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Parental Reporting of Adverse Drug Reactions Associated with Attention-Deficit Hyperactivity Disorder (ADHD) Medications in Children Attending Specialist Paediatric Clinics in the UK

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Abstract

Background: The development of systems to ensure appropriate and informed use of medicines in children is a global priority. Current pharmacovigilance systems, such as the UK Yellow Card Scheme, are limited by opportunistic reporting of adverse drug reactions (ADRs), lack of a denominator and lower than expected reporting rates.

Objective: To develop a pharmacovigilance system able to target specific patient populations such as children, and specific medicines of interest, using specialist medical clinics.

Methods: Between January and March 2010, parents of 578 children (3–16 years of age) receiving pharmacological therapy for attention-deficit hyperactivity disorder and attending a child and adolescent clinic in the UK were sent an ADR questionnaire to elicit information on possible ADRs associated with their child's medication use. Two approaches, free text and a symptom tick list, were used to elicit possible ADRs.

Results: Two hundred and seven questionnaires were returned, of which 200 were evaluable, giving a response rate of 35.9%. 123 questionnaires reported a total of 213 free-text ADRs perceived by the parents to be due to the medications under study. Two-thirds of reported ADRs were considered to be ongoing at the time of reporting. Duration of reported ADRs ranged from 1 week to 3 years. 81 returned questionnaires reported 134 different ADRs for methylphenidate monotherapy. For methylphenidate, the most

frequently reported ADRs were loss of appetite (34.3%), headache (17.9%), mood and emotional problems (14.9%), stomach upset (14.9%), sleep disturbance (10.4%), and rash and other skin problems (5.2%). 467 possible drug-related symptoms were reported using the tick-list approach. Using the tick list, the most frequently reported symptoms were mood and emotional problems (28.1% [131/467]), stomach and abdominal problems (13.3% [62/467]), insomnia (12.8% [60/467]) and lack of appetite (12.6% [59/467]). The symptom tick list identified a broader range of possible adverse effects not reported as free-text ADRs, such as schooling difficulties, hearing problems, cough and blurred vision.

Conclusions: The results of our study demonstrate the feasibility of using specialist clinics to target both at-risk patient populations and/or medicines of interest. We have also clearly demonstrated the practicality and feasibility of parental reporting. Parents reported common and less common ADRs, such as suicidal ideation, using both the free text and symptom tick-list approach.

Background

Attention-deficit hyperactivity disorder (ADHD) is a common neurobehavioural condition,[1] affecting 3–5% of school-aged children,[2] which is characterized by developmentally inappropriate and impairing levels of inattention and/or impulsivity and hyperactivity that is frequently accompanied by significant co-morbidity.[1] In the UK, two classes of pharmacological agent are licensed for the management of ADHD in children: CNS stimulants (methylphenidate and dexamfetamine) and the non-stimulant atomoxetine.[3] Melatonin, which is currently unlicensed for paediatric use, is also commonly used as an adjuvant therapy to manage sleeplessness associated with ADHD.[4] The use of ADHD medication in children is associated with a number of well recognized adverse drug reactions (ADRs),[5] and although the incidence of serious ADRs is relatively small, less serious ADRs are common and may significantly affect the child's quality of life.[5,6] A further issue is the uncertainty surrounding the possible long-term effects of ADHD medicines upon children.[7]

In the UK, the 'Yellow Card Scheme' (YCS), which is run by the Medicines and Healthcare products Regulatory Agency (MHRA), is the spontaneous reporting mechanism for detection of ADRs. The MHRA has added black triangles to the summary of product characteristics for both atomoxetine and melatonin, which typically means these medicines are under extensive review and are being monitored for safety.[8] Although postmarketing spontaneous reporting schemes are the best source of medicines safety information, such schemes are limited by a reliance on opportunistic reporting of ADRs, a lack of a denominator and lower than expected reporting rates.[9] This is particularly true for paediatric medicines, which are frequently prescribed off-label, a practice which itself is associated with an increased incidence of ADRs.[10,11]

To optimize paediatric ADR detection we initially proposed the use of community pharmacies to identify and target the parents of children prescribed ADHD, antidepressant and antiepileptic medications.[12] However, while this approach was successful in stimulating responses from 24% of parents approached, the process was limited by a lower than expected community pharmacist participation rate.

