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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

A pilot study to evaluate a community pharmacy–based monitoring system to identify adverse drug reactions associated with paediatric medicines use

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Abstract
Introduction Current pharmacovigilance systems are limited by spontaneous reporting of adverse drug reactions (ADRs), lack of a denominator, and lower than expected reporting rates. The aim of our study was to undertake a formal pilot evaluation of a community pharmacy–led ADR monitoring system.
Methods The setting was community pharmacies in five Health Boards areas of Scotland. Subjects were parents, guardians, or children presenting prescriptions for children 16 years and under prescribed serotonin specific reuptake inhibitors (SSRI), anticonvulsants, or medicines for the treatment of attention deficit hyperactivity disorder (ADHD). All pharmacies (n=827) were invited to participate. Over a 3-month period they were asked to identify prescriptions for targeted medicines and give out an ADR questionnaire. Questionnaire content included child demography, duration of medicine use, indication, perceived ADRs, and their description and severity. The study was approved by the North of Scotland Research Ethics Committee.
Results Seventy-two community pharmacists (8.7%) agreed to take part. Two hundred and twenty-nine questionnaires were distributed and 55 (24%) completed and returned by parents. Forty-one questionnaires related to ADHD medications, 13 to anticonvulsants, and 1 to an SSRI. Thirty questionnaires reported 44 possible ADRs, 19 of which were related to methylphenidate.
Conclusions The proposed ADR monitoring system identified expected ADRs thus demonstrating face and content validity for our approach. However the process was limited

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What was already known Current pharmacovigilance systems are limited by spontaneous reporting of adverse drug reactions, lack of a denominator, and lower than expected reporting rates. The majority of Yellow Card reports are submitted by healthcare professionals and little is known on the utility of parental, compared to professional, reporting on behalf of children.

What this study adds Community pharmacy–based, prospective adverse drug reaction monitoring scheme identifies the expected range of adverse drug reactions to the target drugs. Almost a quarter of parents approached responded appropriately to the ADR questionnaire. However the application of this approach to ADR monitoring is likely to be limited by low community pharmacist uptake.

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by low community pharmacist participation rates and low questionnaire return rates.

Keywords Adverse drug reactions · Pharmacovigilance · Children · Questionnaire

Introduction

In the UK, the routine system of pharmacovigilance is the Yellow Card Scheme (YCS) operated by the Medicines Healthcare Products Regulatory Agency (MRHA). The YCS has acknowledged limitations including reliance on spontaneous reporting, lack of denominators, and lower than expected reporting rates [1–3]. This is particularly true for adverse drug reactions (ADRs) affecting children, who are frequently prescribed off label medications, known to be associated with an increased incidence of ADRs [4, 5]. Data suggest that ADRs account for 1.5–2.1% of paediatric hospital admissions [6, 7], affect 2.6–9.3% of paediatric inpatients, and 1.5–11.1% of paediatric outpatients [8–10]. Routine prescribing data obtained from General Practice Prescribing databases suggest that in the UK between 120,000 and 880,000 children experience an ADR annually. However current reporting rates for children suggest that only 0.2–1.6% of paediatric ADRs appear to be reported in the UK via the YCS, with, on average, only 2,000 such ADRs reported annually.

Despite the introduction of patient reporting, the majority of Yellow Card reports are submitted by healthcare professionals and little is known on the utility of parental, compared to professional, reporting on behalf of children.

The aim of our study was to pilot and evaluate a community pharmacy–based monitoring system to identify ADRs associated with the use of three groups of high-risk medicines: selective serotonin reuptake inhibitors (SSRIs) [11–13], anticonvulsants [14], and treatments for ADHD including melatonin [15].

Methods

Approval for the study was obtained from the Fife, Forth Valley and Tayside Research Ethics Service and by the NHS Research and Development Committees for all participating Health Board areas. We invited all (n=827) registered community pharmacies within the Grampian (n=127), Lothian (n=180), Tayside and Angus (n=93), Lanarkshire (n=116), and Greater Glasgow Clyde (n=311) Health Board areas to take part. Community pharmacists were asked to prospectively identify all children for whom a prescription for one or more of the target drugs was presented and issue the parent/guardian/child collecting the prescription with a study information leaflet and an ADR questionnaire. An anonymised dispensing label was attached to the ADR questionnaire to accurately identify the drug, strength, and dose.

