A Comparison of Two Antidepressant Tapering Regimens

29 January 2016

NCT02661828

Full Title: A Comparison of Two Antidepressant Tapering Regimens

Short Title: Tapering off Antidepressants

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Draft Date: January 29, 2016

Precis/Abstract:

One hundred adults currently taking an antidepressant for at least four weeks for the treatment of major depressive disorder, an anxiety disorder, obsessive compulsive disorder (OCD) or posttraumatic stress disorder (PTSD) will be randomly assigned to receive one of two different medication tapering regimens. The study will aim to characterize: 1) the clinical characteristics predictive of antidepressant discontinuation symptoms; and 2) which of two tapering regimens is more effective at minimizing antidepressant discontinuation symptoms. Participants will be enrolled in this study ONLY if they no longer wish to take the antidepressant medication they are currently prescribed, due to one of the following reasons: 1) ineffective for symptoms; 2) intolerable side effect; 3) improvement of their illness for sufficient duration that it is clinically appropriate to consider tapering the medication. The study will consist of 4 study visits. At the first visit, all participants will complete a psychiatric interview and questionnaires. The subsequent visits will involve assessment of discontinuation symptoms and mental health symptoms. Upon completion of the antidepressant taper, patients will be assisted in pursuing options for additional treatment if required.

Introduction and Background:

It is widely recognized that abrupt cessation of antidepressant medication (ADM) causes distressing symptoms (known as antidepressant discontinuation symptoms). Discontinuation symptoms can occur regardless of the diagnosis under treatment, whether major depressive disorder (MDD), an anxiety disorder, obsessive compulsive disorder (OCD) or posttraumatic stress disorder (PTSD). These symptoms vary substantially in character, intensity and duration, and there are currently no reliable means of predicting which patients will experience discontinuation symptoms. In most cases these symptoms last less than one week, but occasionally can persist for weeks to months (Fava et al, 2015).

The rates of ADM discontinuation symptoms are not consistent across studies, but the most frequent are as follows:

Symptom	% Patients Experiencing
Worsened mood:	22-45
Irritability/Agitation:	17-35
Anxiety:	12-42
Dizziness:	3-50
Confusion:	10-42
Headache:	13-42

Other less frequent symptoms include vivid dreams, insomnia, nausea, sweating, and electric shock feelings ("zaps"). In rare cases (<1%), suicidal thoughts have occurred (Fava et al, 2015).

An "antidepressant discontinuation syndrome" has been defined in the research literature as the occurrence of 4 or more new or worsened psychic or physical symptoms that arise after stopping an antidepressant (Rosenbaum et al, 1998). Rates of ADM discontinuation syndrome have ranged from 14 – 60% (Baldwin et al, 2006; Khan et al, 2014; Rosenbaum et al, 1998; Sir et al, 2005; Tint et al, 2008).

Most of the research on discontinuation symptoms conducted to date has focused on symptoms arising after cessation of drugs that block the serotonin transporter (selective serotonin reuptake inhibitors, SSRIs, or serotonin norepinephrine reuptake inhibitors, SNRIs). However, before the SSRIs were developed, discontinuation symptoms had been noted to occur with the older tricyclic antidepressants, and case reports have been published for other newer antidepressants that do not affect the serotonin transporter (DIlsaver, et al, 1987). The standard in clinical practice is now to taper off SSRIs and SNRIs, though there is no widely accepted taper rate or protocol to follow when tapering (Ogle et al, 2012). Tapering is often not performed with other classes of antidepressants, though data that could inform clinicians about discontinuation symptoms from those medications is sparse.

Previous controlled studies of antidepressant discontinuation have been conducted on patients who have benefitted from the medication and were willing to be tapered off. The prior randomized discontinuation studies limited to patients who have not responded to their antidepressant had small sample sizes (Tint et al, 2008). Some data suggests that antidepressant side effects at drug initiation may predict eventual treatment response if patients adhere to the medication. It is theorized that certain side effects may reflect the responsivity of biological systems (such as monoamine signaling systems) to the antidepressant (Renoir, 2013). Extending this model to discontinuation suggests that non-responders to medication may have fewer side effects when discontinuing the antidepressant.

