Background and Rationale. Long-term antidepressant use is widespread, yet discontinuation remains challenging due to withdrawal symptoms, prescriber hesitancy, and the lack of standardized tapering protocols.[1,2] Under current discontinuation practices, withdrawal symptoms occur in approximately 56% of patients, with rates as high as 86% reported.[2] Different approaches to tapering may lead to fewer withdrawal symptoms and higher discontinuation rates, however, little is known about the acceptability and effectiveness of different approaches to tapering in clinical practice.[2] Clear and evidence-based tapering guidance is lacking, contributing to prescriber reluctance, prolonging unnecessary medication use, and ultimately failing to provide patients with safe and effective discontinuation strategies.[2]

The proposed pilot pragmatic randomized controlled trial (RCT) addresses these gaps by evaluating a structured proportional tapering (SPT) approach, reducing doses by 10% every two weeks. This method aligns with antidepressants' nonlinear properties, whereby serotonin transporter (SERT) occupancy disproportionately decreases at lower doses, making small reductions essential to prevent withdrawal symptoms.[3] Despite its potential benefits, SPT remains under-studied, leaving providers without clear guidance on its effectiveness and implementation.[3] Current guidelines are vague, generally recommending tapering over a few weeks.[4] A standard tapering (ST) approach would be a 50% dose reduction every 2 weeks. By assessing both patient and provider experiences, we aim to evaluate feasibility, acceptability, and clinical outcomes of SPT compared with ST, to inform best practices for antidepressant deprescribing.

Hypothesis and Specific Aims. Hypothesis: SPT for selective serotonin reuptake inhibitor (SSRI) discontinuation will be feasible and acceptable to both patients and providers at 12 months compared to ST. Aim 1: The primary outcome addresses quality outcomes through feasibility and acceptability of the tapering regimens. Feasibility will be measured through recruitment, retention, and adherence to the assigned tapering regimen through proportion of subjects. Acceptability will be measured through surveys of both subjects and providers. Aim 2: Secondary outcomes address clinical and humanistic outcomes through quality of life measured using Short Form-36; withdrawal symptom severity measured using a 7-point scale weekly (1 = not at all, 7 = very much) and the Discontinuation-Emergent Signs and Symptoms scale biweekly; relapse to SSRI defined by an increase in SSRI dose of at least 30% from the current level; relapse to depression using Patient Health Questionnaire-9 or relapse to anxiety using

Generalized Anxiety Disorder-7 at 3 month intervals; and proportion of subjects who successfully discontinue the SSRI.

Innovation. Current SSRI discontinuation strategies often rely on relatively large dose reductions, despite evidence that a gradual proportional tapering approach better accounts for SERT occupancy and mitigates withdrawal symptoms.[3,4] This study leverages our healthcare system to implement a pilot pragmatic trial which evaluates a pharmacist-led deprescribing protocol. Psychiatry pharmacy residents trained on antidepressant discontinuation can assist with distinguishing withdrawal-mediated effects from unrelated symptoms through clinical evaluation and drug information resources, then adjusting doses accordingly. The pragmatic design of this RCT allows for implementation in routine clinical practice with minimal disruption to care and minimal effort from the subject and provider. Additionally, real-time withdrawal symptoms will be assessed using ecological momentary assessment, a simple automated text messaging system that requires minimal effort from the subject. The pragmatic approach allows us to design a future RCT powered to detect efficacy of SPT.

Proposed Study Design and Methods. In the healthcare system, mental health clinic providers will recruit patients through referral. Once subjects are consented, they will be randomized to SPT or ST and the tapering schedule will be shared with the provider. The SPT group will receive a 10% dose reduction of the previous dose every 2 weeks while the ST group will receive a 50% dose reduction of the previous dose every 2 weeks with cessation at the end of week 6. Liquid formulations will be used for incremental dose adjustments. Following our pragmatic approach, the tapering will be a pharmacist-led protocol managed by providers and aided by pharmacy residents, allowing for implementation within usual care and flexibility in clinical decision-making to address discontinuation issues.

Subjects will be recruited via referral from providers who determine readiness for tapering. Inclusion criteria will be patients on an SSRI who providers deem are ready for tapering. Exclusion criteria will be patients at a high risk of psych complications as determined by providers. Data collection will be through chart reviews as well as surveys completed by both subjects and providers. The sample size will be 40 subjects in each group, with a total of 80 subjects to provide a reasonable estimate of feasibility and acceptability. This is a pilot study, so a smaller sample size is reasonable to see if this new tapering regimen is possible. Statistical analyses will include using a t-test for baseline comparisons, Mann-Whitney U test for feasibility

outcomes, and Wilcoxon signed-rank test for acceptability outcomes. Kaplan Meier Curve, Logistic Regression, and Extended Cox Proportional Hazards Model will be used for secondary outcomes. Limitations include the small sample size, which is insufficiently powered to assess clinical outcomes or efficacy. Additionally, the pragmatic design facilitates real-world implementation but may introduce bias due to the lack of a controlled environment and blinding.

This study will be conducted by providers and residents at the Mental Health Clinic. The timeline of this trial will be month 1-2, study set-up and IRB approval; month 3-8, subject recruitment; month 9-20, randomization and follow up to tapering protocol; month 21-24, data analysis and manuscript writing. Due to the budget constraints, this study is designed to be feasible, hence the pilot pragmatic RCT design. Subject compensation will be $10,000, which will be given based on response participation to surveys throughout the course of follow up. Primary Investigatory Salary will be $8,000, based on 5% of their time. Research Assistant Salary will be $29,000, which will provide 1812 hours at $16/hour for data collection and overall trial management. Data analysis will be $1,000 to analyze the primary and secondary outcome measures. Travel will be $2,000 to assist with dissemination of the results once completed.

Future Impact/Dissemination Plan. The impact of this trial will be to inform the design and sample size of future RCTs to test the efficacy of SPT compared with ST. Our study will pave the way for developing SPT protocols for other psychotropic medications, including antidepressants and sedatives, in pharmacist-led tapering clinics that prioritize individualized, safe tapering strategies. Our dissemination plan includes presenting findings within our healthcare system and at national conferences, such as the American College of Clinical Pharmacy and the American Psychiatric Association. Additionally, we will publish the SPT protocol and findings in peer-reviewed journals, such as the Journal of the American Medical Association Psychiatry or The Lancet Psychiatry.

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