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Lifetime antipsychotic medication and cognitive performance in schizophrenia at age 43 years in a general population birth cohort

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ABSTRACT

This naturalistic study analysed the association between cumulative lifetime antipsychotic dose and cognition in schizophrenia after an average of 16.5 years of illness. Sixty participants with schizophrenia and 191 controls from the Northern Finland Birth Cohort 1966 were assessed at age 43 years with a neurocognitive test battery. Cumulative lifetime antipsychotic dose-years were collected from medical records and interviews. The association between antipsychotic dose-years and a cognitive composite score based on principal component analysis was analysed using linear regression. Higher lifetime antipsychotic dose-years were significantly associated with poorer cognitive composite score, when adjusted for gender, onset age and lifetime hospital treatment days. The effects of typical and atypical antipsychotics did not differ. This is the first report of an association between cumulative lifetime antipsychotic dose and global cognition in midlife schizophrenia. Based on these data, higher lifetime antipsychotic dose-years may be associated with poorer cognitive performance at age 43 years. Potential biases related to the naturalistic design may partly explain the results; nonetheless, it is possible that large antipsychotic doses harm cognition in schizophrenia in the long-term.

1. Introduction

Neurocognitive deficits occur in the majority of persons with schizophrenia (Heinrichs and Zakzanis, 1998; Keefe et al., 2005). They are present before the first psychotic episode, remain relatively stable over the illness course (Bora and Murray, 2014; Zipursky et al., 2013) and are strongly associated with functional outcome (Rajji et al., 2014).

Antipsychotic medication is the foundation of treatment recommendations in schizophrenia, yet the associations of antipsychotic medication with cognition, especially in the long-term, after 5 or more years of illness, remain largely unclear (Husa et al., 2014). The

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cognitive effects of antipsychotic medication have mostly been studied early in the course of illness in relatively short follow-ups ranging from 1 to 3 weeks to 2–3 years. Meta-analyses of these studies have found mild to moderate cognitive improvements associated with the use of both atypical (Désaméricq et al., 2014; Woodward et al., 2005) and typical (Mishara and Goldberg, 2004) antipsychotic medication in schizophrenia.

However, naturalistic, cross-sectional studies have suggested that higher doses of antipsychotics (Élie et al., 2010; Hori et al., 2006; Torniainen et al., 2012) or antipsychotic polypharmacy (Hori et al., 2006) may be associated with poorer cognitive functioning in schizophrenia, supported also by the finding of a positive effect of dose-reduction on cognition (Kawai et al., 2006; Takeuchi et al., 2013).

Very little is known about the effects of antipsychotic medication in the long-term (Leucht et al., 2012). In particular, the effects of several years or lifetime treatment with antipsychotics on global cognition in schizophrenia have not yet been studied. Because many schizophrenia patients receive antipsychotic treatment for several years or permanently, it is imperative to study the effects of not only short-term but also lifelong antipsychotic treatment. Randomised controlled trials (RCTs) are able to primarily determine the efficacy and adverse effects of a treatment, but they do not allow a more detailed and long-term assessment of adverse effects (Young et al., 2015). Naturalistic samples, however, offer an optimal setting for investigating the long-term effects of medication (Wang et al., 2011), that often are impossible to study in RCTs. In the Northern Finland Birth Cohort 1966 (NFBC 1966), higher lifetime cumulative doses of antipsychotic medication were associated with poorer performance at age 34 and a decline in verbal learning and memory between ages 34 and 43 years in schizophrenia (Husa et al., 2014). We wanted to continue this research line to investigate the effects of lifetime cumulative dose of antipsychotic medication on a more comprehensive measure of cognition in midlife in a larger, partly overlapping sample.

This study aimed to analyse the association between cumulative lifetime antipsychotic dose and cross-sectional global cognition in schizophrenia at the age of 43 years. Our hypothesis was that higher lifetime antipsychotic dose would be associated with poorer cognition, even when potential confounders, such as severity and duration of illness, are taken into account.

