Utilisation and outcomes of treatment in Autism Spectrum Disorder

Summary

This thesis explored utilisation and outcomes of treatment in autism spectrum disorder (ASD). ASD is a lifelong neurodevelopmental disorder, characterised by core symptoms of communication deficits, difficulties with social interaction, and restricted and repetitive behaviours. Associated symptoms of autism include obsessions, self-injury, irritability, aggression, and under-reactivity to sensory stimuli. Psychiatric and neurological conditions such as attention deficit/hyperactivity disorder (ADHD), anxiety, depression, epilepsy and bipolar disorder are also more commonly diagnosed in children and adults with autism than in the general population. ASD is typically diagnosed at age 3-4 years in developed countries. Approximately, three to four times as many boys are diagnosed than girls. Up to 1 in 54 children and 1 in 45 adults are diagnosed with ASD in the USA today.

Chapter 1: Introduction, objectives and data

Chapter 1 set out the background to this thesis, by characterising the current ASD treatment landscape and some important knowledge gaps.

The purposes of treatment in ASD should be to minimise core and associated ASD impairments, to maximise daily living skills for independence, and to relieve the impact of problem behaviours.

There are currently no pharmacological treatment options for the core symptoms of ASD. In the USA however, the atypical antipsychotics risperidone and aripiprazole are approved for associated symptoms of irritability and aggression in children and adolescents. These drugs been recommended in clinical guidelines for treatment of aggression or self-injurious behaviours, in order to facilitate daily living, or to allow better adherence to non-drug therapies, but typically only when behavioural interventions have not been successful. These drugs do not have a marketing authorisation in ASD in Europe, yet the United Kingdom National Institute for Health and Care Excellence (NICE) also recommends antipsychotic medications for children with behavioural challenges when non-drug treatments have not helped: so long as these drugs are started by a paediatrician or psychiatrist.

Generally, it is acknowledged that other classes of psychotropic drugs (e.g. antidepressants, anticonvulsants) may be required to manage common psychiatric comorbidities in ASD. A recent systematic review reported median psychotropic drug use estimates of 42% in children and 62% in adults in ASD. The systematic review also pointed to some clear gaps in the literature however. Firstly, the vast majority of studies only focused on North America and used data from over a decade ago. There are limited studies in the adult population and studies generally do not have non-ASD comparator groups to contextualise results.

Drugs used for the treatment of ADHD, such as stimulants and atomoxetine are used frequently in ASD (around 14-19% in children). These drugs have consistently shown medication-induced increases in blood pressure and heart rate, which coupled with case reports, has raised concerns over the potential increased risk of more serious cardiovascular (SCV) events such as stroke, myocardial infarction, and cardiac arrhythmias. Limited observational studies on this topic have produced inconsistent results. Furthermore, this has not been studied in children with ASD.

Children with ASD also commonly use antipsychotic medication (around 17%). Antipsychotics have been associated with increased bone fracture risk in elderly dementia patients, yet the mechanisms leading to increased risks is not clear. For example, it may be due to an increased risk of accidents or falling, or due to a negative impact on bone mineral density. The relationship between antipsychotics and fracture risk has not been well studied in children. However, as risperidone and aripiprazole are commonly used in ASD and have slightly different pharmacological profiles, this setting can offer a unique opportunity to understand possible mechanisms and inform relevant clinical decisions about which treatment to prescribe.

The mainstay of currently recommended treatments for ASD are non-pharmacological in nature, and include behavioural and social-communication based therapies. In a study across 18 European countries, 91% of children with ASD received at least one type of non-drug intervention by age 7 years. Historical uptake of non-drug treatments is also high in the USA, with up to 77% current use. However, there are concerns that children in more rural settings have access to fewer services. Additionally, healthcare expenditures have previously been higher for ASD children with public versus private health insurance, suggesting public insurance may be an advantage for accessing services.

While a number of diagnostic instruments are available to aid a professional diagnosis of ASD, there is little consensus on the most appropriate tools for measuring effects of treatment. Patient or caregiver-reported assessments can offer a quick and cheap option to collect patient symptoms. They may also be administered remotely, for example on a computer or mobile phone. Hence, provided they are validated, they can offer a more sustainable opportunity to evaluate treatment effectiveness over longer periods, and outside controlled clinical trial settings.

This thesis comprised a collection of studies to address various abovementioned knowledge gaps regarding the utilisation and outcomes of treatment in ASD. The objectives were grouped into the following three categories: treatment utilisation patterns, treatment safety, and validation of a new caregiver-reported measure of ASD symptom severity. These categories correspond to Chapters 2 to 4 of the thesis respectively.

