Antidepressant discontinuation in treatment resistant depression

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A B S T R A C T

Treatment-resistant depression (TRD) is a growing problem in psychiatric practice with some 15–20% of depressed patients becoming chronically depressed and perhaps as many as 40% in tertiary settings. Several groups have championed the idea that TRD may be attributed to the long-term treatment with antidepressant drugs (AD). Subjects with the short form of the serotonin transporter gene (both heterozygotes and homozygotes) have an increased risk for depression in the setting of adversity compared to people with the long form. Moreover, these same individuals have a reduced likelihood of responding well to antidepressants, with reports of no response, delayed response, and increased side effects. This hypothesis needs to be examined in a randomized clinical trial. The study will examine the effect of discontinuation versus continuation of serotonergic antidepressants on disease progression in patients with treatment resistant depression. We will recruit 30 subjects and assess the depressive symptoms and disease progression. Genetic testing will be performed to optimize clinical outcome in both groups, but will also be used to evaluate if the short form of the serotonin transporter predicts disease progression and long-term antidepressant treatment response.

1. Introduction

1.1. Background

Major Depressive Disorder (MDD) is a common psychiatric condition that impacts as many as 16% of Americans [1]. While many patients never enter into treatment, the outcome of many that do is frequently suboptimal [2]. Patients who receive treatment and continue to have residual symptoms are at a high risk of having a recurrence, and as many as 50% of treated patients will continue to have residual symptoms [2–4]. Additionally, patients who do respond and experience a recurrence may go on to develop chronic depressive symptoms that are unresponsive to further antidepressant manipulations [5,6].

Treatment-resistant depression (TRD) is a growing problem in psychiatric care with up to 15–20% of depressed patients becoming chronically depressed [7–9] and perhaps as many as 40% in tertiary settings [10]. Furthermore, TRD appears to be increasing faster than generational time [11,12]. TRD has been variously defined as failure to respond to 1 trial of antidepressant monotherapy, failure to respond to 2 or more trials of monotherapy with different antidepressants, or failure to respond to 4 or more trials of different antidepressant therapies, including augmentation, combination, and electroconvulsive therapy (ECT) [5].

The cause of TRD is still poorly understood, and the majority of clinicians believe it is simply a form of severe depressive illness. However, the changing prevalence of TRD, and its apparent expansion in association with the expanding use of antidepressants has led to the idea that antidepressants may have a paradoxical effect [13]. Several groups have championed the idea that TRD may be attributed to the long-term treatment with antidepressant drugs (AD) [11,13–15]. Understanding the potential mechanism of this hypothesized phenomenon may be explained by the short form of the serotonin transporter (5HTTR) [9].

The short form of the 5HTTR is a genetic polymorphism in the non-transcribed promoter region of the *SLC6A4* gene [9]. There is a 44-base-pair insertion/deletion that is respectively called the long (L or l allele) and short (S or s allele) forms of *SLC6A4* or the 5HHTR [9]. The short form of the 5HTTR is associated with roughly a 50% reduction in the number of serotonin transporter units in the synapse compared to those without the short form [16]. Subjects with the short form (both heterozygotes and homozygotes) have an increased risk for depression in the setting of adversity compared to people with the long form [11,12]. Moreover, these same individuals have a reduced likelihood of responding well to antidepressants, with reports of no response, delayed response and increased side effects [11,12]. Similarly, a variant of this allele in which an adenine has been replaced with a guanine

(designated L_G) is also associated with reduced 5-HTTR expression to a level comparable to the short form [17]. When examining effect of genotypes on the course and outcome of depression, the L_G allele is frequently grouped with the S allele.

It is unclear how this increased risk for depression comes about, but neuroplastic changes may play a role. It is known that modification of serotonergic neurotransmission alters arborization of the dendritic tree of serotonergic neurons [12]. The 50% reduction in the number of synaptic serotonin transporters associated with the short form of the serotonin transporter may have many similarities to the chronic 60–85% pharmacological blockade of these transporters that occurs with 5-HT reuptake inhibitors (SRIs) [9]. This suggests that the "s" allele might serve as a model for chronic exposure to a serotonergic AD, particularly when administered to young individuals [11]. In young animals, reducing or eliminating serotonin transporter function causes changes in serotonergic architecture and function and associated increased depressive and anxious behaviors [18,19]. Even in adult animals, it is likely that chronic exposure to antidepressants induces a reduction in serotonergic arborization similar to those that occur in early development of subjects possessing the short form [19].

