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Predictors of clinical trial discontinuation in trichotillomania: a secondary analysis of previous clinical trials

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Abstract

Background Participant discontinuation is a significant challenge in pharmacological trials for trichotillomania (hair-pulling disorder). Attrition in clinical trials reduces statistical power, introduces error, and potentially wastes financial and medical resources. Identifying predictors of discontinuation may help researchers enhance participant retention and improve study outcomes.

Methods Data from five completed pharmacological trials for trichotillomania were aggregated, and participants were classified as either Discontinued or Completed. Differences in demographic and clinical variables between these groups were analyzed using a generalized linear mixed model.

Results Of the 222 participants, 177 (80%) were categorized as the Completed group. Discontinued patients (20%) were more likely to have achieved higher levels of formal education and were more likely to have a history of depression.

Conclusions This study is among the first to examine variables associated with discontinuation rates in trichotillomania trials. The results underscore the importance of addressing educational background and patient history of depression when assessing dropout risk. These findings can guide future research to better support participants at risk of discontinuing treatment.

Keywords Trichotillomania, Dropout, Discontinuation, Clinical trial, Pharmacotherapy

Introduction

Trichotillomania, a psychiatric disorder characterized by the compulsion to pull one's own hair, affects roughly 1–2% of the population [1]. Behavioral therapy with habit-reversal training is currently the most efficacious treatment of trichotillomania symptoms [2]. However, there is currently no FDA-approved medication treatment for trichotillomania. Previously, individual pharmacological clinical trials of trichotillomania have had efficacious results including SSRIs [3] and glutamatergic modulators [4]. However, within these studies discontinuation rates are often elevated (many studies reporting approximately 30–40% of participants discontinue prematurely) [5] and have consistently cited a lack of information regarding reasons for study discontinuation as a major limitation in the existing literature [6–7].

Demographic variables such as age [8] and ethnicity [9] have shown some predictive value in trichotillomania studies in terms of treatment outcome, but their role as predictors of treatment discontinuation remains unclear.

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Looking to other psychiatric disorders, younger patients were shown to have lower rates of retention in clinical trials for substance use disorders, while neither gender nor race/ethnicity demonstrated significant effects [10]. Similarly, younger age has been linked to a higher rate of attrition in trials for depression [11]. Still, these same demographic variables have not been explicitly studied in psychiatric disorders such as OCD or ADHD.

Clinical variables, such as previous treatment, comorbidity, and symptom severity have been shown to influence retention in pharmacological clinical trials for other psychiatric disorders. In clinical trials for obsessive-compulsive disorder (OCD), the presence of generalized anxiety disorder and agoraphobia have been associated with higher rates of treatment discontinuation [12]. Increased symptom severity has been linked to discontinuation in pharmacological trials for alcohol dependence, although this effect was mediated by motivation for change [13].

Despite the significant consequences of clinical trial discontinuation, little is known about the factors contributing to attrition in pharmacological trials in trichotillomania. Clinical trial discontinuation may weaken the statistical power of trials and delay the development of more effective pharmacological treatments. Therefore, identifying predictors of dropout in clinical trials for trichotillomania is essential to designing trials that can better accommodate at-risk patients and improve retention. This study aims to address this gap by investigating potential predictors of discontinuation, including sociodemographic characteristics and clinical variables. We hypothesize that those participants with greater symptom severity would be more like to discontinue a clinical trial.

Methods

Participants

Participants were aggregated from five pharmacological clinical trials performed at the University of Chicago [4, 14, 15, 16, 17]. All studies were double-blind, placebo-controlled pharmacological studies testing the efficacy of various substances as treatment for trichotillomania. These substances included inositol, naltrexone, memantine, N-acetylcysteine (NAC) and dronabinol. All studies ranged from 8 to 12 weeks with five to six total visits throughout the course of the trial. All participants received the diagnosis of trichotillomania based upon the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV/DSM-5). Exclusionary criteria of chosen studies were as follows: unstable medical illness, history of significant neurological disorder, current pregnancy, current thoughts of suicide, lifetime bipolar disorder, dementia or any psychotic disorder, current (past 3-month) substance or alcohol use disorder, recent illegal substance use based on urine toxicology, previous treatment of the drug in question, and current participation in another clinical trial.

