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Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis

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ABSTRACT

Background: Several national guidelines recommend continuous use of antipsychotic medication after a psychotic episode in order to minimize the risk of relapse. However some studies have identified a subgroup of patients who obtain remission of psychotic symptoms while not being on antipsychotic medication for a period of time. This study investigated the long-term outcome and characteristics of patients in remission of psychotic symptoms with no use of antipsychotic medication at the 10-year follow-up.

Methods: The study was a cohort study including 496 patients diagnosed with schizophrenia spectrum disorders (ICD 10: F20 and F22–29). Patients were included in the Danish OPUS Trial and followed up 10 years after inclusion, where patient data was collected on socio-demographic factors, psychopathology, level of functioning and medication.

Findings: 61% of the patients from the original cohort attended the 10-year follow up and 30% of these had remission of psychotic symptoms at the time of the 10-year follow up with no current use of antipsychotic medication. This outcome was associated with female gender, high GAF-F score, participation in the labour market and absence of substance abuse.

Conclusion: Our results describe a subgroup of patients who obtained remission while not being on antipsychotic medication at the 10-year follow-up. The finding calls for further investigation on a more individualized approach to long-term treatment with antipsychotic medication.

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1. Introduction

Schizophrenia is a mental disorder displaying great heterogeneity regarding symptomatology, long-term outcome and functioning (Harrow and Jobe, 2010; Austin et al., 2013). This aspect of diversity calls for a treatment strategy that takes the various outcomes into consideration. Existing guidelines recommend 1–2 years of antipsychotic medication after a first episode psychosis, however continuous use of antipsychotic medication is preferred among multiple episode patients

in order to minimize the risk of relapse. The recommendations are based upon results from randomized clinical trials showing that discontinuation increases the risk of relapse (Takeuchi et al., 2012; Hasan et al., 2013; Leucht et al., 2012).

A recent review on discontinuation has reported trials with relapse rates as high as 79% within 12 months of discontinuation. Yet, none of the trials followed the patients for >3 years and long-term studies are lacking (Zipursky et al., 2013; Emsley et al., 2013). At present, no consensus exists on the optimal duration of antipsychotic medication after remission of psychotic symptoms, but there is a tendency towards recommending long-term treatment (Takeuchi et al., 2012; Hasan et al., 2013; Leucht et al., 2012). A recent study on patients with first-episode psychosis that applied a guided discontinuation/dose reduction strategy revealed that 20% of the patients were able to obtain stable remission without continuous use of antipsychotic medication or dose reduction. Patients who discontinued had twice the relapse rate after 18 months (Wunderink et al., 2007). However, the 7-year follow-up showed no

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significant difference in relapse rate between patients on antipsychotic medication and patients who completed discontinuation or dose reduction (Wunderink et al., 2013).

Since antipsychotic medication can cause adverse effects e.g. extrapyramidal symptoms and a highly increased risk of metabolic syndrome, it is important to identify which patients might be able to obtain stable remission without continuous use of this medication (Leucht et al., 1999; Mitchell et al., 2013). This subgroup is not fully taken into account in the present guidelines and further investigation on long-term perspectives is needed. Regardless of antipsychotic medication, proper management of symptoms both on short and long-term basis is of great importance, since it has a major effect on functional outcome (Cassidy et al., 2010).

The Danish OPUS trial and cohort has investigated patients with a first episode psychosis in a time course of 10 years, which has enabled a thorough investigation on long-term outcome. This study design allows for a large degree of generalizability due to the long follow-up period and the large patient population with a high level of representativity (Petersen et al., 2005). The purpose of this study is to examine the proportion of patients who did not receive antipsychotic medication at the 10-year follow-up and who at the same time had remission of psychotic symptoms. Furthermore, we aim to identify different characteristics associated with this favourable outcome.

2. Methods

2.1. Study design

This study was based on data from the Danish OPUS-cohort, consisting of 578 patients, aged between 18 and 45 years and diagnosed with psychotic illness, i.e. within the F20–F29 spectrum according to the ICD-10. Patients with a diagnosis of schizotypal disorder were excluded from the data set, given that the main focus of this study is on psychotic illness, resulting in a study population of 496 patients.

At the time of recruitment the patients had not received antipsychotic medication for > 12 weeks. The patients were originally recruited to participate in the OPUS trial, which was a randomized clinical trial investigating the effect of an intensive early-intervention program. The recruitment took place in 1998–2000, where individuals with a first episode psychosis were included from major public psychiatric centers in Copenhagen and Aarhus, Denmark. The participants were considered representative of patients with first-episode psychosis since 90% (Aarhus) and 63% (Copenhagen) of all patients from the catchment areas with a registered first-episode psychosis were included in the trial (Petersen et al., 2005; Bertelsen et al., 2008).

