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Protocol

A preliminary evaluation of unified protocol in anxiety disorders in India: a multiple baseline study protocol

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ABSTRACT

Background: Anxiety disorders are highly prevalent with high rates of comorbidity. Single disease protocols have been the predominant choice of psychological treatment, however, there has been an increasing focus on transdiagnostic, shared mechanisms. Unified protocol is an emotion-focused CBT that addresses core vulnerabilities by training individuals in adaptive emotion regulation skills. UP has gained research attention in the management of emotional disorders with its modular approach. A challenge in psychotherapy research has been to understand the mechanisms of interventions and their effect on symptoms. Thus single-case experimental design has the potential to address some of the key questions. We present a research protocol that aims to examine the effectiveness of the unified protocol, using the SCED.
Methods: A single-case experimental design, with multiple baseline assessments, will be employed, with random allocation to 2- or 3-week baselines. Patients with a primary diagnosis of anxiety disorder, consenting to baseline assessments, and stabilized at least for 4 weeks of medication will be recruited. Assessments will be carried out at baseline, post, and three months, in addition to weekly assessments on the primary outcome measure, anxiety by an independent blind rater. Secondary outcomes include intolerance to uncertainty, neuroticism, emotion regulation, and anxiety sensitivity.
Conclusions: The findings of this study would contribute to the empirical status of transdiagnostic interventions in symptom reduction and in addressing shared mechanisms, enhancing its clinical relevance for co-morbid disorders.
Trial Registration: The study has been registered in clinical trials registry of India, No. CTRI/2021/01/030803; 28 January 2021.

Keywords: Transdiagnostic interventions, Unified protocol, Anxiety disorders, Multiple baseline design, Shared mechanism, Emotion regulation

INTRODUCTION

Anxiety disorders are characterized by high rates of comorbidity with other anxiety, mood disorders or their sub-syndromal features.[1] Addressing co-morbidities using single disease protocols which are predominantly used for the treatment of anxiety disorders is challenging.[2] Evidence for common mechanism across disorders from neurobiological studies and from latent structural analysis has led to the development of transdiagnostic interventions that address the core vulnerabilities.[3,4] Neuroticism is one of the general biological vulnerabilities across anxiety disorders.[5] It is defined as a tendency to experience frequent and intense negative emotions in response to various sources of stress. It is also accompanied by low threshold for threat perception and perceived lack of ability to handle situations.[6] The perceived lack of ability to manage emotions and

situations results in aversive reactions further leading to the use of maladaptive emotion regulation strategies such as experiential avoidance, thought suppression, and avoidance that maintain the anxiety.[5] In addition to neuroticism, several other vulnerability factors associated with the development and maintenance of anxiety disorders have been examined in the literature. Amongst these are intolerance to uncertainty (IU) and anxiety sensitivity (AS). IU is defined as the " individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key or sufficient information".[7] IU has both a cognitive (prospective) and a behavioral component (inhibitory). Anxiety sensitivity is described as the fear of the physical, cognitive and social components of anxiety in terms of its harmful consequences.[8] Both anxiety sensitivity and intolerance to uncertainty are considered to be fundamental to anxiety disorders unlike earlier when it was thought to be disorder specific giving rise to the need for transdiagnostic interventions to target them.[9] Unified Protocol is one such transdiagnostic emotion-focused cognitive behavioral intervention that addresses core vulnerabilities through training individuals in adaptive emotion regulation skills. Emotion regulation refers to different processes an individual employs to downregulate or upregulate different emotions.[10] There is evidence to suggest that adaptive emotion regulation skills acquired through UP lead to enduring change in neuroticism.[11] In the last decade, UP has been explored for its effectiveness in symptom reduction across emotional disorders. Meta-analysis of UP based intervention studies for emotional disorders indicates medium to large effect size.[12] However UP has been relatively less studied for its impact on vulnerability factors.[13] Also, considering that transdiagnostic intervention facilitates treatment of multiple co-morbidities and sub-threshold symptoms makes it an important area of research which still remains nascent in India.[14] Studying the vulnerabilities would enable a better understanding about the mechanism of change in UP. In the present study, we aim to examine these objectives using a multiple baseline design- a type of single case experimental design (SCED). While randomized controlled trial (RCT) is considered to be the most superior design for examining treatment efficacy, there are several challenges to conducting RCT, such as high attrition rates, difficulties in blinding patients, feasibility of randomization, challenges in studies with single researchers and other ethical considerations.[15] In this context, use of SCEDs is gaining momentum.[16] SCEDs refer to an experimental design where in the cause-effect relationship between intervention (independent variable) and the outcome (dependent variable) is established in a smaller sample set. SCEDs typically comprise of a baseline phase in which outcomes are measured without the introduction of active intervention and an intervention phase in which a specific intervention is presented. Unlike other experimental designs, the comparison of the outcome is carried out between phases of the same individual rather than between groups.[17] Multiple baseline design (one of the variations of SCED) is a time series design that compares an individual's baseline with the active intervention period and this is replicated across different staggered baseline phases across different subjects, behaviors, and situations.[18] In multiple baselines across subjects design, while one participant enters the intervention, another participant remains at the baseline and eventually enters the intervention. Outcomes are measured repeatedly at both baseline and intervention phases. Within a subject, outcomes are compared between baseline and intervention phase to examine the cause-effect relationship. Between the subjects who belong to different baselines, changes in outcomes following treatment initiation at different timelines are compared.

