The potential of UK clinical databases in enhancing paediatric medication research

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The research potential of many UK clinical databases is not being realized. A recent report published by the Royal College of Paediatrics & Child Health stated that there is a need to build research capacity and support in the area of paediatric pharmacology, with specific emphasis on the use of clinical databases. This article presents the databases available in the UK for medication research and gives some examples of paediatric studies conducted. The databases discussed include the Prescription Pricing Authority database, the General Practice Research Database, IMS Health databases (Medical Data Index, MIDAS Prescribing Insights, Disease-Analyser-Mediplus) and the Yellow Card Scheme. Other databases such as the Medicines Monitoring Unit (MEMO) and the Scottish Primary Care Computer System also have research potential in paediatric pharmacoepidemiology, but their population sizes are relatively small.

Introduction

In a recent study, Black *et al.* found that the audit and research potential of most of UK clinical databases was not being realized and more support was required [1]. Similarly, a report commissioned by the Medical Research Council, UK Department of Health and the Association of the British Pharmaceutical Industry also suggested more research into the use of clinical databases for paediatric medication research is necessary [2].

The Department of Health Standing Medical Advisory Committee in England recommended that children's medication prescribing data should be collected

for evaluation [3]. Moreover, the need for drug utilization studies and pharmacovigilance systems for children was specifically proposed in the draft regulations on medicinal products for paediatric use [4]. Undoubtedly, research capabilities using clinical databases will have to be further developed in order to support the rapidly expanding agenda of paediatric medication research. This article will introduce readers to the key UK clinical databases available in this field of research.

Prescription Pricing Authority

All NHS prescriptions written by general practitioners (GPs) which are dispensed by community pharmacies

Table 1

Cost and training requirements of the clinical databases

Database	Provider details	Cost and training requirements
Prescription Pricing Authority (PPA)	Data available online: http://www.dh.gov.uk/ PublicationsAndStatistics/fs/en	Free for Prescription Cost Analysis data (data released annually in April/May). Explanation of data provided. Knowledge of UK general practice is useful
General Practice Research Database (known as Full Feature-GPRD)	The GPRD Group, The Medicines and Healthcare products Regulatory Agency, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, UK. E-mail: admin@gprd.com	Dependent on level of access, and status of database user. Full access (level 4) for two users (including training) is £300 000. Special rates for academia. Four-day training course provided by the GPRD Group. Knowledge of relational databases and UK general practice is required
IMS Prescribing Insights (MIDAS) including the UK IMS Medical Data Index (MDI)	Mr Peter Stephens VP Public Health Affairs Europe IMS Health, 7 Harewood Avenue, London NW1 6JB, UK e-mail: PStephens@uk.imshealth.com	Dependant on countries and variables required, as well as frequency of updates. Data is projected, so use of statistical confidence tables required
IMS Disease Analyser-Mediplus	IMS Health as above	Dependent on size of dataset required. Full dataset with monthly updates for one work station is £175 000. Separate charge for health economics. Special rates for academia. Knowledge of relational databases and UK general practice required
Yellow Card Scheme	Yellow Card Adverse Drug Reactions Reporting Scheme, The Medicines and Healthcare products Regulatory Agency, CSM Freepost, London SW8 5BR, UK E-mail: info@mhra.gsi.gov.uk	Not yet known

in England are sent to the Prescription Pricing Authority (PPA) for reimbursement. Prescription data are kept in the PPA database, which is the largest of its kind in Europe; over 615 million prescription items are processed per year [5]. The PPA provides information to NHS organizations and legitimate research organizations when specific criteria are met. Table 1 gives details of access to the PPA data.

In general, the raw data from the PPA database is not particularly useful for paediatric medication research as it does not record age; therefore, it would be difficult to study drug use in children.

However, certain medications or formulations are mainly used in children; it is therefore possible to study the prescribing trends over time of such drugs, including methylphenidate. By analysing the methylphenidate prescribing data from the PPA for the years 1998–2004 [6], we are able to show that the use of methylphenidate is increasing (Figure 1). Furthermore, it clearly shows that the use of normal-release preparations was increasing until 2001 and reduced from 2002 onwards. On the

other hand, there was a 22-fold increase in the use of modified-release preparations between 2001 and 2004, and the quantity of prescriptions is expected to continue rising. Therefore, research should be targeted at the clinical efficacy and safety of modified-release methylphenidate.

In conjunction with other research organizations such as the Drug Safety Research Unit (DSRU), the PPA database has greater potential in paediatric drug research. The PPA supplies information to the DSRU on prescriptions for drugs that are being monitored under Prescription Event Monitoring. The information supplied by the PPA includes [7]:

- 1 Patient name, address and gender
- 2 GP name and practice address
- 3 Drug name and quantity prescribed.