All study procedures, including the consent procedure, were carried out in accordance with the Declaration of Helsinki and were approved by the Institutional Review Board of the University of Chicago. After complete description of the previous studies, participants all provided written informed consent.

Assessments

Trial discontinuation was defined as a participant who enrolled in a trial and did not complete the entire treatment as defined in the protocol. Under this definition, participants who terminated early for any reasons would be characterized as having discontinued the trial. Discontinuation was determined by the principal investigator using this standard definition across all studies. Reason for termination was recorded when available.

In addition to demographic information, participants' medical and psychiatric history was collected. Finally, participants also completed the following measurements: NIMH Trichotillomania Severity Scale (NIMH-TSS) [18], a clinician-administered measure of symptom severity over the past 7 days; Quality of Life Inventory (QoLI) [19], a self-report measure of quality of life examining multiple domains; The Massachusetts General Hospital (MGH) Hairpulling Scale [20], a self-report measure of symptom severity over the past week; Sheehan Disability Scale (SDS) [21], a self-report measure of psychosocial impairment due to trichotillomania in these studies; The Mini-International Neuropsychiatric Interview (M.I.N.I.), a clinician- administered assessment of major psychiatric comorbidity [23]; and The Clinical Global Impression Scale (CGI) (including CGI-Severity and CGI-Improvement component), a self-reported and clinican-reported scale of symptom improvement [22]. For particpants in the dropout group, both CGI scores were taken from their last recorded visit to reflect symptom improvement from baseline. All other measurements used the recorded values at first visit as a measure of baseline symptom severity and comorbidities.

Statistical analysis

Discontinuation was treated as a binary variable, thus placing participants into either the Discontinued or the Completed group. A generalized linear mixed-effects model was performed using SPSS with using a binomial distribution with a logit link function with study as a random effect to ensure proper variance between studies. Predictors that were inconsistently collected across studies such as Race/Ethnicity and Employment were excluded from the model. Additionally, variables that had low occurrence rates (i.e., personality and psychotic co-morbidities) or closely collinear with another variable

(MGH and SDS) were also removed from the model. Statistical significance was defined as $p < .05$.

Results

From a total of 222 subjects, 45 (20.3%) did not complete their respective pharmacological clinical trials and thus fell into the "Discontinued" group while the remaining 177 (79.7%) became the "Completers" group. Rates of discontinuation across all 5 trials, reported reasons for discontinuation, full demographic characteristics and predictors of each individual trial are represented in Supplementary Data.

The overall corrected model was significant, F (14, 207) = 1.835, $p = .035$, indicating the predictors meanigfully explain the variability in dropout. Education had a significant effect such that as level of highest education increased, rates of dropout decreased ($F(4, 207) = 3.036$, $p = .018$). More specifically, patients who achieved less than a high school degree were 93% less likely to dropout than patients with a graduate school level degree or higher ($B = 2.601$, $SE = 0.81$, $p < .01$; Fig. 1).

Additionally, patients with a history of depression were significantly more likely to be dropouts ($B = 1.13$, $SE = 0.44$, $p = .011$). In fact, those with a history of depression were 68% more likely to dropout than those without (Fig. 2).

All other variables were found to be not signifiganct (see Supplemental). Variance for the random effect of study was not significant (Estimate = 1.459, SE = 1.258, Z = 1.16, $p = .246$).