The ADR questionnaire was based on one used previously [16] and revised for consistency with the newly introduced patient reporting forms for the YCS. The questionnaire consisted of 23 structured and open questions to collect information on child demography (age, sex, and postcode), duration of medicine use, medical indication, perceived side effects/ADRs (open text), and description and severity of any ADR. Details of any actions taken or outcomes, including discontinuation of medicine, involvement of any healthcare professional, or submission of a Yellow Card were requested. To ensure compatibility with the YCS, the Yellow Card descriptors were used throughout. A tick list of symptoms covering all the major body systems was also included. The questionnaire was reviewed for face and content validity by a panel including clinical pharmacologists, toxicologists, paediatricians, hospital and community pharmacists, and lay people. Parents were asked to return the completed questionnaire whether the child had had an ADR or not.

At the time of this study, routine primary care data indicated that more than 13,000 children were prescribed one of the drugs of interest (3,300 anticonvulsants, 3,100 SSRI, 6,900 treatments for ADHD) annually in Scotland, equating to an average of 11 candidate children per pharmacy (based on 1,150 community pharmacies in Scotland and a typical 4- to 8-week prescription cycle).

Data from the ADR questionnaire were entered into an SPSS (Statistical Package for Social Sciences, version 16.0) database. Descriptive statistics were used to summarise recruitment rate (by Health Board area and by pharmacy), questionnaire response rates, and frequencies of the questionnaire variables.

Results

Response rates

Eight hundred and twenty-seven community pharmacies were approached to take part in this study, and 72 pharmacies were recruited giving a participation rate of 8.7% (72/827). Participating pharmacies distributed 229 ADR questionnaires; 57 completed questionnaires were returned, 2 of which were non-evaluable, giving a response rate of 24%. Forty-two (76.3%) ADR questionnaires were for males, and the median age was 13 [interquartile range (IQR) 9–14] years.

ADHD medication

Twenty-seven (49%) of the questionnaires returned were for children prescribed methylphenidate, of which 19

(70.4%) reported 26 possible ADRs. In order of frequency the ADRs reported were reduced appetite and loss of appetite (n=6, 23%), psychiatric disorders (5, 20%), stomach upset (3, 12%), sleep disturbance (3, 12%), headache (3, 12%). Seven returned ADR questionnaires were for melatonin, only one of which reported a possible ADR, "raised temperature at night". Three of the returned ADR questionnaires were for atomoxetine, one of which reported an ADR, "stomach problems".

Anticonvulsants

Thirteen returned ADR questionnaires were for the anticonvulsants sodium valproate (n=5), carbamazepine (n=3), topiramate (n=2), lamotrigine (n=2), and levetiracetam (n=1). Six (46.1%) of these questionnaires reported suspected ADRs, including drowsiness, dizziness, and weight gain.

SSRI

One ADR questionnaire for an SSRI was returned and this reported a suspected ADR of "nausea".

Severity of reported ADRs

Twenty-seven respondents gave 38 responses to the question "How bad would you say this side effect was?" using descriptors from the Yellow Card. The majority of reported ADRs (39.5%, 15/38) were described as mild-irritating but permitting normal daily function. However 36.8% of ADRs (n=14) were reported as affecting the child's everyday activities and 2.6% (n=1) as requiring hospitalisation.

Action taken and outcome following onset of ADR

Twenty-three respondents gave 38 responses to the question "What action was taken following the onset of the suspected ADR?". For reported ADRs, 65.7% (25) were discussed with their doctor, 7.8% [3] discussed with the community pharmacist, and 5.2% [2] did nothing; 21% (n=8) reported a variety of other actions.

Free text reports of ADRs, duration, and outcome

Thirty of 55 (54.5%) questionnaires reported a total of 44 ADRs perceived to be due to the medication under study (Table 1). When asked the question "Has the side effect stopped?", 28 respondents gave a total of 40 responses to this question. At the time of reporting, 26 ADRs were ongoing, and 14 ADRs were reported as having resolved. The duration of the reported ADRs ranged from 1 week to 6 years.

Symptom list

Eighty-four reports of symptoms possibly associated with medication were recorded by the respondents in 33 of the returned ADR questionnaires. A description of the symptoms is reported in Table 1. Forty-six symptoms were reported for methylphenidate of which the most frequent were mood problems (34.8%, 16), feeding problems (26%, 12), schooling problems (9.3%, 4), and headache (9.3%, 4). Twelve symptoms were reported for dexamfetamine, nine for sodium valproate, five for lamotrogine, four for levetiracetam, three for carbamazepine, three for melatonin, three for atomoxetine, and one for fluoxetine.

