Clozapine CHAMPION-ECHO Educational Study to Improve Clozapine Use

NCT04325386

06/09/2025

CHAMPION PROTOCOL

Contents

INVESTIGATOR

Principal Investigator: Dr. Deanna L. Kelly, PharmD, BCCPP
Professor of Psychiatry
University of Maryland School of Medicine
Director, Treatment Research Program
Maryland Psychiatric Research Center
dlkelly@som.umaryland.edu
410-402-6861

PROJECT SUMMARY

Schizophrenia is one of the leading causes of disability worldwide and the burden of this disease on individual health and society at large is substantial (1). While new pharmacological treatments are emerging, no treatment for schizophrenia has been found to rival the efficacy of clozapine (2-16). Yet, the number of people with schizophrenia who are prescribed clozapine nationally is <5%, despite its recommended use in about 30-50% of people with treatment-resistant schizophrenia (17, 18). Arguably, clozapine is one of the most underutilized evidence-based treatments in psychiatry and optimization of its use could drastically improve patient outcomes and lower treatment costs (19-21). Many barriers contribute to clozapine underutilization; however, our pilot data and data from others show that lack of prescriber competence to use clozapine and challenging logistics for absolute neutrophil count (ANC) monitoring are two of the greatest barriers to

clozapine use (22-25). Further, pilot data shows that prescriber self-reported competence in using clozapine correlates with their prescription of clozapine. Therefore, without improving competence, changes in prescribing of clozapine are unlikely to occur.

In the last 15 years, a unique, structured and empirically validated tele-mentoring model has emerged called Project ECHO (Extension for Community Healthcare Outcomes). ECHO is a "hub" and "spoke" sharing network led by an expert academic team (the "hub") that uses multipoint video-conferencing to conduct virtual clinics with non-expert prescribers (the "spokes") located in areas outside the academic hub site. The use of ECHO has been shown to significantly improve best-practice specialty care in sites that lack expertise in a variety of disease states (26, 27). Importantly, multiple studies have established its efficacy in improving prescriber competence, the "target mechanism" we hypothesize to be linked to increased clozapine prescribing (26, 28-30).

In a randomized controlled design with approximately 26 biweekly sessions over 12 months, we propose to test the effectiveness of an ECHO-based intervention for improving the use of clozapine in people with treatment-resistant schizophrenia. The sessions will include: 1) active dissemination of knowledge and information by an expert "hub" followed by 2) clozapine case presentations and vignettes submitted by the "spokes".

This intervention, ***Clozapine CHAMPION-ECHO (Center for Help and Assistance for Maryland Prescribers-Improving Outcomes Network*** *using* ***E****xtension for* ***C****ommunity* ***H****ealthcare* ***O****utcomes,* will be referred to as *"***CHAMPION"** throughout the application. To minimize ANC monitoring barriers and maximize recruitment, we will provide Food and Drug Administration (FDA)-approved ANC point of care (POC) monitoring devices to all study sites, including those in the control condition (the PI and clinical team has used this previously). We will enroll at least 300 prescribers and additional clinical team members (up to 300) from approximately 60 outpatient mental health clinics (OMHCs) and other treatment sites. Individual prescribers can also enroll. Approximately half the sites/individuals will be randomized to CHAMPION and half randomized to enhanced treatment as usual (ETAU).

SPECIFIC AIMS

Aim 1:

To determine the effect of 12 months of CHAMPION exposure on: a) the clozapine prescribing practices of prescribers/clinical team; and b) the persistence of their patients use of prescribed clozapine. ***Hypothesis 1:*** *Relative to the prescribers randomized to ETAU, prescribers randomized to CHAMPION will significantly increase the proportion of patients in their care who are prescribed clozapine as assessed using Maryland Medicaid prescription data.* ***Hypothesis 2:*** *For patients who are prescribed clozapine, the patients of prescribers randomized to CHAMPION will exhibit significantly greater persistence to clozapine treatment compared to patients of prescribers randomized to ETAU.*

Aim 2:

To determine the effect of 12 months of CHAMPION exposure on prescriber knowledge and self-reported competence of prescribing clozapine and how those mechanisms of change are associated with increased clozapine prescribing and persistence of clozapine use. ***Hypothesis 3:*** *Relative to the prescribers randomized to ETAU, prescribers randomized to CHAMPION will demonstrate significantly increased levels of clozapine knowledge and self-reported competence.* ***Hypothesis 4:*** *Prescriber self-reported competence will mediate the effect of CHAMPION on clozapine prescribing and persistence.*

Exploratory Aims:

To determine the effect of patient race in moderating the effect of 12 months of exposure to CHAMPION on the clozapine prescribing practices of prescribers and objectively measured medication persistence of their patients prescribed clozapine. We will also examine the impact of site and participant characteristics as well as attendance on outcomes.

In summary, if demonstrated to be efficacious, CHAMPION will have significant public impact by increasing the use of clozapine. This project addresses key NIMH priorities including improving access to evidence-based practices, focusing on disparities, and including innovative technologies. This project features a novel intervention, a renowned team of experts and the support of local and national organizations positioned to ensure its success.

PARTICPANTS AND RECRUITMENT AND RETENTION PLAN

Participants and Recruitment and Referral Sources

We will complete all recruitment and enrollment prior to initiation of the intervention. We will enroll 300 prescribers (physicians, nurse practitioners, physician assistants or other doctoral level providers approved to prescribe clozapine in the State of Maryland) as well as other team members at the sites (up to 300). We will recruit prescribers/clinical team from State of Maryland Outpatient Mental Health Centers (OMHC) and other clinical sites. We plan to attempt to enroll approximately 2 OMHCs by county; overall, we plan to enroll approximately 60 sites (approximately 5 prescribers/clinical team per site) with 30 in the CHAMPION group and 30 in the enhanced treatment as usual (TAU) group with N=150 prescribers per group. We may have a few more or less sites to reach the 300 prescriber target for the primary outcome and up to 600 total. We will allow individual prescribers to enroll if they are not affiliated with an enrolled study site, however they will not receive the ANC Point of Care Device, laptop computer, or site stipend. They are eligible for the individual compensation and education benefits if applicable.

Inclusion and Exclusion Criteria

Sites that enroll will have approximately 5 prescribers per site. Other members at the site can enroll. The specific inclusion/exclusion criteria for prescribers includes:

1) Located at a site in the State of Maryland with at least 3 prescribers at the site.
2) Prescribers/clinical team should be licensed in the State of Maryland and have prescribed antipsychotics previously.
3) Between the ages of 22 and 85 years old
4) Willing to agree to try to participate in the CHAMPION sessions
5) Willing to participate in pre- and post-testing
6) Individual prescribers not located at an enrolled study site may enroll with modified benefits.

All sites will benefit from participating in the study, as we will provide free of charge the newly FDA Class II approved Point of Care (POC) monitoring device for absolute neutrophil counts (ANC). We have partnered with the Behavioral Health Administration (BHA) at the State of Maryland Department of Health and are working with the State Core Service Agencies (CSA) and the Clozapine Authorization and Monitoring Program (CAMP) to ensure that we are aware of all clinics in the State that prescribe clozapine and they all receive information

and encouragement from the State of Maryland to participate in the proposed study. We also have access and relationships with the clinics due to our establishment of the Maryland Psychiatric Research Center (MPRC) Practice Research Network (PRN).

The steps for recruitment are as follows:

1) We will develop recruitment materials and flyers describing the study benefits and details to be submitted to IRB. We will advertise on our Facebook and Website pages for the TRP only after IRB approval of advertisements. We will also advertise by Twitter, send an email to the Maryland Psychiatric Association, Department of Psychiatry Newsletter and other outlets in the State, only with IRB approval, for the ads. We will be using #CHAMPION as our hashtag symbol.
2) BHA, the CSA and our research team will do outreach to clinics as well. We will stay in contact with the clinics and personnel once we get them enrolled.
3) All clinics that agree to participate will receive the POC device; training on how to use the device; and access to our REDCap data collection system, which will allow them to participate in two study assessment queries, separated by 12 months, on their knowledge and self-reported competence of using clozapine.
4) All groups will be randomly assigned to receive the CHAMPION intervention or be an enhanced treatment as usual (ETAU) (control site). If they are assigned to CHAMPION, then they will agree to participate in a one-year biweekly (26 session) tele-mentoring program (approximately 1.25 hours each session. They will receive AMA Category 1 PRA CME credit hours (or corresponding CEU) for each session they attend and take the evaluation post-test for the session. CME participants will have to complete an evaluation to receive the credits. This process will be automated, and the University of Maryland Department of Faculty Affairs is partnering with us to provide the CME credits.

We will attempt to enroll OMHCs and clinics from all geographic regions and counties in the State of Maryland. Our goal is to enroll at least two OMHC clinics per county (one randomized to each condition). If we do not get OMHC representation from all counties, then we will open recruitment up to other clinics to apply for participation in the study. We will place an emphasis on underserved and rural areas of Maryland including those with a prominent African-American population; this is a cornerstone to our application. The State of Maryland is unique and well suited for studying and focusing on this minority population. We will have a formal application process, which will be used to select the clinics. Based on the high demand of getting the POC device, the demand for telemedicine for consultation and the demand to get clozapine training (based on our pilot data) we will recommend that the clinics and prescribers/clinical team meet the following criteria:

In our initial outreach/recruitment efforts, we will focus on recruiting clinics from rural counties in order to ensure that we have adequate OMHC representation from rural counties. We will complete this initial outreach effort in the first nine months. Once we enroll these clinics, then we will open recruitment to clinics in non-rural counties.