We used three main sources of real world data throughout the thesis. The first was the MarketScan insurance database which covers de-identified patient-level health data from private ("commercial") and publically (Medicaid) insured populations in the USA. The data covers all billed episodes of care, regardless of the setting. The second database was the Clinical Practice Research Datalink (CPRD) electronic medical record database from the UK. Data is recorded in the primary care setting, although due to the nature of the general practitioner (GP) "gatekeeper" system in the UK, prescriptions should be managed (or at least documented) by the GP even if they started in secondary or tertiary care. The third database was collected via a primary data collection survey study, nested in the Simons Foundation Powering Autism Research for Knowledge (SPARK) platform. SPARK is an online, USA-based research initiative for individuals with ASD and their family members.

Chapter 2: Treatment utilisation in ASD

Chapter 2 focused on the production of up to date estimates of drug and non-drug treatment utilisation in ASD, as well as predictors of use.

Chapter 2.1 was a retrospective, cross-sectional cohort study based in USA MarketScan claims in calendar year 2014. Among 46,943 commercial- and 46,696 Medicaid-insured patients we found substantial annual proportions of psychotropic drug use (64% and 69% respectively). These proportions increased rapidly throughout childhood from 11-25% in the 3-4 years age group to 76-80% in the 12-17 years age group. In adulthood, the proportions roughly plateaued (78-81%). All age groups combined, the most commonly used treatments (commercial-Medicaid) were stimulants (30-32%), antipsychotics (25-35%), antidepressants (33-29%) and hypotensive agents (20-31%). The rate of polypharmacy (two or more treatments concurrently for 30 days) was also high and increased with age (35-44% for all age groups combined, but already 24-36% by age 5-11 years). Medications were most frequently prescribed in conjunction with the indicated psychiatric condition, although over 30% of participants received medication in the absence of a coded psychiatric condition other than ASD. Beyond age and comorbidities, we also found that fee-for-service insurance plans, foster care and White race were associated with higher treatment rates.

Chapter 2.2 was a retrospective, cross-sectional cohort study based in the UK CPRD database in calendar year 2015. Among 10,856 patients, 32% used a psychotropic drug. This is around half the annual proportion observed in the USA, but substantial nonetheless. Also unlike in the USA, treatment rates increased gradually throughout childhood and adulthood years, with small increases in prevalence rate at each increasing age group (11% at age 3-4 years, 26% at age 12-17 years and 44% in adulthood). All age groups combined, the most commonly used treatments were anxiolytics/sedatives/hypnotics (14%), antidepressants (13%) and antipsychotics (8%). Hypotensive agents were used by less than 1% of patients. The rate of polypharmacy was 10% overall, and also increased gradually with age. Presence of psychiatric comorbidities was associated

with treatment use, but similar to the USA, some patents (14%) received psychotropic medication despite having no record of corresponding psychiatric comorbidities. Beyond age and comorbidities, females were more likely to be treated than males. In age, sex, and region matched comparative analysis, we found that psychotropic treatment use, polypharmacy, and healthcare resource use were all substantially higher in ASD than in the general population. However, odds for these outcomes were roughly halved in ASD versus an ADHD-matched cohort. This was primarily driven by the higher frequency of stimulant prescriptions in ADHD (35%) versus ASD (7%).

Chapter 2.3 was a survey study of parents and caregivers of children aged 3-17 years with ASD. The survey was embedded as part of the SPARK platform. We received responses from 5,122 caregivers (45% of invited) on questions regarding their child's use, setting and barriers to care for different non-drug treatment types over the past year (roughly September 2016 to September 2017). Overall, 96% of children received at least one type of non-drug treatment, with the most common being speech and language therapy (SLT; 71%), occupational therapy (OT; 60%) and behavioural therapy (56%). Around 30% of caregivers attended caregiver-training courses. The median intensity of all child-directed treatments combined was 6 hours per week, with behavioural therapy being the most intense (4 hours per week). All treatments were more commonly given in individual rather than group sessions. SLT and OT were more often provided in school, while behavioural therapy and psychological interventions were more frequently provided outside school. Controlling for other factors, behavioural therapy and SLT were significantly more frequent and more intense in metropolitan (urban) than in nonmetropolitan (rural) areas (odds ratios and 95% confidence intervals (OR) were 1.54 (1.30-1.83) for behavioural therapy, and 1.41 (1.17-1.69) for SLT). There were no consistently significant associations between non-drug treatment use and type of insurance coverage (commercial or Medicaid).

