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**Treatment of ADHD in adults – prevalence of discontinuation and associated factors –
results from a cross-sectional analysis of Danish register data**

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Abstract

Background

A growing number of adults are receiving pharmacological treatment for ADHD but a sizable proportion also discontinue or have gaps in treatment. The primary aims of this study were to identify how many patients treated for ADHD in adulthood, have at least one event of discontinuation in treatment and to identify possible associated variables.

Methods

Within the Danish population aged 18-60 years the 1st of January 2013, we identified the number of individuals who had been prescribed ADHD-medication at least once during 1st of January 2002 to 31st of December 2013 using Danish register data. Among those who filed more than one prescription, treatment discontinuation was defined as having more than 211 days between two prescriptions. In crude and adjusted logistic regression analysis, we explored potential associations to discontinuation for variables such as gender, and age at treatment initiation.

Results

In a population of $N=3,165,844$ individuals, $n=42,892$ had received at least one prescription for ADHD medication. Among those with more than one prescription ($N=38,289$), 29.4% had discontinued their treatment at least once, according to our definition of treatment discontinuation. ADHD treatment discontinuation was associated with being male, unemployment, lower educational attainment, receiving incapacity benefits and younger age at treatment initiation ($p<0.001$).

Conclusions

A large proportion of individuals treated for ADHD had at least one discontinuation of treatment according to our definition. Although the present study does not allow for investigating the direction of these effects, nor whether some patients later resumed treatment, having at least one discontinuation was associated with a range of variables relating to e.g. age and gender, and provides an emerging profile for clinicians of patients more likely to discontinue.

Keywords:

ADHD; treatment; compliance; discontinuation; stability

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a chronic condition that often continues into adulthood (Caye et al., 2016), and is associated with an increased risk of for instance developing substance use problems, anxiety disorder, affective disorders (Chang et al. 2016). The prevalence of ADHD in adulthood has been estimated at 2.5% (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). Both stimulant and non-stimulant medication have been found to be effective in reducing core symptoms and some impairments in adults (Cortese et al., 2018; Cunill, Castells, Tobias, & Capellà, 2016) and are recommended in clinical guidelines (NICE, 2018). Studies from national registers also suggest that during periods of active psychopharmacological treatment of patients with ADHD may experience a decrease in risk of negative outcomes such as traffic accidents and engaging in criminal activity (Chang, Lichtenstein, D’Onofrio, Sjölander, & Larsson, 2014; Chang et al., 2017; Lichtenstein et al., 2012).

Due to the persistent and often chronic nature of ADHD symptoms, individuals with ADHD often require long-term pharmacological treatment. Despite the effectiveness of ADHD medications in the short term (Caye, Swanson, Coghill, & Rohde, 2019) treatment discontinuation is common (Gajria et al., 2014). In this and other papers, the terms discontinuation or gaps in treatment need to be considered synonymously, as it is often impossible to conclude whether an episode of discontinuation is permanent or just a gap in treatment unless data covering a vast number of years is accessible. In the literature, discontinuation is often defined as having at least six months or more between prescriptions (Bahmanyar et al. 2013; Pottegaard et al. 2015). High discontinuation rates have been observed across the world (Bhang et al., 2016; Ferrin & Taylor, 2011; Newlove-Delgado, Ford, Hamilton, Stein, & Ukoumunne, 2018; Pottegård et al., 2013; Wang et al., 2016; Wu et al., 2017; Zetterqvist, Asherson, Halldner, Långström, & Larsson, 2013). A large Danish register

based study found that 5.3-14.2% of the Danish population treated with ADHD medication discontinued treatment after having received only one prescription (Pottegård et al., 2013), and among adolescents and adults who initiated treatment 50% had discontinued their treatment after just 1.1-1.8 years (Pottegård et al., 2013).