The aim of the present study was to develop a pharmacovigilance system able to target specific patient populations and specific medicines of interest, using specialist medical clinics. A secondary aim was to compare two different methods for eliciting possible ADRs: free-text reporting and symptom tick list. The specific patient

population we chose to identify was children attending child and adolescent clinics prescribed medicines for the treatment of ADHD.

Method

Following ethical approval, six specialist child and adolescent clinics were approached and agreed to take part in this study. Clinic staff were asked to identify all children under the age of 16 years attending their clinic with a diagnosis of ADHD who were currently prescribed ADHD medication (methylphenidate, dexamfetamine, atomoxetine and melatonin).

To ensure anonymity and confidentiality, the research team had no access to clinic databases or contact with parents/guardians. A personalized invitation letter together with a participant information leaflet and a previously validated ADR questionnaire[12] were sent directly to the parents of identified children from the child's medical consultant.

The Adverse Drug Reaction (ADR) Questionnaire

The ADR questionnaire, which had been previously validated in two community pharmacy studies and amended in light of comments from parents prior to use, consisted of 22 structured and open questions to collect information on child demography (current age, sex and postcode), duration of medicine use, medical indication, free-text description of perceived ADRs, together with severity, outcome and parental actions (see Supplement Digital Content 1, http://links.adisonline.com/DSZ/A36).[12-14] Prior to use, the amended questionnaire was further assessed by a group of 12 healthcare professionals consisting of pharmacists, clinical pharmacologists, doctors and nurses. To ensure compatibility with the YCS, Yellow Card descriptors were used throughout. A tick list of symptoms possibly related to the medication was also included in the ADR questionnaire to elicit further information on possible ADRs. This list consisted of domains such as stomach or schooling problems, previously identified from MHRA Yellow Card report data for ADHD medications. Such an approach has been used by other studies assessing the frequency of ADRs in a variety of patient populations.[15,16]

Data Collection

To minimize respondent bias, the importance of returning the questionnaire even if there had been no ADR was stressed in the parent information leaflet. To enhance parental response, parents/guardians could either complete and return the questionnaire by post, or call the researcher to describe their response by telephone. The research team was not allowed to provide parents/guardians with information or advice on the identification and management of possible ADRs. If such information was requested, the parents/guardians were referred to their child's general practitioner (GP), specialist consultant or the National Health Service (NHS) 24-hour helpline. A reminder letter and questionnaire were sent to all participants 4 weeks after the initial invitation letter.

Data Analysis

Questionnaire data were entered and analysed using SPSS v.17.0 (IBM Corporation, Somers, NY, USA). Simple descriptive statistics were used to summarize the response rate by drug, ADR data and comparison of free text and symptom tick-list reporting.

Approval for the study was obtained from The North of Scotland Research Ethics Committee, and R&D approval was secured from local NHS committees.

Results

Response Rate

A total of 750 children were identified by clinic staff using the clinic electronic patient list; however, 172 children were either no longer prescribed pharmacological treatments or no longer registered as active at the clinics, leaving 578 children suitable for study inclusion. Study packs were sent to the parents of 578 children currently prescribed ADHD medications (figure 1). Within

