ORIGINAL CONTRIBUTION

An inventory of European data sources for the long-term safety evaluation of methylphenidate

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Abstract To compile an inventory of European health-care databases with potential to study long-term effects of methylphenidate (MPH) in patients with attention deficit hyperactivity disorder (ADHD). Potential databases were identified through expert opinion, the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, and literature search. An online survey was conducted among database providers/coordinators to ascertain the databases' appropriateness for inclusion into the inventory. It included questions about database characteristics, sample size, availability of information on drug exposure, clinical data and accessibility. Forty-two databases from 11 countries were identified and their coordinators invited to participate; responses were obtained for 22 (52.4 %) databases of which 15 record ADHD diagnoses. Eleven had sufficient data on ADHD diagnosis, drug exposure, and at least one type of outcome information (symptoms/clinical events, weight, height, blood pressure, heart rate) to assess MPH safety. These were Aarhus University Prescription Database, Danish National Birth Cohort (Denmark); German Health Interview and Examination Survey for Children and Adolescents; Health Search

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Database Thales, Italian ADHD Register, Lombardy Region ADHD Database (Italy); Avon Longitudinal Study of Parents and Children, General Practice Research Database, The Health Improvement Network, QResearch (UK) and IMS Disease Analyzer (UK, Germany, France). Of the 20 databases with no responses, information on seven from publications and/or websites was obtained; Pedianet and the Integrated Primary Care Information database were considered suitable. Many European healthcare databases can be used for multinational long-term safety studies of MPH. Methodological research is underway to investigate the feasibility of their pooling and analysis.

Background

As a first-line pharmacological therapy for attention deficit hyperactivity disorder (ADHD), methylphenidate (MPH) is widely prescribed in children and adolescents and to a lesser extent to adults. The efficacy of MPH in ADHD has been robustly demonstrated in randomised controlled trials with approximately 70 % of children, adolescents and adults showing a therapeutic response [1]. Other effective drugs for ADHD are the potent psychostimulant dexamfetamine and atomoxetine, a selective noradrenaline reuptake inhibitor. Although the medications for ADHD are generally well-tolerated, commonly reported adverse effects include neurological effects (such as headache, insomnia), gastroenterological effects (loss of appetite, nausea and vomiting, abdominal pain), psychiatric effects

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(mood, anxiety) and chronic effects such as growth restriction and increases in blood pressure [2, 3]. In order to control the acute and chronic adverse effects of medication, often patients on long-term (>1 year) drug treatment have a structured interruption of treatment (known as a drug holiday). This allows monitoring to ensure medication is still effective, and assessment of whether the balance between adverse effects and therapeutic effects favours the continuation of treatment [3].

In 2006, there were safety concerns reported about the use of amfetamines and MPH as treatments for ADHD, specifically with respect to cardiovascular safety of these products [4]. In 2007, the European Commission requested a referral to the Committee for Medicinal Products for Human Use (CHMP) under Article 31 of Directive 2001/83/EC, as amended, for MPH because of safety concerns [5]. The CHMP concluded that insufficient was known about the long-term adverse effects of MPH on growth, sexual development, the neurological system, psychiatric states and the cardiovascular system, and further assessment is needed. In January 2009, the European Medicines Agency (EMA) concluded that the benefit–risk ratio of methylphenidate in the authorised indication remains favourable, but more data are needed on the long-term effects in children, adolescents and young adults [6]. In response to the CHMP's concerns, the ADDUCE (Attention deficit hyperactivity disorder drugs use chronic effects) research team was formed by a consortium of experts in the fields of ADHD, drug safety, neuro-psychopharmacology and cardiovascular research. The ADDUCE project, funded under the European Union's 7th Framework Programme, will use pharmacoepidemiological research methods to investigate the long-term adverse effects of MPH on growth, the neurological system (including cognition and motivation), psychiatric states and the cardiovascular system in children, adolescents and adults. The methodologies employed will be the acquisition and analysis of existing patient databases, a 2-year prospective cohort study of MPH-treated patients and two control groups, and a cross-sectional study in late adolescents and young adults. A methodological overview of the ADDUCE project is provided by the website (http://adhd-adduce.org).

Electronic health care databases, comprising patient data, drug prescription data, patient outcomes and information on confounding variables, potentially provide valuable resources to examine associations between drug use and long-term adverse effects. A survey published in 2008 showed that many European healthcare databases had enormous potential for use in paediatric drug utilisation and safety studies [7]. The use of electronic health records was also recommended by the EMA when conducting post-authorisation drug utilisation and safety studies [8].