A systematic review on medication discontinuation in patients with ADHD (Gajria et al., 2014) highlighted the heterogeneity and complexity of the factors leading to discontinuing treatment. Lack of symptom control, dosing inconvenience, social stigma associated with ADHD medication, and the patient's attitude, beliefs and knowledge about medication are all cited as common reasons for medication discontinuation (Brinkman et al. 2012; Gajria et al., 2014).

Few studies have explored medication discontinuation in naturalistic follow-up data in order to investigate which patient or treatment variables are associated with discontinuation. Studies have identified the transition from childhood to adolescence and adolescence to adulthood as an at risk period (Pottegård et al., 2013; Zetterqvist et al., 2013). There is conflicting evidence about whether there are gender-differences or an impact of comorbid psychopathology on treatment discontinuation (Bahmanyar et al., 2013; Kooij et al., 2013; Soendergaard et al., 2016). For adults with ADHD, the decision to discontinue pharmacological treatment for ADHD is often taken without medical consultation, but discontinuation can also be related to lack of access to continuous care as well as side-effects, and perceived lack of efficacy (Matheson et al., 2013).

Aims

Given the conflicting results of previous studies, especially those that have explored treatment discontinuation using naturalistic follow-up, this study aimed to analyse a large Danish dataset based on administrative data of adults in treatment with ADHD medication. The primary aims

of the study were to characterise individuals receiving treatment with ADHD medication in adulthood, and to estimate variables associated with at least one discontinuation.:

Materials and methods

Design

The present study is study was a descriptive study, based on data from a range of Danish national health and social registers (Erlangsen & Fedyszyn, 2015). The data had been extracted, organised, and delivered by Statistics Denmark in two separate datasets without individual level data (microdata). This limited the level of detail of analysis, and restricted the authors to using the predefined variables.

The two datasets differed in sample size due to restrictions from Statistics Denmark, specifying that all cells had to include a minimum of five observations, which is the reason why sample size differed between the two datasets. The first dataset is the main dataset used in this paper and contained data on 3,165,844 adults. This first data-set contained all the information, presented in this paper, except for data about participants' employment status and whether they received incapacity benefits. The second data-set included data on 3,163,332 adults and was used only to provide information about employment status and incapacity benefits.

Population

This study included information on the Danish population aged 18-60 years on the 1st of January 2013. Data from the National Prescription Registry (NPR), which contains information

on prescriptions dating back to 1995, was used to define ADHD treatment. In Denmark, initiation of pharmacological treatment with ADHD medications is a task exclusively undertaken by trained psychiatrists or licensed neurologists, or paediatricians. The majority of services are organized within the public health care system in outpatient services. Patients access services through referral from e.g. a general practitioner (GP). Assessment and treatment is funded by public health care, and prescribed medication is subsidised by the state (maximum annual expenses typically do not exceed 550 Euro).

The definitions used to identify ADHD treatment and other variables are outlined below.

Variable description

ADHD-medication

The NPR was used to define a range of variables containing information on ADHD drug prescription. ADHD-medication use was defined as having claimed at least one prescription for ADHD medication during 1st of January 2002 to 31st of December 2013. ADHD drugs were identified by using the Anatomical Therapeutic Chemical Classification System codes (ATC). All medication types under the ATC code N06BA (including e.g. dexamphetamine, methylphenidate, atomoxetine and lisdexamphetamine) were included, except N06BA01 (amphetamine) and N06BA07 (Modafinil), as these two drugs are not indicated for ADHD treatment in Denmark. Despite including almost the entire range of drugs under ATC code N06BA, statistics from the Danish Health Data Authority (medstat.dk) identify that the vast majority of treated adults during 2002-2013 were treated with methylphenidate (Table 1). As presented in table 1, atomoxetine was first used in ADHD treatment from year 2006, and during our observation period atomoxetine became the second most frequently prescribed drug for treatment of ADHD in adults. Lisdexamphetamine was introduced in 2013. Thus only a

smaller proportion of the adult population in treatment with ADHD medications during the period covered by the dataset, would have received medication other than methylphenidate and atomoxetine..

