



# Clozapine use in childhood and adolescent schizophrenia: A nationwide population-based study



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## Abstract

Early onset schizophrenia (EOS) begins in childhood or adolescence. EOS is associated with poor treatment response and may benefit from timely use of clozapine. This study aimed to identify the predictors of clozapine use in EOS and characterize the clinical profile and outcome of clozapine-treated youths with schizophrenia. We conducted a nationwide population-based study using linked data from Danish medical registries. We examined all incident cases of EOS (i.e., cases diagnosed prior to their 18th birthday) between December 31st 1994 and December 31st 2006 and characterized their demographic, clinical and treatment profiles. We then used multivariable cox proportional hazard models to identify predictors of clozapine treatment in this patient population. We identified 662 EOS cases (1.9% of all schizophrenia cases), of whom 108 (17.6%) had commenced clozapine by December 31st 2008. Patients had on average 3 antipsychotic trials prior to clozapine initiation. The mean interval between first antipsychotic treatment and clozapine initiation was 3.2 (2.9) years. Older age at diagnosis of schizophrenia [HR=1.2, 95% CI (1.05–1.4),  $p=0.01$ ], family history of schizophrenia [HR=2.1, 95% CI (1.1–3.04),  $p=0.02$ ] and attempted suicide [HR=1.8, 95% CI (1.1–3.04),  $p=0.02$ ] emerged as significant predictors of clozapine use. The majority of patients ( $n=96$ , 88.8%) prescribed

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clozapine appeared to have a favorable clinical response as indicated by continued prescription redemption and improved occupational outcomes. Our findings support current recommendations for the timely use of clozapine in EOS.

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## 1. Introduction

A significant proportion of individuals with schizophrenia present during childhood or adolescence. Childhood onset schizophrenia (COS), defined as schizophrenia diagnosed before the age of 13 years, is rare and affects about 1:40,000 children (Gochman et al., 2011). Adolescent onset schizophrenia (AOS) is more common as approximately 5% of cases present between the ages of 13 and 17 years (Cannon et al., 1999). The term early-onset schizophrenia (EOS) is commonly used when referring to both COS and AOS.

EOS is diagnosed using the same criteria as adult onset schizophrenia and lies on the same neurobiological continuum (Rapoport et al., 2005). Compared to the adult onset cases, EOS is associated with more pronounced developmental and premorbid deviance (Vourdas et al., 2003) and greater genetic loading evidenced by higher prevalence of family history of psychosis (Ahn et al., 2013), increased rates of genetic abnormalities, particularly copy number variations (Addington and Rapoport, 2009), and possibly more penetrant common risk-conferring polymorphisms (Addington and Rapoport, 2009). Substance abuse, particularly use of cannabis in early adolescence, appears to be more prevalent in EOS (Kumra et al., 2005), may precipitate the earlier onset of psychosis (Schimmelmann et al., 2012; Large et al., 2011), and lead to greater symptom severity and poor treatment response (Kumra et al., 2005). The effect of these risk factors may be further exacerbated by urbanicity (Kuepper et al., 2011) and social adversity (Heinz et al., 2013).

EOS is also associated with unfavorable clinical and psychosocial outcome (Röpcke and Eggers, 2005; Remschmidt et al., 2007; Schimmelmann et al., 2007; Vyas et al., 2007). A further concern is increased suicidality, particularly in adolescent patients (Jarbin and Von Knorring, 2004; Falcone et al., 2010; Shoval et al., 2006; Sanchez-Gistau et al., 2013). Up to 32% of AOS patients may attempt suicide prior to their first admission (Falcone et al., 2010; Shoval et al., 2006), up to 12% in the two years following the first admission (Sanchez-Gistau et al., 2013) and approximately 25% in the subsequent ten years (Jarbin and Von Knorring, 2004). Moreover, the 10-year prevalence of completed suicide in EOS following the first admission is reported to be as high as 5% (Jarbin and Von Knorring, 2004).

Antipsychotic medication is the mainstay treatment for EOS as is the case with adult onset cases. However, antipsychotic agents, regardless of pharmacological class, are only partially effective in EOS with acute response rates ranging from 34% to 50% (Sikich et al., 2008; Findling et al., 2010). The prevalence of poor treatment responders in EOS is therefore consistently high (Sikich et al., 2008; Findling et al., 2010). As clozapine has shown superior efficacy in treatment-resistant adult patients with schizophrenia, several clinical trials and observational studies have examined its efficacy and tolerability in EOS

(Schneider et al., 2014). We have recently reviewed this literature (Schneider et al., 2014) which shows that clozapine is associated with significant symptomatic relief and sustained clinical improvement in EOS. These benefits need to be balanced against a wide-range of clozapine-induced adverse drug reactions (ADRs) that necessitate close monitoring of patients' physical health. The most common ADRs in EOS are sedation and hypersalivation (reported in 90% of patients), followed by enuresis and constipation (up to 60%) (Schneider et al., 2014). Weight gain and metabolic changes are also relatively common (8–22%) but emergent diabetes is infrequent (<6%) (Schneider et al., 2014). Although hematological ADRs are potentially the most concerning, neutropenia occurs in a small minority of EOS patients (6–15%) and is usually transient while agranulocytosis is rare (<0.1%) (Schneider et al., 2014). There are no reports of fatalities in this age group. The average all-cause discontinuation rate of clozapine in EOS is very low (<6%) (Schneider et al., 2014).

The most recent international guidelines recommend the use of clozapine in refractory EOS and provide a clear framework for ADR monitoring (McClellan et al., 2013; NICE, 2013). Despite this, the use of clozapine in EOS is generally thought to be both limited and delayed. For example, less than 0.4% of all clozapine prescriptions in the UK are for EOS patients (Cirulli, 2005) and nearly 40% of psychiatrists working in child and adolescent inpatient units have never prescribed clozapine (Cirulli, 2005). This suggests that clinical decision-making in connection to clozapine initiation in EOS is influenced by variables beyond clinical response or tolerability. However, systematic data addressing this issue are currently lacking. Accordingly, the purpose of this study was to identify the clinical features that predict clozapine treatment in EOS. We hypothesized that age at diagnosis, suicidality and cannabis abuse may emerge as significant predictors of clozapine treatment and that the influence of these factors may be modified by sex, urbanicity, and social adversity.

## 2. Experimental procedures

### 2.1. Case identification

We used linked data from the Danish Psychiatric Central Research Register (DPCR) (Mors et al., 2011), the National Prescription Database (Kildemoes et al., 2011), the Danish Civil Registration System (CRS) (Pedersen et al., 2006) and the Integrated Database for Labor Market Research (IDA) (Munk-Jørgensen and Østergaard, 2011).

The DPCR covers the entire Danish population including immigrants and contains information on all admissions to inpatient psychiatric facilities since 1969 and all visits to specialty outpatient and emergency services since 1995 (Mors et al., 2011; Munk-Jørgensen and Østergaard, 2011). Diagnoses both for patients and their first-degree relatives followed the International Classification of Diseases, 8th revision (ICD-8) (WHO, 1967) till 1994 and the 10th revision (ICD-10) (WHO, 1992) thereafter. We used the DPCR to identify all patients with schizophrenia

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