experimental condition

Participants in the experimental condition will receive the EMPOWER-ED website information over the telephone and by email. They will be able to access the EMPOWER-ED protocol on any platform (e.g., smartphone, desktop, tablet) that they choose. Based on the original EMPOWER protocol, the EMPOWER-ED protocol will consist of: a self-assessment of risks associated with long-term benzodiazepine use, information on the evidence for benzodiazepine-related harms (Fig. 2), knowledge statements designed to create ambivalence about the safety of benzodiazepines, education about drug interactions, vignettes of peers who have successfully stopped using benzodiazepines to support participants’ self-efficacy to change (Fig. 3), information about equally or more effective therapeutic alternatives for sleep difficulties and/or anxiety (Fig. 4) and recommendations for self-tapering.

Participants will have the option of generating a taper schedule should they decide that they would like to reduce or discontinue their benzodiazepines. To produce the taper schedule, participants will first enter their current daily benzodiazepine dose and frequency of dose. Participants are then asked to enter their desired date for starting the taper and to verify information entered including current dose each time they take their medication. This verification process allows participants to correct any incorrect information initially entered about their benzodiazepine use prior to generating the personalized taper schedule. After verification, EMPOWER-ED will generate a taper schedule based on the information provided. The tapering schedule will last up to 21 weeks with each day’s target pill consumption graphically displayed on a calendar (e.g., full-pill, half-pill, quarter pill, or no pill for each time they take their medication).

All participants’ enrolled in the study will have a note indicating their study involvement including their condition assignment uploaded to their medical chart that is accessible by their primary care provider. The EMPOWER-ED materials will encourage all participants to notify their primary care physician of their decision to taper their benzodiazepines and provide practical tips for managing the taper process including when to contact their prescribing provider. The study team will also provide the phone number to a study physician should participants have questions about any concerning symptoms during their taper.

2.7. Control condition

Participants assigned to the control condition will be asked to continue to follow any provider recommendations regarding their benzodiazepine use. Control participants will also be informed that if the EMPOWER-ED materials have an effect, they will be made available to them at the end of the study (i.e., at 12-months follow-up).

2.8. Data collection

Participants in both conditions will be asked to complete a 30–45 min interview over the telephone at baseline and at six-month follow-up. We will also collect data from the VHA centralized databases on participants’ benzodiazepine use at baseline, six-month and 12-month follow-up. The study will collect demographic data including age, sex and gender identity, race/ethnicity, current marital, occupational and housing status and education at baseline. We will also collect data on participants’ readiness to make a change in their benzodiazepine use (1 = not ready to change, 10 = trying to change) using the single item readiness ruler [23] and use the 5-item Severity of Dependence Scale.

Fig. 2. Self-assessment of risks associated with long-term benzodiazepine use and education on potential harms.
(SDS) modified for benzodiazepine use to assess dependence at baseline and three month follow-up [24]. The SDS assesses the degree of dependence experienced by participants using different types of drugs in the past month (e.g., did you worry about your use of benzodiazepines? and did you wish you could stop?). SDS items can be summed to generate a summary score with higher scores indicating more drug dependence [24]. These variables will be explored as potential moderators of intervention effects should EMPOWER-ED be found to be effective.

2.9. Outcomes

We preregistered two primary outcomes: cessation of benzodiazepines and dose reduction of benzodiazepines at six-month follow-up. Cessation is defined as the absence of a benzodiazepine prescription renewal in the three months prior to follow-up, and dose reduction is defined as a 25% or greater decrease in benzodiazepine use sustained for three months or more at follow-up. All participants who cease benzodiazepines entirely will be included with those who achieve 25% or more reduction.

We will collect data from two sources to examine our primary outcomes. First, we will follow the approach used in the original EMPOWER study and use administrative data to assess reductions in benzodiazepine use. Second, we will collect participants’ self-report data on their benzodiazepine use at baseline and six-month follow-up, using the six-month Timeline Followback method [25]. The TimeLine Followback is
a valid calendar-based method that asks participants to retrospectively recall their drug use (e.g., yes or no, daily dosage, drug name) up to two years prior to the interview date. This data source will allow us to determine the existence of any additional benzodiazepine prescriptions (e.g., from a non-VHA provider) and/or whether any additional benzodiazepine use occurred between baseline and six-month follow-up that was not captured in the administrative data. For both data sources, all doses of different benzodiazepines used will be converted to lorazepam equivalents and the baseline dose will be defined as the average daily dose in the six-months prior to randomization.