[Table 1 near here]

Discontinuation

In case a patient had more than one prescription recorded, data from NPR was used to identify the number of individuals with at least one discontinuation of treatment. Discontinuation was defined as having more than 211 days between two prescriptions. This definition approximates that of previous studies using 180 days between prescriptions as a means of defining discontinuation (Bahmanyar et al. 2013, Pottegaard et al. 2015), and therefore a gap of this duration must be considered a crude, but conservative definition. Discontinuation status was defined as a binary variable (No discontinuation or at least one discontinuation).

Since the dataset did not include microdata, we had no access to information about duration of treatment, nor information about whether patients stopped or started treatment again after a gap.

Age at first prescription for ADHD medication

From the NPR another variable specifying age at first ADHD medication prescription was available. To form this variable, information for the entire period of coverage available in the NPR (1995-2013) had been used to form five mutually exclusive categories for age at first prescription; i) 0-10 years, ii) 11-17 years, iii) 18-25 years, iv) 26-36 years, and v) 37 years or older.

Age of the sample

Using the Danish Population Registry age at the 1st of January 2013 was identified. This data was used to construct four mutually exclusive categories; i) age 18-24 years, ii) age 25-30 years, iii) age 31-45 years and iv) age 46-60 years.

Highest achieved education

Using the Danish Education Registry (DER), the highest achieved education level by October 2012 of the sample was defined. Data on highest achieved education was obtained by November 2012, since there is a delay in the update of the DER. Highest achieved educational level was categorized into six mutually exclusive categories; i) Elementary school (0-10th grade), ii) high-school, iii) Vocational training, iv) short education (typically 1 to 2 years in addition to high school or vocational training) (v) middle-long education (bachelor degree, master degree or further) or vi) Missing.

Employment status

Using the Registry on the Danish Workforce the employment status of the population by November 2012 was identified. This data was used to form three categories; i) Employed, ii) unemployed (includes unemployed individuals on income support and other temporary benefits), and iii) outside the workforce (including for instance students and people on retirement benefits).

Income support

Statistics Denmark provided information on individuals who received income support based on data from the registry of public benefits. A binary variable was provided from Statistics Denmark that specified whether a person had received income support for more than six consecutive months (182 days) during the time-period 2007-2013. In Denmark, state benefits are a government provided income replacement given to unemployed citizens who are not members of an unemployment insurance fund.

Incapacity benefits

Statistics Denmark provided information on individuals receiving incapacity benefits based on data from the registry of public benefits. A binary variable was provided from Statistics Denmark that specified whether a person had received incapacity benefits for more than three consecutive months (91 days) during the time-period 2007-2013. In Denmark, people who are employed, self-employed or unemployed can receive incapacity benefits if they are unable to work for a shorter or longer period of time due to for instance illness.

Treatment with selective serotonin reuptake inhibitors (SSRI)

As an indicator of comorbidity, this study obtained information about SSRI treatment history. To identify a treatment history with SSRI, data from NPR during 1995-2013 was used to identify the ATC codes N06A and N05B. This period covers all the years data has been collected for the NPR. Using this data, two variables had been formed; i) ever treated with SSRI (yes/no), and ii) treated with SSRI prior to first ADHD prescription (yes/no)

Statistical analysis

Data was analysed descriptively reporting N and percentages for all variables. In our analyses concerning adults receiving treatment for ADHD, data was stratified on age groups at the 1st of January 2013. Binary logistic regression analyses were performed to identify potential variables associated with discontinuation. In these analyses, we estimated the crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI). In the adjusted analyses, the following variables were entered: gender, age at first prescription for ADHD medication, lifetime SSRI treatment history, educational achievement and income support. Due to the limited number of observations in some subcategories in the variable on educational achievement, we collapsed short, middle and long educations into one category, and left out subjects missing information on educational achievement. In all analyses the alpha level were set at 0.05. The data was analysed using SPSS 25th edition (IBM corp, 2017).

