Overcoming obstacles to implementation of an interventional clinical trial on chronic psychotic disorders in Tanzania

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•Abstract

•Introduction: Chronic psychotic disorders (CPDs) such as schizophrenia occur world-wide and cause significant burden, reduced quality of life, functional impairment and premature mortality. Stigma and persistent disability, which usually begin early in life, profoundly and negatively impact people with CPD as well as their families and communities. Lower and middle income countries (LMICs) including nations in Sub-Saharan Africa (SSA) experience disproportionate burden due to poor adherence with evidence-based medication treatments, pervasive stigma, and lack of workforce capacity. In spite of the growing burden caused by CPD in SSA, there are numerous obstacles to research implementation and very few completed prospective clinical trials that can inform care.

•Methods: This ongoing project is using a multi-stage process to develop and test a person-centered CPD care approach that will be practical and effective in Tanzania, generalizable to other countries in SSA, and develop research capacity for future efforts in clinical trials. The study team includes investigators from Muhimbili University of Health and Allied Sciences and Muhimbili National Hospital in Dar es Salaam, Tanzania, and from Case Western Reserve University (CWRU), Ohio, USA, and builds upon a successful behavioral + medication approach for high-risk individuals with CPD developed at CWRU.

•Results: Steps in the 3-phase/3-aim project are: 1) A mixed-methods (quantitative + qualitative) needs assessment regarding barriers and facilitators to CPD care in Tanzania; 2) Refinement of a brief, customized adherence enhancement approach (CAE) to improve adherence and mental health outcomes in Tanzanians with CPD, and 3.) Establishment of a clinical trials infrastructure, adequately trained staff, and data tools/procedures preparatory to implementation of a randomized controlled trial (RCT) using the adapted CAE approach combined with long-acting injectable antipsychotic medication (LAI) in Tanzanians with CPD.

•The Phase 1/Aim 1, mixed-methods analysis involves 100 individuals with CPD to better understand antipsychotic adherence barriers and attitudes. Phase 1 methods include evaluation of common reasons for non-adherence, as well as stakeholder input regarding preferred approaches for treatment and adherence promotion. In Phase 2/Aim 2, CAE is being culturally and linguistically adapted for the Tanzanian setting. In Phase 3/Aim 3 appropriate outcome measures will be selected, staff will be trained in study and measure implementation, and the intervention will be finalized for delivery. Finally, the adapted CAE approach combined with LAI will be evaluated in a 6-month prospective clinical trial format.

•Conclusions: Taken together, this ongoing project is targeting common obstacles to clinical trials implementation in SSA,and will setthe stage for a futurelarge-scale RCT that has substantial potential for positive public health impact should preliminary methods and outcomes prove promising.

Introduction

CPDs such as schizophrenia occur world-wide and cause significant burden characterized by reduced quality of life, functional impairment and premature mortality. Although CPDs manifest globally, LMICs experience disproportionate burden due to pervasive stigma, care access problems and lack of workforce capacity. Antipsychotic medications are a cornerstone of treatment for CPD. In SSA, poor medication adherence is seen in approximately half of individuals with CPD and is a major driver of relapse. Long-acting injectable antipsychotic (LAI) medication is a potentially attractive treatment alternative to daily oral antipsychotic medication. It can improve adherence but needs to be combined with a quality behavioral program to modify long-term attitudes and behaviors. This study team includes experts in mental health treatment research, qualitative methods and psychopharmacology from Muhimbili University in Dar es Salaam, Tanzania and from Case Western Reserve University (CWRU), Ohio, U.S.A. The ongoing project will refine an adherence enhancement approach called Customized Adherence Enhancement combined with LAI (CAE-L) that has been demonstrated to improve outcomes in high-risk group CPD in the U.S.

Approach

Phase 1: Mixed-methods (quantitative + qualitative) assessment of barriers to adherence among 100 Tanzanians with CPD which will inform an approach for optimizing adherence with evidence-based care. Quantitative data is supplemented by qualitative data from focus groups (family members, care providers) and individual interviews (patients).

Phase 2: Adapt a curriculum-driven customized adherence enhancement (CAE) approach to improve treatment adherence in CPD to be culturally& linguistically appropriate for this setting.

Phase 3: Prospective, 6-month uncontrolled pilot of adapted CAE + LAI to establish a clinical trial infrastructure, adequately trained staff, and data tools/procedures preparatory to implementation of a future randomized controlled interventional CAE trial.

Tanzania site

Muhimbili National HospitalPsychiatry Department is a 70-bed facility located in urban Dar es Salaam, Tanzania. It is one of two psychiatric national referral centers and serves a population of approximately 4.5 million. Approximately 75% of patients are rural dwelling individuals who live by agriculture/farming. There is a large outpatient clinic. Follow-up clinics are also held at the district level in 4 facilities; most are stable back-referrals from clinics run by psychiatric nurses.