1.2. Hypothesis

The hypothesis underlying the current study is that TRD may be secondary to the long-term use of antidepressants and that TRD might improve with discontinuation of serotonergic antidepressants. Additionally, it is thought that this outcome is more likely to occur in subjects who possess the short form of the serotonin transporter or L_G allele. It is believed that the greatest likelihood of reversing AD drug effects would be in individuals who have been exposed to ADs for a limited duration, but still "chronically," as might occur in tardive dyskinesia [11,12] Because antidepressants magnify the changes caused by the short form genotype, subjects with the long form of the serotonin transporter may have a more limited response to antidepressant discontinuation.

2. Methods

2.1. Proposed study

In this study, we will attempt to compare disease progression in patients with TRD after slow taper and discontinuation of serotonergic antidepressants over 8 weeks (and possibly shifting them to other categories of antidepressants, i.e., medications that work through dopamine or norepinephrine, or by reducing the serotonin signal rather than increasing synaptic serotonin, as might be accomplished with low dose, sub-antipsychotic doses of some second-generation antipsychotics) versus TRD patients who continue on serotonergic antidepressants (which is current standard of care). We will also try to determine if the short form of the serotonin transporter or L_G allele is preferentially associated with improvement after antidepressant discontinuation in TRD patients.

2.2. Study design

This is a prospective, randomized, controlled, discontinuation study (Fig. 1) which will be performed at one site. The plan is to recruit 30 patients with MDD (meeting Diagnostic and Statistics Manual-5 criteria for major depressive illness as confirmed with the MINI [Table 1]) who have been using serotonergic antidepressants as treatment of depression for at least 2 years but not more than 4 years. We will recruit only subjects with TRD, utilizing the definition of TRD as a minimum of 2 treatment failures of adequate antidepressant courses as confirmed historically by the patient and by using a self-rated scale: Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ). The patients will also be evaluated for the proposed

diagnostic criteria of "tardive dysphoria" or antidepressant-induced depressive symptoms [19]. The investigators will note if the patient has melancholia or mixed depression as we perform our diagnostic evaluation to determine if such patients are overrepresented in our sample. The patients will be randomized to either discontinue serotonergic antidepressants (and possibly shift to other antidepressant categories that were proven to be effective in treating depression, such as pramipexole, bupropion, modafinil, armodafinil, quetiapine, aripiprazole, lurasidone, brexpiprazole or mood stabilizers) or continue on antidepressant medications (controls, and possibly have the same set of medications added to their serotoninergic antidepressant treatment and/or have their antidepressant changed to another antidepressant) on a 1:1 basis with a predetermined schedule (Fig. 1).

As is the standard of care, both groups will have access to other treatment measures of treating TRD; these treatment measures will be equally used in both groups (for example, if aripiprazole is used, it will be added to an antidepressant in the control group, which reflects the standard of care; or will be used without an antidepressant in the experimental group). The study duration is 8 months (Table 1).

Several scales will be collected at the baseline and throughout the study (Table 2). The person performing the data collection (rater) will be blind to the randomization of the patient for the entire duration of the study. The treating clinician and study coordinator and the patients themselves will be aware of the randomization group. Patients will be repeatedly instructed not to reveal their randomization to the rater.

Note that all patients will undergo genetic testing since this is becoming the standard of care for TRD [26,27].

2.3. Inclusion criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

- Subject must be a man or woman 18–70 years of age, inclusive.
- Subject must meet criteria for a major depressive disorder as confirmed by the MINI.
- Subject must have a current Treatment-Resistant Depression as defined below.
- Subject must have been taking serotonergic antidepressants (any medication that increases the concentration of synaptic serotonin such as serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors) for at least 2 years but not more than 4 years, and have failed 2 previous medication trials for the current episode (using MGH-ATRQ).
- Current MADRS score must be $\geq$ 25.
- Subject must be medically stable.
- Female subjects must have a negative urine pregnancy test at screening, and agree to use a birth control method to avoid pregnancy during the study.
- Each subject must sign an informed consent form indicating that he/she understands the purpose of the study and the procedures required and are willing to participate in the study.
- Subject must be able to participate in symptom measurement.

2.4. Exclusion criteria

Any potential subject who meets any of the following criteria must be excluded from participating in the study.