METHODS

Study design and location

A multiple baseline across-subjects design with time series analysis will be followed.[20] Patients will be recruited from out-patient services of National Institute Of Mental Health and Neurosciences, Bangalore, India.

Sample size estimation

There are no specific guidelines with respect to sample size estimation in multiple baseline design, however considering the reported attrition rate in Cognitive Behavioral Therapy, a sample of 42 patients with a primary diagnosis of anxiety disorders will be recruited from outpatient services of the National Institute of Mental Health and Neurosciences, Bengaluru.[19]

Inclusion criteria

Patients with a primary diagnosis of anxiety disorder as per DSM-V criteria, aged between 18-55 years, providing consent for baseline phase and have been stabilized on medication 4 weeks prior to the baseline phase will be recruited.[20]

Exclusion criteria

Primary diagnosis of schizophrenia, bipolar affective disorder, patients with high suicidal risk, co-morbid severe depression with psychotic symptoms, obsessive compulsive disorder, current psychoactive substance dependence (except nicotine dependence), primary diagnosis of depression with secondary anxiety symptoms, having received structured psychotherapy of more than 8 sessions in the last 6 months will be excluded.

Screening measures

Structured clinical interview for DSM-5 disorders-clinical version (SCID-5-CV):[21] It is a semi-structured interview based on DSM-5 that enables the clinician to

confirm the primary diagnosis and co-morbidities. Structured clinical interview for DSM-5- personality disorders (SCID-5 PD); it is a semi-structured interview used for assessing the DSM-V personality disorders in a categorical manner.[22] It will be administered by the researcher to document presence of personality disorders considering the transdiagnostic nature of the intervention.

TIMEPOINT**	Study period								
	Screening	Allocation to baseline	Post-allocation					Post intervention	
	$-t_1$	0	t_1	t_2	t_3	t_4	t_{18}	t_{1month}	$t_{3\ month}$
ENROLMENT									
Eligibility screen	X								
Informed consent	X								
Clinical monitoring	X	X	X	X	X	X	X		
Allocation		X							
INTERVENTIONS									
Unified Protocol after 2-week baseline					◆—	——	—◆		
Unified Protocol after 3-week baseline						◆—	—◆		
ASSESSMENTS									
SCID-5-CV, SCID-5-PD	X								
ASI-3, DERS, IUS, EPQ, SDS,CGI			X			X	etc.	X	X
HAM-A, HAM-D, OASIS, ODSIS			X	X	X	X	etc.	X	X
HCS					X	X	etc.	X	X

Figure 1: SPIRIT diagram (standard protocol items for reporting clinical trials) for the schedule of enrollment, interventions and assessment.