Previous studies have demonstrated that healthcare databases can be used to investigate certain adverse effects of MPH. Gau et al. used the National Health Insurance database (Taiwan) to assess the association between MPH use and psychiatric disorders in 2,109 children and adolescents with new onset ADHD between 1999 and 2003 matching 1:4 with non-ADHD controls. In this study, MPH use was associated with the occurrence of bipolar disorder (adjusted hazard ratio (HR), 4.1; 95 % CI 1.7, 9.7, $p < 0.05$) [9]. McCarthy et al. aimed to estimate the mortality rates associated with stimulant and non-stimulant treatment prescription using the UK General Practice Research Database (GPRD). Compared with the general population, there was a 162-fold increased risk of completed suicide in patients aged 11–14 years using psychostimulants or atomoxetine (standardized mortality ratio: 161.91 [95 % CI 19.61, 584.88]) [10]. Recently, four large US health-plan databases of insurance claims were combined to assess the use of ADHD drugs and the risk of serious cardiovascular events (sudden cardiac death, myocardial infarction, stroke) in children and young adults [11]. A total of 81 serious cardiovascular events were confirmed from over 2.5 million person-years of follow-up giving an incidence of 3.1 events per 100,000 person-years in the study cohort. Among current users of ADHD drugs, there was no increased risk of serious cardiovascular events when compared with non-users (adjusted HR, 0.75; 95 % CI 0.31, 1.85), and there was no evidence of increased risk for methylphenidate (adjusted HR, 0.96; 95 % CI 0.31, 2.97). Another study of claims data (Medicaid) from 28 US states found that the treatment of children aged 3–18 years with MPH or mixed amfetamine salts was not significantly associated with an increased short-term risk of severe cardiac events [12]. However, both US studies were unable to assess the long-term safety of stimulant treatment due to their short follow-up of 2 years [11, 12].

On the basis of these examples, we judged that analysis of existing health care databases might be useful to study the association between MPH use and long-term adverse events. Although this might not be possible for all adverse events of interest (e.g. sleep abnormalities), such databases may provide important health information relevant for the systematic study of side effects. However, many studies performed in Europe have been limited in their power and scope by the use of a single data source. Cooper et al. [11] demonstrated the value of using multiple existing databases in the US to obtain large sample sizes to study the safety of ADHD drugs; adopting a similar approach in Europe may be valuable if the issues concerning the pooling of such databases could be overcome. Our previous work has shown this to be feasible [13–16]. Hence, the aim of this study is to compile an inventory of existing European databases which can be used to study the effects of long-term MPH use in patients with ADHD.

Methods

There were a number of steps taken to achieve our aim.

First, a list of all known potentially relevant European databases with individual patient information was collated. A range of different methods were used to identify eligible databases: from those listed on the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), a systematic review of the published literature (including conference proceedings [17]) and finally, by nominations from members of the ADDUCE Consortium.

Second, a questionnaire comprising 33 questions to collect detailed database information was designed (by SI, TB, MLM, SM, AN and ICKW) and implemented using a web-based data collection tool (SurveyMonkey™). A request to complete the questionnaire survey was sent to the providers/coordinators of the identified databases. Information collected on each database comprised general information on the database (name, country), a description of the nature of the database (e.g. longitudinal/patient record database, disease registry, cross-sectional, observational data survey), characteristics and sample size (such as number of investigators, database starting date, and number of patients), availability of data on the exposure to medication and on symptoms and clinical events and accessibility. Examples of questions are "Is information available on ADHD diagnosis?"; "Which of the following data are recorded in the database? Weight, height, blood pressure, heart rate" and "What system is used to code diagnoses?"

Third, databases were categorised with respect to their potential suitability for investigating the long-term safety of MPH based on the availability of individual patient information. Our criteria were based on the basic data elements that are required for pharmacoepidemiologic research using healthcare databases [18]. To be useful for the investigation of the long-term safety of MPH use for ADHD, databases had to record information about the following clinical aspects of individual patients: ADHD diagnosis, MPH exposure (dose and duration), exposure to other medications, potential adverse outcomes (such as effects on height and weight, blood pressure, heart rate) and other symptoms/clinical events. Furthermore, information on the structure and standardisation of data, costs to access the database, completeness of clinical and drug information and previous applications in research or validation studies were considered. The ability to combine with data from other sources was also assessed based on whether

the database used unique patient identifiers (to allow for record linkage) and coding systems for diagnoses, clinical events and medications prescribed.

Last, detailed information of all databases without survey responses were sought from publications and the websites of their data providers/coordinators, where possible information collated were based on that requested in the survey questions. The databases were then assessed for their potential suitability using similar criteria to those used above.