- Subject has a current DSM-5 diagnosis of bipolar disorder or has a positive screening for bipolar disorder by MINI or MDQ.
- Subject has a current DSM-5 diagnosis of schizophrenia, schizoaffective disorder, autistic disorder, or intellectual disability.
- Subject has psychosis or severe personality disorders.
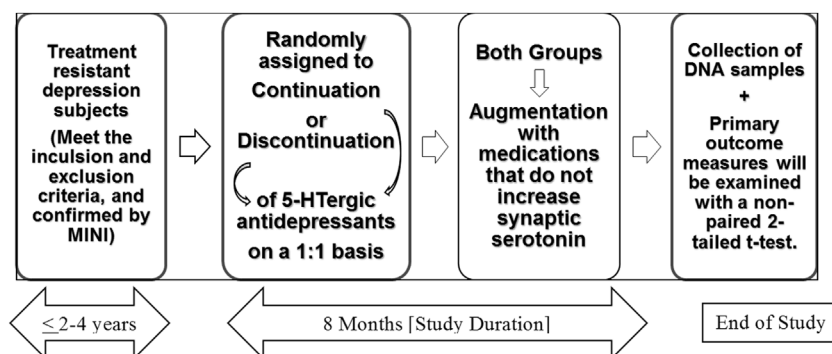- Subject has a substance use disorder (except for nicotine or

Fig. 1. The clinical study examining disease progression of TRD after discontinuation of serotonergic antidepressants.

Table 1

The sequence of study activities. All visits will be 4 weeks ± 1 week apart.

Visit # Activity	Screening	Baseline	AD taper	Maintenance	Study End
	1	2	3–4	5–9	10
Clinical History	✓				
MDQ	✓				
MINI	✓				
MADRS		✓	✓	✓	✓
HAM-A		✓	✓	✓	✓
C-SSRS		✓	✓	✓	✓
SDS		✓	✓	✓	✓

cannabis) within 3 months prior to screening or has a positive drug screen test for any recreational drugs at the time of screening.

- Subject has evidence of any clinically significant, unstable medical problems that may create a safety risk for a subject, interfere with study participation, or make results difficult to interpret.
- Subject is at imminent risk of suicide according to the investigator's clinical judgment and/or a Columbia-Suicide Severity Rating Scale (C-SSRS) ≥ 3 or more at any time in the study.
- Subject is a woman who is pregnant, breast-feeding or planning to become pregnant while enrolled in the study.
- Subject has any condition (according to the investigator) for which participation will not be in the best interest of the subject or it can prevent, limit or confound the protocol-specified assessments.

2.5. Genotyping protocol

2.5.1. Collection materials
Four sterile swabs and a sealable envelope.

2.5.2. Collection procedure

- The patient must not have had anything to eat or drink but water for at least 30 min prior to DNA collection.
- The sterile swabs will be scraped firmly against the inside of one cheek for at least 30 s, then scraped on the opposite cheek for

another 30 s (1 swab = 1 Minute). The process will be repeated with another three swabs.
- The swabs will air-dry upright for approximately 1 h after collection. After air-drying, place tip-end first into the envelope. Storage until shipping will be at room temperature, away from direct light.

2.6. Data analysis

The primary outcome measure is to compare the difference of response as measured by the MADRS between both groups. Two comparisons will be performed. The first comparison will evaluate the end period of the study, i.e., the MADRS score on the final visit. The second will evaluate the long-term effect of treatment by comparing the average MADRS score from midpoint to end of study.

The primary outcome measures will be evaluated with a non-paired, two-tailed t-test. A probability (P) value of ≤ 0.05 will indicate statistical significance.

Secondary outcome measures will include similar evaluations for the HAM-A, C-SSRS, and the SDS.

Regarding the gene testing, all subjects with homozygous and heterozygous low expression alleles will be combined as one group, and all high expression subjects will be the other group. One-way ANOVAs will be conducted for each genotype group, with genotype group as the independent variable (IV) and MADRS and HAM-A scores as the dependent variables (DV). A probability (P) value of ≤ 0.05 will indicate statistical significance.

Since it is an exploratory analysis, the number of 30 subjects with 15 in each group will be sufficient with a moderate power of 0.7.

2.7. Limitations

In theory, the "cleanest" version of the study would very slowly taper patients with TRD off their serotonergic agents and then follow them closely off all treatment for at least a few weeks, seeing whether (as hypothesized) they improve off the medication; however, such a design would be associated with ethical and legal issues, thus it could be a step for the future in a bigger study when more data are available.

It is important to mention that there are many hypotheses which try

Table 2

Scales to be used in the study and the purpose of each scale.