SCID-5-CV:Structured Clinical Interview for DSM-5 Disorders- Clinical Version, SCID-5-PD:Structured Clinical Interview for DSM-5 Personality Disorders- Patient Edition, HAM-A: Hamilton Anxiety Rating Scale, OASIS: Overall Anxiety Severity and Impairment Scale, HAM-D: Hamilton Depression Rating Scale, ODSIS: Overall Depression Severity And Impairment Scale, ASI-3: Anxiety Sensitivity Index-3, IUS: Intolerance to Uncertainty Scale, DERS: Difficulties in Emotion Regulation Scale, EPQ: Eysenck Personality Questionnaire, SDS: Sheehan Disability Scale, HCS: Homework Compliance Scale, CGI: Clinical Global Impression scale.

Primary outcome anxiety measures

Hamilton anxiety rating scale (HAM-A) is a clinician rated scale used to assess the severity of anxiety.[23] It will be assessed by an independent rater. Overall anxiety severity and impairment scale (OASIS) is a self-report measure used to assess level of anxiety on a weekly basis in terms of frequency, intensity, avoidance, interference with socio-occupational functioning.[24]

Depression

Hamilton depression rating scale (HAM-D) is a clinician rated scale used to assess the severity of depressive symptoms.[25] It will be assessed by an independent rater. Overall depression severity and impairment scale (ODSIS) is a self-report measure used to measure the level of depression on a weekly basis in terms of frequency, intensity, level of disinterest, interference with socio-occupational functioning.[26]

Treatment response

Clinical global impression scale (CGI) is a three-item scale to assess treatment response in psychiatric patients.[27] In the present study severity and global improvement items will be administered by an independent rater.

Secondary outcome measures

Anxiety sensitivity index-3 (ASI-3) is a self-report measure to assess the three dimensions of anxiety sensitivity; physical, social, cognitive.[28] Intolerance to uncertainty scale (IUS) is a 12 item self-report measure with the items assessing inhibitory and prospective IU.[29] Difficulties in emotion regulation scale (DERS) is a 18 item self-report measure to assess difficulties in regulating emotions, namely lack of awareness, clarity, non-acceptance of emotions, difficulty engaging in goal directed behaviors, impulsive behaviors in response to distress, lack of strategies to manage emotions.[30] Eysenck personality questionnaire (EPQ): Neuroticism subscale of the questionnaire with 12 items will be used to assess neuroticism.[31]

Functional impairment

Sheehan disability scale (SDS) is a brief self-report tool to rate the effect of the symptoms on work, social and family responsibilities on a 10-point visual analogue scale.[32]

Homework compliance

Homework compliance scale (HCS) is a two-item scale used to assess the quantity and quality of homework compliance.[33] Items for the quality of homework will be developed in accordance with Unified Protocol and would be rated by the researcher prior to each session.

Intervention

Unified protocol is an emotion-based CBT with 8 modules, 5 of which are core modules. The treatment begins with functional assessment and an introduction to the treatment. The five core modules of UP include mindful emotion awareness, cognitive flexibility, identifying and modifying emotion driven behaviors and action tendencies, such as avoidance and safety behaviours, increasing awareness and tolerance of physical sensation, using exercises like symptom induction and exposure to emotions, with present focused non-judgmental awareness, cognitive reappraisal and without any form of avoidance. In addition to core modules, UP also have modules covering common therapeutic factors like enabling goal setting and maintaining motivation, increase understanding regarding the function of emotions, recognizing accomplishments and maintaining gains (Table 1). Each of the modules contain specific activities to enhance skill acquisition and learning.

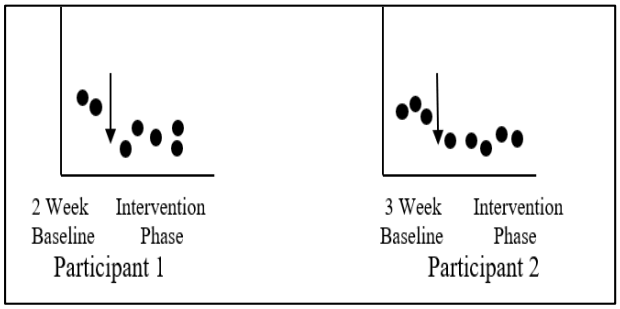

Figure 2: Multiple baseline design across subjects.