Pre-registered secondary outcomes include anxiety symptoms, sleep quality and overall health and quality of life collected at baseline and 6-month follow-up. Anxiety symptoms will be measured by the Generalized Anxiety Disorder Scale [26]. This seven-item scale asks about the presence and severity of seven symptoms (e.g., feeling on edge, having trouble relaxing) and includes an omnibus item rating that is the extent to which any of the seven symptoms has made it difficult “to do your work, take care of things at home, or get along with other people”. The secondary outcome will be the sum of the seven items assessing anxiety symptoms. Sleep quality will be measured by the Patient-Reported Outcomes Measurement System brief sleep disturbance scale [27]. This eight-item scale assesses degree of difficulty falling asleep, degree to which sleep is refreshing, and ability to stay asleep through the night. A secondary outcome will be the sum of the eight items assessing sleep quality. Overall health and quality of life will be measured by the RAND Veterans Short Form-12 measure [28], which consists of items assessing global emotional and physical well-being and function (e.g., “How much time in the past four weeks did you have a lot of energy?”). “Compared to one year ago, how would you rate your physical health today?”). Global domains of emotional and physical well-being and health will be used to measure this secondary outcome.

The final secondary outcomes are cessation and 25% decrease of benzodiazepine use at 12-months follow-up; unlike the prior measures these data will be collected using administrative data (resource constraints prevent assessing this by interview). Benzodiazepine cessation and reduction at 6-month, as opposed to 12-month, are chosen as the primary outcomes in an attempt to replicate findings from the original EMPOWER study in Canada [19]. No other 12-month outcome data will be gathered.

3. Statistical methods

The randomization scheme will be checked by comparing baseline variables with known or suspected prognostic importance between the experimental and control group using bivariate analyses. If the proportion of variables with significant differences between groups is greater than .05, an imbalance between the two groups is suspected. We will then run the models with and without those variables that caused imbalance between the groups included and compare the results. If the results from both approaches are essentially the same, we will use the models without those variables included. Otherwise, we will adjust those variables in the models. Linearity between continuous variables and outcomes will be checked. If the relationship is not linear, other appropriate functional forms (e.g., quadratic) will be assessed or the variable will be changed to categorical. Proportions of missing values will be assessed and multiple imputation method will be used for missing values if necessary and if the missing at random assumption is deemed reasonable.

Descriptive statistics will be calculated to examine data distributions. Tests for distributional assumptions (e.g., normality) for continuous variables will also be performed. Bivariate analyses will be performed for categorical variables using a Chi-square test, for continuous normally distributed variables using independent t-test and for non-normally distributed continuous variables using nonparametric Wilcoxon rank-sum test. For primary outcomes of benzodiazepine discontinuation and 25% dose reduction at 6-month follow-up, we will use logistic regression models to examine the effect of EMPOWER-ED on the proportions of participants with discontinuation and dose reduction. The models will be run first with the indicator variable for EMPOWER-ED versus control conditions only plus baseline outcomes. Then the models will be run again with the covariates identified in the bivariate analysis added. The results from both models will be compared.

The same approach will be used to examine any impact of the intervention on the three secondary outcomes assessing function (anxiety, sleep quality, and quality of life) at 6-month follow-up. General or generalized linear models will be used depending on whether outcomes are normally distributed or not.

In addition, to examine secondary outcomes of benzodiazepine discontinuation and 25% dose reduction at 12-month follow-up, we will use generalized estimating equations (GEE) models or generalized linear mixed models, with data collected at 6-months, to examine the effect of EMPOWER-ED on the proportions of participants with discontinuation and dose reduction to account for the repeated measures within each participant. All the models will include the indicator variable for EMPOWER-ED versus control conditions, time representing 6- and 12-month follow-ups and covariates identified in bivariate analysis. The baseline benzodiazepine use (i.e., average daily dose) variable will be adjusted. The interaction between the indicator variable and time will be examined and dropped from the models if statistically non-significant. SAS 9.4 will be used in all the analyses.

3.1. Economic analysis

We will estimate the average cost of the intervention. For each participant, we will summarize their care utilization and cost data. We will then perform a budget impact analysis of the intervention, comparing all health care costs for each condition, including the costs of delivering EMPOWER-ED. We will not include costs of developing the intervention or administrative overhead [29]. Assuming also, that EMPOWER-ED may affect both immediate decisions about benzodiazepine use as well as decisions about other health care in the near future, we will analyze changes in all health care utilization and costs incurred within the 12-months before and the 12-months following randomization. We will also compare costs incurred in the first 6-months to those incurred in the second 6-months.

We will analyze the subsequent cost impacts of the intervention, using both the simple cost comparison and multivariate regression methods. For the mean cost comparison, we will estimate the average costs of health care utilization by type of care (e.g., inpatient, outpatient, pharmacy) for the experimental and control group, respectively. We will also estimate the average costs by type of care separately for the two outcome groups: patients with complete cessation for three or more months and patients with 25% or more dose reduction compared to baseline. Due to the skewed distribution of cost data, we will use a two-part regression model (logit for the first part and generalized linear model for the second part) to evaluate the marginal effect of EMPOWER-ED on costs and resource utilization [30,31]. For the regression analysis, we will include demographic and risk adjustment variables in the regression models and examine the impact of complete cessation and 25% or more dose reduction on health care costs by type of care.