Discussion

The goal of this study was to identify variables associated with discontinuation from pharmacological trials for adults with trichotillomania. It was expected that demographic and clinical variables may be predictive of attrition and our results partially supported these hypotheses. Regarding demographic variables, only education level was found to be a significant predictor of dropout. This trend appears to be driven by the low number of dropouts from lower education attainment. It is possible that attaining a higher level of education equips patients with greater knowledge or greater financial or schedule flexibility to search for alternatives if a patient decides they no longer wish to continue with a trial. This finding is consistent with the previous literature [24] in which

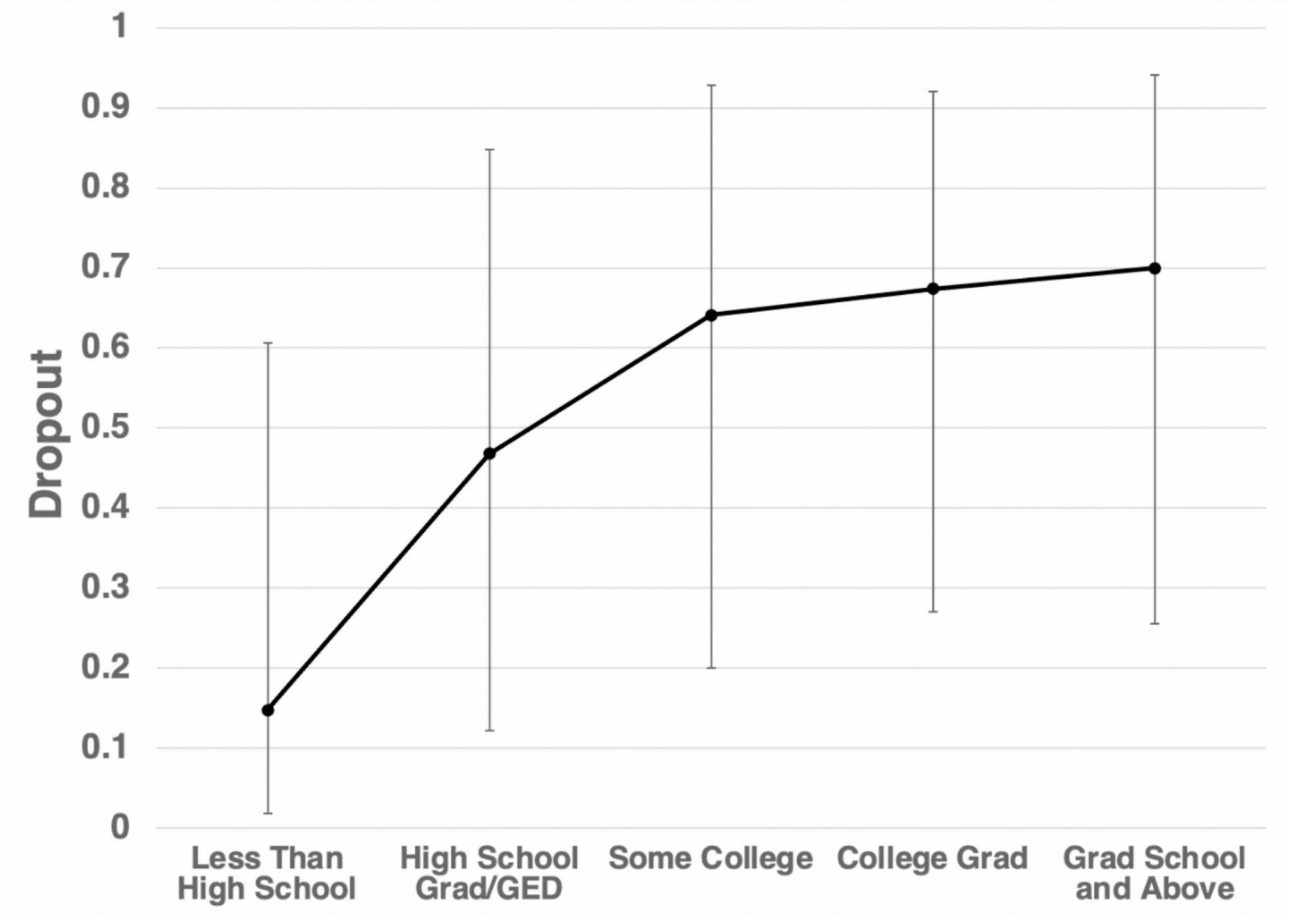

Fig. 1 Estimated Dropout Means of Education

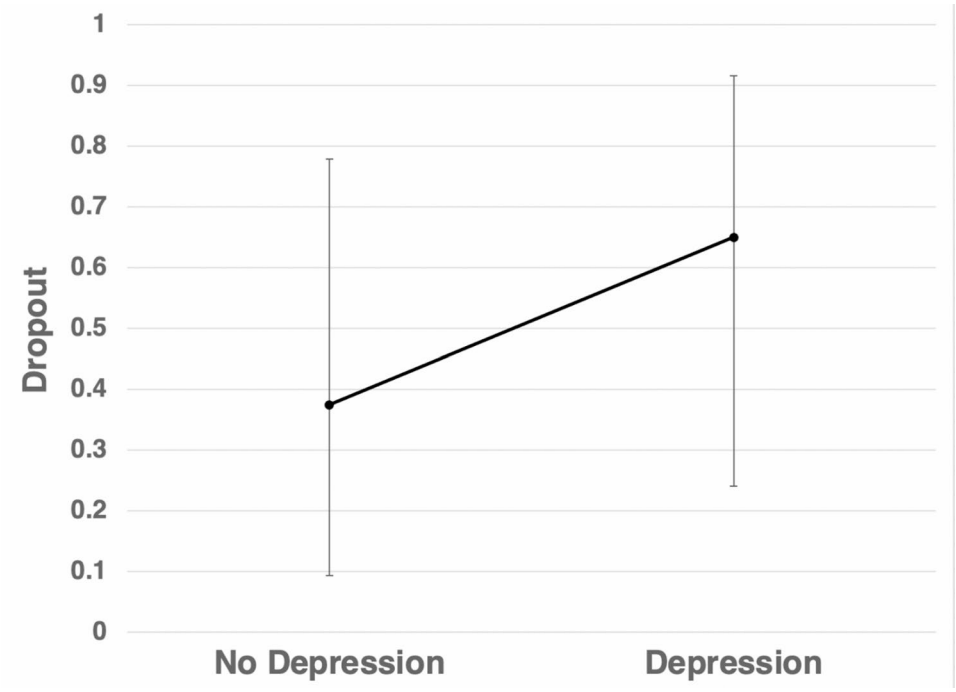

Fig. 2 Estimated Dropout Means of History of Depression

education level was associated with discontinuation in a behavioral trial for depression. Unlike various other disorder studies [10–11], age of those who discontinued did not differ significantly from those who completed the trials. However, consistent with prior with literature [10], gender did not significantly predict dropout. Due to protocol differences, race/ethnicity was not collected for a majority of the studies and thus had to be excluded from our model. It is also worth noting that the majority of participants in these studies were female and Caucasian. This relative lack of diversity further limits our ability to discern the use of gender and race/ethnicity as predictors for discontinuation.

With regrads to co-morbidities, patients with a history of depression were more likely to dropout. Depression has not been previously implicated as a predictor of dropout in prior literature. However, within the context of a randomized control trial this finding could have a few explanations. Patients with a history of depression may begin to feel hopelessness about their treatment earlier in the trial resulting in dropout. Alternatively, increased fatigue or lower motivation would make paitents with depression more likely to be lost to follow up. In contrast to prior literature that previously implicated both lower [25] and higher [26] baseline symptom severity in attrition, symptom severity of trichotillomania patients was not found to be a significant predictor of dropout. Similarly, presence of adverse events also did not significantly predict dropout. Taken together, this seems to indicate that attrition is not necessarily dependent upon the response to treatment by itself nor by the negative effects that some patients experienced during the trial.