Clinical trends at the study site

In 2015, there were 1,636 patients (1,099 men (67.2% total), 537 women) admitted to psychiatry. Most of patients lived within a 15 kilometer radius of the clinic a 1-3 bus commute which costs about US$1.20 round-trip. This is typical for urban and outlying zones of Dar es Salaam. Hospital discharge diagnosis were schizophrenia (32.4%), schizophreniform disorder (11%), manic depressive psychosis (35.3%), cannabis-induced psychosis (9.8%) ethanol-induced state (2.9%), delusional disorder (1.2%), major depressive disorder (8.7%) and general anxiety disorder (0.6%). The most commonly prescribed discharge medication was oral haloperidol (75% of patients). There were 16 % treated with the LAI fluphenazine decanoate. Antipsychotic side effects were managed with trihexyphenidyl (Artane). Few patients received second-generation antipsychotic medication such as risperidone and quetiapine.

Study Population

Patients ≥ age 18 with schizophrenia or schizoaffective disorder . Eligible patients must agree to receive LAI and must be able to participate in research.

Exclusion Criteria:

1.) LAI immediately prior to enrollment, or those intolerance/resistance to LAI
2.) Medical conditions that would interfere with ability to participate in the trial
3.) Physical dependence on substances
4.) Immediate risk of harm to self or others
5.) Pregnancy or lactation

Behavioral intervention

CAE is flexibly delivered in up to 4 treatment modules whose use is determined based upon an individual's reasons for non-adherence (adherence barriers) identified at baseline. The modules are Psycho-education focused on medication and consequences of missing medication, Modified Motivational Enhancement Therapy (MET) to address non-adherence related to substance use, Communication with Providers to facilitate appropriate treatment expectations and optimize management of feared or experienced side effects, and Medication Routines intended to incorporate medication-taking into lifestyle. Prior to delivering CAE, adherence barriers are evaluated with two standardized measures, the Rating of Medication Influences (ROMI) and the Attitudes toward Mood Stabilizers Questionnaire (AMSQ).

LAI

Patients on oral haloperidol will be switched to haloperidol decanoate. Individuals not on antipsychotic at the time of screening assessment or who are on a different antipsychotic will receive an oral tolerance test (OTT) consisting of up to 14 days of oral haloperidol approximately 1.5-4.5mg/day as per clinical trends at the study site.

Preliminary Results

Phase 1:

- As most previous conducted research was focused on management of HIV and related mental health complications, few staff had experience with standardized psychosis evaluation instruments. Training included didactic presentation, video viewing & interactive discussion.
- Multidisciplinary discussion/consensus quickly yielded research instrument selection that included streamlining the assessment battery for diagnostic and psychotic symptom evaluation. Semi-structured evaluations with clear descriptors /anchor points were overwhelmingly preferred.
- Comorbidity evaluation de-emphasized substance use disorder assessment, expanded medical evaluation including HIV testing for all participants
- Semi-structured qualitative interview guide developed jointly by Tanzanian and U.S. investigators
- Oral 2nd generation antipsychotics are prescribed to some individuals, however no2nd generation drugs are in use in this setting
- Social workers are the preferred staff to deliver the behavioral intervention vs. nurses as they are present at the treatment sites and more likely to be available to spend time delivering the intervention .

Conclusions

CPD causes extensive burden in SSA. Care approaches that pre-emptively address cultural and logistic factors have potential to improve outcomes and be amenable to broader scale-up in resource-limited settings.

Table 1: Study schedule of events:

Procedure	Screen*	Baseline*	W 1	W 5	W 9	W 13	W 17	W 21	W 25
Informed consent/inclusion & exclusion assessment	X								
Diagnostic evaluation, MINI	X								
TRQ	X	X				X			X
Demographics	X								
Adherence vulnerabilities :ROMI, AMQ	X								X
Laboratory testing, EKG	X		X***						X
Physician Exam		X							X
Primary outcomes: TRQ, LAI injection frequency		X				X			X
Secondary outcomes:		X				X			X
Adherence attitudes : DAI									
CPD Symptoms: PANSS, CGI									
Health Resource Use									
Social functioning: SOFAS									
Standardized side effects: ESRS-A									
Alcohol and Drugs: AUDIT									
Weight and vitals, Reported side effects	X	X	X	X	X	X	X	X	X
Pt Acceptability & Satisfaction									X
CAE intervention		X	X	X	X	X	X	X	X
Injection		X	X**	X	X	X	X	X	X
Clinician assessment			X	X	X	X	X	X	X

* Screening and baseline assessments may be completed in a single visit if it is more convenient for the participant
** May require additional baseline booster injection depending on dosage

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