Results

Sample description

In the main dataset based on N=3,165,844 individuals, N=42,892 had received at least one prescription for ADHD medications, and N=3,122,952 had not received treatment for ADHD during the period of data-coverage (See flowchart in Figure 1). A description of the sample of treated and untreated individuals is presented in Table 2. Treated individuals were more likely to be male, to be younger, and to have achieved less education. They were also more likely to be unemployed, to have received both income support and incapacity benefits, and to have received SSRI treatment during their lifetime. For individuals treated with ADHD medications 10.7% had received only one prescription. Of those treated who had more than one prescription (N=38,289), 29.4% had discontinued their treatment at least once, according to our conservative definition of treatment discontinuation.

[Table 2 and Figure 1 near here]

Description and comparison of males and females treated for ADHD

This, and the remaining part of the analyses, focus on the population of those treated for ADHD, who had more than one prescription (N=38,298). Table 3 and Table 4 presents descriptives stratified for age category and gender, and we include comparisons of genders by age.

First, for the outcome variable of interest, we observed that males were significantly more likely to have at least one discontinuation compared to females across all age-categories ($p<0.001$) except for those age 46-60 years, where no significant difference was detected ($p=0.679$). The proportion with at least one discontinuation was higher among the youngest age-group, and differences between the genders diminished when looking across the age-categories.

Across the age categories, females were significantly older at first prescription ($p<0.001$), and more likely to have received SSRI treatment prior to initiating ADHD treatment and lifetime ($p<0.001$). The prevalence of lifetime SSRI use was remarkably high for both genders across all age-categories, for instance 66.9% in males and 85.2% in females in those aged 25-30 years the 1st of January 2013. Females also tended to have higher educational attainments compared to males ($p<0.001$). For instance, in males aged 25-30 years and 31-45 years, 2.2 to 8.7% had middle-long educations, while the corresponding finding in females was 8.1 to 18.5%. In contrast, males were significantly more likely to have only the state mandatory elementary school as highest educational attainment (e.g. 65.8% of males vs. 59.9% of females in the age-group 25-30 years), but considering that the sample consisted of adults, the proportion with no formal education was large

for both genders. Males were significantly more likely to be employed compared to females, whereas a higher proportion of females were outside the workforce at the time the data was collected. For income support, more females ages 18-24 years and 25-30 years had received income ($p<0.001$) compared to males, but there was no significant difference between genders for those aged 31-45 years ($p=0.750$). Among those aged 46-60 years, more males compared to females had received income support ($p=0.007$), despite the small differences in absolute numbers (17.1% vs. 14.2%). However, a greater number of females aged 31-45 and 46-60 years received incapacity benefits ($p<0.001$).

[Table 3 and 4 near here]

Variables associated with treatment discontinuation

Since we observed a number of differences between genders (e.g. age at treatment initiation and educational attainment), we decided to estimate crude and adjusted estimates of the various variables association to treatment discontinuation (See table 5).

In the crude analyses the estimate of gender naturally followed the pattern observed in the descriptive analyses with males being 20 to 50% more likely to have discontinued compared to females for those age 18-24, 25-30 and 31-45 years, and with no significant gender-differences for those age 46-60 years. Adjusting the analyses for all the variables in the model, reduced the difference such that the association of male gender and discontinuation was only increased by 10-20%, yet still significant, for those age 18-24, 25-30 and 31-45.