Chapter 3: Safety evaluation of treatments in children

Chapter 3 explored safety concerns of two commonly used drug classes in children with ASD.

Chapter 3.1 consisted of two case-control studies, nested within respective cohorts of ADHD and ASD children aged 3-18 years. In these groups, we evaluated the relationship between serious cardiovascular (SCV) events and current use of ADHD medications. ADHD medications were atomoxetine and stimulants (such as amphetamine, methylphenidate, lisdexamfetamine). We defined cases by a composite SCV outcome of stroke, myocardial infarction, or serious cardiac arrhythmia, and for each case, we matched ten controls on age, sex, and insurance type. We used the MarketScan commercial (years 2000-2016) and Medicaid (years 2012-2016) data. We identified 2,240,774 children for the ADHD cohort and 326,221 children for the ASD cohort. Overall, incidence rates of SCV events was extremely low: 3.1 per 100,000 patient years in the ADHD cohort and 5.6 per 100,000 patient years in the ASD cohort. For ADHD, 33.9% of cases (63 of 186) versus 32.2% of controls (598 of 1,860) were exposed, which yielded an OR of

1.08 (0.78-1.49). For ASD, 12.5% of cases (6 of 48) versus 22.1% of controls (106 of 480) were exposed (OR 0.49 (0.20-1.20)). Covariate-adjusted results and results for individual outcomes and other exposure definitions were also consistent with no increased risk of SCV events. In short, we found no evidence of increased SCV risk in children and adolescents with ADHD or ASD exposed to ADHD medications.

Chapter 3.2 was a propensity score matched cohort study to compare the risk of fracture among children aged 2-18 years with ASD using either risperidone or aripiprazole. We identified 3,312 new users of each drug from the MarketScan Medicaid data between years 2013 and 2018. The main exposure was continued use of aripiprazole or risperidone over time. Over the full duration of follow-up (median 10 months in both cohorts), incidence rates of any fracture per 1,000 patient-years were 23.2 for risperidone and 38.4 for aripiprazole. The hazard ratio and 95% confidence interval (HR) was 0.60 (0.44-0.83). Risks were similar between cohorts throughout the first 180 days on treatment, but significantly higher in the aripiprazole group thereafter. Extremity fractures drove most of the increased risk, with the biggest differences in lower leg and ankle fractures. Differences widened for children aged 10 years or younger (HR 0.47 (0.30-0.74)). In short, compared to aripiprazole, risperidone was associated with 40% lower risk of fracture.

Chapter 4: Validation of caregiver reported ASD severity

Chapter 4 was dedicated to the psychometric validation of the Autism Impact Measure (AIM): a new caregiver reported assessment for the severity of ASD symptoms in children. The AIM was completed online by 5,001 caregivers from the SPARK cohort during September and October 2017, and the study sample are a subset of those caregivers surveyed in Chapter 2.3. Children were aged 3-17 years. This study demonstrated the AIM's ability to discriminate between "known-groups" of children with different symptom severity, estimated thresholds for clinically important responses and confirmed internal and external validity of the measure. We also confirmed meaningful and distinct domains of the AIM including ASD core symptoms of communication deficits, difficulties with social interactions and repetitive behaviours. Importantly, this study showed the AIM is a valid tool, which can be quickly completed in a remote setting by caregivers on computer and mobile devices (median time: 7 minutes).

Chapter 5: General discussion

Chapter 5 provided a summary and critical reflection on the main body of the thesis. It included a lengthy summary of the main findings placed into a broader context, a critical evaluation of epidemiological methods used and considerations for future research and implications. Please see the relevant section of this thesis for further details.

Conclusion

This thesis demonstrates that the treatment landscape in ASD is varied with many drug and non-drug treatment options commonly used. The likelihood of accessing and receiving

these treatments is dependent on more than just health status, and is also associated with increased age, country of residence, female gender (in the UK), and urbanisation of residence, fee-for-service healthcare plans, race, and foster care status (in the USA). We showed that serious cardiovascular events were not associated with ADHD medication for most children with ASD. Compared to risperidone, long-term aripiprazole use in ASD was associated with increased risk of fractures, especially for children under age 10 years. Finally, the Autism Impact Measure (AIM) offers a valid, quick and inexpensive method for caregivers to report their child's severity of core autism symptoms.

In the coming years, as the treatment landscape in ASD continues to evolve, epidemiology and real world databases (both primary and secondary data use) will continue to compliment clinical trials in helping to understand real life experiences of how people with ASD access and use treatments, as well as the risks and benefits of doing so.