Scales	Purpose	Reference
Montgomery-Asberg Depression Rating Scale (MADRS)	Measures depressive symptoms	[20]
Hamilton Anxiety Rating Scale (HAM-A)	Measures anxiety symptoms	[21]
Columbia-Suicide Severity Rating Scale (C-SSRS)	Measures intensity of suicidal ideations	[22]
Mood Disorder Questionnaire (MDQ)	Screening for bipolar disorder	[23]
Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ)	Screening for treatment resistance in major depressive disorder	[24]
Sheehan Disability Scale (SDS)	Measures level of function or dysfunction	[25]
Mini International Neuropsychiatric Interview (MINI)	A diagnostic questionnaire	[34]
Diagnostic Criteria for Tardive Dysphoria	To validate the diagnostic criteria of tardive dysphoria	[19]

to explain the pathogenesis of depression and mechanisms of action of antidepressants. For example, there is increasing evidence that inflammatory processes and cytokines such as nuclear factor kappa B (NF-κB) are common in depressed patient [28]. Similarly, there may be anomalies in neural plasticity and disruption of cell survival that are reflected, in part, by peripheral brain-derived neurotrophic factor levels; more traditionally, stress response as reflected in hypothalamic-pituitary-adrenal (HPA) axis dysfunction [29]. Our focus on the potential effects on the possible prodepressant effects of antidepressants is borne out of the importance of that possibility for our patients and treatment practices.

We also acknowledge that comorbid conditions such as cannabis use will increase variability. In Louisville, where this study will be performed, cannabis use is so common, that it would be nearly impossible to recruit the target sample if we excluded cannabis users.

3. Discussion

TRD has been a devastating issue in psychiatric settings. In this study, we are exploring the hypothesis that antidepressants might be a major contributor to the development of TRD state. The short form of the serotonin transporter is a natural genetic variant that manifests as a reduction in the number of serotonin reuptake pumps. The fact that inhibition of this same pump is important for the action of most ADs is an important clue to the understanding of TRD. This is because possession of the short form of the serotonin transporter *increases* the risk for depression in the setting of adversity [9]. The additive effect of the short form polymorphism to prolonged antidepressant exposure may underlie onset of TRD. Consequently, the short form may be a clinical predictor of development of TRD and response to antidepressant discontinuation as a therapeutic strategy.

The allele frequency of the short form has a global variation ranging from 11% in African population, 35–61% of Native Americans and reaching up to 70% in East Asians [9]. There also appears to be variation in its effects. For example, while the short form may predict poor antidepressant response in Europeans and North Americans, it does not in East Asians [9]. It is not known why this is the case, but it would suggest that it is important to keep track of ancestry of study participants.

We modeled the study design around similarities of TRD to tardive dyskinesia and the proposed concept of tardive dysphoria [9,11,12]. We specifically limited the duration of chronic depressive symptoms to 4 years because, as in tardive dyskinesia, it is anticipated that the depressive symptoms would be reversible early, after their onset, but would become irreversible when they persist for long periods of time [9,11,12]. According to the hypothesis underlying this study, it is expected that patients discontinuing serotonergic ADs will ultimately have lower MADRS scores compared to patients who will continue ADs. This is akin to the waning of abnormal movements after an antipsychotic is discontinued in tardive dyskinesia. It is difficult to predict whom among subjects with or without the short form, will experience the most significant reduction of MADRS scores with antidepressant discontinuation. However, we anticipate that there will be a significant difference between individuals with and without the short form. Patients with the short form, who will discontinue serotonergic antidepressants, are expected to experience reduction in their anxiety scores and improvement in functionality compared to patients with the short form who will continue serotonergic antidepressants. If the above expectations are met, it will open the door for more research studies on AD discontinuation and its applicability on patients with TRD and/or people who possess the short form.

The concept of ADs being pro-depressant is difficult for clinicians to accept. Some of this is because of the power of language: it is more difficult to believe that an "antidepressant" causes depression than to believe that a "serotonin-reuptake inhibitor" might cause depression [30]. Additionally, clinicians have the *intent* to improve or prevent

depression, so they are less able to believe that their actions may be causing the depression. This is the same effect that increases clinician-observed response in blinded non-placebo trials [31,32]. These, and other factors, create the non-evidence-based belief that ADs cannot induce depression. However, this belief needs to be examined, and randomized discontinuation studies may reveal this to be the case in unipolar TRD, as they have in bipolar depression [33].

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Conflicts of interest

Dr. El-Mallakh has research funding from Janssen and Sage, but not for the current study. He also serves as a speaker for Allergan, Janssen, Lundbeck, Neurocrine, Otsuka, Takeda, and Teva. None of the other authors have conflicts of interest to report.

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