With age 18-24 years at treatment initiation as the reference category, adjusted analyses identified that earlier treatment initiation, was associated with a 3-6 times higher likelihood of discontinuation for those age 18-24 years in 2013, whereas for those age 25-30 years in 2013, initiating treatment younger than age 18-24 years increased the likelihood approximately 2-3 times. Although the analyses for those age 25-30 years indicate that the likelihood of discontinuation was higher in those who initiated treatment at age 11-17 years relative to those who initiated at age 0-10 years of age, it is crucial to note from Table 3, that only a minority had initiated at age 0-10 years, and that confidence intervals were overlapping. Across age categories 25-30 years and 31-45 years, having initiated treatment at an older age than 18-24 years was associated with an estimated 70% in the adjusted analyses. Lifetime history of SSRI treatment was not clearly associated with treatment discontinuation across the age-categories, although we observed a 30% increased risk of discontinuation among those aged 31-45 years in the adjusted model. For those aged 18-24 and 46-60 years no clear significant patterns were observed for the association of educational attainment to the outcome, but for those aged 25-30 years and 31-45 years there was a trend towards lower risk of discontinuation around 20-30% when having a higher educational level than elementary school, but no dose-response relationship could be observed. Finally, across all age-categories, except those aged 46-60 years, having a history of receiving income support for at least six consecutive months was associated with a 10-50% greater likelihood of at least one discontinuation in adjusted analyses.

[Table 5 near here]

Discussion

Based on the available datasets, we identified that the Danish population of adults the 1st of January 2013 who had received prescriptions for ADHD medications during 2002 to 2013, appeared disadvantaged. A finding that is in line with a recent study, showing that adults with ADHD also report lower levels of quality of life, compared to healthy controls (Thorell, Holst, Sjöwall, 2019). Despite the fact, that those who had received treatment for ADHD were much younger cohort, they had a much larger prevalence of lifetime SSRI use (68.0 vs. 27.3%). Also, they more often had received income support for at least six consecutive months (30.9 vs. 4.5%), and were more likely to have received incapacity benefits (18.6% vs. 10.6%). As many increase their educational levels during their 20ties and 30ties, this variable should be interpreted with caution. However, we did observe that 60.3% of the treated adults had only elementary school as their highest educational achievement. This is noteworthy, as data from Statistics Denmark (freely available at <https://www.statistikbanken.dk/UDDAKT10>) on age at education completion for 2012/2013 show, that adolescents leave elementary school in Denmark at ages 15-17 years moving on to high-school or vocational training which the majority complete at ages 18-20. So even among those age 18-24 years in 2013, a large proportion would have been expected to have graduated high-school or vocational training if following the general Danish education trajectories. The findings are however in line with prospective studies from for instance register based studies from the Nordic countries (Chang et al. 2015; Keilow et al. 2018; Jangmo et al. 2019; Lichtenstein et al. 2012; Mohr-Jensen et al. 2019). These register studies also indicate, that although treatment of ADHD has been found to be associated with improved outcomes (see e.g. Chang et al. 2015; Jangmo et al. 2019; Lichtenstein et al. 2012, Mohr-Jensen et al. 2019) differences between those with and without ADHD still persist.

It is relevant to notice, that the majority of our sample initiated treatment in adulthood. In Denmark as in other countries, most individuals with ADHD are diagnosed and initiate treatment in mid-

childhood to early adolescence (Jensen & Steinhausen 2015; Pottegaard et al. 2012). However, as our sample consisted of individuals born at the earliest in 1995, most individuals in the sample were children during a time, where knowledge and awareness of ADHD in Denmark was limited, and no clear diagnostic criteria for ADHD were available. This also means, that those individuals who are treated in our sample could potentially be a more impaired subgroup with persisting ADHD. Furthermore, it is important to note, that the NPR only started to include data on prescriptions of all kinds in 1995. Thus a small proportion of the sample could have started treatment prior to 1995, but without this having been recorded. However, the prevalence of medication use in the start/mid 1990ies was very low for all age groups, in particular in adolescent and adult populations (Pottegaard et al. 2012), so the risk of misclassification will be minimal.

In this register study, we identified that in our entire sample of treated adults 10.7% had received only one prescription of ADHD medication. Furthermore, we found that a total of 26.2%, amongst those with two prescriptions or more, had at least one treatment discontinuation. Although excluding those with only one prescription from the remaining part of the analyses, could have introduced a bias, we decided to do so, as many reasons could have led them to stop early. Therefore, the findings concerning prevalence of discontinuation and variables associated with discontinuation only applies to patients who receive at least two prescriptions.