Procedure

Patients meeting DSM-V criteria for anxiety disorders and consenting to participate will be screened using SCID-5-CV and SCID-5-PD.[20,21] Patients will be randomly allotted to either a two- or three-week baseline. Block randomization will be used to allot patients evenly between 2- and 3-week baseline. Computer generated random number will be used for randomization. During the baseline period, patients will be assessed on the primary (severity of anxiety symptoms) and secondary outcomes (anxiety sensitivity, emotion regulation, intolerance to uncertainty, neuroticism), severity of co-morbid depression, functional impairment along with clinical evaluation, functional analysis and clinical monitoring. After the baseline phase, UP will be initiated. During the intervention phase, primary outcome will be measured on a weekly basis (independent rater and self-report) and secondary outcomes will be measured after each module (Figure 3). Concomitant psychotropic medications would be kept stable during the baseline and intervention phase. However, treatment changes would be allowed in the post-intervention phase and it will be documented. Patients who complete 80% of the total number of sessions would be considered completers and patients who attend less than 20% of the sessions would be considered drop-outs. A CGI score of 1 (very much improved) or 2 (improved) after the intervention would be considered as improved in the present study.

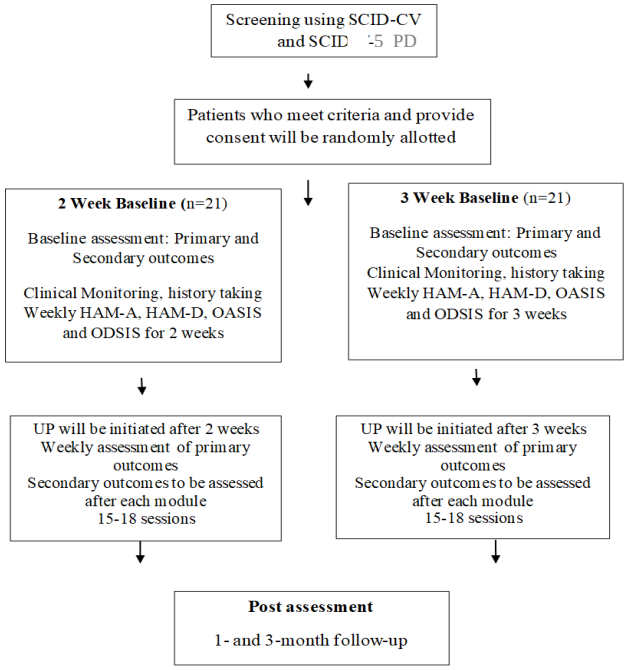

Figure 3: Flowchart of the study.

Treatment adherence and competence

The treatment guidelines for unified protocol in emotional disorders will be used to develop the session-by-session module. Treatment adherence will be ascertained through case supervision with supervisors (PMS and SS), in implementing the principles and techniques of unified protocol, and through online supervision from experts of centre for anxiety and depressive disorders.

Therapist training and treatment fidelity

Intervention will be carried out by the first author (AB) who will be the primary therapist, under the supervision of the second authors (PM and SS). The primary therapist is a clinical psychologist with two years of post-graduate training in clinical psychology. In addition,, the therapist has received online training in unified protocol offered by Centre for Anxiety and related disorders, Boston.[34] Since UP is based on the principles of CBT, basic training in CBT is considered to be sufficient to offer therapy from a UP framework. Therapist adherence to treatment will be

assessed by rating of randomly selected session transcripts by experts based on a checklist of UP components**.** The timeline of enrolment, assessments and intervention are presented in Figure 1.

Table 1: Modules of unified protocol.

Modules	Description
Module 1	Functional assessment and introduction to treatment
Module 2	Goal setting and maintaining motivation
Module 3	Understanding emotions
Module 4*:	Mindful emotion awareness
Module 5*:	Cognitive flexibility
Module 6*	Countering emotion driven behaviors
Module 7*:	Getting comfortable with physical sensations
Module 8*	Emotion exposure

***Highlighted modules are the core modules of UP

Study period

The protocol has been designed as a part of the doctoral program that runs for a 5-year period of time between January, 2020 to December 2024. The study is currently in phase of data collection.