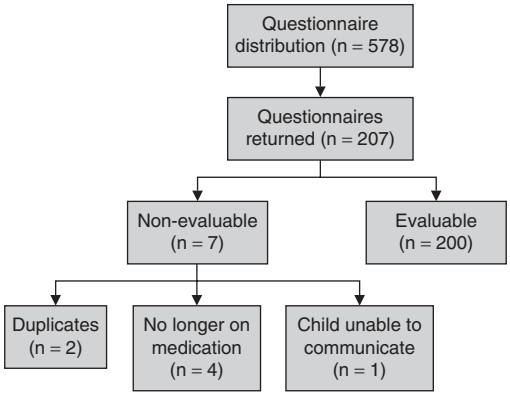

Fig. 1. Study flow chart describing the adverse drug reaction questionnaire distribution and return.

a 2-month period, 207 completed questionnaires were returned, giving a response rate of 35.9%. Of the 207 questionnaires, seven were non-evaluable, of which four were for children no longer on medication, two were duplicates and one was for a child unable to communicate and describe ADRs.

ADR Questionnaire

Of the 200 evaluable questionnaires, 61.5% (123/200) reported free-text ADRs (84.5% [104] male, median age 11 years, interquartile range 9–13) [table I]. Seventy-five percent (124) of questionnaires were for monotherapy and the remainder for multiple therapies. Children prescribed multiple therapies were not excluded from the study. Only three reports of ADRs were made using the dedicated phone line (2.4%). Thirty-six (36/200 [18.4%], six female) of the questionnaires, all for monotherapy, contained no free-text ADR or symptom reports and 41 (41/200 [20.6%]) reported no free-text ADRs but did report symptoms in the tick-list section.

Free-Text Reports of ADRs, Duration and Outcome

One hundred and twenty-three questionnaires (61.5%) reported a total of 213 free-text ADRs perceived to be due to the medications under study (table I), of which 62.4% (133) were reported as ongoing and 30% (64) as resolved (information not supplied for 16 ADR reports). The duration of the reported ADRs varied between 1 week and 3 years.

Study Medications

The majority of questionnaires (80% [160/200]) were for methylphenidate preparations either as mono- or polytherapy. Methylphenidate as monotherapy was the study drug most frequently associated with an ADR report. Eighty-one returned questionnaires reported 134 different free-text ADRs for methylphenidate alone, of which 60.4% (81/134) were described by parents as unresolved (table I). Fifty percent (40) of these questionnaires referred to the immediate-release formulation only and accounted for 49.6% (67) of free-text ADR reports; 40.7% (33) to the prolonged-release formulation only accounting for

Table I. Reported free-text adverse drug reactions (ADRs) and outcome

Medicine(s)	No. of reports with ADRs	Total no. of ADRs	No. resolved[a]	No. not resolved[a]
Methylphenidate	81	134	42	81
Methylphenidate + melatonin	13	24	8	16
Atomoxetine	9	15	5	8
Methylphenidate + atomoxetine	12	26	6	18
Dexamfetamine	3	5	2	3
Dexamfetamine + melatonin	2	4	1	3
Dexamfetamine + atomoxetine	1	1		1
Risperidone	1	2		1
Dexamfetamine + methylphenidate	1	2		2
Total	**123**	**213**	**64**	**133**

a The number of ADRs resolved and not resolved may not add up to the total number of ADRs reported as some reports were missing.

Table II. Frequency and description of free-text adverse drug reaction (ADR) reports for methylphenidate as monotherapy