METHODS

Overview of the Study Design

Our study outcomes are all individual participant outcomes and randomized by sites to ensure we have enough Athelas devices to pass out. We will randomize the individuals by site (N = 60 sites, approximately 3-5 prescribers per site) randomized controlled effectiveness trial to assess if CHAMPION (150 prescribers) significantly increases clozapine prescribing, persistence, knowledge and self-reported competence compared to Enhanced Treatment as Usual (ETAU, N = 30 sites, 150 prescribers). We may have participants from more

than 60 sites and more than 300 enrollments to reach the target of 300 prescribers. In addition, individual prescribers signing up will also be randomized to the two conditions. .

We will assess provider level outcomes (knowledge and self-reported competence) immediately before and after the intervention (12 months) and patient level prescribing outcomes (from administrative data) for the year prior to the intervention, during the year of the intervention and for the year following the intervention. This will allow us to estimate the baseline level of clozapine prescribing, the impact during the intervention year and the sustainability of any effects during the year after the intervention is no longer active.

Randomization Procedures

Randomization will occur at the site level for enrolled sites and individual level for prescribers not at enrolled sites. There are NO site outcomes, this randomization allows for the devices to be given to providers in groups to ensure all groups can get a device. The randomization schedule will be created by the study statistician using a randomized block design (block = rural/urban/suburban). We will randomly assign each clinic/prescriber into one of the two study groups using a 1 (CHAMPION) to 1 (ETAU) assignment. Random assignment will occur after agency recruitment and prescriber baseline assessments are completed.

CHAMPION Intervention Condition

Sites included in the CHAMPION will receive the POC ANC device to use during the 12-month study (and for 12 months post intervention) as well as access to clozapine consultation as described in the ETAU condition for 12 months during the intervention and 12 months follow-up. In addition, approximately half of the CHAMPION sites/individuals will receive biweekly ECHO telementoring education sessions. These telementoring sessions will occur simultaneously for all intervention sites and may consist of one or two identical sessions during the week. Each session will consist of a 15-20-minute didactic period on specific topics which will be followed by approximately 1 hour of site supplied case and patient consultations. All the prescribers and the clinicians at the sites are welcome to attend the online session even if they enroll for study inclusion or not. Attendance will be tracked by the study team at the beginning of each session.

The session will conclude with a discussion and question and answer period. At the end of the session the team of clozapine experts will provide a written summary of treatment recommendations regarding the cases. Each CHAMPION session will have at least one clozapine expert delivering the didactic topic and at least 2 additional clozapine experts providing mentoring for the case-based consultation session. This will allow us to call upon the diverse group of experts in our proposed study personnel. We will complement the sessions with dissemination of any relevant publications, toolkits and tips.

Enhanced Treatment as Usual (ETAU) Condition and Justification

Clinics randomized to ETAU will receive (1) a Point of Care (POC) device to use during the 12 months intervention for ANC monitoring and 12 months post intervention , and (2) access to the MPRC clozapine team for consultation and questions during this time period. First, we will provide an Athelas One POC monitoring device, which has just received FDA class II clearance, to each clinic in order to provide easy and immediate results for the ANC and other white blood cell count results needed for the mandatory FDA monitoring requirements associated with clozapine prescribing. We have installed the device and provided training on its use in 3 sites; these sites have performed over 220 ANC measurements using this novel technology. The Athelas One POC monitoring device provides ANC results using a small drop of capillary blood drawn by a quick fingerstick and drop placed on a slide (unlimited supply to be supplied for free); the fingerstick can be done in the clinic and mitigates against having to refer the patient to another site for their blood draw. The

device images and automatically analyzes the cells morphologically with machine learning and pathologist oversight, and then generates a final count report, which is highly correlated to national reference laboratory values For the ease of each prescriber and healthcare team, the returned ANC values can be entered automatically into the FDA mandated Clozapine Risk and Mitigation Evaluation System (REMS), which is the required and often cumbersome system of reporting the weekly ANC values. All sites will receive a laptop that can receive the ANC result with a simple log-in to the website and secure password. We will have the study coordinator (already familiar and using Athelas One) to set up the device at all of the sites and be available for any troubleshooting or questions. Athelas has also pledged to be available to help with all devices. The devices will be available for routine use for all clozapine patients during the study. There will be no charge for the devices and Athelas will help with Medicaid billing to receive payment for time of use. Individual prescribers enrolling and not affiliated with a site will not have access to the device. Following the conclusion of the observation period in August of 2023 we will work with the sites to transition the Athelas devices to their own custody and will work with sites to make arrangements with Athelas

Second, we will disseminate a centralized MPRC phone number and email contact to all 60 sites and individual prescribers for questions and consultative questions for clozapine starting at the CHAMPION randomization and continuing throughout the entire study period. At the conclusion of the entire grant funding we will post all ECHO sessions and make them available to the ETAU sites.

Medicaid Data and Security

We will be getting Medicaid Data from the Hilltop Institute www.hilltopinstitute.org

The Hilltop Institute at the University of Maryland, Baltimore County (UMBC), is a non-partisan health research organization dedicated to advancing the health and wellbeing of people and communities. Hilltop conducts research, analysis, and evaluations on behalf of government agencies, foundations, and nonprofit organizations at the national, state, and local levels. Hilltop is committed to addressing complex issues through informed, objective, and innovative research and analysis.

Formed in 1994 as the Center for Health Program Development and Management in a unique collaboration with the Maryland Medicaid program, Hilltop was instrumental in the 1997 launch of HealthChoice, Maryland’s Medicaid managed care program. Since its inception, Hilltop has maintained a nationally recognized partnership with the Maryland Department of Health to analyze state health policies and develop solutions for the Maryland Medicaid program.

Hilltop developed and manages a data warehouse containing Maryland’s Medicaid claims and encounter data. Hilltop processes and warehouses data on service utilization by more than 1,200,000 Medicaid enrollees and Medicaid payments totaling over $7 billion. Hilltop currently processes and archives more than 12 million records each month. These records are used to generate standardized and customized reviews of Maryland’s Medicaid system. Among Maryland Medicaid enrollees are approximately 105,000 individuals who are also eligible for Medicare (Medicare-Medicaid enrollees). Since 2002, CMS has provided Hilltop with Medicare claims corresponding to those Medicare-Medicaid enrollees, which Hilltop refines and maintains. Hilltop is also expert in linking Medicare and Medicaid data to study issues that affect Medicare-Medicaid enrollees.

The Hilltop institute maintains private and secure files and will be transferring requested data to the University of Maryland School of Medicine, Division of Services Research only through a secure file transfer protocol, Accellion. All data kept at the Division of Services Research are strictly confidential and secure.

Data Elements will include:

We will begin to collect data retrospectively for one year prior to the start of the CHAMPION intervention. This is slated to occur in approximately June of 2021 for the period of December of 2019 onward. We will collect data until one year after the CHAMPION ends or around June of 2023. Thus, we will be examining Medicaid data for a period of December 2019 to December of 2023 approximately.

The elements we will be collecting include collecting Maryland Medicaid recipient data for those who are over the age of 18. We are asking for data on those with a 295 diagnosis so we can examine antipsychotic and clozapine treatment. We anticipate approximately 350,000 antipsychotic prescriptions and 75,000 clozapine prescriptions annually.

We will have participant ID to link records for examining adherence and persistence. Thus, we will have Medicaid enrollment and demographic data, inpatient and outpatient claims data, other professional fee services, pharmacy data and provider information. The provider linkage is needed to link the knowledge and competence testing to rates of prescribing. Specifically, this includes:

Date of Service	Dates for prescription
Drug Name	Identification of antipsychotic name
Drug Formulation	Route of administration of type of antipsychotic
Strength	Dose of the Antipsychotic
Quantity	Number dispensed
Participant's Medicaid ID	Identification number of the patient
Claims data	Inpatient and Outpatient services for 295 diagnosis
Age	Age of patient
Zip code	Zip code where living
Race	Race
Prescriber ID	Prescriber identification number
Prescriber zip code	Zip code of where the prescriber resides
Prescriber county	County where the prescriber resides

HMIS Data and Security

CHAMPION PROTOCOL

In a randomized controlled design with 26 biweekly sessions over 12 months, we were funded by the National Institute of Mental Health (NIMH) to test the effectiveness of an ECHO-based intervention for improving the use of clozapine in people with treatment-resistant schizophrenia. This intervention, *Clozapine CHAMPION-ECHO (Center for Help and Assistance for Maryland Prescribers- Improving Outcomes Network using **E**xtension for **C**ommunity **H**ealthcare **O**utcomes,* is referred to as "CHAMPION." We are measuring antipsychotic prescribing before, during and after the intervention period as the primary study outcome. Statewide Medicaid data from Maryland is the prime source of prescribing data for this study.

We completed recruitment of study sites/prescribers/clinicians in 2021 and included approximately 278 prescribers. The intervention concluded in August of 2022. We have an existing Data Use Agreement for the Medicaid data component with the Hilltop Institute and MDH and that data collection is progressing as planned.