Discussion

The study demonstrated that a community pharmacy–based, prospective adverse drug reaction monitoring scheme identified the expected range of adverse drug reactions to the target drugs, demonstrating its validity. To our knowledge this is the first pharmacovigilance study to target community-based paediatric populations prescribed specific medicines of interest via community pharmacies. Our study has several limitations including low pharmacy and pharmacist participation rates, a situation which was exacerbated by a lower than expected questionnaire distribution rate, factors which limit the generalisability of our findings.

The design of the current study did not permit the reasons for pharmacy non-participation to be determined, however a similar approach using financial incentivisation has been demonstrated to have a positive effect in other pharmacy-based research studies [17, 18]. Although UK community pharmacists are encouraged to contribute to the YCS, it is not explicitly included in their NHS contractual framework. However the framework does include as a core component a public health service which comprises poster campaigns, smoking cessation advice and treatment, provision of emergency hormonal contraception and chlamydia detection and treatment. Consideration should possibly be given to including ADR monitoring and reporting in this framework with associated remuneration. However further research into those factors influencing pharmacy involvement in pharmacovigilance and pharmacovigilance related research is required.

Twenty-four percent of parents/guardians returned the ADR questionnaire, which is less than the predicted rate of 40% suggested in our previous study [16]. The medicines involved in the current study were prescribed for psychiatric, neurological, and behavioural conditions, and the nature of these conditions may have reduced parental response rates. Nonetheless, the return rate of 24% would, if scaled up to the whole population, produce significantly greater

Table 1 Free text ADR reports, medicine-related symptoms, prescribed medicines, and child demographics

Medicine(s) prescribed	Prescribed daily dose	Age (years)	Sex	Free text reported ADRs	Duration of ADRs	Severity	ADR now resolved	Recovery of child from ADR	Reported tick list symptoms
Methylphenidate	10 mg	5	M	Sleeping problems	–	2	Yes	Recovered completely	–
Methylphenidate	54 mg	12	M	Loss of appetite	6 years	3	No	Recovered but some lasting effects	Constipation, headache, very slow weight gain, mood change, struggled at school
				Affect growth	6 years	3	No	Recovered but some lasting effects	
				Depression	On/off	–	Yes	–	
Methylphenidate	18 mg	12	M	Weight gain	Always	2	No	No improvement	–
				Poor sleep	Always	3	No	No improvement	
Methylphenidate	36 mg	13	M	Stomach cramp	Everyday (all)	1	No	Other	Mild cramping, difficulty getting to sleep
				Loss of appetite		1	No		
				Difficulty getting to sleep		1	No		
Methylphenidate and sodium valproate	10 mg 300 mg	6	M	Hallucination (hearing and seeing things that were not there)	2–3 months	2	Yes	Getting better	Irritation, bad mood, hearing voices and noises, scared of classroom (seeing monsters)
Methylphenidate	18 mg	16	M	Headache	1 week	2	Yes	Other	Nausea, no appetite
Methylphenidate	20 mg	13	M	Reduced appetite	2 years	1	Yes	Recovered completely	Slight weight loss
Methylphenidate	54 mg	13	M	–	–	–	–	–	Weight loss, no appetite, can't set to sleep
Methylphenidate	20 mg	12	M	Stomach upset	Day-day	2	No	Other	Sore head, weepy, doesn't feel hungry, mood change
				Violent out bursts	Frequently		No	Other	
Methylphenidate	30 mg	9	M	Loss of appetite	Most days	2	No	Other	Headache first week only, mild weight loss, sleeping and schooling problems, dryness of mouth
				Rebound hyperactivity	Most evenings	2	–	Other	
Methylphenidate	5 mg	12	M	Alopecia	–	–	–	Other	Headache
Methylphenidate	18 mg	12	M	Trouble sleeping	–	2	Yes	Recovered completely	–
Methylphenidate	36 mg	13	M	Headache	6 months	3	Yes	Recovered completely	Bit tearful at times, lack of appetite
				Stomach ache	6 months	3	Yes		
Methylphenidate and melatonin	10 mg	7	M	Decreased appetite	Continually	1	No	No improvement	
Methylphenidate	5 mg	9	F	Headache	1 week	1	Yes	Getting better	Mood problems
Methylphenidate	20 mg	15	F	–	–	–	–	–	Low confidence, sleeping problems
Methylphenidate	15 mg	7	F	Mood swings	From evening	1	No	–	Weight loss, schooling problem
Methylphenidate and melatonin	70 mg 18 mg	14	M	Reduced appetite	Years	–	No	–	Regular headache, gets down, slow weight gain, sleeping problems, poor behaviour at school, mood change