Results

Response to the survey

Forty-two databases from 11 European countries were identified and their providers/coordinators were invited to participate in the survey (Fig. 1). Responses were obtained from 22 (52.4 %) database coordinators/providers in seven European countries (Table 1). Seven of these 22 databases did not contain information on ADHD diagnosis; therefore, 15 databases were included in the detailed assessment. Table 2 provides detailed information of the participating databases. Only one database had an incomplete response

to the survey (Generation R study), however, it was possible to obtain some of the missing details from the literature [19, 20]. There was information on over 4.5 million children and adolescents in these 15 databases (of which just over 23,000 from six databases are reported to have ADHD), this is an overestimate due to the possibility that patients and/or their clinicians can contribute information to more than one database. For example, there is an overlap between GPRD and The Health Improvement Network (THIN), where 66 % of contributing practices in THIN also contribute to GPRD between 2001 and 2008 [21].

Type of database

Most of the selected databases are longitudinal/patient record databases ($n = 11$). Two are ADHD specific patient cohorts (Lombardy Region ADHD Database and the Italian ADHD Register). One is a prescription information database (Aarhus University Prescription Database) and one is a cross-sectional, observational data survey (German Health Interview and Examination Survey for Children and Adolescents; KiGGS). Three databases could be linked to various other registries through unique patient identifiers (Aarhus University Prescription Database, Swedish National Health Data Registers and the National Psychiatric
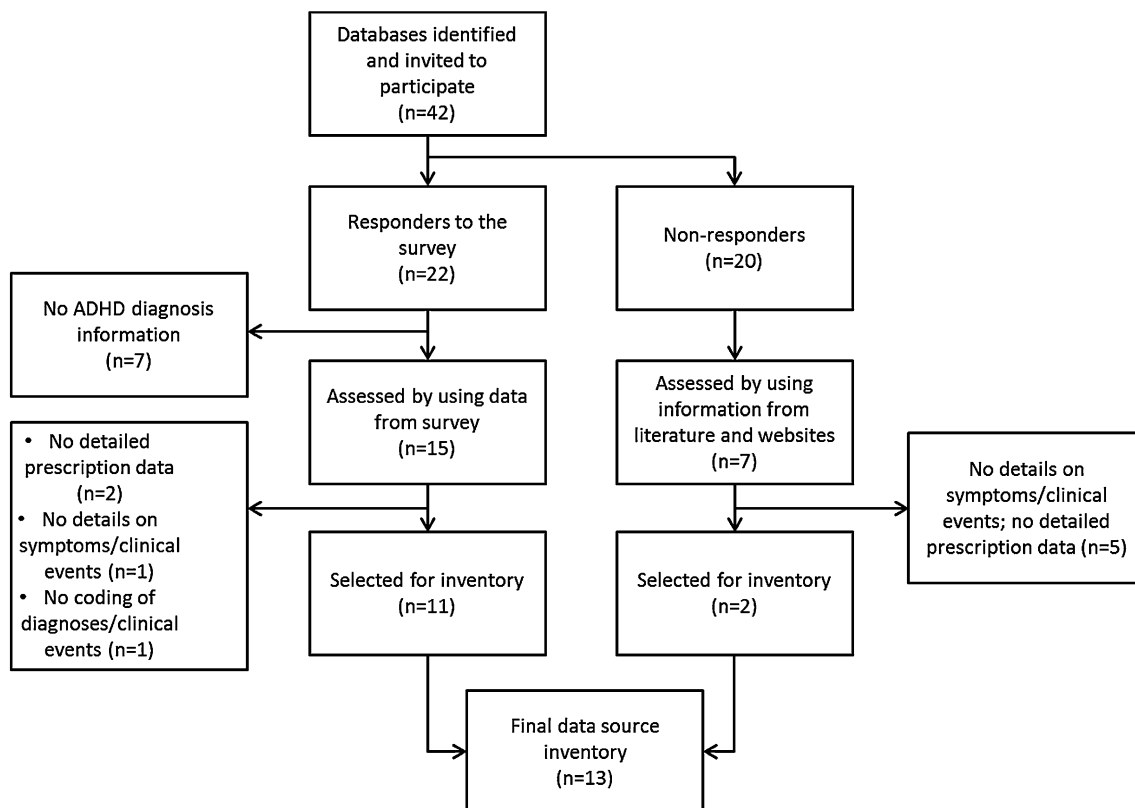