We included clinics and hospitals from around the State of Maryland, and staff and prescribers from State of Maryland inpatient psychiatric facilities also participated. Inpatient prescribing data are not contained in Maryland Medicaid prescription data. **Therefore, we must obtain inpatient prescribing records for antipsychotis (not protected health information) from the state hospital facilities via the Hospital Management Information System (HMIS).**

SCOPE OF DATA:

Time Period:
We are requesting hospital prescription records of antipsychotic prescribing from HMIS and Eastern Shore Hospital (outside HMIS)) for the dates of January 1, 2020 to July 31, 2023. This will enable us to examine prescribing patterns during three time periods:

Pre-intervention period: January 1, 2020-July 31, 2021
Intervention period: August 1, 2021 – July 31, 2022
Post-intervention period: August 1, 2022 – July 31, 2023

Variables and Acquisition:
The variables we are requesting include those in the following table and represent NO protected health information (PHI). HMIS personnel will code patient name, prescriber name and date of birth to client ID, NPI number and age, respectively. Instead of prescriber names we want to receive the prescriber NPI which will also enable a linkage to the Medicaid data we've already obtained (separate approval and data use agreement). NPI numbers are not considered protected health information (see https://npiregistry.cms.hhs.gov/search). We also do not want to receive individual patient names though if there are Medicaid identification number we would want that.

HMIS Variable	Eastern Shore Variable*
Client ID and ANR# and Medicaid ID if applicable (do not want patient name)	Entity name SS#
Sex	Gender (M/F)
Admission Date	Admiss Date
Age (recoded from DOB)	Age (recoded from DOB)
Start date of Medication	Start date and order date
DC date of Medication	
End date of Medication	Stop date
Gen name	
Strength	
Drug form	
Sig	Sig comment

Admin qty	
Prescriber NPI (Coded from prescriber name)	Prescriber NPI (Coded from Entity name (doc))
DH date (discharge date)	DH date
Location	
Inst (Institution)	
Diagnosis	
Race	

*Eastern Shore Hospital has different variable names

Data Storage and Protection:
No PHI will be sent. All downloaded data will be stored at the University of Maryland Division of Psychiatric Services Research on a virtual computer server maintained by Information Technology staff who provides these services for the University of Maryland School of Medicine, Department of Psychiatry. We have a Certificate of Confidentiality from the Federal Government that protects all research data from subpoena.

Approvals:

We have received UMB and MDH approval to collect these variables from an amendment to a fully approved IRB approved study for the collection of human subject data. We will send data to a team member with a Maryland.gov email address and no data will be shared outside the research team.

Other Data:

We will also collect deidentified prescribing data from Gladstone as they do not participate in Medicaid or HMIS. The same security provisions as above will apply.

Assessments

We will be collecting data before and after the 12- month CHAMPION. The assessments include:

1. Demographic, degree, NPI number and general information about practice and education (all participants, baseline only)
2. Multiple Choice Questions on clozapine knowledge (all participants)
3. Self-reported competence for clozapine use (prescribers only)
4. Survey on intervention (all participants, endpoint only)

STUDY TIMELINE

Our grant proposes approximately 4 years of study. In the first year, we will recruit all the study sites, set up the CHAMPION sites and finalize the CHAMPION intervention. Additionally, we will capture Medicaid data for a one-year period. In the second year, we will start the CHAMPION intervention, which will run for one full year. We will complete the administration of the intervention in the second quarter of the third year. In years 2 and 3, we will collect Medicaid data for the 12 months following the intervention, then initiate analyses. The schematic below details the approximately study timeline visually.

Year	**Year 1**				**Year 2**				**Year 3**				**Year 4**			
Quarter (Q)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**

CHAMPION PROTOCOL

Set up Medicaid Contract with Hilltop Institute																
Set up videoconferencing and iECHO																
2 Team Members trained on Project ECHO in New Mexico, ensure they have reviewed our materials and methods																
Validate the questions																
Initial meetings with BHA and OMHCs																
Organization of Project ECHO team																
Project ECHO team meetings																
Meet with OMHCs																
IRB approvals																
Period of Medicaid Data Collection 1 (After IRB approval) (Aim)1																
Website/Portal Development for REDCap																
Meet with the SAMSHA/APA group																
Uploading clozapine materials, guidelines into iECHO																
Advertising materials, BHA and CSAs send info																
Meet with all OMHCs and prescriber groups																
Send letters and emails to all prescribers/clinical team within CSA																
Install POC devices and training																
Provide ongoing POC help																
ECHO team available for phone or email consultation																

Enrollment 300 prescribers/clinical team and Pre-testing ECHO																
ECHO Lecture series announcement																
Randomization by Statistician																
OK to begin from ECHO headquarters and final check of all details																
Assessment of Baseline Knowledge and Self-Reported Efficacy (Aim 2)																
Clozapine CHAMPION ECHO Intervention																
Travel to national and regional meetings																
Analysis of Medicaid Data for primary aim																
Analysis of Secondary and Exploratory aims.																
Archive ECHO lectures for website at end of 12 months																
Period of Medicaid Data Collection 2 (Aim 1)																
Post Testing on Knowledge and Self-Reported Competence (Aim 2)																
Meetings with NASHMPD																
Analysis of Project ECHO Post data																
Make videotaped ECHOs available to all participants once 12-month Medicaid data completed.																
National Webinar with NASHMPD and APA CSS SMI																
Submit symposium abstract to national																

meetings, e.g. IPS, SIRS																
Data Repository Submission																

STATISTICAL DESIGN AND POWER

Primary Outcomes

Specific Aim 1: The primary outcome examines Maryland Medicaid (and HMIS for inpatient) prescription data, which will be used to assess the increase in the proportion of patients treated with clozapine for those in the care of prescribers/clinical team randomized to the CHAMPION relative to the ETAU condition. We will also examine persistence in the use of clozapine for patients who are prescribed clozapine under the care of prescribers/clinical team randomized to CHAMPION compared to prescribers/clinical team randomized to the ETAU. The specific outcome assessments using Medicaid data include:

a. Proportion of clozapine prescriptions: Clozapine prescribing rates will be calculated from Medicaid prescription data. National Prescriber Identification (NPI) numbers will be used to identify the antipsychotic prescription records for each prescriber in the study. The denominator will be the number of unique individuals with a diagnosis of schizophrenia who had at least 1 prescription for an antipsychotic during each time period (12 months prior to start of study, during active study participation, and 12 months after the intervention period ends). For each individual in the sample, an indicator will be created that reflects whether the person had any prescription for clozapine during each of the time periods.

b. Persistence to clozapine: Incident episodes of clozapine prescriptions will be identified by a 90 day look back period to identify a new episode of care. Persistence will be measured as the duration of the clozapine episode (in days) from the date of the first prescription record until the first gap of more than 45 days between prescriptions. Prescribing gaps will be calculated by first adding the days' supply to the dispensing date of each prescription to identify the date the prescription should be exhausted. Days that the patient is hospitalized will not be included in the calculation of episode duration. The first gap in prescribing of 46 days or more will be considered a discontinuation of the medication. An episode will only be right censored at the study endpoint, otherwise an episode can continue into the next time period. If a person has more than 1 episode of clozapine use during any time period, we will select the first episode.

Specific Aim 2: We will measure two educational outcomes: self-reported competence of prescribers/clinical team in using clozapine and knowledge associated with clozapine treatment. These will both be measured before and after the 12-month intervention period. These outcomes have been selected, because they are measurable and pilot data has already established that prescribers/clinical team will rate competence and answer questions on clozapine knowledge. In addition, we will pilot-test all questions and review the self-reported competence measure prior to the administration of the CHAMPION intervention.

a. Competence: Our measurement of competence will be based upon self-report assessment guided by Bandura's theory of self-efficacy (2, 3) and we are using a definition of competence as "the perceived self-efficacy rating of one's judgment to use clozapine"(2, 4). We will use a Visual Analog Scale (VAS) (0-100 mm) will serve as the primary outcome. Self-reported competence ratings will be evaluated for the overall use of clozapine and for each of the CHAMPION session topic areas. The VAS format has been found to be superior

to using a standard Likert scale for self-reported competence evaluation (2). Self-efficacy ratings of competence have been shown to be increased in a mental health ECHO model (6); are recommended as a measure for approaching measurement of practice outcomes (7); and, when using VAS to measure self-efficacy competence, have been found to be a reliable and valid measure for this construct (8-10).

b. Knowledge: We will use multiple-choice questions (MCQ) to assess knowledge. The knowledge-based test questions will consist of 52 questions that will cover 2 questions per 26 topic areas and will conform to best practices and guidelines for design of the questions (11). MCQ have been used to assess knowledge with ECHO models (6, 12) and are known to be a reliable and valid measure for measuring knowledge (11). The total score will range from 0-52 correct answers.

Power

Hypothesis 1: Considering the intent to treat (ITT) approach to analyses, we will be able to assess administrative data prescription records for all prescriber participants regardless of their level of participation in the CHAMPION intervention sessions or other research data collections efforts. Missing data will be a concern only for those time periods where prescriber participants were not practicing in the Maryland public health system (before or after the intervention time period). We assume that we will have administrative data records from at least 85% of the prescribers/clinical team across all time points. We calculated the needed sample size using PASS version 13 (13) for independent proportions in a clustered-randomized design with the following specifications: alpha-level = .05, power = .80, effect size (h) = .39 (small to medium) and ICC = .01 (prescribers/clinical team nested within site). Effect size is based on estimating an 11% improvement in the rate of clozapine prescribing in CHAMPION; e.g. a 4% rate of clozapine prescribing in the ETAU group and a 15% rate in the CHAMPION condition. The required sample size is 254 based on clusters of 4-5 prescribers/clinical team per site.

Hypothesis 2: Even with a conservative estimate of the number of patients per prescriber on clozapine, a high ICC (.20) for patients nested within prescriber, and a small effect (d = .3), the power to detect differences in clozapine persistence between conditions is greater than 95%.

Hypothesis 3: Although the variables for hypothesis 3 are normally distributed, the specifications are the same and the power calculations are identical to those noted above. Based on literature described in Approach section 10 above, we anticipate changes in knowledge and competence to be large (>.8).