In this population of adults with at least two prescriptions, we identified that the proportion who discontinued was between 22.1 to 39.7% in males and 30.8 to 21.0% in females. After adjusting the association of gender and treatment discontinuation (for age at first prescription, SSRI treatment history, educational achievement and history of receiving income support), males were still more likely to have discontinued among those aged 18-24, 25-30 and 31-45 years . Previous studies have

suggested that female gender may predict treatment dropout (Kooij et al., 2013; Wang et al., 2016), but the literature on gender differences and treatment dropout is not consistent (Bahmanyar et al., 2013; Soendergaard et al., 2016). However, it is important to note that when analyses were adjusted for the age of treatment initiation, the association of male sex was only slightly elevated. This observation underscore the importance of considering that gender effects can be complex to interpret, as differences may be mediated by e.g. age at initiating treatment. This is relevant to consider, as females have been observed to get diagnosed and thus likely treated later than males (Bang Madsen, 2017; Jensen & Steinhausen, 2015) and since our analyses indicated that younger age at treatment initiation was significantly associated with treatment discontinuation. However, since we did not have data that allowed us to control for the duration of treatment in this study, this finding needs to be interpreted with care. As those who initiated treatment early, also had longer duration of follow-up time, the observation could simply be related to differences in time at risk. Previous studies that have been able to take time in treatment into consideration, do however find that in particular during adolescence and young adulthood the risk of discontinuing treatment is high (Pottegård et al., 2013; Zetterqvist et al., 2013). If we consider, that for instance adolescence is a period with heightened risk of treatment discontinuation, and not just an artefact of duration of treatment, the question is why those who start treatment at a young age, are more likely to discontinue their treatment. This could be related to lack of continuation of care between child and adolescent and adult mental health services, fear of stigma, or lack of knowledge about why they should take medication, to name just a few potential reasons (Gajria et al., 2014). Data from surveys among adolescents treated for ADHD do suggest, that adolescents may more often deviate from their treatment plan and that perception of the necessity of taking medication, as well as the experience of side-effects may affect treatment adherence (Brinkman et al. 2010; Emilsson, Gustafsson, Öhnström, & Marteinsdottir, 2017; Kosse, Bouvy, Philbert, de Vries, & Koster, 2017).

A survey among 181 Dutch adolescents in treatment for ADHD found that 48.1% of adolescents reported that they deviated from the prescribed dosing regimen and 60.2% occasionally discontinued medication during weekends or holidays (Kosse et al., 2017). In the sample, 83% of adolescents expressed low necessity and low concerns toward ADHD medication, a tendency the authors described as an “indifferent attitude”(Kosse et al., 2017). A Swedish study on adolescents has identified that side-effects and necessity-concern scores on the Beliefs about Medicines (BMQ) questionnaire correlate significantly with medication adherence (Emilsson et al., 2017). The nature of our dataset did not allow us to investigate how many of those e.g. adolescents and young adults who discontinued treatment, started again at a later point during their development. In other words, we are left uncertain about whether discontinuation was temporary or permanent. A recent longitudinal study based on data from the UK Clinical Practice Research Datalink suggests that less than 10% of adolescents who stop their treatment initiate it again in young adulthood (Newlove-Delgado et al. 2019). Whether this can also be observed in for instance Denmark, will be an important question for future studies. Also, we have no knowledge about whether some of those who initiated treatment in childhood may have outgrown the need for treatment.