2.2. Assessments

Extensive follow-up assessments were carried out 1, 2, 5 and 10 years after the initiation of the OPUS trial. At each follow-up demographic data, vocational and social status were obtained. The psychiatric diagnoses at baseline were verified applying Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). SCAN-interviews were also used to identify substance abuse at all follow-ups. Psychotic and negative symptoms were assessed using the Scale of Assessment of Positive Symptoms (SAPS) and the Scale of Assessment Negative Symptoms (SANS) covering symptoms 3 months prior to the interview at the 10-year follow-up (Andreasen et al., 2005). The examiners were all trained in the use of SCAN, SANS and SAPS, and common ratings were conducted throughout the follow-up period to ensure reliability. In addition to the psychiatric assessments, a reading test “Danish Adult Reading Test” (DART), corresponding to National Adult Reading Test, was conducted at the 5-year follow-up to assess premorbid IQ level (Hjorthøj et al., 2013).

To evaluate the level of functioning, we used a subdivided version of Global Assessment of Functioning, where GAF-S and GAF-F were

separate (Endicott et al., 1976). The duration of untreated psychosis (DUP) was estimated using the Interview for Retrospective Assessment of Onset of Schizophrenia (Häfner et al., 1992). Moreover, patient interviews covering the intake of antipsychotic medication and the level of compliance regarding all psychopharmacological medication were conducted at each follow-up.

2.3. Definition of outcome: Remitted-off-medication, Remitted-on-medication, Non-remitted-off-medication and Non-remitted-on-medication

To evaluate the long-term relationship between the use of antipsychotic medication and psychotic symptoms, we divided the patients' outcome into four groups: Remitted-off-medication, Remitted-on-medication, Non-remitted-off-medication and Non-remitted-on-medication (Table 1). The grouping of the patients was based on two parameters: scores in the SAPS interview and intake of antipsychotic medication. To be considered non-psychotic, the global scores for hallucinations, delusions, bizarre behavior or thought disorder should be lower than 3. This cut-off value corresponded to the widely acknowledged Andreasen-criteria for remission (Andreasen et al., 2005). In order to be considered in the category of patients on antipsychotic medication, the patient had to have a regular use on daily basis or as depot medication. Patients who did not take their prescribed antipsychotic medication at all were considered completely non-compliant and were allocated into one of the two groups with no use of medication (Remitted-off-medication, Non-remitted-off-medication).

The patients in the Remitted-off-medication group did not use antipsychotic medication on a daily basis and were rated non-psychotic. Non-psychotic patients who did have a daily intake of antipsychotic medication were categorized as Remitted-on-medication. Patients who were rated as psychotic and without using antipsychotic medication regularly were defined as Non-remitted-off-medication, while the patients who were medicated with antipsychotic medication, but still had psychotic symptoms were considered Non-remitted-on-medication (Table 1).

2.4. Statistics

Statistical analyses were conducted using SPSS 20.0. In order to calculate odds ratios for a better outcome the 4 groups were transformed into an ordinal variable, where Remitted-off-medication was considered the best outcome, Remitted-on-medication as the second best followed by Non-remitted-off-medication and finally Non-remitted-on-medication considered as the worst outcome. Univariable and multivariable analyses were carried out using ordinal logistic regression and a *p*-value below 0.05 was considered significant. The variables included were the baseline variables gender, age, age of onset, DUP, High school degree and diagnosis. Variables from the 10-year follow-up included vocational status, negative dimension, GAF-F and substance abuse. Additionally one variable from the 5-year follow-up, DART, (only conducted at the 5-year follow-up) was included. When conducting multivariable analyses on GAF-F and vocational status, the two variables were left out of each other's logistic regression due to co-linearity. Furthermore the variable negative dimension was left out of the

Table 1

Categorization of the 303 participants into remitted-off-medication, remitted-on-medication, non-remitted-off-medication and non-remitted-on-medication:

	No antipsychotic medication	Regular use of antipsychotic medication
Non-psychotic global scores* < 3	Remitted-off-medication	Remitted-on-medication
Psychotic global scores* > 2	Non-remitted-off-medication	Non-remitted-on-medication

Global scores* = global scores on hallucination, delusion, bizarre behavior or thought disorder from the SAPS interview at year 10.

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