Quantification of early treatment discontinuation: a retrospective analysis on 4,810 participants to CNS clinical trials

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SUBMISSION DETAILS

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Methodological Issue Being Addressed This work aims at precisely quantifying the magnitude and temporality of early treatment discontinuation, across countries and dosing frequencies. To do so, electronic medication adherence data from previous CNS clinical trials were combined and analyzed using Kaplan-Meier survival curves.

Introduction Early treatment discontinuation is frequent in clinical trials (40% of participants discontinue within 1 year) and must be considered when planning and running such a trial. The usual approach is to recruit around 20% additional participants to compensate, costing $44,000 per single additional participant in a CNS trial.

Electronic recording of medication intakes can be performed using smart medication packages: bottle caps, blisters, injectors, inhalers, pill dispensers... Such packages electronically record a timestamp each time a participant uses their medication. The resulting data allows to (1) quantify how well a participant follows the prescribed regimen, and (2) determine the exact day on which the last dose is taken, which is more precise than other approaches for estimating time to treatment discontinuation.

Methods Electronic medication intake data from past clinical trials were collected, anonymized (at participant, drug, sponsor, site, and smart package levels), harmonized, and pooled. Selected trials were a convenience sample of recent trials in which AARDEX Group was involved for the data analysis.

Using electronic medication intake data, the actual time on treatment was derived for each participant. The event of interest was early treatment discontinuation, for whatever reason. When available, sponsor-provided information about who dropped out from the study was used. When such data was not available, early treatment discontinuation status was determined by comparing the duration on treatment to the expected follow-up duration. A Kaplan-Meier survival curve was built from the pooled dataset.

Implementation adherence, i.e., how well a participant took the medication, was computed as the proportion of prescribed doses taken while on treatment. A Cox regression was performed with implementation adherence as a predictor of early treatment discontinuation.

Results Data from 7 studies were included, performed between 2019 and 2025. These studies enrolled a median number of 801 participants (Q1: 299.5, Q3, 1129); total: 4,810 participants. Dosing frequency was mostly once (58%) or twice (42%) daily. The median expected follow-up duration was 365 days (Q1: 244, Q3: 896). The median one-year persistence was 69%. Six percent of participants never initiated the treatment.

A worse implementation adherence was significantly associated to a higher risk of early treatment discontinuation (coefficient = -1.3, $p < 0.005$). In other words, participants with 80% implementation adherence had 14% more chance of discontinuing treatment early than those with 90% implementation adherence.

This study is the first to report a meta-analysis of persistence to CNS trials specifically. Previous studies reported persistence pooled across several therapeutic areas. The results that were reported in these general studies are consistent with the present one. In particular, the rate of early treatment discontinuation is similar for CNS trials and for trials in other therapeutic areas.

Conclusion Early treatment discontinuation is common, even in the controlled environment of CNS clinical trials. Implementation and early discontinuation are inter-related. These findings highlight the importance of continuously monitoring and improving medication adherence.

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Keywords

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medication adherence
treatment discontinuation
early discontinuation

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