Clinical practice would be enhanced if predictors of difficulty tapering ADM could be identified. Currently, very little is known about which patients are likely to develop discontinuation symptoms. The most consistently replicated finding is that the long half-life antidepressant fluoxetine is associated with fewer discontinuation symptoms than the short half-life agent paroxetine. However, discontinuation symptoms are known to arise with fluoxetine cessation, and both these drugs are SSRIs. Identification of patients who will or will not develop difficulty coming off antidepressants is of significant clinical importance because tapers that are longer or shorter than necessary can negatively impact patient care.

This study will aim to assess the frequency of discontinuation symptoms across all classes of antidepressants among patients who have not responded to medication. Only patients who wish to be tapered off their medication will be eligible to participate.

Objectives:

There are two primary objectives to this study:

AIM 1: Compare the tolerability of two antidepressant tapering regimens.

Hypothesis 1. Tapering antidepressant dose over two weeks will be associated a lower incidence of antidepressant discontinuation symptoms than tapering over one week.

Hypothesis 2. Discontinuing medications that inhibit the serotonin transporter (SSRIs and SNRIs) will show greater difference in the frequency of discontinuation symptoms between the two week and one-week tapering regimens than medications that do not inhibit the serotonin transporter.

AIM 2: Identify demographic and clinical features that predict the emergence of antidepressant discontinuation symptoms.

Hypothesis 2. SSRIs and SNRIs will be associated with greater numbers of discontinuation symptoms compared to non-SSRI/SNRI medications.

Hypothesis 1. Duration of treatment will positively associated with the number of discontinuation symptoms.

Study Design and Methods:

Sample

The sample will include 125 subjects currently taking an FDA-approved antidepressant. We anticipate an approximate screen fail rate of 20%, allowing for 100 subjects to enter randomization.

Inclusion Criteria:

1. Male or female, age 18-75
2. Currently taking an FDA-approved antidepressant for at least four weeks.
3. Primary psychiatric diagnosis of major depressive disorder, an anxiety disorder, OCD, or PTSD.
4. Ability to read and understand English language

Exclusion Criteria for all Subjects;

1. Has met criteria at any time during their life for a primary psychotic disorder (e.g. schizophrenia), or dementia.
2. Meets criteria for DSM-5-defined substance use disorder within three months of the screening visit.
3. Currently taking two or more antidepressants.
4. Presents with a clinically significant suicide risk, as assessed by a study physician.
5. Presence of any unstable or central nervous system-related medical illness that would interfere with cognition or participation.
6. Women who are currently pregnant or lactating, or plan to become pregnant during the study.

Setting

The setting of the study will occur in the Mood and Anxiety Disorders Program research clinic at the Emory University Executive Park campus.

Recruitment

Patients will be recruited through advertisements and clinician referral.

Procedures

The study consists of four visits.

Visit 1.

Visit 1 commences with the informed consent discussion and signing the informed consent form for the study. Subsequently, the following procedures will be performed:

1. Demographic information
2. Psychiatric interview and MINI.
3. Clinician ratings of symptoms: MADRS, HAMA
4. Clinician rating of suicidality: CSSRS
5. Clinician assessment of discontinuation symptoms present at baseline: DESS
6. Vital signs (temperature, height, weight, blood pressure, pulse)
7. Urine pregnancy test for women of child-bearing potential.
8. Medical History
9. Past psychiatric treatment history
10. Review of concomitant medications and supplements
11. Review of recall of side effects experienced when starting the antidepressant.
12. Patient questionnaires: DEBS, Q-LES-Q, BIS

Participants with internet access, either by cell phone or computer, will be asked to record their mood symptoms daily on the self-report Scale for Anxiety and Depression (SAD). This is a free internet app available at sad.ecu.edu. Participants will use their de-identified study ID code as their login name to preserve confidentiality. After completing the scale in the office at Visit 1, participants will complete the SAD daily until Visit 4. Participants who lack internet access will be given paper versions of the form to fill out each day.

Upon completion of these components, the patient will be randomized to either Taper A or Taper B (see below). The physician will discuss the tapering process with the patient.