Fig. 1 Survey and database assessment schematic flowchart

Table 1 Databases identified and invited to participate in the survey

Country	Purpose of database	Database	Website	Response	Information from websites and literature
Denmark	PM	National Psychiatric Central Register	www.psykiatriskforskning.dk/research/central-research-register/	Yes	No
Denmark	PM/Admin	Odense Pharmacoepidemiological Database	www.sdu.dk	Yes	No
Denmark	PM/Admin	Aarhus University Prescription Database	kea.au.dk/en/informaticsand statistics/researchdatabases/theprescriptiondatabases/	Yes	No
Denmark	RC	The Danish National Birth Cohort (DNBC)	www.dnbc.dk/	Yes	No
Finland	PM/Admin	Prescription register	www.kela.fi	No	Yes
Finland	RC	The Finnish Northern Finland Birth Cohort (NFBC) 1986 study	kelo.oulu.fi/NFBC/	No	Yes
Germany	RC	The German Health Interview and Examination Survey for Children and Adolescents (KiGGS)	www.rki.de	Yes	No
Germany	PM	The German Population Based Long-Term Follow-up of ADHD	www.bips.uni-bremen.de	No	Yes
Italy	PM	Pedianet	www.pedianet.it/	No	Yes
Italy	PM	Sistema Informativo Sanitario Regionale Database-FVG region	www.regione.fvg.it	No	No
Italy	PM	Health Search Database Thales—CSD LPD (HSD)	www.healthsearch.it/	Yes	No
Italy	PM	Tuscany Regional database	www.arsanita.toscana.it	No	No
Italy	PM	Lombardy Regional ADHD database	givitiweb.marionegri.it/Centres/Public/ADHD/Default.aspx	Yes	No
Italy	PM	ARNO Observatory	osservatorioarno.cineca.org/arnoeng.htm	No	No
Italy	PM	The National ADHD Registry	www.farmaco-iss.org/	Yes	No
Netherlands	PM	Integrated Primary Care Information Database (IPCI)	www.ipci.nl	No	Yes
Netherlands	PM	PHARMO-Record-Linkage-System	www.pharmo.nl	Yes	No
Netherlands	PM	InterAction database	www.iadb.nl	Yes	No
Netherlands	RC	The Dutch KOALA Birth Cohort Study	www.koala-study.nl	Yes	No
Netherlands	RC	The Dutch TRAILS study		No	No
Netherlands	RC	The Dutch Generation R study	www.generationr.nl/	Yes	No
Norway	PM	The Norwegian Prescription Database	www.norpd.no/	Yes	No
Portugal	RC	Centro de Estudos e Avaliação em Saúde (Centre for Health Studies and Evaluation) (CEFAR)		No	No
Sweden	PM	Swedish Medical Birth Register	www.socialstyrelsen.se	Yes	No
Sweden	PM	Swedish National Health Data Registers	www.socialstyrelsen.se	Yes	No
Sweden	RC	The Swedish All Babies in Southeast Sweden	www.abis-studien.se/	No	No
Spain	PM	Base de datos para la Investigacion Farmacoepidemiologica en Atencion Primaria (BIFAP)	www.bifap.org/	No	No
UK	PM	General Practice Research Database (GPRD) (now part of Clinical Practice Research Datalink)	www.cprd.com/	Yes	No
UK	PM	The Health Improvement Network Data (THIN)	csdmruk.cegedim.com/	Yes	No
UK	PMS	Prescription Event Monitoring (PEM)	www.dsru.org/pem	Yes	No
UK	Admin	Prescription Pricing Authority (PPA)	www.nhsbsa.nhs.uk/PrescriptionServices.aspx	No	No

Table 1 continued

Country	Purpose of database	Database	Website	Response	Information from websites and literature
UK	PM	QResearch	www.qresearch.org/	Yes	No
UK	PM	Scottish Programme for Improving Clinical Effectiveness in Primary Care (SPICE) formerly known as GPASS (General Practice Administration System for Scotland)	www.abdn.ac.uk/iahs/uploads/files/PCI.pdf	No	No
UK	PM	Medicines Monitoring Unit (MEMO)	www.dundee.ac.uk/memo/	No	No
UK	RC	The Avon Longitudinal Study of Parents and Children (ALSPAC)	www.bristol.ac.uk/alspac/	Yes	No
UK	RC	The 1970 British Cohort Study	www.cls.ioe.ac.uk/bcs70	No	Yes
UK	RC	The Millennium Cohort Study	www.cls.ioe.ac.uk/mcs	No	Yes
UK	RC	The 2004 British Child and Adolescent Mental Health Survey		No	No
UK	RC	The Scottish SEATON Study	www.abdn.ac.uk/seatonstudy/	Yes	No
European	RC	The ADHD Observational Research in Europe		No	No
European	RC	The International Muti-Center ADHD Genetics (IMAGE) Project		No	No
UK, France, Germany	PM	IMS Disease Analyzer (IMS DA)	www.imshealth.com/	Yes	No

PM Patient management and/or disease surveillance, *RC* Research cohort, *Admin* administrative database for reimbursement and/or renumeration of prescriptions, *PMS* post-marketing surveillance

Central Register). The purpose of data collection of the majority of databases was for patient management and disease surveillance (*n* = 10); the remaining five are research cohorts: Danish National Birth Cohort (DNBC), KiGGS, Generation R Study, Dutch Child, Parent and health: Lifestyle and Genetic constitution (KOALA) Birth Cohort Study and Avon Longitudinal Study of Parents and Children (ALSPAC).