Hypothesis 4: Using the values above and the SAS macro from O'Rourke and MacKinnon (14), the power to detect indirect effects (mediation) will be greater than .80 when using the bias corrected bootstrap procedure when paths a and b are at least 0.3 (small to medium effects anticipated).

Statistical Analyses Overview

All data will be screened for errors using frequency and contingency tables and univariate and bivariate plots before formal analysis. These informal plots and summaries will allow us to be cognizant of data distribution characteristics before building regression models. We anticipate that our dependent variables will either have a distribution that is relatively bell-shaped or can be transformed to be relatively bell-shaped. Site will be included in all models as a random effect. Prescriber is nested within intervention arm, by design, and will be specified as a random effect in all analyses that include patient level data. The intercept will be designated as random to account for the non-independence across time point when appropriate. SAS PROC MIXED or GLIMIX will be used for the analyses described below (15).

Missing Data

All analyses will be conducted within an ITT framework. As described above, missing data for hypotheses 1 and 2 will be limited due to the use of Medicaid prescription records for those outcomes. For hypotheses 3 and 4, we will compare the baseline characteristics of the prescribers/clinical team who drop out prior to completing the 12-month assessment to those prescribers/clinical team who do complete the assessment. If necessary, we will investigate how estimates/results change over a range of several plausible assumptions regarding the missing mechanism together with multiple imputations to most accurately capture existent random variability.

Multiple Comparisons

To control for Type I errors, we will use the sequential Bonferroni-type procedure for dependent hypothesis tests of Benjamini and Hochberg (16) to control the false discovery rate at 5%. The false discovery rate is the expected (or on average) proportion of falsely rejected hypotheses. This procedure will be applied to the family of tests on the multiple associated measures corresponding to each aim. We will also control for if randomized to site or individual.

Analyses for Each Specific Aim and Hypothesis

Specific Aim 1: To determine the effect of 12 months of exposure to CHAMPION on the clozapine prescribing practices of prescriber participants and the objectively measured medication persistence of the patients prescribed clozapine.

Specific Aim 1, Hypothesis 1: *Relative to the prescribers/clinical team randomized to the ETAU condition (POC and consultation), prescribers/clinical team randomized to CHAMPION will significantly increase the proportion of patients in their care who are prescribed clozapine, as assessed using Maryland Medicaid prescription data.* Clozapine prescribing will be measured as the proportion of patients with any clozapine prescriptions (See Approach 5a). We will use a mixed-effects, 2-level model generalized linear mixed model (SAS Proc GLIMIX, log link) with percent adherence as the dependent variable and treatment group (CHAMPION/ETAU), time (pre-CHAMPION year (t=1), CHAMPION year (t=2), follow-up CHAMPION year (t=3), and time by treatment group as the independent variables of interest. However, since the main outcome will be calculated at t=3, a contrast statement, within the context of the full model, will be used to compare the two treatment conditions at t = 3, controlling for baseline, to test the primary hypothesis with a random site effect to account for intra-site correlation (ICC). The test of hypothesis 1 will operationally be the test of whether the coefficient of the CHAMPION/ETAU condition term is significantly >0 (two-sided test) at time t = 3. Post hoc analyses will use the same model to test effects at t = 2.

Specific Aim 1, Hypothesis 2: *For patients who are prescribed clozapine, the patients of prescribers/clinical team randomized to CHAMPION will exhibit significantly greater persistence to clozapine treatment compared to patients of prescribers/clinical team randomized to the ETAU condition, as assessed using Maryland Medicaid prescription data.* Persistence (Approach Section 5b) will be measured as number of days of clozapine use. An episode will be identified as having begun during the 1 year prior to CHAMPION, during CHAMPION, or in the year after CHAMPION ends. A person can only have one episode in each of the time periods. We will use a generalized linear mixed-effects, 3-level model (SAS Proc GLIMIX, Poisson link), with a random site and a random prescriber effect to account for within site and within prescriber correlation (ICC). The longitudinal portion of the model will be treated as described for hypothesis 1. The test of hypothesis 2 will

operationally be the test of whether the coefficient of the CHAMPION/ETAU condition term is significantly greater than zero (two-sided test) at time 3. Post hoc analyses will use the same model to test for effects at time 2.

Specific Aim 2: To determine the effect of 12 months of exposure to the CHAMPION intervention on the knowledge and self-reported competence of prescribers/clinical team prescribing clozapine and how those mechanisms of change are associated with increased clozapine prescribing and persistence.

Specific Aim 2, Hypothesis 3: *Relative to the prescribers/clinical team randomized to the ETAU condition, prescribers/clinical team randomized to CHAMPION will demonstrate significantly increased levels of knowledge (correct number of MCQs) and self-reported competence (mean score on 0-100 mm VAS).* Knowledge and competence are continuous measures that can be assumed to be normally distributed. Transformations will be used if necessary. They will be measured at two time points (baseline and end of the 1-year CHAMPION. A General Linear Mixed Model (Proc MIXED) will be used to estimate the effects of the two groups on change in knowledge and competence with site as a random effect. The test of hypothesis 3 will operationally be the test of whether the coefficient of the CHAMPION/ETAU condition term is significantly greater than zero (two-sided test) at the post CHAMPION time point controlling for baseline. In exploratory analyses, we will examine individual competence scores related to outcomes as above while controlling for multiple comparisons.

Specific Aim 2, Hypothesis 4: *Prescriber self-reported competence will mediate the effect of the CHAMPION on clozapine prescribing and persistence.* A separate model will be used for each outcome. The independent variable will be group assignment, the dependent variable will be rate of clozapine prescribing during the year following CHAMPION and the persistence of clozapine episodes, and the mediator will be the overall self-reported competence score (0-100 mm VAS) measured at 12 months, controlling for baseline. We will use the product of coefficients approach to test mediation. The rationale behind this method is that mediation depends on the extent to which the independent variable changes the mediator (i.e., path a), and the extent to which the mediator affects the outcome variable (i.e., path b). The PROCESS (17) macro for SAS will be used to generate 95% bias corrected confidence intervals for the relative indirect effects and other parameters.

Exploratory Analyses

We will examine the role of race in moderating the effects of *CHAMPION.* To determine whether there was differential benefit of the program for the AA patients, race and interaction terms (time by race) will be added to the models described above. Despite our previous work, it is possible that increases in prescribing will not occur similarly between AA and Caucasian patients, however, we will use data collected to adapt future iterations of the topics related to AA if we do not see similar improvements in prescribing. Specifically, we will examine the two competence questions related to AA and ascertain the relationship of these specific measures to prescribing for AA and Caucasian patients. We will also look at other variables by site and patient that may contribute to outcomes and will analyze the other clinicians and examine.

We will also explore the satisfaction of the POC device to clozapine prescribing.

PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement, Characteristics, and Design

We anticipate including a total of 300 individual prescriber participants as our target enrollment but also can enroll up to 300 clinical team for the secondary analyses at approximately 60 outpatient Mental Health Clinics (OMHC) in the State of Maryland for the one-year intervention versus enhanced treatment as usual (TAU) (control) (1:1 randomization; 30 sites and 150 individual prescribers per group). This would include up to 600 people enrolled in the study. Additionally, individual prescribers not located at study sites can enroll in the study with limited benefits.

All research team members involved in this study are required to receive training in the protection of human subjects. This includes both Good Clinical Practices at University of Maryland and the Collaborative Institutional Training Initiative (CITI). All work with human subjects (State of Maryland clinicians) will be conducted by the Principal Investigators and study team at the Maryland Psychiatric Research Center (MPRC) and its affiliated team.

Source of Research Materials

Project ECHO has an application available for tracking some data for standardized data collection and programming. We will use **iECHO,** a teleECHO clinic management application that is provided by the University of New Mexico to streamline information about clinic participation, reference material, continuing medical education materials (CME), etc. iECHO is the web-based, proprietary teleECHO program management software and database developed and managed by the ECHO Institute. Due to its key role in tracking the movement, iECHO usage is mandatory for partners conducting Project ECHO activities. Non-exclusive right and license to use iECHO in conducting Project ECHO activities is provided to each partner at no cost per the Project ECHO Intellectual Property Terms of Use Agreement. The software will specifically organize, manage, track, and report on the programmatic components of our Clozapine CHAMPION ECHO. iECHO is not designed to store Protected Heath Information (PHI) and PHI will never be entered into iECHO. The specific data collected includes program administrative data, attendance records for participants and facilitators, case presentation metrics, didactic presentations, and program documents. iECHO organizes data into 4 primary categories: organizations, contacts, programs, and resources.

Additionally, prescriber self-reported competence and knowledge assessments will be completed and entered into a secured web-based database to which all prescribers/clinical team will be granted access through a secure link in REDCap. Prescribers/clinical team will be given access to enter the system through a secure remote, web-based portal. Once in the system, they will be able to access the informational sheet They will also complete the baseline and 12-month Multiple Choice Questions (MCQ) and the Clozapine Competence Visual Analog Scale (VAS) assessments. This system will be backed up by routine project-copy and downloaded as a structured .csv file on a monthly basis. Each account will have a secure login and password and a centralized person from the Education Core to be available to answer and help with all login and data entry queries.

Additionally, for those participating in CHAMPION, we can administer the session evaluations needed to earn CME (or CEU) credits. We will include here the link for the Cloud CME assessments that may be earned at each of the 26 sessions (http://cloud-cme.com/).

We will be collecting demographic and some basic information on training and employment from prescribers/clinical team. We will plan to collect 1) current age, 2) current employment status, 3) current educational attainment and type of practitioner, 4) sex, 5) years in practice, 6) ethnicity, and other demographic variables related to education and practice. We will collect contact information and will specify in the informational sheet that we will be sending reminders and information by email, phone or text.