Visit 2

Visit 2 occurs 1 week after initiating the antidepressant taper. The following procedures will be performed:

1. Clinician ratings of symptoms: MADRS, HAMA
2. Clinician rating of suicidality: CSSRS
3. Clinician assessment of discontinuation symptoms: DESS, PWC-20
4. Vital signs (temperature, height, weight, blood pressure, pulse)
5. Review of concomitant medications and supplements
6. Review of adverse events

7. Patient questionnaires: DEBS, BIS, PGI-C

Visit 3:

Visit 3 occurs 2 weeks after initiating the antidepressant taper. The following procedures will be performed:

1. Clinician ratings of symptoms: MADRS, HAMA
2. Clinician rating of suicidality: CSSRS
3. Clinician assessment of discontinuation symptoms: DESS, PWC-20
4. Vital signs (temperature, height, weight, blood pressure, pulse)
5. Review of concomitant medications and supplements
6. Review of adverse events
7. Patient questionnaires: DEBS, BIS, PGI-C

Visit 4:

Visit 4 occurs 3 weeks after initiating the antidepressant taper. The following procedures will be performed:

1. Clinician ratings of symptoms: MADRS, HAMA
2. Clinician rating of suicidality: CSSRS
3. Clinician assessment of discontinuation symptoms: DESS, PWC-20
4. Vital signs (temperature, height, weight, blood pressure, pulse)
5. Review of concomitant medications and supplements
6. Review of adverse events
7. Patient questionnaires: DEBS, BIS, PGI-C, Q-LES-Q
8. Planning of transition of care.
9. Download of SAD daily scale data from website sad.ecu.edu.

Multiple potential referral options will be discussed, depending on the patient's improvement and insurance status. Final referral selected will be based on the patient's preference. Options include referral to a primary care physician, psychiatrist, therapist, community mental health center, or other research studies. If necessary, patients may be seen for 1 or 2 post-study follow-up visits until their care transfer is completed.

Schedule of Events:

BIS: Barratt Impulsiveness Scale; CSSRS: Columbia Suicide Severity Rating Scale; DEBS: Dunlop Emotional Blunting Scale; DESS: Discontinuation Emergent Signs and Symptoms; HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview; PGI-C: Patient Global Impression, Change; PWC-20: Physician Withdrawal Checklist; Q-LES-Q: Quality of Life Satisfaction Questionnaire

Visit Number	**V1**	**V2**	**V3**	**V4**
Day	**0**	**7**	**14**	**21**
Informed consent	X			
Demographics	X			
Vital signs	X	X	X	X
Weight	X			X
Psych/Medical History	X			
MINI v.7.0	X			
Clinician Ratings				
MADRS	X	X	X	X
HAMA	X	X	X	X
DESS	X	X	X	X
PWC-20		X	X	X
Patient Ratings				
DEBS	X	X	X	X
BIS	X	X	X	X
Q-LES-Q	X			X
PGI-C		X	X	X
SAD (Daily)	X	X	X	X
Safety Measures				
Concomitant Meds	X	X	X	X
Adverse Events		X	X	X
CSSRS	X	X	X	X

Taper Regimens:

Taper A:
Days 1-7: Take 50% of baseline dose
Days 8-14: Take 25% of baseline dose
Day 15: Stop antidepressant

Taper B:
Days 1-3: Take 50% of baseline dose
Days 4-7: Take 25% of baseline dose
Day 8: Stop antidepressant

Monitoring for Suicidality
The emergence of suicidal thoughts or behaviors are not considered part of antidepressant discontinuation symptoms, but rather are thought to reflect the breakthrough of a new depressive episode. Patients who do not believe their antidepressant is helping them may nevertheless experience worsening depression with discontinuation of the medication. Therefore, we will conduct a standardized assessment for suicidal ideation or behavior, the CSSRS, at every study visit. Any patient who exhibits and increase in suicidal ideation, any form of suicidal behavior, or about whom the study physician has concern for their safety will be immediately withdrawn from the study and treated as clinically appropriate.