Drug exposure

Almost all databases contain information on prescribed medicines; Generation R Study does not collect details on prescriptions or drug exposure. One (Lombardy Region ADHD Database) has information on MPH and atomoxetine only. Most (*n* = 14) include information on medical diagnosis and the indication for prescription drugs. Four databases (National Psychiatric Central Register, Generation R study, Swedish National Health Data Registers, and ALSPAC) contain limited information on dosage and duration of treatment. The Anatomical Therapeutic Chemical classification system (ATC) is commonly used to classify medications; 10 of the 15 databases use this coding scheme [22, 23]. Multilex is a UK drug terminology system used to classify medications and is used in the GPRD and THIN databases. Only one database (KOALA) currently does not use a medication coding system.

Clinical outcomes

Full clinical data (symptoms and clinical events, weight and height, blood pressure and heart rate) are available in eight databases [KiGGS, Italian ADHD Register, Lombardy Region ADHD register, KOALA, ALSPAC, GPRD, THIN, and IMS Disease Analyzer (IMS DA)]. The International Classification of Diseases 10th Revision (ICD-10) is used as the diagnoses/clinical event coding system in six databases (Aarhus University Prescription Database, DNBC, National Psychiatric Central Register, Swedish National Health Data Registers, ALSPAC, and IMS DA) [24]. Read Clinical Terms (a UK hierarchical classification system) is used in four UK databases (GPRD, THIN, QResearch, and IMS DA). One database, Health Search Database Thales (HSD), uses ICD-9 to code diagnoses and clinical events.

Other variables

The diagnostic process for ADHD and hyperkinetic disorder includes the recognition of specific behavioural and attentional symptoms per criteria of either the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) [25] or ICD-10. However, these symptoms are also found in disorders other than ADHD [26, 27]. Therefore, information on whether the ADHD diagnosis

Table 2 Detailed information of the participating databases which record ADHD diagnoses

Name of database	Aarhus	DNBC	National Psychiatric Central Register	KiGGS	HSD	Italian ADHD Register	Lombardy Region ADHD Database
Country	Denmark	Denmark	Denmark	Germany	Italy	Italy	Italy
Type of database	Prescription Information Databases[a]	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database[a]	Cross-sectional, Observational Data Survey	Longitudinal/Patient Record Database	ADHD specific patient cohort	ADHD specific patient cohort
Number of Investigators	N/A	N/A	N/A	5	700	84	18
Starting year	1994	1996	1969	2003	1996	2007	2007
End year	Ongoing	Ongoing	Ongoing	2006	Ongoing	Ongoing	Ongoing
Estimated no.							
Male (no. Of ADHD)	10,000 (50)	48,000 (N/A)	633,385 (N/A)	8,985 (710)	760,000 (114)	2,000	201
Female (no. of ADHD)	10,000 (0)	46,000 (N/A)		8,656 (156)	850,000 (20)	244	28
Prescriptions							
Medication	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medication Code	ATC	ATC	ATC	ATC	ATC	ATC	Only atomoxetine and methylphenidate
Indication	No	No	No	Yes	Yes	Yes	Yes
Dosage	Yes	Yes	No	Yes	Yes	Yes	Yes
Duration	Yes	Yes	No	Yes	Yes	Yes	Yes
Outcomes/confounders							
Weight	No	Yes	No	Yes	Yes	Yes	Yes
Height	No	Yes	No	Yes	Yes	Yes	Yes
Blood pressure	No	No	No	Yes	Yes	Yes	Yes
Heart rate	No	No	No	Yes	No	Yes	Yes
Medical diagnosis	Yes[a]	Yes	Yes	Yes	Yes	Yes	Yes
Symptoms/clinical events	Yes[a]	Yes	Yes	Yes	Yes	Yes	Yes
Diagnoses/clinical events code	ICD-10	ICD-10	ICD-10, ICD-8	Parent reported clinician based information on ADHD	ICD-9CM	MedDRA	List of co-morbidities
Validation of ADHD diagnosis via	N/A	Comparison with SDQ	ICD-10	Comparison with SDQ	ICD9-CM and further validation required	DSM-IV	DSM-IV
Medical examinations	Yes	No	Yes	Yes	Yes	Yes	Yes
Ethnicity	Yes	No	Yes	Yes	No	No	No
Genetic information	No	Yes	No	No	No	No	No
Data access							
Via academic collaboration	N/A	Yes	Yes	Yes	Yes	No	Yes
By paying a fee	N/A	Yes	No	Yes	Yes	Yes	Yes