Plan of analysis

Visual analysis is the predominant method of analysis in SCED. Major factors to be established through visual analysis are; change in the outcome variable, whether the change runs in parallel to the introduction of the treatment, whether the change is statistically and clinically significant.[35] Stability during the baseline and visual depiction of change in slope indicates change, comparison with different baselines and change in slope after treatment introduction indicates causal relation.[36] In addition to visual inspection, reliable change index (RCI) is also commonly used in multiple baseline design. RCI indicates the reliability of change in scores and it is calculated using the test-retest reliability of the scale. Reliable change index indicates whether change in scores across time period is clinically significant.[37]

DISCUSSION

We report a research protocol, aimed at gathering preliminary evidence for effectiveness of unified protocol as a transdiagnostic intervention in the Indian clinical setting. By assessing and monitoring vulnerability factors during intervention, we would be able to understand the effect of UP on transdiagnostic variables. This has not been explored extensively in literature on UP, even though UP is designed to address core vulnerabilities. Single Case Experimental design enables the researcher to address these objectives through periodic assessment and monitoring of outcome variables across the intervention. It is hypothesized that various modules of Unified Protocol address different processes of emotion regulation such as situation selection, modification, attention deployment, cognitive reappraisal and response modulation.[38] More effective affect regulatory process is expected to bring about enduring change in vulnerabilities such as neuroticism, intolerance to uncertainty, anxiety sensitivity. Intolerance to uncertainty is addressed implicitly through mindful engagement with uncertainty, flexibility in interpreting ambiguous stimuli, approach behaviors in response to behavioral inhibition.[39] Various components of anxiety sensitivity will be explicitly addressed through interoceptive exposure exercises, combined with other emotion regulation skills acquired in UP.[40] Thus, skills are not mutually exclusive, they have an additive effect on symptom reduction. Although there is considerable amount of ongoing research in UP, RCTs are primarily used. Multiple baseline design would enable us to understand the effect of modules independently. The study will also help in understanding the feasibility of the multiple baseline design in Indian setting. Internal validity is established by randomization to multiple baselines, use of independent raters for assessment, assessing the inter-rater reliability. The multiple baseline design could be a robust alternative to an open-label design, and for psychotherapy research with single therapists as each subject serves as their own controls. Further, this design would improve the external validity of the single-group study. Single case designs are gaining status as an experimental design.[17] It is also feasible to evaluate individual variations in response to intervention through multiple baseline design. Among the few studies that look at the effect of UP on transdiagnostic variables, most studies employ a pre-post design.[41] The study would also be first of its kind in India examining the effect of Unified Protocol on transdiagnostic variables during the course of intervention using a multiple baseline design. The strengths of the study are employment of multiple assessments conducted by an independent rater to track the trajectory of change. Limitations include delivery of the intervention by a single therapist and difficulty in establishing stability of scores. Even though a minimum of 2-week baseline is considered adequate to establish stability in the baseline phase, the nature of the primary outcome (anxiety) is such that it fluctuates as a function of day-to-day stressors, thereby making it difficult to establish stability in scores. Further, there is little consensus currently regarding appropriate statistical analysis in single case design, thereby making it challenging to report cause-effect relation from the data.

CONCLUSION

The present study would enable us to understand the effectiveness of UP in the Indian setting and provide a framework for addressing co-morbidities in emotional disorders, in place of the Single Disease Protocol. This would reduce the burden on health care services by considering the high co-morbidity and relapse rates. The core vulnerabilities examined in the study have clinical

relevance for the origin and maintenance of anxiety disorders. The understanding of the trajectory of the transdiagnostic variables during intervention would help us to examine the malleability of core vulnerabilities and mechanisms of change in UP, thus contributing to the empirical evidence of UP as a transdiagnostic intervention. The SCED, further offers an advantage in examining these objectives across individuals.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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