In a previous study, the DSRU successfully researched the off-label use (licensed drugs used outside of the license terms) of new medications (black triangle drugs in the UK) in primary care [8]. Over 690 000

Figure 1

Total quantity of methylphenidate prescribed by General Practitioners in England [6]. Normal release (■), modified release (■), total (□)

patients and 63 newly marketed medications were included; 9081 (1.3%) of these were children and 15 256 (2.2%) were adolescents. This study has shown that although only a small proportion (10%) of newly marketed drugs were licensed for use in children, 22% of children received drugs 'off label' during the first few years that the drug was marketed and a small number of children and adolescents were given drugs contraindicated in these age ranges.

General Practice Research Database

The General Practice Research Database (GPRD) is the world's largest computerized database of anonymized patient data from general practice. It contains over 35 million patient years of data. The GPRD has been collecting patient records in the UK continuously since 1987 and it currently collects information on approximately 3 million patients, equivalent to almost 5% of the UK population. Data are provided by contributing general practices from all around the UK [9]. There were 877 802 children (under 18) in GPRD in 2002 and 1.3 million prescriptions were issued for this cohort in 2002 (Personal communication, GPRD).

Information collected from GPs includes:

- Demographics, including year of birth and gender of patient (information on ethnic group is not collected).
- Medical diagnosis, including comments.
- All prescriptions.
- Events leading to withdrawal of a drug or treatment.
- Referrals to hospitals.
- Treatment outcomes, including hospital discharge reports where patients are referred to hospital for treatment.

- Miscellaneous patient care information, e.g. smoking status, height, weight, immunizations, laboratory results.

GPRD has the existing capability for conducting paediatric drug utilization and pharmacovigilance studies because it contains both demographic and clinical details of patients. Furthermore, the large size of the database population makes it possible to study rare adverse events. Further details on access, cost and training are provided in Table 1.

Our research team has recently conducted a drug utilization study of antidepressant use in children and adolescents [10]. The results show that the use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents has increased significantly between 1992 and 2001, whilst the use of tricyclic antidepressants has been falling in the UK (Figure 2).

The GPRD was also used to investigate the link between the MMR vaccine and autism [11]; the results did not support the association between the use of the vaccine and autism. A further case – control study reached a similar conclusion [12].

However, in our antidepressant study, we identified some mothers of 0–3-year-olds who were prescribed antidepressants on their children's medical records [10]. This is a hazard for those who use the GPRD to study medication use in young children, as it could lead to an overestimation of prevalence, particularly in this group of patients.

IMS Health Databases

IMS is an international healthcare information company, specializing in the collection and interpretation of

Figure 2

Proportions of antidepressant (ATD) users aged 0–18 years by calendar year and drug group*. Data from General Practice Research database [10]. TCA users (■), Tricyclic antidepressant; SSRI users (▨), selective serotonin reuptake inhibitors; MAOI users (□), monoamine oxidase inhibitors; other ATDs users (▩) comprise flupentixol, mirtazapine, nefazodone, reboxetine, tryptophan and venlafaxine

Figure 3

Psychotropic medication prescriptions given to patients aged 0–17 years by country and year [14]. Year 2000 (■), year 2001 (▨), year 2002 (□) *USA data is by ten thousand prescriptions, **Statistically different between the years 2000 and 2002

anonymized health information, and often the only source of information on aspects of medicine utilization within and outside the UK, as well as across the world. These complex, secure databases represent an invaluable source of paediatric pharmacoepidemiology. Table 1 provides details on cost of and access to these databases.

IMS Medical Data Index

The Medical Data Index (MDI) is an audit drawn from the de-identified records of 500 GPs in the UK. Since 1994, prescribing data have been collected continuously from the practice computers of 500 GPs. The data of sampled doctors are then adjusted according to specific stratifications (e.g. region), and a projected national total of prescriptions data per year are calculated [13].

Unlike the PPA database, the MDI contains the age of patients, therefore it is possible to study paediatric drug utilization. We recently conducted a utilization study, which confirmed that there was a 68% increase in pae-

diatric psychotropic prescriptions in the UK between 2000 and 2002 [13]. The study also showed a significant increase in paediatric psychotropic prescriptions compared with adults during the same period of time.

IMS prescribing Insights

The IMS Prescribing Insights (MIDAS) contains prescribing data from 11 major countries. MIDAS is an audit drawn from a representative sample of medical practitioners in each country. As with MDI, data of sampled doctors are adjusted according to specific stratifications and projected national totals of prescriptions are calculated for each country [14].

After our research team studied the prescribing trends of paediatric psychotropic drugs in the UK [13], we used MIDAS to investigate the pattern of paediatric psychotropic prescriptions in eight other countries. We found very similar trends in all nine countries (Figure 3) [14], so we concluded that increased prescribing of psychotropic medications is a global issue.