Table 2 continued

Name of database	Generation R Study	KOALA	Swedish National Health Data Registers	ALSPAC	GPRD	THIN	QResearch	IMS DA
Country	Netherlands	Netherlands	Sweden	UK	UK	UK	UK	UK, France and Germany
Type of database	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database[a]	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database
Number of Investigators	5	3	N/A	1	600	495	600	>100
Starting year	2002	2000	2005	1990	1987	2003	1990	1991
End year	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Estimated no.								
Male (no. Of ADHD)	3,000 (N/A)	1,400 (N/A)	32,000 (N/A)	5,000 (N/A)	2,000,000 (12,000)	1,713,823 (N/A)	200,000 (N/A)	2,500,000 (N/A[c])
Female (no. of ADHD)	3,000 (N/A)	1,400 (N/A)	18,000 (N/A)	5,000 (N/A)	2,000,000 (8,000)	1,750,216 (N/A)	200,000 (N/A)	2,500,000 (N/A[c])
Prescriptions								
Medication	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medication Code	N/A	Not yet determined[b]	ATC	ATC	Multilex	ATC, Multilex	EMIS drug database	ATC, Read
Indication	N/A	No	No	Yes	Yes	No	No	Yes
Dosage	N/A	Yes	Yes	No	Yes	Yes	Yes	Yes
Duration	N/A	Yes	No	Yes	Yes	Yes	Yes	Yes
Outcomes/confounders								
Weight	Yes[d]	Yes	No	Yes	Yes	Yes	No	Yes
Height	Yes[d]	Yes	No	Yes	Yes	Yes	No	Yes
Blood pressure	Yes[d]	Yes	No	Yes	Yes	Yes	No	Yes
Heart rate	Yes[d]	Yes	No	Yes	Yes	Yes	No	Yes
Medical diagnosis	Yes[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Symptoms/clinical events	Yes[d]	Yes	No	Yes	Yes	Yes	No	Yes
Diagnoses/clinical events code	N/A	Not yet determined[b]	ICD-10	ICD-10, ALSPAC generated	Read	Read	Read	ICD-10, Read
Validation of ADHD diagnosis via	CBCL & DSM-IV[e]	Not yet determined[b]	Uncertain	Traits and DAWBA questionnaire	GP questionnaire	GP questionnaires	None	None
Medical examinations	Yes[d]	No	No	No	Yes	Yes	No	Yes
Ethnicity	Yes[d]	Yes	Yes	Yes	Yes	No	Yes	Yes
Genetic information	Yes[d]	No	No	Yes	No	No	No	No
Data access								
Via academic collaboration	Yes[d]	Yes	Yes	Yes	No	No	No	Yes
By paying a fee	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

ATC Anatomical Therapeutic Chemical classification system, *CBCL* Child Behaviour Checklist, *DAWBA* Development and Well-Being Assessment, *DSM-IV* Diagnostic and Statistical Manual of mental disorders, 4th edition, *GP* general practitioner, *ICD* International Classification of Diseases, *MedDRA* Medical Dictionary for Regulatory Activities, *Read* Read Clinical terms, *SDQ* Strengths and Difficulties Questionnaire, *N/A* not available

[a] Linkable to other registries through unique identifiers of the patients

[b] Future follow-up in 2012

[c] the number of ADHD patients can be supplied on personal request

[d] from [19]

[e] from [20]

had been validated is important. For two databases (Italian ADHD Register and Lombardy Region ADHD Database), clinicians use DSM-IV criteria to confirm diagnoses. In DNBC and KiGGS, ADHD diagnosis is supported by the scores from Strengths and Difficulties Questionnaire (SDQ) [28], which has a scale measuring ADHD symptoms. Questionnaires to general practitioners (GPs) can be used to obtain further information on diagnosis in the GPRD and THIN databases.

Nine databases include information on ethnicity. Three databases (DNBC, National Psychiatric Central Register, and ALSPAC) also collect genetic information.

Previous applications of databases in the field of research in paediatrics and/or ADHD

The Italian ADHD Register has been previously used in studies on medication safety in ADHD patients [29–31]. The GPRD and THIN databases have been used to study the safety and use of ADHD drug treatment [10, 32, 33]. Data from KiGGS has been used in a number of paediatric studies, including those investigating the prevalence of mental health disorders, such as ADHD and drug treatment [34, 35]. ALSPAC has been widely studied and has numerous publications in paediatric research but none in ADHD.

Data access

All databases apart from one can be accessed either by paying a fee and/or via academic collaboration. Nine of them (DNBC, National Psychiatric Central Register, KiGGS, HSD, Lombardy Region ADHD Database, KOALA, Swedish National Health Data Registers, ALSPAC, IMS DA) can be accessed via academic collaboration. The means to access the Aarhus University Prescription Database was not reported in the survey, but the literature states project-specific permission from the Danish Data Protection Agency is required and any data-linkage studies (which would be necessary to obtain outcome data) need approval from the Danish National Board of Health [36].