All forms are identified within this database by a unique participant ID number, participant initials, protocol ID number and acronym, together with the protocol phase and visit. The protocol data collection schedule is kept in a database table and is used to monitor the progress of participants through the protocol, missing assessments, and other protocol deviations during the study. Data entry screens incorporate range checks or lists of valid responses for each item. Prescriber confidentiality is maintained by restricting study data access to specified study personnel. Most authorized personnel will have read-only access and write/edit access will be restricted to data entry and data management staff assigned to the study. An electronic audit trail records all changes to the database once data have been entered. The database resides on a cloud-based server, and all server data are backed up several times weekly. Access to the server from outside the MPRC is restricted by a firewall. Norton Anti-Virus software, updated automatically whenever new virus data files are provided, is installed on the server and all computers are linked to the server. For HMIS data no identifying data will be collected outside MDThink.

Separately, as the primary aim revolves around the change in clozapine prescribing, we will partner with the Hilltop Institute to obtain prescriptions of clozapine from prescribers/clinical team located at OMHCs with those of prescribers/clinical team from enhanced TAU sites in the State of Maryland. These datasets will be captured in HIPAA-compliant database and transferred securely via Accellion (UMB secure file transfer protocol, FTP) to the MPRC and the Division for Psychiatric Services Research at UMB, were they will be stored in HIPAA-compliant manner.

Potential Risks and Protections Against Risks

Prescriber participant risks associated with the study are minimal.

Participation in the CHAMPION sessions: Participation in the sessions may be tiring or boring. The sessions involve a time component of about 1.25 hours and this could be challenging to busy clinicians or jeopardize billing time to clinicians and offices. It is possible prescribers/clinical team may feel embarrassed if they ask questions and show their lack of knowledge in front of other prescriber peers. These are not mandatory.

Study assessments: The participant will be reminded that they can refuse to answer any question that makes them uncomfortable. Prescribers/clinical team may feel inadequate or embarrassed if they do not know answers to the questions. There is a slight risk of breach of confidentiality. All data will be coded with an ID number that is unique. All data will be labeled by ID only. Only the study team will have access to the link between the ID and participant's name. Data containing names and personal information will never be included in published materials.

Medicaid data: There is a slight risk of breach of confidentiality. All data will be coded with a unique ID number. All data will be labeled by ID only and all data will be carefully transferred and stored. Only the study team will have access to the link between the ID and participant's name. Data containing names and personal information will never be included in published materials.

Recruitment and Informational Sheet

Recruitment procedures have been described in the Recruitment and Retention Plan above.

Enrollmentwill occur electronically. The State of Maryland IRB will rely on the UMB IRB for this study. The informational sheet contains the risks and benefits of the study, but participants are not required to sign. The

participant is free to withdraw from the study at any time. Prescribers/clinical team will be informed in the informational sheet that the information they provide will be kept confidential except within the research team and how that confidentiality will be ensured. They will be told that their records are filed by a number, not by name, and that all records are kept in secure servers or locked files accessible only to research personnel.

Protection Against Risk: Participants and their data are safeguarded from undue risk by procedures listed in the informational sheet which describes how we ensure confidentiality and minimize possible risks associated with the study. Each is described below.

a) *Informational Sheet*: This study if considered exempt will not require informed consent. We will, however, provide an informational sheet where participants will be advised fully of the study procedures, the amount of time required of them, the possible risks and benefits, the voluntary nature of their participation, their right to refuse participation without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator. The informational sheet will state that that we may share de-identified subject data with a clinical trial data repository maintained by the National Institute of Mental Health, using procedures outlined in NIH NOT-MH-14-015 (http://grants1.nih.gov/grants/guide/notice-files/NOT-MH-14-015.html). This repository will allow other researchers access to data from this clinical trial, with the assurance that the participant's individual name or other identifying information will not be included in the data shared with other researchers.

b) *Confidentiality*: In the informational sheet participants will be told that the information they provide, and all findings will be kept strictly confidential, with access limited to the research staff, with one exception: state or federal regulatory personnel and legal advocacy organizations authorized by law will have access to review records. Data collected with identifying information will be stored in locked cabinets or in password-protected computer files. Participant identity will not be revealed in the presentation or publication of any results. All staff working on the project will be educated about the importance of strictly respecting patient confidentiality.

c) *Research Procedures*: Described above are the potential risks of the research procedures and specific measures to minimize each of those risks. Below are general safeguards that will be used to minimize risks. These include termination of participants from research participation if it is believed that such participation endangers their welfare.

Potential Benefits of the Proposed Research to Human Subjects and Others

Benefits to Maximize Enrollment

Reaching our recruitment goals is paramount to our success. We have many strategies in place to reach our participant enrollment goals. This summarizes the benefits that will be given to maximize the likelihood that busy prescribers/clinical team will participate:

1) All participating sites will receive the POC ANC monitoring device. Athelas, the company will give each clinic at no charge and will help with sites for Medicaid billing so that sites can receive compensation for patients enrolled
2) All participating sites and individual prescribers will receive a centralized phone number and email for questions and consultation advice from the clozapine team
3) All participating sites will receive a laptop to ensure that, if randomized, they can participate in the telementoring CHAMPION sessions and if not randomized, has a means to complete the baseline and endpoint assessments and use for watching CHAMPION sessions when granted permission at the end of this study.

4) All prescriber participants that complete the baseline and 12-month competence and knowledge assessments will receive compensation for their time and effort to complete these assessments. For other team members participating (nonprescriber) knowledge and competence is optional. They will also receive compensation for time and effort.
5) All prescribers/clinical team randomized to CHAMPION can get 1.25 PRA Category 1 CME (or equivalent CEU credits) for participation. These will be available online through https:/cloud-cme.com
6) All sites randomized to the CHAMPION will receive a stipend for snacks and drinks and organizing the CHAMPION sessions.
7) All sites will receive the Clozapine Handbook authored by Jonathan Meyer and Stephen Stahl.

Thus, we feel as if we have created an exciting opportunity for sites to participate and have several enhanced pieces included to maximize recruitment and eliminate the logistics of getting weekly ANC blood draws.

The prescribers/clinical team that are randomized to the CHAMPION have the benefit of improving knowledge and self-reported competence with clozapine through active discussion, interactions and cases. Others have reported the benefits of the social environment for the prescribers/clinical team. They are included together in one virtual room where everyone can interact. This social environment has benefits of camaraderie and satisfaction. Other benefits reported have been increased career satisfaction and improved staff interactions and communication. Lastly, the benefits include time savings on complex cases that would involve coordination for referral or phone calls under other circumstances.

However, the indirect benefits to patients with serious mental illness and psychotic disorders in the State of Maryland are more considerable, as we believe that this study will increase prescriber self-reported competence and use of this superior antipsychotic medication. Patients may receive clozapine trials or be maintained more successfully than in the past. This could improve outcomes and may decrease hospitalizations and emergency room visits. It may lead to better job productivity and a host of other possible outcomes known to be associated with the path to remission and recovery. Also, unnecessary treatments with non-evidence-based treatments and long wait times for care could all be improved.

While financial compensation will be provided for the time and effort that participants provide and a stipend to the sites to organize snacks at the time of the CHAMPION, this is not considered a benefit of study participation.

Importance of the Knowledge to Be Gained

The risks that this study poses to participants are reasonable in relation to the anticipated benefits and potential heuristic value of the research. This study has the potential to improve clozapine prescribing, improve lives of many patients and decrease overall health system costs. We will learn if an ECHO intervention, CHAMPION, is effective for improving clozapine prescribing and we will understand if this effect can be mediated by prescriber self-reported competence scores. Given the importance of the information to be gained and the low risks, we feel this project has a high importance on knowledge to be gained.

We believe the risks of this study are far outweighed by the potential benefits to the participants and their patients with schizophrenia and that this will demonstrate an effective and sustainable way to improve the treatment of these patients

Data and Safety Monitoring Plan

This study puts forth a randomized double-blind trial where prescribers/clinical team of antipsychotic medications will be the enrolled population. The study is an educational intervention and no biophysiological intervention will be performed; being a minimal risk study. No Data Safety Monitoring Board (DSMB) is required but the PI and team will monitor this study as described below.

Roles and Responsibilities

The DSMP holds the Principal Investigator (PI) responsible for overall data and safety monitoring, sharing her responsibility with coinvestigators. The PI will review trial data yearly at minimum but will review any and all safety or confidentiality issues promptly should they arise. We will have an ombudsmen for this study. This will allow prescribers/clinical team at sites to report if they feel they have issues with other participants during the videoconferencing calls. These complaints will be brought to the PI and committee to discuss and a plan made for addressing any problems within 7 days of the complaint. We will also have a full-time coordinator who will manage and ensure participants receive CME and stipends in a timely fashion.

Reportable Events

Serious adverse events, unexpected adverse events, and non-serious adverse events will be reported according to NIH/NIMH, University of Maryland, and Federal guidelines. The PI and will receive all SAE reports within 24 hours of their occurrence (albeit unlikely). All serious adverse events (SAEs) will be reported to the PI, the University of Maryland School of Medicine IRB, if required by IRB guidelines, and the appropriate NIMH program officer per University and Federal regulations. If the incidence of any reported problem or event occurs, we will examine all as we do not anticipate adverse events or side effects as with a pharmacologic intervention. In the event any pattern emerges in either treatment group, the PI and coinvestigators will determine whether possible protocol modifications are required to minimize the further occurrence of such events.

Clinical Trials.Gov Requirements

The study will be registered on ClinicalTrials.gov prior to the enrollment of prescriber participants.

