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Unified Protocol for the Discontinuation of Long-term Serotonin Reuptake Inhibitors in Obsessive Compulsive Disorder: Study Protocol and Methods

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Abstract

Obsessive-compulsive disorder (OCD) is chronic psychiatric disorder associated with high rates of functional impairment and decreased quality of life. Although serotonin reuptake inhibitors have demonstrated efficacy in the treatment of OCD, little data is available to guide clinicians on how to manage these medications long-term. Cognitive-behavioral approaches provide a promising avenue for helping OCD patients discontinue maintenance SRIs while minimizing the potential for symptom worsening. This manuscript describes the rationale and methods for pilot feasibility study designed to a unified, cognitive-behavioral strategy for discontinuing long-term SRIs in OCD. The aims of the study are (1) to evaluate the feasibility and acceptability of research procedures and interventions, (2) to test the efficacy of this treatment relative to an enhanced control condition and (3) to investigate the role of distress tolerance in both taper completion and clinical outcome. Our central aim is to investigate whether this approach improves discontinue outcomes relative to an enhanced control condition. Identifying optimal long-term treatment strategies for this population is needed to guide clinicians managing this often-chronic disorder.

Keywords

obsessive compulsive disorder; medication; anxiety; taper

1. Introduction

Obsessive-compulsive disorder (OCD) is a chronic, costly, and often disabling psychiatric disorder affecting 1.6 to 2.3% of the general population [1,2]. OCD is associated with significant morbidity, high rates of functional impairment, and markedly decreased quality of life. [3,4] Despite increased recognition of its public health significance, surprisingly little

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is known about how to optimize long-term treatment of the disorder. Serotonin reuptake inhibitors (SRIs) are the most commonly prescribed medications for OCD [5] with large observational studies estimating lifetime utilization at over 90% in treatment-seeking populations [6,7]. Although widely used and efficacious [8–10], SRI use long-term is associated with adverse side effects [11–14], as well as problems with adherence and financial burden [15,16]. Additional potential challenges include continuation of medication during pregnancy [17] and potential drug interactions [13]. Thus, maintenance SRI treatment may not be an ideal long-term approach and some patients may want or need to discontinue pharmacologic treatment.

However, there have been few controlled studies examining discontinuation in OCD patients maintained on SRIs longer than one year. Controlled short-term SRI discontinuation studies highlight a moderate-to-high risk of OCD symptom reoccurrence following abrupt or rapid discontinuation [18–20]. These findings, however, are inconsistent with naturalistic observations suggesting that the majority of OCD patients discontinue maintenance SRIs without significant symptom worsening [7]. Furthermore, abrupt discontinuation of SRIs is at odds with clinical practice and American Psychiatric Association guidelines recommending slow taper [21]. Additional, more systematic data are needed on the likelihood and nature of clinical worsening following slow taper of SRIs. Indeed, the evaluation of strategies to mitigate the possible clinical burdens of SRI discontinuation is a promising avenue for improving long-term treatment outcome for the disorder.

We have designed a pilot study to test a treatment that combines a slow SRI taper with an intervention that targets the emotional avoidance and catastrophic thinking patterns that both maintain OCD symptoms and may impede successful discontinuation. The primary aim of this study is to test feasibility, acceptability, and preliminary efficacy of a unified, transdiagnostic cognitive-behavioral protocol [22] in improving both discontinuation success and outcome. Cognitive behavioral therapy (CBT) is an efficacious and effective treatment for OCD with improvement that persists long-term [23–25]. CBT-based approaches have shown promise for facilitating medication discontinuation in anxiety disorders [26,27]; however, studies of OCD have remain largely unaddressed. Moreover, no studies to date have focused specifically on long-term SRIs, despite frequent use in OCD populations and the challenges presented by maintenance treatment.

This manuscript describes the study design and procedures for a pilot randomized controlled trial investigating the feasibility, acceptability, and efficacy of a unified, cognitive behavioral protocol (UP) [22] approach for discontinuing long-term SRIs in OCD.