Assessment of non-responding databases

We obtained information on seven additional databases whose coordinators did not reply to the survey. These were Prescription Register (Finland), The Finish Northern Finland Birth Cohort (NFBC) 1986 study, The German Population Based Long-Term Follow-up of ADHD, Pedianet (Italy), Integrated Primary Care Information Database (IPCI; Netherlands), The 1970 British Cohort Study and The Millennium Cohort Study (UK). These databases were appraised using the same criteria as above with information

obtained from database websites and published literature (Table 3).

Type of database

Three of these seven databases are longitudinal/patient record databases (the German Population Based Long-Term Follow-up of ADHD, Pedianet and IPCI). Three are longitudinal birth cohorts (NFBC, the 1970 British Cohort Study, and The Millennium Cohort Study). Only one database is a prescription information database [Prescription Register (Finland)].

Drug exposure

Only two of the databases include information on indication of prescription and/or medical diagnosis (Pedianet and IPCI). Information on dosage and duration of prescription is available in Pedianet and IPCI, and both use the WHO ATC classification system [22].

Clinical outcomes

Information on weight and height is found in Pedianet, IPCI, the 1970 British Cohort Study and the Millennium Cohort Study. Two databases provide information on medical diagnosis and symptoms/clinical events (Pedianet and IPCI). Only IPCI classifies diagnoses/clinical events using the International Classification of Primary Care (ICPC) code [37].

Other variables, previous applications in research and data access

Due to limited information on these databases, the availability of data on confounding variables and data accessibility cannot be assessed. There is one study using Pedianet to investigate the safety of paediatric drugs [38]. No studies of paediatric drug safety using the IPCI database could be identified in the literature. However, both databases have been previously used to study paediatric drug use [13–16]. A study describing the incidence and prevalence of ADHD and drug treatment for ADHD using The German Population Based Long-term Follow-Up of ADHD database has been conducted [39].

Selection of data source inventory

According to our criteria for suitability, 11 of the 15 responding databases were considered to have potential value for the long-term safety evaluation of MPH. These are Aarhus University Prescription Database, DNBC,

Table 3 Detailed information obtained from literature and websites of non-responding databases

Name of database	Prescription register	The Finish Northern Finland Birth Cohort (NFBC) 1986 study	The German population based long-term follow-up of ADHD	Pedianet	Integrated primary care information database (IPCI)	The 1970 British cohort study	The millennium cohort study
Country	Finland	Finland	Germany	Italy	Netherlands	UK	UK
Type of database	Prescription Information Database	Longitudinal 1-year birth cohort	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database	Longitudinal/Patient Record Database	Longitudinal study	Longitudinal study
Number of investigators	N/A	N/A	N/A	300 paediatricians	150 GPs	N/A	N/A
Starting year	1994	1985	2010	1998	1992	1970	2000
End year	Ongoing	1986	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Estimated no. of individuals	480,000 (0–18 years)	9,400	30,000	106,554 (0–14 years)[a]	>1,000,000 (161,108 of 0–18 years)[b]	15,500	18,800
Prescriptions							
Medication code	ATC	N/A	N/A	ATC	ATC	N/A	N/A
Indication of prescription	Limited	N/A	N/A	No	Yes	N/A	N/A
Dosage of prescription	Limited	N/A	N/A	Yes	Yes	N/A	N/A
Duration of prescription	No	N/A	N/A	Yes	Yes	N/A	N/A
Outcomes/confounders							
Weight	No	N/A	N/A	Yes	Yes	Yes	Yes
Height	No	N/A	N/A	Yes	Yes	Yes	Yes
Blood pressure	No	Yes	N/A	N/A	Yes	N/A	N/A
Heart rate	No	Yes	N/A	N/A	N/A	N/A	N/A
Medical diagnosis	No	Limited	N/A	Yes	Yes	N/A	N/A
Symptoms/clinical events	No	Limited	N/A	Yes	Yes	Limited	Limited
Diagnoses/clinical events code	N/A	N/A	N/A	N/A	ICPC	N/A	N/A
ADHD diagnosis tool	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Medical examinations	No	Limited	N/A	Yes	Yes	Limited	Limited
Ethnicity	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 3 continued

Name of database	Prescription register	The Finish Northern Finland Birth Cohort (NFBC) 1986 study	The German population based long-term follow-up of ADHD	Pedianet	Integrated primary care information database (IPCI)	The 1970 British cohort study	The millennium cohort study
Genetic information	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Data access							
Via academic collaboration	N/A	N/A	N/A	N/A	N/A	N/A	N/A
By paying a fee	N/A	N/A	N/A	N/A	N/A	N/A	N/A

N/A not available, *GPs* general practices, *ICPC* the international classification of primary care

[a] in year 2008

[b] in year 2004

KiGGS, HSD, Italian ADHD Register, Lombardy Region ADHD Database, ALSPAC, GPRD, THIN, QResearch and IMS DA. Of the non-responding databases, Pedianet and IPCI were considered potentially suitable. Hence, 13 databases were included in our data source inventory.