Inclusion or women, minorities and children

This project specifically targets clozapine prescribing. As such, only persons who are old enough to have completed medical, nurse practitioner, physician assistant, or other relevant health care training and provide mental health care to patients in Maryland will be eligible for inclusion. Thus, children shall be excluded from this study and we will target the ranges of 22 -85 years to cover the range of prescribers/clinical team in the State of Maryland. This study does not involve any biophysiological interventions, so there are no issues with including women regardless of reproductive status. Women and minority prescribers/clinical team will be eligible for recruitment and inclusion. We estimate that, based on available gender data for psychiatrists and nurse practitioners, approximately 40-50% of those eligible for enrollment will be women providers. Although Maryland is a state diverse in ethnicity, a better indicator of minority provider estimates would be the nationwide data on prescribers/clinical team with our state ethnicity breakdown taken into account. Thus, we estimate potential recruitment of up to 8% Hispanic, 20% Black, 18% Asian, and smaller percentages of American India and Hawaiian Pacific Islanders. All efforts will be made to include women and minorities in this study.

Compensation

All prescriber participants who enroll will receive $100 by check, cash or giftcard after the baseline and the 12-month assessments ($200 total) at the conclusion of the CHAMPION for their time completing thee knowledge and competence assessments. All non-prescriber clinicians receive $25 for their participation at each assessment ($50 total). Each site will receive a POC monitoring device and laptop and each site will be given a stipend of $1000 at the beginning when three prescribers have been enrolled at the site. This is approximately $40 for drinks and food for each session, or in the case of being in the ETAU group for group snacks as well. Individual prescribers who enroll and are not affiliated with an enrolled site will be eligible for the CME/CEU credits, and will receive the $100 compensation at the beginning and end of the study ($200 total).

Consultation Service (Not part of research aims)

As a service component to support the project, a consultation phone line and email address will allow participants in the study and other people outside the study to ask for advice or questions. This service is not part of the study aims of this research study. We maintain information on callers around the state for purposes of returning calls and quality improvement. All calls will be answered or sent to an expert to help answer. For quality improvement purposes we will track number of calls and types of calls. This information could be used to improve call procedures and provide the best ways to help with specific clozapine questions.

REFERENCES:

1. Chong HY, Teoh SL, Wu DB, Kotirum S, Chiou CF, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr Dis Treat. 2016;12:357-73.
2. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry. 1999;156(7):990-9.
3. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry. 2001;158(4):518-26.
4. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. Schizophr Res. 2002;56(1-2):1-10.
5. Moncrieff J. Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. Br J Psychiatry. 2003;183:161-6.
6. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J, Association AP, Guidelines SCoP. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(2 Suppl):1-56.
7. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RS, Davis CE, Severe J, Hsiao JK, Investigators C. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163(4):600-10.
8. Moore TA, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, Essock SM, Finnerty M, Marder SR, Miller DD, McEvoy JP, Robinson DG, Schooler NR, Shon SP, Stroup TS, Miller AL. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry. 2007;68(11):1751-62.

9. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71-93.
10. Barnes TR. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2011;25(5):567-620.
11. Citrome L. A systematic review of meta-analyses of the efficacy of oral atypical antipsychotics for the treatment of adult patients with schizophrenia. Expert Opin Pharmacother. 2012;13(11):1545-73.
12. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-62.
13. Osser DN, Roudsari MJ, Manschreck T. The psychopharmacology algorithm project at the Harvard South Shore Program: an update on schizophrenia. Harv Rev Psychiatry. 2013;21(1):18-40.
14. Sinclair D, Adams CE. Treatment resistant schizophrenia: a comprehensive survey of randomised controlled trials. BMC Psychiatry. 2014;14:253.
15. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the Pharmacotherapy of Schizophrenia in Adults. Can J Psychiatry. 2017;62(9):604-16.
16. Psychosis and schizophrenia in adults: prevention and management; National Clinical Practice Guidelines Number CG178National Institute for Clinical Excellence (NICE) 2014 January 21, 2019: Available from: https://www.nice.org.uk/guidance/CG178.
17. Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. Clin Schizophr Relat Psychoses. 2012;6(3):134-44.
18. Torrey EF, Knable M, Quanbeck C, Davis J. Clozapine for Treating Schizophrenia: A Comparison Of The StatesTreatment Advocacy Center 2015: Available from: https://www.treatmentadvocacycenter.org/evidence-and-research/studies.
19. Goren JL, Meterko M, Williams S, Young GJ, Baker E, Chou CH, Kilbourne AM, Bauer MS. Antipsychotic prescribing pathways, polypharmacy, and clozapine use in treatment of schizophrenia. Psychiatr Serv. 2013;64(6):527-33.
20. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res. 2012;138(1):18-28.
21. Velligan DI, Carroll C, Lage MJ, Fairman K. Outcomes of medicaid beneficiaries with schizophrenia receiving clozapine only or antipsychotic combinations. Psychiatr Serv. 2015;66(2):127-33.
22. Fayek M, Flowers C, Signorelli D, Simpson G. Psychopharmacology: underuse of evidence-based treatments in psychiatry. Psychiatr Serv. 2003;54(11):1453-4, 6.
23. Kelly DL, Dixon LB, Kreyenbuhl JA, Medoff D, Lehman AF, Love RC, Brown CH, Conley RR. Clozapine utilization and outcomes by race in a public mental health system: 1994-2000. J Clin Psychiatry. 2006;67(9):1404-11.
24. O'Brien A. Starting clozapine in the community: a UK perspective. CNS Drugs. 2004;18(13):845-52.
25. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol. 2010;24(7):965-71.
26. Katzman JG, Galloway K, Olivas C, McCoy-Stafford K, Duhigg D, Comerci G, Kalishman S, Buckenmaier CC, McGhee L, Joltes K, Bradford A, Shelley B, Hernandez J, Arora S. Expanding Health Care Access Through Education: Dissemination and Implementation of the ECHO Model. Mil Med. 2016;181(3):227-35.
27. Sequist TD. Ensuring equal access to specialty care. N Engl J Med. 2011;364(23):2258-9.
28. Ball S, Wilson B, Ober S, McHaourab A. SCAN-ECHO for Pain Management: Implementing a Regional Telementoring Training for Primary Care Providers. Pain Med. 2018;19(2):262-8.

29. Wood BR, Unruh KT, Martinez-Paz N, Annese M, Ramers CB, Harrington RD, Dhanireddy S, Kimmerly L, Scott JD, Spach DH. Impact of a Telehealth Program That Delivers Remote Consultation and Longitudinal Mentorship to Community HIV Providers. Open Forum Infect Dis. 2016;3(3):ofw123.
30. Zhou C, Crawford A, Serhal E, Kurdyak P, Sockalingam S. The Impact of Project ECHO on Participant and Patient Outcomes: A Systematic Review. Acad Med. 2016;91(10):1439-61.
31. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, Bloomfield MA, Bressan RA, Buchanan RW, Carpenter WT, Castle DJ, Citrome L, Daskalakis ZJ, Davidson M, Drake RJ, Dursun S, Ebdrup BH, Elkis H, Falkai P, Fleischacker WW, Gadelha A, Gaughran F, Glenthoj BY, Graff-Guerrero A, Hallak JE, Honer WG, Kennedy J, Kinon BJ, Lawrie SM, Lee J, Leweke FM, MacCabe JH, McNabb CB, Meltzer H, Moller HJ, Nakajima S, Pantelis C, Reis Marques T, Remington G, Rossell SL, Russell BR, Siu CO, Suzuki T, Sommer IE, Taylor D, Thomas N, Ucok A, Umbricht D, Walters JT, Kane J, Correll CU. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry. 2017;174(3):216-29.
32. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45(9):789-96.
33. Warnez S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry. 2014;14:102.
34. Okhuijsen-Pfeifer C, Huijsman EAH, Hasan A, Sommer IEC, Leucht S, Kahn RS, Luykx JJ. Clozapine as a first- or second-line treatment in schizophrenia: a systematic review and meta-analysis. Acta Psychiatr Scand. 2018;138(4):281-8.
35. Excellence NIfHaC. Psychosis and Schizophrenia in Adults: Prevention and Management. 2014.
36. Argo T, Crismon M, Miller A, Moore T, Bendele S, Suehs B. Texas Medication Algorithm Project Procedural Manual: Schizophrenia AlgorithmAustin: Texas Department of State Health Services 2008 January 31, 2019: Available from: . https://jpshealthnet.org/sites/default/files/tmapalgorithmforschizophrenia.pdf.
37. Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, Remington G. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. J Clin Psychiatry. 2011;72(11):1439-44.
38. Conley RR, Kelly DL, Lambert TJ, Love RC. Comparison of clozapine use in Maryland and in Victoria, Australia. Psychiatr Serv. 2005;56(3):320-3.
39. Lieberman JA. Maximizing clozapine therapy: managing side effects. J Clin Psychiatry. 1998;59 Suppl 3:38-43.
40. Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. J Clin Psychiatry. 2003;64(1):30-4.
41. Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration--New York metropolitan region. Schizophr Bull. 2002;28(1):31-42.
42. Xiang YT, Wang CY, Si TM, Lee EH, He YL, Ungvari GS, Chiu HF, Shinfuku N, Yang SY, Chong MY, Kua EH, Fujii S, Sim K, Yong MK, Trivedi JK, Chung EK, Udomratn P, Chee KY, Sartorius N, Dixon LB, Kreyenbuhl JA, Tan CH. Clozapine use in schizophrenia: findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. Aust N Z J Psychiatry. 2011;45(11):968-75.
43. Bachmann CJ, Aagaard L, Bernardo M, Brandt L, Cartabia M, Clavenna A, Coma Fusté A, Furu K, Garuoliené K, Hoffmann F, Hollingworth S, Huybrechts KF, Kalverdijk LJ, Kawakami K, Kieler H, Kinoshita T, López SC, Machado-Alba JE, Machado-Duque ME, Mahesri M, Nishtala PS, Piovani D, Reutfors J, Saastamoinen LK, Sato I, Schuiling-Veninga CCM, Shyu YC, Siskind D, Skurtveit S, Verdoux H, Wang LJ, Zara Yahni C, Zoëga H, Taylor D. International trends in clozapine use: a study in 17 countries. Acta Psychiatr Scand. 2017;136(1):37-51.
44. Torrey EF, Knable, M.B., Quanbeck, C., Davis, J.M. Clozapine for Treating Schizophrenia: A Comparison Of The States. Treatment Advocacy Center: Affairs OoRaP; 2015.

45. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry. 2012;201(6):481-5.
46. Alessi-Severini S, Le Dorze JA, Nguyen D, Honcharik P, Eleff M. Clozapine prescribing in a Canadian outpatient population. PLoS One. 2013;8(12):e83539.
47. Thien K, O'Donoghue B. Delays and barriers to the commencement of clozapine in eligible people with a psychotic disorder: A literature review. Early Interv Psychiatry. 2019;13(1):18-23.
48. Heald A, Livingston M, Yung A, De Hert MA. Prescribing in schizophrenia and psychosis: Increasing polypharmacy over time. Hum Psychopharmacol. 2017;32(2).
49. Misawa F, Shimizu K, Fujii Y, Miyata R, Koshiishi F, Kobayashi M, Shida H, Oguchi Y, Okumura Y, Ito H, Kayama M, Kashima H. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects?: a cross-sectional study. BMC Psychiatry. 2011;11:118.
50. Mallinger JB, Fisher SG, Brown T, Lamberti JS. Racial disparities in the use of second-generation antipsychotics for the treatment of schizophrenia. Psychiatr Serv. 2006;57(1):133-6.
51. Copeland LA, Zeber JE, Valenstein M, Blow FC. Racial disparity in the use of atypical antipsychotic medications among veterans. Am J Psychiatry. 2003;160(10):1817-22.
52. Kelly DL, Kreyenbuhl J, Dixon L, Love RC, Medoff D, Conley RR. Clozapine underutilization and discontinuation in African Americans due to leucopenia. Schizophr Bull. 2007;33(5):1221-4.
53. Moeller FG, Chen YW, Steinberg JL, Petty F, Ripper GW, Shah N, Garver DL. Risk factors for clozapine discontinuation among 805 patients in the VA hospital system. Ann Clin Psychiatry. 1995;7(4):167-73.
54. Pai NB, Vella SC. Reason for clozapine cessation. Acta Psychiatr Scand. 2012;125(1):39-44.
55. Das-Munshi J, Bhugra D, Crawford MJ. Ethnic minority inequalities in access to treatments for schizophrenia and schizoaffective disorders: findings from a nationally representative cross-sectional study. BMC Med. 2018;16(1):55.
56. Paz Z, Nails M, Ziv E. The genetics of benign neutropenia. Isr Med Assoc J. 2011;13(10):625-9.
57. Crosslin DR, McDavid A, Weston N, Nelson SC, Zheng X, Hart E, de Andrade M, Kullo IJ, McCarty CA, Doheny KF, Pugh E, Kho A, Hayes MG, Pretel S, Saip A, Ritchie MD, Crawford DC, Crane PK, Newton K, Li R, Mirel DB, Crenshaw A, Larson EB, Carlson CS, Jarvik GP. Genetic variants associated with the white blood cell count in 13,923 subjects in the eMERGE Network. Hum Genet. 2012;131(4):639-52.
58. Nalls MA, Wilson JG, Patterson NJ, Tandon A, Zmuda JM, Huntsman S, Garcia M, Hu D, Li R, Beamer BA, Patel KV, Akylbekova EL, Files JC, Hardy CL, Buxbaum SG, Taylor HA, Reich D, Harris TB, Ziv E. Admixture mapping of white cell count: genetic locus responsible for lower white blood cell count in the Health ABC and Jackson Heart studies. Am J Hum Genet. 2008;82(1):81-7.
59. Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. A map of human genome variation from population-scale sequencing. Nature. 2010;467(7319):1061-73.
60. Reich D, Nalls MA, Kao WH, Akylbekova EL, Tandon A, Patterson N, Mullikin J, Hsueh WC, Cheng CY, Coresh J, Boerwinkle E, Li M, Waliszewska A, Neubauer J, Li R, Leak TS, Ekunwe L, Files JC, Hardy CL, Zmuda JM, Taylor HA, Ziv E, Harris TB, Wilson JG. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. PLoS Genet. 2009;5(1):e1000360.
61. Thobakgale CF, Ndung'u T. Neutrophil counts in persons of African origin. Curr Opin Hematol. 2014;21(1):50-7.
62. Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? J Lab Clin Med. 1999;133(1):15-22.
63. Denic S, Showqi S, Klein C, Takala M, Nagelkerke N, Agarwal MM. Prevalence, phenotype and inheritance of benign neutropenia in Arabs. BMC Blood Disord. 2009;9:3.
64. Richardson CM, Davis EA, Vyas GR, DiPaula BA, McMahon RP, Kelly DL. Evaluation of the Safety of Clozapine Use in Patients With Benign Neutropenia. J Clin Psychiatry. 2016;77(11):e1454-e9.
65. Kelly DL, Ben-Yoav H, Payne GF, Winkler TE, Chocron SE, Kim E, Kitchen C, Stock V, Vyas G, Love RC, Wehring HJ, Sullivan KM, Feldman S, Liu F, McMahon RP, Ghodssi R. Blood Draw Barriers for

Treatment with Clozapine and Development of a Point-of-Care Monitoring Device. Clin Schizophr Relat Psychoses. 2018;12(1):23-30.
66. Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. Acta Psychiatr Scand. 2014;130(1):16-24.
67. Tungaraza TE, Farooq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. Ther Adv Psychopharmacol. 2015;5(2):88-96.
68. Mustafa FA, Burke JG, Abukmeil SS, Scanlon JJ, Cox M. "Schizophrenia past clozapine": reasons for clozapine discontinuation, mortality, and alternative antipsychotic prescribing. Pharmacopsychiatry. 2015;48(1):11-4.
69. Taylor D, Shapland L, Laverick G, Bond J, Munro J. Clozapine - a survey of patient perceptions. The Psychiatrist. 2000;24(12):450-2.
70. Hodge K, Jespersen S. Side-effects and treatment with clozapine: a comparison between the views of consumers and their clinicians. Int J Ment Health Nurs. 2008;17(1):2-8.
71. Farooq S, Choudry A, Cohen D, Naeem F, Ayub M. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. BJPsych Bull. 2019;43(1):8-16.
72. Verdoux H, Quiles C, Bachmann CJ, Siskind D. Prescriber and institutional barriers and facilitators of clozapine use: A systematic review. Schizophr Res. 2018;201:10-9.
73. Freudenreich O, Henderson DC, Sanders KM, Goff DC. Training in a clozapine clinic for psychiatry residents: a plea and suggestions for implementation. Acad Psychiatry. 2013;37(1):27-30.
74. Falzer PR, Garman DM. Optimizing clozapine through clinical decision making. Acta Psychiatr Scand. 2012;126(1):47-58.
75. Curry B, Palmer E, Mounce C, Smith G, Shah V. Assessing prescribing practices of clozapine before and after the implementation of an updated risk evaluation and mitigation strategy. Ment Health Clin. 2018;8(2):63-7.
76. Farhadian S, Yee MV, Christopher ML. Fostering the use of clozapine in the severely mentally ill through academic detailing. Mental Health Clinician. 2011;1(5):94-8.
77. Carruthers J, Radigan M, Erlich MD, Gu G, Wang R, Frimpong EY, Essock SM, Olfson M, Castillo EG, Miller GA, Sederer LI, Stroup TS. An Initiative to Improve Clozapine Prescribing in New York State. Psychiatr Serv. 2016;67(4):369-71.
78. Goren JL, Rose AJ, Engle RL, Smith EG, Christopher ML, Rickles NM, Semla TP, McCullough MB. Organizational Characteristics of Veterans Affairs Clinics With High and Low Utilization of Clozapine. Psychiatr Serv. 2016;67(11):1189-96.
79. Giguere A, Legare F, Grimshaw J, Turcotte S, Fiander M, Grudniewicz A, Makosso-Kallyth S, Wolf FM, Farmer AP, Gagnon MP. Printed educational materials: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2012;10:CD004398.
80. Forsetlund L, Bjorndal A, Rashidian A, Jamtvedt G, O'Brien MA, Wolf F, Davis D, Odgaard-Jensen J, Oxman AD. Continuing education meetings and workshops: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2009(2):CD003030.
81. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, O'Brien MA, Johansen M, Grimshaw J, Oxman AD. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2012(6):CD000259.
82. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, Forsetlund L, Bainbridge D, Freemantle N, Davis DA, Haynes RB, Harvey EL. Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2007(4):CD000409.
83. Stetler CB, Damschroder LJ, Helfrich CD, Hagedorn HJ. A Guide for applying a revised version of the PARIHS framework for implementation. Implement Sci. 2011;6:99.
84. Arora S, Geppert CM, Kalishman S, Dion D, Pullara F, Bjeletich B, Simpson G, Alverson DC, Moore LB, Kuhl D, Scaletti JV. Academic health center management of chronic diseases through knowledge networks: Project ECHO. Acad Med. 2007;82(2):154-60.

