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Why do indiviuals with schizophrenia drop out of observational clinical trials?

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ABSTRACT

Randomized controlled trials (RCTs) and observational studies frequently differ with regard to study dropouts. The present naturalistic follow-up investigation aimed to shed a light on this issue by evaluating the time to and the reasons for study dropout in patients suffering from schizophrenia who started monotherapy with an oral new-generation antipsychotic. To this end, psychopathological symptoms and safety data were assessed in 194 patients who were followed up to a maximum observation period of twelve months. 9.3% of study participants completed the study. The mean time to study dropout was 2.6 ± 2.7 months with almost two thirds of patients dropping out within three months. 44.3% discontinued medication at the date of study dropout, the remainders dropped out due to withdrawal of written consent, logistic reasons, or nonappearance to the study visit ("loss to follow-up"), which were not necessarily to be equated with cessation of the antipsychotic. These findings indicate that in contrast to RCTs, dropout of observational studies is not necessarily associated with drug discontinuation. Accordingly, systematic differences between trial designs need to be considered when interpreting the results of clinical trials.

1. Introduction

The efficacy of antipsychotic drugs in the short-term and maintenance treatment of schizophrenia has been documented in numerous clinical trials (Hasan et al., 2012, 2013). Nevertheless, discontinuation of antipsychotic medication is a common phenomenon and has been used as a measure of ineffectiveness in the management of schizophrenia, because it reflects both the physician's and patient's judgement of drug efficacy, safety, and tolerability (Kahn et al., 2008; Lieberman et al., 2005).

Several antipsychotic effectiveness trials, including the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) (Lieberman et al., 2005) and the European First Episode Schizophrenia Trial (EUFEST) (Kahn et al., 2008) have used drug discontinuation as the primary outcome measure. Generally, the use of new-generation antipsychotic medication has been associated with lower dropout rates than first-generation treatments (Rabinowitz et al., 2009). However, due to selection bias and high attrition rates (Hofer et al., 2000) data from randomized studies are not easily generalizable to optimal antipsychotic drug treatment in everyday clinical practice. For example, 74% of patients included in CATIE discontinued treatment within 18 months of observation, whereas patients who were treated in a naturalistic setting stopped treatment at a much lower rate of 45.5% within the same time frame (Vita et al., 2012). Amongst others, these inconsistencies have been hypothesized to result from differences in study design. It has to be noted, however, that due to abstaining from symptom selection or a placebo arm, CATIE is not a typical randomized controlled trial (RCT), and a recent naturalistic 18-months study reported on discontinuation of treatment in up to 90% of patients (Chan et al., 2017).

In a retrospective study with naturalistic design, Pai and Vella (2012) found that approximately half of 151 patients ceased treatment with clozapine within the first six months of treatment and only one third continued therapy beyond twelve months. Notably, own decision (40%) and non-compliance (36%) were the main reasons for cessation, followed by medical complications (17%), poor response (3%), and other reasons (4%). Due to the exceptional role of clozapine in treating patients who respond poorly to other antipsychotics and due to its complex safety profile these findings clearly apply to a special patient population and are not attributable to all individuals suffering from schizophrenia.

Obviously, the definition of dropouts differs considerably between studies. In some instances, they present the primary outcome variable of interest, in others, they are only superficially described and treated

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as missing values in final analyses. Within the rigorous procedure of RCTs, this issue is generally given more attention than in studies applying a naturalistic design, which are related closer to everyday clinical practice. In any case, understanding the reasons behind dropping out of a study greatly contributes to understanding and interpreting the results of clinical trials. Therefore, the purpose of this naturalistic follow-up investigation was to evaluate the time to and the reasons for study dropout in schizophrenia patients who started monotherapy with an oral new-generation antipsychotic except for clozapine.

2. Methods

The data utilized in this post-hoc analysis were based on a study designed to build a drug monitoring register. From October 1997 to September 2010 patients aged between 18 and 65 years who were treated in an in- or outpatient unit of the Department of Psychiatry, Psychotherapy and Psychosomatics of the Medical University Innsbruck were allocated to the study when starting monotherapy with an oral new-generation antipsychotic except for clozapine. The diagnostic criteria of a schizophrenia spectrum disorder according to ICD-10 served as a basis for study inclusion. Diagnoses were confirmed using chart information and reports from the referring clinicians. Following discharge from the hospital participants who had been recruited at an inpatient unit were treated at a specialized outpatient clinic. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the Medical University Innsbruck. All patients gave written informed consent for study participation.