IMS Disease Analyser-Mediplus

Disease Analyser-Mediplus collects de-identified practice records of more than 500 GPs in the UK. Currently, there are 3 million active patients registered with contributing GPs. The information allows analysis by diagnosis and links prescriptions to diagnosis. Information on test results, referrals and outcomes allows analysis of care pathways and the efficacy of particular treatment approaches.

There is very good correlation between the database population and the UK population in terms of age and male-to-female ratio. The panel of GPs is broadly representative of the UK population, although there is under-representation of smaller practices and of practices in Scotland and Northern Ireland, and there is a slight over-representation of younger doctors.

The following information is available:

- Diagnoses by Read code (mapped to ICD-10)
- Diagnoses linked to treatment
- Test results linked to diagnosis
- Anonymized patient age (in years only) and sex
- Treatment linked to cost
- Referrals
- International comparisons.

The Disease Analyser-Mediplus database has similar potential to the GPRD in paediatric drug utilization and pharmacovigilance research, which should be explored further.

Yellow Card Scheme

The Yellow Card Scheme was established in 1964 as a result of the thalidomide tragedy. Since then, the system has become one of the major international pharmacovigilance resources. The Yellow Card Scheme is run jointly by the Medicines and Healthcare products Regulatory Agency (MHRA) (the regulatory agency) and the Committee on Safety of Medicines (CSM) (an expert advisory committee to the MHRA).

Since 1991, the Yellow Card Scheme has been enhanced by a new computer system, the ADROIT (Adverse Drug Reaction On-line Information Tracking) system. ADROIT is different from other databases. It stores not only the details of the report, but also the image of the Yellow Card in the optical system; multiple users can view any yellow card on the screen at the same time.

The system receives approximately 20 000 yellow cards each year and more than 400 000 reports of suspected adverse drug reactions (ADRs) have been submitted on a voluntary basis by doctors, dentists, pharmacists, coroners and nurses and by pharmaceutical

companies under statutory obligations [15]. There are a number of quality assurance steps to ensure a high quality of data. Data from the year 2000 showed that 43 000 reports out of the total database were for children [16]. The MHRA estimated that about 8% of the yellow card reports in 1997 and 1998 were for those aged under 18 years [17].

The data on fatal suspected paediatric ADRs were reviewed by Clarkson and Choonara [16]; they have shown that 0.8% of yellow cards for children had a fatal outcome. A wide range of drugs were reported as being associated with children's deaths; anticonvulsants were found to have the highest number of fatal reports (78 out of 390 reports).

The MHRA has just conducted an independent review of access to the Yellow Card Scheme. The review recommended 'the MHRA should open access to the Yellow Card database, and should maximize the release of data from the Scheme for independent research subject to appropriate safeguards' [17]. It is anticipated that more research on paediatric drug safety using Yellow Card data will be conducted in the future. Further contact details for the Yellow Card Scheme are provided in Table 1.

Other databases

Databases such as MEMO (the Medicines Monitoring Unit) in Tayside [18] and the Scottish Primary Care Computer System (GPASS) [19] also have potential in paediatric pharmacoepidemiology. These databases are relatively small, so they are useful for studying medications that are widely used in children, such as corticosteroids in children with asthma [19].

There are other databases which could be useful for researching treatments of specific diseases or healthcare settings such as the Biologics & New Drugs Registry run by the British Society for Paediatric and Adolescent Rheumatologists, which contains information on the use of etanercept (Enbrel®) by patients with juvenile idiopathic arthritis [20]. Other examples include PICAnet (Paediatric Intensive Care Audit Network), which records treatment details of all critically ill children in NHS Paediatric Intensive Care Units in England and Wales [21]; UK Cystic Fibrosis Database in Dundee [22]; and UK Pain Database (PainDB) in Southampton, which collects data on behalf of members of the Pain Society [23].

Limitations

Each of these databases has enormous research potential, but they also have limitations to be aware of. We have already alluded to a few weaknesses, and some are

detailed in previous work [10, 14]. These include (but are not pertinent to all): nonspecific or missing diagnoses; no indication data for prescriptions; lack of prescription duration or dosage data; no information on compliance and adherence. The Yellow Card Scheme relies on spontaneous reporting, so cannot be used to estimate incidence rates of ADRs.

Summary

The NHS is a unique healthcare system which allows many powerful clinical databases to be developed; these databases have great potential for paediatric medication research. The future 'European Parliament and Council Regulation (EC) on medicinal products for paediatric use' is likely to stimulate research and development of paediatric pharmacoepidemiology and greater use of the above-mentioned databases is anticipated.

Competing interests

None declared.

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