Our data identified that a large proportion of individuals treated for ADHD had a history of treatment with SSRIs. Across our age-categories 36.0 to 85.1% of males and 60.4 to 91.6% of females had a history of receiving SSRI treatment.. Thus, the prevalence of SSRI use was quite substantial within our sample, but is important to consider that since the vast majority of cases initiated treatment in adulthood, the data will not generalise to patients diagnosed and treated in childhood and followed prospectively. However, ADHD has been found to increase the risk of developing e.g. depression (Chang et al. 2016), but there is also evidence to suggest that ADHD sometimes may be overlooked in clinical assessments when depression is present. A Swedish study

of individuals diagnosed with ADHD adulthood found that 41% had been in contact with psychiatric services prior to their first ADHD diagnosis, and that time from first contact to services to first ADHD diagnosis was a mean of 3.1 years ($SD=4.8$) and ranged from 0 to 25 years (Nylander et al. 2012). Of those with prior contacts, 38% were registered with a diagnosis of an affective disorder and 30% with an anxiety disorder (Nylander et al. 2012). Thus, it is not unlikely that the high prevalence of SSRI use we observed can be related to consequences of undetected ADHD as well as the more general risk of internalizing disorders associated with struggles associated to having ADHD. In the adjusted regression models, we did not observe a consistent association of treatment with discontinuation. Any possible associations would therefore be speculative. Unfortunately, data was not available in a format that allowed us to identify the temporal overlap between ADHD treatment and treatment with SSRI but we encourage that future studies will look into whether contaminant treatment with e.g. SSRIs and other psychotropics may be associated with treatment stability or instability. A study by Bahmanyar et al. (2013) has identified that treatment with other psychotropic medications is associated with an increased risk of gaps in treatment, but also, that this finding became insignificant after controlling for gender, age, comorbidity and frequency of hospital contact. Although there is an increased risk of depression and anxiety disorders in individuals with ADHD, it would have been interesting to also observe effects for other classes of psychotropics and comorbid psychiatric disorders, but these data were unfortunately not available to us in the predefined dataset.

We also observed a trend towards increased discontinuation and low educational achievement and income support. It is important to interpret these findings with caution. The results could suggest that discontinuation of treatment could be associated with a poorer outcome on these variables. Yet, it is equally likely that those who discontinue treatment represent a more vulnerable subgroup of patients who have poorer prerequisites for continuing care. Treatment of ADHD has been

associated with improved academic outcomes (Jangmo et al. 2019; Keilow, Holm, & Fallesen, 2018). When looking at the literature concerning predictors for treatment continuation or adherence, some have found that a higher educational attainment is associated with better adherence (Semerci, Taskiran, Tufan, & Şanlı, 2016; Sobanski et al., 2014), while others find the opposite or no association (Kooij et al., 2013; Soendergaard et al., 2016). We believe that it is worthwhile to study these variables as predictors of treatment continuation in more detail in future studies, while at the same time taking into consideration the impact of age at treatment initiation etc. Furthermore, future research should address the role of pharmacological treatment in the educational and occupational outcomes of adults with ADHD.

While the study of nationwide registers can help us monitor, how many patients discontinue treatment, data from registers cannot help us understand why so many decided to discontinue the treatment. As mentioned previously the decision to discontinue treatment could be made by the prescribing physician, on agreement between the patient and the prescribing physician, patients could decide to stop themselves, or discontinuation could occur without anyone actively deciding to end treatment. The study by Matheson et al. (2013) highlights the complexity of the issue (Matheson et al., 2013). In their qualitative interviews with 30 adult patients with ADHD they identified that the mechanisms leading to discontinuation of treatment were varied. Some of the interviewed patients reported that discontinuation occurred due to factors relating to the core symptoms of ADHD, such as missing appointments and forgetting to take medication. Some actively chose to take a temporary break in treatment, while others experienced that discontinuation was unwillingly forced upon them e.g. because of encountering reluctance from general practitioners towards providing follow-up care, or that transition from child and adolescent mental health services to adult services were delayed or not carried through. (Matheson et al., 2013). In

order to obtain more information about what may underlie the large discontinuation rates observed in Denmark and other countries (Newlove-Delgado et al., 2018; Pottegård, Bjerregaard, Kortegaard, & Zoëga, 2015; Wang et al., 2016), it is relevant to design and conduct naturalistic follow-up studies of patients initiating treatment and recording on which grounds treatment end, including both qualitative and quantitative data.