These findings must also be interpreted within the context of the current state of trichotillomania treatment. Currently there are no FDA-approved pharmacological treatments specifically for trichotillomania. Moreover, it is arguably more difficult to find a health professional for treatment of trichotillomania than for more common disorders such as depression or anxiety. Due to these more limited options, participants who join trichotillomania trials may be more inclined to stay the course of the trial. If true, this may provide a possible explanation as to why factors that had previously been implicated in attrition of pharmacological trials of other psychiatric disorders such as age or symptom severity did not follow the same trend with trichotillomania patients.

There are limitations to the current study, particularly sample size and demographics. While the current study chose to aggregate trials from a singular site, it would be beneficial to aggregate more trials such as Doughtery et al. (2006) [27] or van American et al. (2010) [28], especially to enroll a more diverse and representative patient population. As such, generalizability of the current study may be limited. Furthermore, by treating dropout as a binary, our ability to capture the nuances of timing and reasoning for dropout. While we attempted to address this problem by analyzing dropouts before and after the halfway point of their respective study, it is still a relatively narrow view of attrition.

Regrading the model, the creation of the generalized linear mixed model required the exclusion of many of our collected variables due to missing values and collinearity. This limited our ability to properly address all our potential predictors at once, notably race/ethnicity, employment and other measures of symptom severity. Ideally, thorough collection of these demographic and clinical factors in their entirety would allow for proper assessment of their importance in attrition. Additionally, it must be noted that the confidence intervals of both education and history of depression are somewhat large, possibly due to limited sample size or the nature of our binary dependent variable. Finally, future studies should also consider pursuing other demographic variables such as socioeconomic status as well as other cognitive measures such as the Barrett Impulsive Scale or Start Stop Task. Impulsivity, a related cognitive measure to inhibition response, is common hallmark of trichotillomania and thus may also play a role in patient discontinuation.

Still, the problem of trial discontinuation remains prominent in trichotillomania studies. Overall, there was a 23% dropout rate among participants with an almost equal number of particpants dropping out before (52%) and after (48%) the midway point. This indiscriminate dropout temporally suggests that length of trial is not a significant factor when it comes to dropout. Taken together with the fact that group assignment and presence of adverse events also were not implicated in rates of discontinuation, most participants appear willing to tolerate the current double-blinded methodology of clinical trials. The main reason cited for participants "dropping out" from our aggregated trials was not due to the design of the trials themselves, but rather due to loss to follow up or not showing up to check-ins. While it may not be possible to intervene in a patients' prior education attainment or history of depression, it is vital that researchers recognize and combat these factors with intentional efforts to provide additional support. Interventions may include clear communication and expectation setting reinforced throughout the trial, more flexible scheduling and increased check-ins offered over telephone or telehealth in order to more actively evaluate patient feelings of potential attrition and intervene before becoming lost to follow up.

Conclusion

As pharmacological trials for trichotillomania continue to advance, addressing participant dropout is crucial. To the best of our knowledge, our study is among the first to specifically examine dropout in trichotillomania patients, revealing that study dropout was associated with participants with higher educational attainment and a history of depression. In recognizing these trends, researchers should implement strategies such as more frequent check-ins or to improve retention of participants that fall into these categories, leading to more robust and diverse clinical trial data and better outcomes for future studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-07360-8.

Supplementary Material 1

Author contributions

TL and JEG designed and implemented the study. TL drafted the article. Both authors revised and edited the article. TL performed data analysis.

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Data availability

The dataset generated and/or analyzed during the current study are not publicly available due to subject confidentiality but is available from the corresponding author on reasonable request and with a data sharing agreement in place.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the University of Chicago approved all of the previous studies and the consent statements. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. After complete description of the previous studies, participants all provided written informed consent.

Consent for publication

Both authors consent for publication.

Competing interests

Dr. Grant has received research grants from Janssen, Boehringer Ingelheim, and Biohaven Pharmaceuticals. He receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies and has received royalties from Oxford University Press, American Psychiatric Publishing, Inc., Norton Press, and McGraw Hill. Mr. Lam reports no conflicts.

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