2. Study design and aims

This study was funded by the National Institutes of Mental Health (MH100444) and is registered on clinical trials.gov (NCT02103621). The Institutional Review Boards at Butler Hospital and Brown University approved all study procedures, which are described below.

2.1. Design overview

This study is a 14-week, Stage 1b, single site study designed to evaluate the feasibility, acceptability, and preliminary efficacy of two strategies for discontinuing long-term SRIs in OCD. Thus, this study was designed to evaluate the feasibility of conducting a two-arm pilot randomized controlled trial with participants randomized to the UP or an enhanced taper and monitoring control condition (TAP-M). Primary and secondary outcomes are assessed after the 14-week acute treatment phase (post-treatment), after the two-month booster phase (post-booster) and at 6-month follow-up. Figure 1 provides an overview of the study design.

2.2. Specific aims

The specific aims and hypotheses for this pilot trial are as follows:

1. To examine the feasibility and acceptability of research procedures and treatment interventions.
2. To test the efficacy of the UP at facilitating discontinuation of long-term SRIs in OCD. We hypothesize that patients receiving UP will be less likely to experience symptom worsening during SRI discontinuation, and less likely to resume SRIs during a 6-month follow-up compared to TAP-M.
3. To examine the relationship of distress tolerance to taper completion. We hypothesize: a) baseline levels of distress tolerance will predict successful taper completion, and b) individuals receiving UP will show greater increases in distress tolerance following treatment compared to TAP-M.

2.3. Participant selection, recruitment and retention

Eligibility criteria for this ongoing pilot trial (target N = 30) include: (1) Age 18 or older, (2) Presence of mild to moderate OCD symptom, (3) Long-term maintenance on SRI dose that has not increased due to significant clinical worsening in the two years prior to enrollment, (4) Agreement from patient's treating clinician that SRI discontinuation is clinically appropriate (e.g., not contraindicated and represents a next logical step in their patient's care), and (5) Ability to provide written informed consent. Exclusion criteria include: (1) Clinically significant suicidality or a suicide attempt within the past year, (2) Presence of any clinical features warranting a higher level of care than outpatient treatment, (3) Current or recent (past 6 months) substance use disorder, (4) History of psychotic disorder or bipolar disorder, (5) Moderate to severe depression, as indicated by a Hamilton Rating Scale for Depression (17-item) ≥ 14 [28] or recent major depressive episode (past 6 months), (6) History of severe OCD (YBOCS ≥ 28), (7) Prior adverse experience with SRI discontinuation (e.g., discontinuation syndrome, severe exacerbation of anxiety or mood symptoms), (8) Primary compulsive hoarding, given research distinguishing the symptom profile from OCD and the more limited efficacy of CBT-based treatments in hoarding populations [29] (9) Concomitant psychosocial treatment w/proven efficacy in the treatment of OCD, (10) Adequate trial of exposure-based treatment in the past 5 years, and (11) Use of non-SRI psychotropic medications for OCD in the 3 months prior to enrollment.

Participants are recruited primarily from the OCD Program at Butler Hospital, a program with a long-standing history of both research and treatment. Recruitment also consists of printed advertisements (e.g., flyers), letters to community-based clinicians soliciting referrals, online advertisements through the hospital website and Facebook, radio advertisements, and presentations to local primary care and outpatient psychiatry offices. Research assistants (RAs) screen participants for preliminary eligibility and those who meet initial eligibility criteria are brought into the clinic for an in-person evaluation where informed consent is obtained. The current study employs several measures to minimize attrition, including frequent contact with participants for the duration of the study, including reminder calls prior to study appointments. In addition, as part of the informed consent process, participants are asked to provide contact information for two individuals who could help us locate them if we lose contact.

2.4. Randomization

Following eligibility determination, participants are randomly assigned to either the intervention (UP) or enhanced control condition (TAP-M). Urn randomization is used to assign participants [30] in a 1:1 allocation while stratifying treatment assignment on baseline level of OCD severity (cutoff on the YBOCS = 16) [31]. Level of OCD symptomatology at baseline (pre-intervention) is likely a prognostic factor affecting severity and discontinuation outcomes [7] and therefore is controlled during randomization.