2. Methods

2.1. Sample

2.1.1. Participants

The participants of this study were members of the Northern Finland Birth Cohort 1966. The NFBC 1966 is an unselected, general population birth cohort identified during mid-pregnancy based on an expected delivery date during 1966 in the provinces of Lapland and Oulu. It comprises 12 058 live-born children, representing 96% of all births in the region (Rantakallio, 1969). Permission to gather data was obtained from the Ministry of Social and Health Affairs. The study design was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.1.2. Case identification

The NFBC 1966 members with a lifetime psychosis diagnosis were identified using data from national registers. Psychosis diagnoses by the end of 1997 were detected from the Care Register for Health Care (formerly Finnish Hospital Discharge Register) and these diagnoses were validated using hospital notes (Isohanni et al., 1997; Moilanen et al., 2003). In addition, newer psychosis cases were detected based on Care Register for Health Care on those registered first time for a psychosis between 1998 and 2008; Social Insurance Institution of Finland register data on sick leaves or disability pensions due to psychosis, or the right to reimbursement for psychoactive medication due to psychosis by the end of 2008; or having reported a psychosis or current antipsychotic use (at least 300 mg chlorpromazine equivalent) in 1997 in a questionnaire data collection (Haapea et al., 2010).

Based on this procedure, 257 NFBC 1966 members with a psychosis diagnosis and known address were invited and 99 (38.5%) individuals participated in a psychiatric interview and examination in 2008–2011 at an average age of 43 years. The examination included the SCID I interview (First et al., 2002) leading to DSM-IV lifetime diagnosis. Based on diagnostic interview and information from national registers, 69 individuals had a diagnosis of schizophrenia spectrum disorder. In the end, 60 (87.0%) were able to complete the cognitive test battery and had adequate information on antipsychotic medication. Of these 50 (83%) had a DSM-IV lifetime diagnosis of schizophrenia, 6 (10%) schizoaffective, 2 (3%) schizophreniform and 2 (3%) delusional disorder. Hereafter, the term schizophrenia is used for schizophrenia and other schizophrenia spectrum disorders. Part of this sample (40 cases, 67%) went through the same diagnostic interviews as well at 34 years of age when participating in another psychiatric examination where we analysed associations between lifetime antipsychotic medication and change of verbal learning and memory in schizophrenia between ages 34 and 43 years (Husa et al., 2014). The mean duration of illness of the sample was 16.5 years (SD 6.0) and average age was 43.1 years (SD 0.8).

In addition, 450 non-psychotic NFBC 1966 members from all around Finland were invited to participate in the same psychiatric interviews and cognitive assessment in 2008–2011. 191 (42.4%) control subjects with an average age of 43.8 years (SD 0.8) and available cognitive test results were included in the final analyses.

Written informed consent was obtained from all cases and controls. Participating cases did not differ from non-participating cases in gender, number of cumulative lifetime hospital treatment days or occupational status. Compared to non-participants, participating cases had significantly lower education (basic education 28% vs. 15%, secondary education 62% vs. 85%, tertiary education 10% vs. 0%) ($p=0.001$), lower age of illness onset (mean 30.1 years vs. 26.6 years) ($p=0.002$), they were more often on a disability pension (26% vs. 50%) ($p=0.001$), and had more often diagnosis of narrow schizophrenia (68% vs. 84%) ($p=0.024$). Participating controls did not differ from all non-psychotic members of the NFBC 1966 in gender, education or disability pension status. Compared to non-participants, participating controls were more often working (71% vs. 95%) ($p < 0.001$).

2.2. Data on antipsychotic medication

Information on the lifetime use of antipsychotic medication, until the day the person was examined in the 43-year study, was gathered in 2007–2014 by a careful review of hospital, outpatient and health centre medical records of all cases from everywhere in Finland. This information was used to calculate the cumulative lifetime antipsychotic dose, expressed as dose-years of a daily dose of 100 mg chlorpromazine equivalent. Medication data was not only based on prescribed medication but if there was indication that a patient had not taken medication it was taken into account in the estimation of lifetime doses. This procedure is described in more detail in our previous work (Husa et al., 2014). Additionally, current and earlier use of antipsychotic and other psychiatric medication was ascertained in an interview in the 43-year study.

2.3. Neuropsychological assessment and cognitive composite score

The neurocognitive performance of all cases and controls was evaluated using a cognitive test battery comprising the Abstraction Inhibition and Working Memory task (AIM; Glahn et al., 2000), California Verbal Learning Test (CVLT; Delis et al., 1987), Visual