Discussion

From our survey, we identified 13 sources of electronic health care records in Europe which have potential value in investigating the long-term effects of MPH treatment in patients with ADHD. These databases were selected because they record basic data elements required to conduct drug safety studies; these include validated ADHD diagnosis (or at least the ability to confirm diagnosis), other diagnoses and clinical events, exposure to MPH, and exposure to any other medications and potential adverse clinical outcomes. These data are rich resources, easily accessible, sourced from real-life practice, with the potential to provide large study populations for the long-term safety evaluation of MPH. Many are longitudinal in nature, which is essential for the long-term follow-up of patients.

However, it is generally recognised that existing sources of data (including those we have identified) may have several limitations such as selection bias, lack of control or comparison group, missing data (or limited detailed clinical information) [18], small sample sizes and issues of quality control in data collection. For example, the selection of an un-medicated group of ADHD patients from the 13 data cohorts may be challenging due to the small numbers of patients that exist (and would also affect prospective cohort studies). Some data may be unrecorded because the purpose of the database did not require it, such as details of pubertal maturation, specific psychiatric rating scales, measurements of brain function and activity (EEG, fMRI), or risk factors such as developmental history, parental history of medical and psychiatric problems and life events. Other data may not be routinely entered at specific time intervals (e.g. height, weight, blood pressure, heart rate). Missing data may restrict the ability of some data sources to be used to study specific long-term effects (such as developmental or psychiatric effects), or even threaten the reliability and validity of results, especially if confounding variables are unavailable. Misclassified diagnoses or outcomes can also affect the validity of a study. The issue of small sample sizes could be overcome if data are pooled to form larger cohorts. These issues are not pertinent to all of the selected data sources in our inventory, but they all should be carefully considered (and addressed) when selecting data sources for our drug safety research.

After consideration of these general limitations, the ADDUCE Consortium proposed that high quality data should be collected in a large prospective cohort study of patients with ADHD and their controls. This cohort study would collect specific information at set time points on efficacy measures of MPH, growth, coordination, psychiatric effects (using rating scales such as DAWBA—Developmental and Well-being Assessment modules), neurological effects (rating scales, measures of brain function and activity), as well as patient demographics, family and personal medical, psychiatric and medication histories and physical examinations (including cardiac examinations). Much of these data are not recorded in the existing data sources of our inventory. However, there are also limitations to primary data collection of a large prospective cohort; it is time- and resource-consuming, and recruitment of a sufficiently large sample size to allow the study of rare effects of MPH may be difficult. Hence studies of large existing databases (single or pooled) in our inventory would complement those of the prospective cohort.

There are opportunities to exploit the databases that we have identified in our inventory; in particular, the combination of healthcare databases can potentially generate sample sizes and statistical power for large-scale drug safety studies [7]. European colleagues have recently pooled eight existing electronic healthcare databases covering four countries to generate an early signal detection system by creating a database platform using a common data framework (EU-ADR) [40]. The different clinical terminologies of the databases (e.g. Read Clinical Terms, ICD-9) can be mapped using a biomedical terminology integration system, Unified Medical Language System®. This generated a study population of almost 20 million individuals with just under 60 million person-years of data. Five of these databases are included in our inventory (Aarhus University Prescription Database, HSD, QResearch, Pedianet and IPCI) [40]. However, the amalgamation of existing databases is complex and goes beyond issues of data structures and sources. There are ethical issues concerning the processing of anonymised healthcare data and national diversity in healthcare provision and practice [7, 40]. Also, some of the limitations described above such as the issue of data quality still remain, which affect the choice of analytical methods. Database providers may wish to improve the quality and completeness of recording by the end-user and increase the availability of more specific detailed clinical information (such as the results of diagnostic tests) [18] to enhance the research value of their databases. Despite the complexity of such a task, the EU-ADR project [40] and other studies [11] demonstrate that combining diverse databases of heterogeneous populations is feasible for drug safety research, with vast potential for further work.

Conclusion

There are 13 European databases of birth cohorts or electronic healthcare records included in the ADDUCE data inventory, which have potential value individually or pooled for the evaluation of the long-term safety of MPH treatment in patients with ADHD. They are rich sources of data from real-life settings and easily accessible. However, there are limitations in utilising existing sources of data including small sample sizes, missing data and poor data quality. The pooling of existing data sources presents opportunities for large-scale safety studies of MPH in the future; its feasibility is currently under investigation but data quality and analysis, ethical issues and national differences in healthcare provision need to be considered.

relationships. All authors declared that they have no financial interests that may be relevant to the submitted work.

Appendix: Adduce consortium

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