3. Study Interventions and Taper Schedule

Table 1 provides a summary of study visits and taper protocol

3.1. Unified Protocol

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP) [22] is an empirically supported, cognitive-behavioral treatment that has been described extensively elsewhere [32–34]. Briefly, the UP builds upon five core treatment modules that are transdiagnostic in their application: (a) increasing emotional awareness, (b) building cognitive flexibility, (c) identifying and preventing patterns of emotional avoidance and maladaptive emotion-driven behaviors, (d) increasing awareness and tolerance of emotion-related physical sensations, and (e) situational and interoceptive emotion-focused exposure. While OCD symptoms are the primary focus of the treatment in this study, attention is given to co-occurring anxiety and mood disorder as warranted by the patient's symptom presentation [35]. The UP was selected because it is specifically designed to address the broad experience of dysphoric and distressing states, catastrophic thinking patterns, and comorbidity that may prevent patients with OCD from successfully discontinuing SRIs. The format of treatment consists of 45–60 minute individual sessions over fourteen weeks. These weekly sessions are followed by 4 biweekly booster sessions designed to help consolidate gains and support participants in the months following SRI taper.

3.2. Taper and Monitoring

The taper and monitoring (TAP-M) condition is designed to provide assessment, monitoring, and non-specific support. This enhanced control condition allows us to: 1) control for the

patient's expectation that they are receiving an intervention; 2) approximate for number and frequency of study visits; 3) increase systematic monitoring of patient progress. Taper and monitoring focuses on providing support for SRI discontinuation by troubleshooting patient concerns, encouraging health behaviors, and monitoring OCD symptomatology. Consistent with the UP condition, TAP-M is administered over 14 weekly sessions, which are then followed by 4 biweekly booster sessions.

3.3. Taper Protocol and Schedule

Serotonin reuptake inhibitors are tapered over a 12-week period by study psychiatrists with expertise in the pharmacologic treatment of OCD. Psychiatrists meet with patients biweekly for 15-minutes during this acute discontinuation period and then as needed thereafter. During these visits, psychiatrists discuss patient concerns regarding discontinuation. They also monitor adverse events, clinical states, and the patient's physical/medical condition, consistent with their usual clinical practice. The taper is non-blinded by design, as this study aims to pilot an intervention hypothesized to limit symptom recurrence by providing strategies to help patients tolerate distress that may arise due to patients' awareness of SRI discontinuation (e.g., catastrophic thoughts around likelihood of abrupt symptom reoccurrence, misinterpretation of interoceptive cues). For all SRIs except fluoxetine, medication dose is reduced to 50% of baseline by the end of week 4, 25% of baseline by the end of week 8, and discontinued by the end of week 12. Due to its extended half-life, fluoxetine is discontinued by the end of week 4 [21]. Consistent with American Psychiatric Association treatment guidelines [21], SRIs are tapered slowly, at a rate consistent with that used in clinical practice.

3.4. Monitoring of Treatment Integrity

All treatment sessions, including psychiatrist visits, are audio-recorded to monitor treatment fidelity. Fifteen percent of audiotapes will be randomly selected for review by an independent evaluator using fidelity scales adapted from a prior large-scale randomized controlled trial [32]. These scales are designed to assess four aspects of the clinician's conduct: (1) adherence to the treatment protocol, (2) avoidance of proscribed interventions, (3) skill in administering treatment components, and (4) general competence in delivering the intervention. In addition to clinician adherence, several measures of patient adherence are utilized. This includes data on session attendance including presence and duration, assessment of concomitant medication usage or psychotherapy, and patient report of adherence to the taper protocol.

4. Assessments

Measures selected for this study mirror those commonly used in treatment outcome trials for OCD [24,36,37] and are consistent with international expert consensus guidelines for determining treatment response [38]. These measures include those for screening and eligibility, assessing feasibility, acceptability and patient satisfaction, monitoring patient safety, and determining primary and secondary clinical outcomes. Unless otherwise specified, all measures –including primary and secondary outcome measures – are

administered and collected by Ph.D.-level independent evaluators (IEs) naive to study condition.