85. Arora S, Kalishman SG, Thornton KA, Komaromy MS, Katzman JG, Struminger BB, Rayburn WF. Project ECHO: A Telementoring Network Model for Continuing Professional Development. J Contin Educ Health Prof. 2017;37(4):239-44.
86. Project ECHO Hubs (Global)University of New Mexico January 19, 2019: Available from: https://echo.unm.edu/locations-2/echo-hubs-superhubs-global/.
87. Arora S, Kalishman S, Thornton K, Dion D, Murata G, Deming P, Parish B, Brown J, Komaromy M, Colleran K. Expanding access to hepatitis C virus treatment—Extension for Community Healthcare Outcomes (ECHO) project: disruptive innovation in specialty care. Hepatology. 2010;52(3):1124-33.
88. Pajares F, Hartley J, Valiante G. Response format in writing self-efficacy assessment: Greater discrimination increases prediction. Measurement and evaluation in counseling and development. 2001;33(4):214.
89. Sockalingam S, Arena A, Serhal E, Mohri L, Alloo J, Crawford A. Building provincial mental health capacity in primary care: an evaluation of a project ECHO mental health program. Academic Psychiatry. 2018;42(4):451-7.
90. Cofta-Woerpel L, Lam C, Reitzel LR, Wilson W, Karam-Hage M, Beneventi D, Cofer J, Baker E, Wetter DW, Cinciripini PM, Blalock J. A tele-mentoring tobacco cessation case consultation and education model for healthcare providers in community mental health centers. Cogent Med. 2018;5(1).
91. Lewiecki EM, Rochelle R, Bouchonville MF, 2nd, Chafey DH, Olenginski TP, Arora S. Leveraging Scarce Resources With Bone Health TeleECHO to Improve the Care of Osteoporosis. J Endocr Soc. 2017;1(12):1428-34.
92. Anderson D, Zlateva I, Davis B, Bifulco L, Giannotti T, Coman E, Spegman D. Improving Pain Care with Project ECHO in Community Health Centers. Pain Med. 2017;18(10):1882-9.
93. Gordon SE, Dufour AB, Monti SM, Mattison ML, Catic AG, Thomas CP, Lipsitz LA. Impact of a Videoconference Educational Intervention on Physical Restraint and Antipsychotic Use in Nursing Homes: Results From the ECHO-AGE Pilot Study. J Am Med Dir Assoc. 2016;17(6):553-6.
94. Hager B, Hasselberg M, Arzubi E, Betlinski J, Duncan M, Richman J, Raney LE. Leveraging Behavioral Health Expertise: Practices and Potential of the Project ECHO Approach to Virtually Integrating Care in Underserved Areas. Psychiatr Serv. 2018;69(4):366-9.
95. Komaromy M, Bartlett J, Manis K, Arora S. Enhanced Primary Care Treatment of Behavioral Disorders With ECHO Case-Based Learning. Psychiatr Serv. 2017;68(9):873-5.
96. Stewart RW, Whiteman LN, Strouse JJ, Carroll CP, Lanzkron S. Improving Inpatient Care for Individuals with Sickle Cell Disease Using the Project ECHO Model. South Med J. 2016;109(9):568-9.
97. Sayre GG, Haverhals LM, Ball S, Stevenson L, Battaglia C, Aron DC, Kirsh S, Helfrich CD, Au D. Adopting SCAN-ECHO: The providers' experiences. Healthc (Amst). 2017;5(1-2):29-33.
98. Sethi MS, Meena K, Krishnamurthy S, Agrawal S, Xavier B. Hybrid Training: e-learning model in Promotion of Mental Health. Journal of Mental Health Education. 2017(1):1-4.
99. Sockalingam S, Arena A, Serhal E, Mohri L, Alloo J, Crawford A. Building Provincial Mental Health Capacity in Primary Care: An Evaluation of a Project ECHO Mental Health Program. Acad Psychiatry. 2018;42(4):451-7.
100. Bandura A. Guide for constructing self-efficacy scales. Self-efficacy beliefs of adolescents. 2006;5(1):307-37.
101. Kelly DL, Freudenreich O, Sayer MA, Love RC. Addressing Barriers to Clozapine Underutilization: A National Effort. Psychiatr Serv. 2018;69(2):224-7.
102. Love RC, Kelly DL, Freudenreich O, Sayer M, Sanders KM, McLean MF, Adair DK, Hepburn B, Sims B, Walker AJ, Gordon SY. Clozapine underutilization:Addressing the barriersNational Association of State Mental Health Porgram Directors (NASMHPD) 2016 January 30, 2019: Available from: http://www.nasmhpd.org/sites/default/files/Assessment%201_Clozapine%20Underutilization.pdf.
103. Quick Facts: MarylandUnited States Census Bureau January 18, 2019: Available from: https://www.census.gov/quickfacts/fact/table/md/PST045217.
104. Petterson SM, Rayburn WF, Liaw WR. When Do Primary Care Physicians Retire? Implications for Workforce Projections. Ann Fam Med. 2016;14(4):344-9.

105. Moore Jr DE, Green JS, Gallis HA. Achieving desired results and improved outcomes: integrating planning and assessment throughout learning activities. Journal of continuing education in the health professions. 2009;29(1):1-15.
106. Stewart J, O'halloran C, Barton JR, Singleton SJ, Harrigan P, Spencer J. Clarifying the concepts of confidence and competence to produce appropriate self-evaluation measurement scales. Medical education. 2000;34(11):903-9.
107. Murdock JE, Neafsey PJ. Self-efficacy measurements: an approach for predicting practice outcomes in continuing education? The Journal of Continuing Education in Nursing. 1995;26(4):158-65.
108. Turner NM, Van De Leemput AJ, Draaisma JM, Oosterveld P, Ten Cate OTJ. Validity of the visual analogue scale as an instrument to measure self-efficacy in resuscitation skills. Medical education. 2008;42(5):503-11.
109. May BA, Limandri BJ. Instrument development of the self-efficacy scale for abused women. Research in nursing & health. 2004;27(3):208-14.
110. Kalichman SC, Cain D, Fuhrel A, Eaton L, Di Fonzo K, Ertl T. Assessing medication adherence self-efficacy among low-literacy patients: development of a pictographic visual analogue scale. Health Education Research. 2004;20(1):24-35.
111. Al-Rukban MO. Guidelines for the construction of multiple choice questions tests. J Family Community Med. 2006;13(3):125-33.
112. Beste LA, Mattox EA, Pichler R, Young BA, Au DH, Kirsh SF, Germani MW, Hedeen A, Harp BK, Chang MF. Primary Care Team Members Report Greater Individual Benefits from Long- Versus Short-Term Specialty Telemedicine Mentorship. Telemed J E Health. 2016;22(8):699-706.
113. Colleran K, Harding E, Kipp BJ, Zurawski A, MacMillan B, Jelinkova L, Kalishman S, Dion D, Som D, Arora S. Building capacity to reduce disparities in diabetes: training community health workers using an integrated distance learning model. Diabetes Educ. 2012;38(3):386-96.
114. Bouchonville MF, Hager BW, Kirk JB, Qualls CR, Arora S. Endo Echo Improves Primary Care Provider and Community Health Worker Self-Efficacy in Complex Diabetes Management in Medically Underserved Communities. Endocr Pract. 2018;24(1):40-6.
115. Hintze J. NCSS, LLC. Kaysville, Utah USA. 2014.
116. O'Rourke HP, MacKinnon DP. When the test of mediation is more powerful than the test of the total effect. Behavior research methods. 2015;47(2):424-42.
117. SAS/SAT 14.1 User's GuideSAS Institute 2015 January 19, 2019: Available from: https://support.sas.com/documentation/onlinedoc/stat/141/plm.pdf.
118. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B (Methodological). 1995;57(1):289-300.
119. Hayes AF, Preacher KJ. Statistical mediation analysis with a multicategorical independent variable. Br J Math Stat Psychol. 2014;67(3):451-70.
120. The Psychiatric Shortage: Causes and SolutionsNational Council for Behavioral Health 2017 January 18, 2019: Available from: https://www.thenationalcouncil.org/wp-content/uploads/2017/03/Psychiatric-Shortage_National-Council-.pdf
121. Shelley BM, Katzman JG, Comerci GD, Jr., Duhigg DJ, Olivas C, Kalishman S, Monette R, Britt M, Flatow-Trujillo L, Arora S. ECHO Pain Curriculum: Balancing Mandated Continuing Education With the Needs of Rural Health Care Practitioners. J Contin Educ Health Prof. 2017;37(3):190-4.
122. Flynn DM, Eaton LH, McQuinn H, Alden A, Meins AR, Rue T, Tauben DJ, Doorenbos AZ. TelePain: Primary Care Chronic Pain Management through Weekly Didactic and Case-based Telementoring. Contemp Clin Trials Commun. 2017;8:162-6.
123. Williams T, Purvis TL. Development of an outpatient pharmacist-managed clozapine clinic. Am J Health Syst Pharm. 2012;69(14):1192-5.
124. Gage H, Family H, Murphy F, Williams P, Sutton J, Taylor D. Comparison of sole nurse and team-delivered community clozapine services for people with treatment-resistant schizophrenia. J Adv Nurs. 2015;71(3):547-58.

125. Clark SR, Wilton L, Baune BT, Procter N, Hustig H. A state-wide quality improvement system utilising nurse-led clinics for clozapine management. Australas Psychiatry. 2014;22(3):254-9.