Table 1 (continued)

Medicine(s) prescribed	Prescribed daily dose	Age (years)	Sex	Free text reported ADRs	Duration of ADRs	Severity	ADR now resolved	Recovery of child from ADR	Reported tick list symptoms
Methylphenidate	5 mg	8	M	Tiredness	Days	1	Yes	Recovered completely	Wanted to sleep most the day
Methylphenidate	36 mg	13	M	–	–	–	–	–	Blurred vision for 2 weeks
Methylphenidate	5 mg	14	M	Itchiness	When first prescribed	2	Yes	Recovered completely	Mild stomach pain, weight gain despite reduced appetite, schooling problems
Methylphenidate	28 mg	9	M	–	–	–	–	–	Night terrors for 20 nights
Melatonin	3 mg	12	M		–	–	–	–	Bedwetting, poor concentration
Melatonin	3 mg	3	M	Slight raised temperature	First few weeks	1	Yes	Recovered completely	
Dexamfetamine	5 mg	16	M	–	–	–	–	–	Not sleeping well
Dexamfetamine	5 mg	12	F	Loss of appetite	Always	1	No	No improvement	Tummy pain, headache, slight depression
Dexamfetamine	5 mg	9	M	Could affect weight	–	–	–	–	Constipation, no appetite, schooling problems
Dexamfetamine	20 mg	9	M	Make him eat more	–	1	No	No improvement	Mood problems, very dry skin, bedwetting, bad concentration, mood change
Atomoxetine	30 mg	11	M	–	–	–	–	–	Sickness in the morning, coldness in his foot
Atomoxetine	18 mg	10	M	Sickness	–	1	No	Recovered completely; stopped medicine	Headache, mood problems, poor appetite
Carbamazepine	440 mg	7	F	–	–	–	–	–	Excess tiredness
Carbamazepine and lamotrigine	400 mg	13	F	Tiredness	3 years	2	No	Getting better	Headache, rash
Lamotrigine	15 mg	4	F	Mood swings	Every day	2	No	No improvement	Leg cramps, sore right eye, sore throat, insomnia, limited concentration
				Constipation	Every day	2	No	No improvement	
Sodium valproate and topiramate	560 mg	14	M	Drowsiness	3 years	3	Yes	Recovered completely	Constipation, very sleepy
Sodium valproate	640 mg	5	M	Increased appetite	4 months	1	No	–	–
				Weight gain	4 months	–	No	–	
Sodium valproate	920 mg	8	M	–	–	–	–	–	Gets tired, schooling problems, mood change
Sodium valproate	480 mg	3	F	Tiredness	Continuous (all)	4	No	Other	Tantrums and mood swings, disturbed sleep, withdrawn, aggressive
				Tantrums		3	No		
				Loss of concentration		3	–		
Levetircetam and diazepam suppositories	1 g; 10 mg	12	M	Dizzy	3 weeks (all)	2	No		Very bad tempered, hearing problems, learning difficulties, very moody
				Tired		2	No		
				Headache		2	No		
Fluoxetine and methylphenidate	16 mg	13	M	Nausea	–	1	Yes	Recovered completely	Nausea

(–) indicates no response. Exact free text wording of the parents was used. Severity of ADRs: *1* mild, *2* uncomfortable, *3* bad enough to affect child's activity, *4* bad enough for child to be admitted to hospital

returns than currently implemented pharmacovigilance systems. In Scotland, paediatric Yellow Card ADR reports currently number approximately 200 per year, while in the UK a total of 906 ADR and 13 fatal ADR reports were received by the MHRA for methylphenidate between October 1964 and October 2009. Despite the low community pharmacy uptake in this study we generated 72 suspected ADRs or medicine-related symptoms for methylphenidate during a 3-month data collection period.

Our approach generated a number of responses, mostly for methylphenidate. Importantly, not all parents/guardians had been informed of these potential ADRs by their health professionals and, in some, the ADRs were still an issue of concern long after the start of therapy and the initial occurrence of the ADR. The ADR monitoring system we propose has potential for targeted monitoring and reporting of ADRs if parent/guardian recruitment and response can be enhanced.

Conclusions

The monitoring system utilised identified expected ADRs for the study medicines and produced frequencies which were similar to those reported in the literature, thus demonstrating face and content validity. Although the process was limited by the low community pharmacist and parent participation rate, such an approach could enhance and complement current ADR monitoring/reporting systems and generate new data likely to have a positive impact on paediatric patient safety.

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