4.1. Eligibility Determination and Diagnostic Assessment

OCD symptoms are assessed for the determination of eligibility at intake using the clinician-rated Yale Brown Obsessive-Compulsive Scale and Symptom Checklist (YBOCS) [31,39], the gold-standard for OCD assessment. In addition, intake diagnoses are established using the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I) [40]. The SCID-I is utilized for eligibility determination at intake and is a secondary outcome measure at post-treatment, post-booster, and 6-month follow-up assessments. Treatment history is assessed using the medication and treatment history interview from the Longitudinal Interval Follow-up Evaluation [41]. This interview provides a retrospective report of patients' medication history on a weekly basis including medication type, dose, and duration as well as the use of hospitalization, or day treatment, and modalities of psychotherapy. The Hamilton Rating Scale for Depression (HRSD) [28], a 17-item semi-structured interview, is administered to assess depression severity. Finally, consistent with medication discontinuation studies, the Clinical Global Impression Scale (CGI) [42] is used to provide a clinician rating of OCD and global severity and improvement.

4.2. Weekly monitoring of symptoms and participant safety

Participants are monitored on a weekly basis for symptom worsening during the acute discontinuation phase and biweekly during the booster phase of this study. This assessment, conducted by a trained RA prior to each study visit, includes the clinician-rated YBOCS severity scale, HRSD, and CGI ratings of OCD and global symptom change. In addition, side effects associated with SRI discontinuation are monitored using a modified version of the self-report Discontinuation-Emergent Signs and Symptoms checklist (DESS) [43]. The RA flags any significant symptom worsening, which is then followed-up upon by the treating psychiatrist.

The criteria for determining significant symptom worsening and initiation of rescue treatment were developed *a priori* and are follows: (1) 25% or greater increase of baseline Y-BOCS score, (2) plus a Y-BOCS ≥ 16 , and (3) a score of much worse or very much worse on the CGI. This definition requires participants to meet full criteria for OCD, which is associated with a cut-point of 16 on the YBOCS. This combined criteria also accounts for the fact that participants with lower scores at randomization might more easily worsen when solely using a percentage definition [44]. Any participant meeting these criteria for 2 consecutive weeks – ensuring that the symptom exacerbation is stable rather than a random fluctuation or temporary lapse—are considered to have significantly worsened and referred for doctor's choice rescue treatment (e.g., reinstitution of SRI). Participants can also be withdrawn from the trial for any of the following reasons: (1) A significantly deteriorating clinical course, such as the emergence of active suicidal ideation or a need for hospitalization, (2) emergence of significant depressive symptoms defined HRSD ≥ 18 , (3) a two-point increase on global CGI, and (4) participant decision to withdraw.

4.3. Primary outcomes

4.3.1. Feasibility, Acceptability and Participant Satisfaction—Measures of feasibility include the ability to recruit the intended population from outpatient, hospital, and tertiary care settings, participant willingness to be randomized, and session attendance. In addition to the widely used Client Satisfaction Questionnaire-8 (CSQ-8) [45] a study-specific questionnaire was also created to gain participants' feedback about the acceptability of UP and TAP-M including how the treatment might be improved, made more feasible, or made more relevant for patients discontinuing SRIs. This interview includes questions about recruitment, consent, assessment, and other research procedures, as well as ways to improve these procedures. To maintain the blind of the IEs, these acceptability and satisfaction measures are administered at the end of the acute treatment period (week 14) by RAs not otherwise involved in the study. Finally, the Credibility/Expectancy Questionnaire (CEQ) [46] is administered at session 2 to measure the credibility of treatment rationale and expectancy for improvement. The CEQ has shown to be predictive of clinical outcomes in previous treatment trials [46] and was adapted to include questions on expectancies regarding the likelihood of successful SRI discontinuation.

4.3.2. Clinical outcomes—The YBOCS is the primary clinical outcome measure at post-treatment, post-booster, and 6-month follow-up assessments. In addition, significant symptom worsening resulting in the institution of rescue treatment and/or participant withdrawal is considered a primary clinical outcome.