While the present study cannot help us identify who decided to discontinue the treatment and why, the discussion above does suggest that some variables are associated with higher discontinuation prevalence.

Strengths and limitations

The strengths of the present study was that the descriptive analyses were based on a large population based dataset of all adults aged 18-60 years on the 1st of January 2013 in the Danish population. Thus, the dataset is representative of this specific population, since the national Danish registers are believed to be complete with high quality data (Erlangsen & Fedyszyn, 2015). Thus, we were for instance able to include data on a large population of both males and females, and the risk of selection and attrition bias is minimal, compared to what is usually possible to obtain in prospective follow-up studies of patients.

Some of the limitations of this study have been discussed throughout the paper, but additional limitations will be outlined below. Although our dataset covered a longer period the data ended in 2013. Thus, it is uncertain to what extent for instance prevalence of discontinuation is still the same. Research on Danish datasets has identified that during 2000 to 2012 the number of patients who failed to fill a second prescription within six months after initiating treatment had dropped for adults (Pottegaard et al. 2015), but whether this translates into more persistent treatment patterns during long-term follow-up is uncertain, but should be a focus in future studies. A general limitation was

that our analysis was restricted to the predefined variables in the existing datasets including only aggregated data. For instance, in the study, discontinuation was defined as at least 211 days elapsing between two prescriptions. Due to the nature of data analysed we were not able to use alternative definitions of discontinuation to see if estimates of the proportion who discontinue treatment, altered as a function of the definition used. It may be relevant to use more than one definition of treatment discontinuation in future studies, in particular since results from previous studies suggest that adolescents and adults may use medication more flexible by e.g. not taking medication every day, during weekends or holidays (Kosse et al., 2017; Matheson et al., 2013) which could affect the frequency of prescription renewals. Furthermore, we were not able to see how many of those who discontinued eventually started treatment again, or study the duration of intermittent medication breaks. Therefore, it is uncertain how many of those registered as having discontinued treatment, were persistent or simply had a single gap in treatment. It may be relevant that future studies also address whether risk-factors for persistent rather than intermittent treatment discontinuation are the same in order to improve our understanding.

Furthermore, our dataset did not contain information about other relevant clinical variables such as the impact of comorbidity, frequency of hospital contacts, severity or complexity of the patient's condition. The impact of such variables on treatment stability are relevant to study in future as the literature is sparse and inconclusive. One study suggests that psychiatric comorbidity with e.g. internalising disorders, but not psychopathology in general, may be associated with lower risk of discontinuation (Soendergaard et al., 2016). In contrast, the study by Bahmanyar (2013) suggests that presence of any comorbid psychiatric disorder may increase the risk of a gap in treatment even when controlling for other background factors (Bahmanyar et al., 2013). The study by Bahmanyar also suggest a lower risk of treatment gaps among individuals with more frequent contacts to

hospitals (Bahmanyar et al., 2013), which could be a proxy for the whether the patient has access to and attend routine follow-up in specialized care. Finally while we have concentrate our discussion on treatment and discontinuation in adulthood, for some of the sample, treatment and therefore discontinuation may have occurred in childhood.

Conclusion

The results of this nationwide cross-sectional study support the results from previous studies by finding, that a sizeable proportion of patients who initiate pharmacological treatment for ADHD discontinue their treatment, at least temporarily. Our analyses suggest that younger age at treatment initiation is associated with treatment discontinuation but whether this is related to the duration of treatment or to discontinuations occurring more frequently during periods of transitioning from for instance adolescence to adulthood cannot be answered here. Furthermore, the data does suggest, that treatment discontinuation is associated with higher level of treatment with SSRI and poor outcomes, although the findings cannot make claims about causation. The study underscore the importance of conducting more research on this topic to identify patient and health care organization factors linked to premature discontinuation. In addition, the study highlights the need for greater efforts to support patients with ADHD on medication to avoid treatment discontinuation when relevant and provide additional information that would help support clinicians prescribing practice.

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