Operationalized Discontinuation Criteria for Suicidality:
Research participants are exited from the study should any of the following occur:

- Any emergent CSSRS defined suicidal behavior
- A suicidal ideation score of 5 (indicating active suicidal ideation with specific plan and some level of intent) on the CSSRS
- In the absence of a CSSRS suicidal ideation score of 5 or CSSRS-defined suicidal behavior, the investigator determines the patient to have a significant short-term risk for a suicide attempt.

Randomization:
Patients will be randomized in a 1:1 manner to Taper A or Taper B. Randomization will be stratified based on mechanism of action of drug (serotonin reuptake inhibitor or not). The two randomization schedules will be created prior to study commencement by a staff member not involved in the clinical components or data analytic components of the study. Randomization assignments will be placed in numbered and sealed envelopes, and opened sequentially for each subject who qualifies for randomization at Visit 1.

Included Medications:
The patient will be responsible for the cost of the antidepressant prescription (if necessary) and going to a pharmacy to get the prescription filled. Antidepressant medications eligible for discontinuation in this protocol include the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone or vortioxetine), SNRIs (desvenlafaxine, duloxetine, levomilnacipran, venlafaxine) and other classes (amitriptyline, bupropion, desipramine, doxepin, mirtazapine, nefazodone, nortriptyline, phenelzine, selegiline, or tranylcypromine). Clomipramine, a tricyclic antidepressant approved for the treatment of OCD, will also be included, but will be classed as an SSRI

for this study because inhibition of the serotonin transporter is its primary therapeutic mechanism.

Measures

Clinician-Rated:

1. The Mini International Neuropsychiatric Interview (MINI, Sheehan et al, 1998), will be used to assess psychiatric diagnoses, which will be confirmed by an interview with a study psychiatrist.
2. The Montgomery Asberg Depression Rating Scale (MADRS, Montgomery & Åsberg, 1979) will assess clinical depressive symptoms.
3. The Hamilton Anxiety Rating Scale (HAMA, Hamilton, 1959) will assess clinical anxiety symptoms.
4. The Discontinuation Emergent Signs and Symptoms (DESS, Rosenthal et al, 1998) questionnaire will assess the frequency of discontinuation symptoms.
5. The Physician Withdrawal Checklist (PWC-20, Rickels et al, 2008) will assess the intensity of discontinuation symptoms.
6. The Columbia Suicide Severity Rating Scale (CSSRS, Posner et al, 2007) will assess for the emergence of any suicidal ideation or behaviors during antidepressant tapering.

Patient-Rated:

1. The Barratt Impulsiveness Scale (BIS, Patton et al, 1995) will assess impulsivity.
2. The Dunlop Emotional Blunting Scale (DEBS) will assess for changes in emotional reactivity.
3. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q, Endicott et al, 1993)
4. The Patient Global Impressions- Change (PGI-C) will assess the patient's overall perceived level of mental health compared to baseline.
5. Scale for Anxiety and Depression (SAD). This 17-item scale is a self-report questionnaire asking about 17 common symptoms of depression over the past 24 hours and anxiety rated on a 1-10 visual analogue scale. The SAD is completed daily, providing a more fine-grained analysis of symptom change over short periods, such as tapering of antidepressants. The scale is accessed through a free internet app and takes approximately 3 minutes to complete.

Payment:

Patients will receive no compensation for participating in this study.

Outcomes:

Primary outcome:

The primary outcome is the change in the DESS, defined as the number of symptoms that are either new or worsened compared to baseline at Visit 4.

Secondary outcomes include:

1. Change in the PWC-20 from baseline to Visit 4
2. Number of patients who meet criteria for antidepressant discontinuation syndrome, defined as ≥4 new or worsened DESS symptoms, at visit during the study.

3. 3. Change in SAD daily score from baseline to peak SAD score during the taper period.