4.4. Secondary outcomes and putative mechanisms of change

In conjunction with the primary feasibility and clinical outcomes, secondary outcomes focused on quality and life and functioning are obtained at baseline (prior to randomization), at post-treatment and at the 6-month follow-up assessment. Quality of life is evaluated by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) short form [47] a widely used measure assessing 8 domains of quality of life. The 5-item Work and Social Adjustment Scale (WSAS) [48] is used to assess the degree of interference caused by the patient's OCD symptoms in the areas of work, home management, social leisure, private leisure, and family relationships. The third exploratory aim of this study is to investigate the relationship of distress tolerance to taper completion. The ability to tolerate distress negative emotional states has long been associated with the development and maintenance of psychopathology [49–51] as well as difficulties discontinuing or withdrawing from psychiatric medications as well as drugs of abuse [49]. Thus, it is not surprising that distress tolerance is central to the theoretical basis of numerous therapeutic approaches [49]. Indeed, increasing patients' ability to confront and experience uncomfortable emotions adaptively (non-avoidance) represents a putative mechanism underlying change in the UP [52]. As such, this study investigates whether differences in distress tolerance predict discontinuation outcome more generally, and to pilot distress tolerance as a potential mechanism by which the UP serves to improve discontinuation success. Perceived ability to tolerate emotional distress is assessed with the 15-item self-report Distress Tolerance Scale (DTS) [53] at baseline, mid-treatment (week 7), post-treatment and follow-up.

4.5. Assessment Training

All independent evaluators are Ph.D.-level researchers with extensive prior diagnostic assessment experience. Regardless of familiarity with study assessment measures, all IEs receive additional training on the primary clinical outcome measures prior to conducting study assessments. This includes viewing and rating YBOCS training created by one of the study investigators, also a developer of this measure (S.A.R.). Prior to conducting interviews, IEs must meet a reliability threshold ($ICC = .80$) with established raters. To ensure that valid and reliable data are collected, all interviews are audio-recorded for review. RAs follow our standard training protocol under the direction of the study investigators and the Clinical Assessment and Training Unit at Brown University. This structured training protocol consists of a graduated set of tasks and experiences, beginning with reading relevant papers, studying instruments and instruction booklets, multi-day didactics, watching training tapes, and reviewing suggestions for handling common interviewing problems. RAs are closely supervised during these training sessions and during their initial interviews by the principal investigator (C.L.B.) and OCD research staff. Following training, all assessments are audiotaped for ongoing reliability monitoring.

5. Data Management and Statistical Analysis Plan

5.1. Data collection, management, and assurance of quality

REDCap (Research Electronic Data Capture) [54] is used for data collection, entry and management. REDCap is a secure, password-protected web application designed to support data capture for research studies that includes several features to reduce the amount of missing data and optimize data quality. Paper self-report questionnaires are available if participants prefer, or in the case of technological failure. With the exception of the SCID-I, data from interview-administered measures are entered directly into REDCap by the independent evaluator. Data from the SCID-I are first recorded on paper forms and then are entered into REDCap and verified by research staff. Several data monitoring procedures are implemented to ensure data quality: (1) double data entry for all data recorded on paper forms, (2) systematically recording study notes-to-file in the case of any event that threatens data integrity, and (3) routine internal audits confirming proper informed consent, accurate completion of data forms and documentation of missing data. In addition, a data monitoring and safety board (DSMB) established at the start of the study, provides external monitoring of data integrity.

5.2. Data analysis plan and power considerations

The primary aim of this randomized controlled pilot trial is to evaluate the feasibility and acceptability of both the UP and TAP-M arms to inform a larger investigation. In the past, PIs have used pilot data to estimate an effect size to assist in future power calculations. Although widely adopted, Kraemer et al. [55] emphasized the limitations of this practice due to the likelihood of a large standard error surrounding the effect size estimate. In light of these concerns, we will primarily focus on descriptive statistics to examine both feasibility/acceptability and clinical outcomes. This includes examining rates of study recruitment, participants' willingness to be randomized, session attendance, and patient satisfaction. Additionally, we will compare rates of successful taper completion, symptom worsening,

and resumption of SRI during follow-up across the two conditions. We will also examine differences in means of key variables (e.g., YBOCS, HRSD) across baseline, 14 (post-treatment), 23 (post-booster) and 48-week (6-month follow-up) time points. We will calculate effect sizes (Cohen's *d*) and the associated 95% confidence intervals, in order to understand the precision (or lack thereof) of these estimates. We recognize that, due to the likely size of these CIs, these analyses most likely will not permit definitive conclusions. Thus, the primary goal of this pilot trial is to establish the feasibility and acceptability of the treatment design and interventions in order to support a larger, more definitive trial.