We will estimate the budgetary impact for the study site. We will measure labor costs associated with delivering and maintaining the intervention. We will extrapolate from this site to create projections for other VHA medical facilities based on the prevalence of patients on long-term benzodiazepines. This will allow us to estimate the budget impact of diffusing the EMPOWER-ED materials throughout VHA as well as beyond it.

4. Discussion

Digital interventions have substantial potential to serve as broadly
accessible, low-cost sources of behavior change support for individuals who use addictive substances. However, most of such interventions available on the Internet have not been evaluated, and many others have only been evaluated on populations which are not broadly representative of the whole. The EMPOWER-ED trial thus has potential to advance the science and clinical practice in both respects, while simultaneously engaging in a fundamental but often neglected task for addiction science: replication of clinical trial findings.

The other potential contributions of this evaluation are twofold. First, benzodiazepines are a strangely neglected topic in the addiction field [32], with little effort being expended to understand and intervene with long-term users. Like the EMPOWER trial itself, the present study evaluating EMPOWER-ED will help fill this gap in understanding. Second, by focusing on a high-need population, namely US military veterans, this project can reasonably hope to reduce health disparities in the United States as well as we hope in other countries.

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Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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References
[1] M.A. Steinman, M. Low, R.D. Balicer, E. Shadmi, Epidemic use of benzodiazepines among older adults in Israel: epidemiology and leverage points for improvement, J. Gen. Intern. Med. 32 (8) (2017) 891–899.
[2] S. Taylor, F. Anand, P. Birkhunwsh, F. Greaves, M. Kelleher, J. Knight, C. Perkins, A. Tran, M. White, J. Marsden, Dependence and Withdrawal Associated with Some Prescribed Medicines: an Evidence Review, Public Health England, London, 2019.
[3] M.A. Bachhuber, S. Hennessey, C.O. Cunningham, J.L. Starrels, Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013, Am. J. Publ. Health 106 (2016) 668–688.
[4] A. Lembo, J. Papac, K. Humphreys, Our other prescription drug problem, N. Engl. J. Med. 378 (8) (2018) 693–695.
[5] U.S. Department of Veterans Affairs. Veterans Health Administration, PBM Academic Detailing Service. Benzodiazepine risks: are you aware of the possible risks? [from taking benzodiazepine]. https://www.phv.va.gov/PBM-AcademicDetailingService/Documents/Benzodiazepine_Provider_AD%20RiskDiscussionGuide.pdf. (Accessed 13 January 2021).
[6] S. Billioti de Gage, B. Béguin, F. Bazin, et al., Benzodiazepine use and risk of dementia: prospective population based study, BMJ 345 (2012), e6231, Published 2012 Sep 27.
[7] T.W. Park, M.R. Larochelle, R. Saitz, et al., Associations between prescribed benzodiazepines, overdose death and buprenorphine discontinuation among people receiving buprenorphine, Addiction 115 (5) (2020) 924–932, https://doi.org/10.1111/add.14886.
[8] T.W. Park, M.R. Larochelle, R. Saitz, N. Wang, D. Bernson, A.Y. Walley, Associations between prescribed benzodiazepines, overdose death and buprenorphine among people receiving buprenorphine, Addiction 115 (5) (2020) 924–932.
[9] E.C. Sun, A. Dixit, K. Humphreys, B.D. Darnell, L.C. Baker, S. Mackey, Association between concurrent use of prescription opioids and benzodiazepine with overdose: a retrospective analysis, BMJ 356 (2017) 766.
[10] D. Poyares, C. Guillenmaul, M.M. Ohayon, et al., Chronic benzodiazepine usage and withdrawal in insomnia patients, J. Psychiatr. Res. 38 (3) (2004) 327–334.
[11] R.L. Gould, M.C. Coulson, N. Patel, E. Highton-Williamson, R.J. Howard, Interventions for reducing benzodiazepine use in older people: meta-analysis of randomized controlled trials, Br. J. Psychiatry 204 (2) (2014) 98–107.