Patients who had been pre-treated with antipsychotics were included into the study after a wash-out period of 3–5 days in those on oral treatment and one injection interval in those on long-acting injectable medication. Exclusion criteria included unmanaged somatic illness and concomitant antipsychotic medication. Antipsychotics were chosen by the psychiatrists treating the patients, dosing followed clinical needs. Benzodiazepines were permitted to treat agitation, anxiety or sleep disturbances, biperiden/propranolol for extrapyramidal symptoms, akathisia as well as hypersalivation, and antidepressants and mood stabilizers to counteract clinically significant mood swings.

Symptom severity and side effects of medication were rated by using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987), respectively. The UKU Side Effect Rating Scale comprises a total of 48 symptoms, arranged into four groups: psychic, neurological, autonomic, and other side effects. Each symptom is scored on a severity scale and the rater assesses whether the report is best attributed to a side effect (rated as improbable, possible or probable) or related to the disease. Ratings were completed by psychiatrists belonging to a trained schizophrenia research team. In addition, metabolic syndrome, liver and renal functions, differential blood count, prolactin level, and electrocardiogram were monitored regularly.

Compliance was regularly assessed by clinical interviews and plasma level monitoring (for details, see Rettenbacher et al., 2004; Kaufmann et al., 2016). Patients were assessed at baseline, on a weekly basis during the first six weeks of treatment, at week 8, and at monthly intervals thereafter. The maximum observation period was twelve months.

The reasons for study dropout were categorized into “poor response” (based on both the physician's and patient's judgement), “non-compliance” (drug adherence less than 80% according to clinical interview + an observed plasma level being lower than the expected plasma level of the antipsychotic drug measured), “side effects”, “suicide”, “withdrawal of written consent”, “logistic reasons” (i.e. relocation or continuing treatment at another facility), and “nonappearance”. The former three reasons were equivalent to stopping the current treatment, whereas the latter three were not necessarily associated with subsequent treatment discontinuation and were summarized under the category “loss to follow-up”.

2.1. Statistical methods

Prior to the analysis, all metric outcome variables were scrutinized for deviations from normality by investigating their skewness. If skewness values exceeded 1 or −1, variables were subjected to a “normalizing” transformation (logarithm or square root). One-way analysis of variance was applied to compare groups on metric variables (time to study dropout, PANSS baseline score, and change in PANSS). Analysis of covariance was used to analyze changes in PANSS score by dropout reason, adjusting for PANSS baseline scores.

Moreover, Cox regression analysis was used to identify variables affecting time to dropout. Potential predictors considered were age, sex, duration of illness, type of antipsychotic medication, PANSS total score at baseline and change of PANSS total score. The latter variable was considered as a time-dependent covariate where time was split into four intervals (baseline, weeks 2–4, months 2–3, months 4–12) and changes of mean PANSS scores between adjacent time intervals were used in the analysis. The forward stepwise selection method was applied for the identification of significant predictors. The censoring variable was defined such that treatment discontinuations were counted as events, whereas dropouts due to loss to follow-up were regarded as censored observations.

In addition, separate Cox regression analyses for the three individual reasons for treatment discontinuation were performed: poor response, side effects, and non-compliance. For this purpose, the censoring variable had to be redefined, counting only those patients as events who dropped out for the reason in question and regarding all other dropouts as censored.

3. Results

3.1. Sample characteristics

Demographic and clinical characteristics of the study sample are summarized in Table 1. Altogether, 194 patients (59.3% males) with a mean age of 35.5 years and a mean duration of illness of 7.4 years were included into the study. Baseline symptomatology was moderate. All new-generation antipsychotics that are approved in Austria were used. Olanzapine was prescribed most frequently, followed by amisulpride, and risperidone.

3.2. Time to dropout

Fig. 1 illustrates the percentage of patients dropping out of the study over time. Altogether, the mean time to dropout was 2.6 ± 2.7 months (treatment discontinuation: 2.5 ± 2.8 months, loss to follow-up: 2.6 ± 2.6 months). 30.6% of patients dropped out within the first month (treatment discontinuation: 14.4%, loss to follow-up: 16.2%), further 30.9% during months 2 and 3 (treatment discontinuation: 13.9%, loss to follow-up: 17%), 16% during months 4–6 (treatment discontinuation: 6.2%, loss to follow-up: 9.8%), and 12.9% during months 7–12 (treatment discontinuation: 5.7%, loss to follow-up: 7.2%). A small proportion of 9.3% continued on treatment beyond twelve months. As shown in Table 1, the time to dropout did not differ between dropout categories.

3.3. Reason for dropout

Fig. 2 displays the reasons for dropout. A total of 90.7% of study dropouts were recorded. Among these, 44.3% dropped out due to discontinuing medication, 1 patient committed suicide. The majority of patients (54.1%) dropped out due to loss to follow-up. Altogether, patients who dropped out over the course of the study had a significantly higher mean PANSS total score both at baseline and at last observation