6. Managing participant safety

Monitoring participant safety is paramount in this investigation. Therefore, in addition to the weekly assessment of participant safety detailed above, an external DSMB was established to monitor participant safety and data integrity. The DSMB consists of 4 independent MD or PhD-level board members with expertise in OCD clinical trials, statistical methodology, and medication discontinuation in psychiatric populations. The DSMB meets on a biannual basis to review expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the prior 6 months, any adverse events or serious adverse events (SAEs), and any actions or changes with respect to the protocol. This review is to ensure that participant risk continues to not outweigh study benefits. In addition, the DSMB is available to convene outside of the appointed meeting schedule, if necessary, due to concerns regarding a particular patient, or due to any disconcerting developments in participants' experiences during study. If non-serious adverse events occur at a higher rate in one condition than the other, then the DSMB will make appropriate recommendations for changes to the protocol, if indicated. If SAEs occur at a significantly higher rate in one condition than the other, then the DSMB might consider terminating the trial, if changes to the protocol are unlikely to address the high occurrence of SAEs. A report generated from each of these meetings is retained at the study sites, is forwarded to the IRB, and included in the annual report to NIH.

7. Discussion

Sizeable progress has been made in behavioral and pharmacologic treatments for OCD [56,57], however, there remain significant questions regarding the long-term management of the disorder. This study provides an initial empirical evaluation of whether OCD patients maintained long-term on SRIs can discontinue without symptom exacerbation and examines a potential strategy to increase discontinuation success amongst the range of OCD patients seeking to discontinue. Indeed, this pilot trial aims to test a Unified Protocol approach for discontinuing long-term SRIs in OCD that addresses the emotional avoidance and catastrophic thinking patterns that both maintain the disorder and impede successful discontinuation. Thus, this randomized trial will provide a first step towards identifying optimal long-term treatment strategies for this population, with the overarching goal of improving outcomes for this disabling disorder. There are some limitations to our study design. While our inclusion and exclusion criteria are designed to maximize the safety of participants in this trial, it limits our ability to generalize our results to more severe patient populations or those with high degrees of comorbidity. Second, due to our sample size we

are not able to test for potential differences in outcome between SRIs with different half-lives or discontinuation symptom profiles. Several key questions also remain for future studies including, for example, whether the effects of an emotion-based treatment generalize to discontinuation of other classes of medications such as benzodiazepines or can be more broadly utilized for the range of patients with emotional disorders seeking to discontinue SRIs. The next step after this pilot trial—if hypotheses are supported—will be to conduct a stage 2 trial consisting of a larger randomized controlled trial to investigate efficacy as well as test potential mediators of treatment effects. In addition, it will be important to determine the cost-effectiveness of study interventions relative to continued pharmacotherapy.

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Figure 1.

Overview of Study Design

UP = Unified Protocol for Transdiagnostic Treatment of Emotional Disorders; TAP-M = Taper and Monitoring

Table 1

Summary of Study Timeline

	BL	Acute Treatment															PT	Booster				PB	6M
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	20	22	23	48	
UP/TAP-M		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x			
Psychiatrist			x		x		x		x		x		x		x		as needed						
Symptom Monitoring		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x			
Independent Evaluation	x															x					x	x	
SRI taper goal (% of BL)	100				50				25				0										

Note: BL = baseline, PT = post treatment assessment, PB= post booster assessment, 6M= 6 month follow-up assessment, UP = Unified Protocol, TAP-M = taper and monitoring, SRI = serotonin reuptake inhibitor