[12] C. Garnett, M. Oldham, C. Angus, E. Beard, R. Burton, M. Field, et al., Evaluating the effectiveness of the smartphone app, Drink Less, compared with the NHS alcohol advice webpage, for the reduction of alcohol consumption among hazardous and harmful adult drinkers in the UK at 6-month follow-up: protocol for a randomised controlled trial, Addiction (2020 Oct 17), https://doi.org/10.1111/add.15227 (Epub ahead of print).
[13] Y.T.D. Cheung, C.H.H. Chan, K.S. Ho, W.P. Fok, M. Conway, C.H.K. Wong, et al., Effectiveness of WhatsApp online group discussion for smoking relapse prevention: protocol for a pragmatic randomized controlled trial, Addiction 115 (9) (2020) 1777–1785.
[14] J. Cunningham, T.C. Wild, J. Cordingley, T. van Mierlo, K. Humphreys, A randomized controlled trial of Internet-based intervention for alcohol abusers, Addiction 104 (12) (2009) 2023–2032.
[15] J.A. Cunningham, C. Neighbors, T.C. Wild, K. Humphreys, Ultra-brief intervention for problem drinkers: results from a randomized controlled trial, PLoS One 7 (10) (2012), e48003.
[16] C.R. Erbes, R. Sinson, E. Kuhn, M. Polusny, J. Urban, J. Hoffman, et al., Access, utilization and interest in mHealth applications among veterans receiving outpatient care for PTSD, Mil. Med. 179 (11) (2014) 1218–1222.
[17] A. Klee, M. Stacy, R. Rosenheck, L. Harkness, J. Tsai, Interest in technology-based therapies hampered by lack of awareness and distrust among veterans with serious mental illnesses, Psychiatr. Rehabil. J. 39 (2) (2016) 173–179.
[18] L.J. Damschroder, H.J. Dargad, A guiding framework and approach for implementation research in substance use disorders treatment, Psychol. Addict. Behav. 25 (2) (2011) 194–205.
[19] C. Tannenbaum, P. Marin, R. Tamblyn, A. Benedetti, S. Ahmed, Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial, JAMA Intern. Med. 174 (6) (2014) 890–896.
[20] Correspondence with VA Pharmacy Benefits Management, 2017.
[21] Cucciare, M.A., Abraham, T., Kemp, L., White, P., Marchant, K., Hagedorn, H., Humphreys, K. Adapting the Eliminating Medications through Patient Ownership (EMPOWER) protocol to promote benzodiazepine cessation among US military Veterans: an iterative, qualitative approach. J. Med. Internet Res., (in press).
[22] N. Boumparis, E. Karyotaki, M.P. Schaub, P. Cuijpers, H. Riper, Internet interventions for adult illicit substance users: a meta-analysis, Addiction 112 (9) (2017) 1521–1532.
[23] M. Hesse, The Readiness Ruler as a measure of readiness to change poly-drug use in drug abusers, Harm Reduct. J. 3 (3) (2006). Published 2006 Jan 25.
[24] C. de las Cuevas, E.J. Sanchez, J.A. De La Fuente, J. Padilla, J.C. Bennraeger, The Severity of Dependence Scale (SDS) as screening test for benzodiazepine dependence: SDS validation study, Addiction 95 (2) (2000) 245–250.
[25] National Institute on Drug Abuse, CTN common data elements. Instrument: timeline Followback method assessment. https://ctn.drugabuse.gov/ctncde/ctnDataDefinitions/nida/CTN/Docs/924.pdf. (Accessed 13 January 2021).
[26] R.L. Spitzer, K. Kroenke, J.B.W. Williams, B. Lowe, A brief measure for assessing generalized anxiety disorder: the GAD-7, Arch. Intern. Med. 166 (10) (2006) 1092–1097.
[27] L. Yu, D.J. Buysse, A. Germain, D.E. Moul, A. Stover, N.E. Dodds, et al., Development of short forms from the PROMIS sleep disturbance and sleep related impairment item banks, Behav. Sleep Med. 10 (1) (2012) 6–24.

[28] B.D. Schalet, N.E. Rothrock, R.D. Hays, L.E. Kazis, K.F. Cook, J.P. Rutsohn, et al., Linking physical and mental health summary scores from the veterans RAND 12-item health survey (VR-12) to the PROMIS global health scale, J. Gen. Intern. Med. 30 (10) (2015) 1524–1530.

[29] J.A. Mauskopf, S.D. Sullivan, L. Annemans, J. Caro, C.D. Mullins, M. Nuijten, et al., Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices—budget impact analysis, Value Health 10 (5) (2007) 336–347.

[30] F. Belotti, P. Ich, W.G. Manning, E.C. Norton, Twopm: Two-part models, STATA J. 15 (1) (2015) 3–20.

[31] B. Mihaylova, A. Briggs, A. O’Hagan, S.G. Thompson, Review of statistical methods for analysing healthcare resources and costs, Health Econ. 20 (8) (2011) 897–916.

[32] A. Schmitz, Benzodiazepines: the time for systematic change is now, Addiction 116 (2) (2021) 219–221.