Statistical Analysis:

The primary analyses will be carried out on a modified intent to treat (ITT) sample, which will include all randomized patients who returned for at least one post-randomization study visit. The primary outcome variable is change in DESS score, defined as the number of symptoms that are either new or worsened at Visit 4 compared to baseline (Visit 1). For patients who terminate early the principle of last observation carried forward will be used. If amount of change for the total sample is non-normally distributed, raw change will be log-transformed to approximate a normal distribution before parametric tests are conducted. The primary analysis analyzing the taper groups will be an overall, 2-way ANCOVA, with appropriate covariates, on change in DESS score. Treatment groups will be compared on baseline variables that have a potential relationship to amount of change with the DESS. These include duration in months on ADM, dose equivalents of ADM at Visit 1, gender, age, Visit 1 HAMA score, Visit 1 MADRS score, and comorbid anxiety disorder. Only those Baseline variables that differ among randomized treatment groups at $P<0.10$ and are significantly associated with the primary outcome variable for the entire sample will be entered into the analysis as covariates.

Secondary analyses will include a similar 2-way ANCOVA assessing change from baseline in PWC-20 and SAD peak daily scores between the two taper groups following the same analytic plan as for the DESS. The proportion of patients experiencing the ADM discontinuation syndrome in each taper arm will be compared by Chi-Square test. The frequency of individual discontinuation symptoms between the two taper arms will be assessed using Fisher's Exact Test.

Power Calculation:

An sample size of 48 patients per taper group provides 80% power to detect a clinically meaningful difference of 1.0 points on the DESS, with a standard deviation of 1.75 (at two-sided $\alpha=.05$). With 49 subjects per taper group, we will have 70% power to detect a difference of 20% (10% vs 30%) incidence in ADM discontinuation syndrome.

Adverse event reporting:

Risks to participation

Risks to participation include experiencing side effects from the taking or discontinuing antidepressant medications. All study antidepressants share some risks, including headache, nausea, anxiety, sleep and appetite disturbance. In patients under age 25, antidepressant initiation and dose increase has been associated with a small increased risk of developing thoughts of self-harm or suicidal ideas.

Benefits to subject or future benefits

Patients who participate will receive an expert psychiatric assessment and treatment. With treatment, patients may be able to come off ineffective or no longer desired antidepressant medication. Patients will have the benefit of participating in a clinical trial that could inform future treatment of patients with antidepressants.

Training:

No training will be necessary for the rating scales used in this study because all research personnel involved in this project as they are currently trained and involved in ongoing clinical trials with mentally ill patients.

Confidentiality:

Patient's confidentiality will be maintained throughout the duration of their study participation. Patient files will be kept in locked offices, and the computerized data is kept on password-protected computers in the locked Mood and Anxiety Disorders Program offices.

Informed consent:

At the screening visit, patients will be provided with an informed consent form that will outline the risks and benefits of participating in this study. It will also outline which assessments occur at the various study visits.

Plans to inform participants of new findings or research results that might affect health:

If new findings emerge regarding risks or benefits of the study medications used in our study, patients will be informed of this information as soon as possible and reminded of their ability to continue participation in the study at their own will.

Data and safety monitoring plan (DSMP):

The tapering regimens provided in this protocol are consistent with standard-of-care for MDD, OCD, PTSD and anxiety disorders. It is expected that some patients will experience the known antidepressant discontinuation symptoms – these will not be classified as adverse events. Any unanticipated mental or physical symptoms that are not anticipated as adverse events (i.e., not listed on the DESS scale), or any breaches of confidentiality or other social harms will be coded as adverse events. We will review the adverse event data twice-yearly to evaluate whether unexpected frequencies of adverse events are occurring.

Plans for data management and monitoring:

Data will be stored on an Excel spreadsheet on a password-protected computer, stored in our research clinic.

Pharmaceutical, biologic, and device information:

Package inserts for the antidepressants that could be used in the study are available at http://dailymed.nlm.nih.gov/dailymed/about.cfm

APPENDICIES

Questionnaires and scales attached include:

Hamilton Anxiety Rating Scale (HAM-A)
Montgomery Asberg Depression Rating Scale (MADRS)
Dunlop Emotional Blunting Scale (DEBS)
Barratt Impulsiveness Scale (BIS)
Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q)
Mini Neuropsychiatry Interview, Version 7.0 (MINI)
Discontinuation Emergent Signs and Symptoms (DESS)
Physician Withdrawal Checklist (PWC-20)
Columbia Suicide Severity Rating Scale (CSSRS)
Scale for Anxiety and Depression (paper version)

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