Reported ADRs	No. and frequency of ADR [n (%)]	Children's age [y (median, IQR)]	Sex (n)	Dose associated with ADR [mg; median (IQR)]	Duration of ADR [wk; median (IQR)]	Severity	Resolved (yes, no)
Lack of appetite	46 (34.3)	11 (9–14)	4 F, 42 M	45 (20–60)	24 (24–24)	12 mild, 21 uncomfortable, 4 affect child's daily activities, 9 missing	Yes (n = 4), no (n = 35), 7 missing
Headache	24 (17.9)	11 (9–12)	24 M	30 (20–56)	4 (2–5)	10 mild, 8 uncomfortable, 6 missing	Yes (n = 11), no (n = 11), 2 missing
Mood and emotional problems	20 (14.9)	10 (9–12)	1 F, 19 M	40 (20–50)	8 (4–24)	2 mild, 9 uncomfortable, 6 affect child's daily activities, 3 missing	Yes (n = 5), no (n = 13), 2 missing
Stomach upset and abdominal problems	20 (14.9)	10 (8–13)	1 F, 19 M	30 (15–30)	4 (3–8)	7 mild, 8 uncomfortable, 1 affects child's daily activity, 4 missing	Yes (n = 10), no (n = 6), 4 missing
Insomnia	14 (10.4)	11 (9–12)	2 F, 14 M	46 (30–60)	24 (5–24)	4 mild, 6 uncomfortable, 1 affects child's daily activity, 3 missing	Yes (n = 3), no (n = 10), 1 missing
Skin problems	7 (5.2)	10 (9–11)	7 M	30 (30–54)	24 (4–24)	5 mild, 2 uncomfortable	Yes (n = 2), no (n = 5)

F = female; **IQR** = interquartile range; **M** = male.

41.5% (56) of ADR reports; and 9.8% (8) to both, accounting for 8.9% of ADR reports. For methylphenidate monotherapy, the most frequently reported ADRs were loss of appetite (46/134 [34.3%]), headache (24/134 [17.9%]), mood and emotional problems (20/134 [14.9%]), stomach upset (20/134 [14.9%]), sleep disturbance (14/134 [10.4%]), and rash and other skin problems (7/134 [5.2%]) [table II]. Nine questionnaires reported 15 ADRs for atomoxetine and three questionnaires reported five ADRs for dexamfetamine, both as monotherapy. One questionnaire reported two ADRs for risperidone. Twenty-nine questionnaires for polytherapy reported 57 different ADRs, which could not be directly attributed to any single agent.

Severity of Reported ADRs

The question ''How bad would you say the side effect was'', was completed by parents for 90.1% (192) of the reported ADRs. The majority, 45.3% (87/192), were described as uncomfortable but permitting normal daily function, 30.2% (58) as mild or slightly uncomfortable, 24% (46) as bad enough to affect the child's everyday activities and one as life threatening (suicidal ideation with atomoxetine).

Action Taken Following Onset of ADR

One hundred and seventy-two responses were given to the question ''What did you do about the side effect.'' The GP was consulted for 55.8% (96) of reported ADRs, a nurse for 11.0% (19), the pharmacist for 5.2% (9) and no action was taken for 9.3% (16) of ADRs. For 12.2% (21) of ADRs the medication was either changed or the dose reduced by the doctor, and for 6.4% (11) of ADR reports the child stopped the medication themselves.

Outcome Following ADR

When asked ''How is the child who had the side effect'', parents responded for 147 of the 213 reported ADRs (69%). For 55.1% (81) of the reported ADRs parents reported that the child was not improving, for 18.4% (27) parents reported

that the child had recovered completely, for 20.4% (30) parents reported that they were getting better and for 6.1% (9) parents reported that the child had recovered but had lasting side effects.

Symptom Tick List

One hundred and sixty-three questionnaires returned 467 possible drug-related symptoms using the symptom tick list (table III). Methylphenidate as monotherapy was linked to 305 reported symptoms. For all study medications, the most frequently reported symptoms were mood and emotional problems (28.1% [131/467]), stomach and abdominal problems (13.3% [62/467]), insomnia (12.8% [60/467]) and lack of appetite (12.6% [59/467]). Two-thirds of free-text reports for ADRs (141/213 [66.2%]) were also reported by parents on the symptom tick list. However, 69.7% (324) of symptoms reported using the tick list were not reported as free-text ADRs. The symptom tick list identified a broader range of possible adverse effects not reported as free-text ADRs, such as schooling difficulties, hearing problems, cough and blurred vision. Furthermore, for methylphenidate, symptoms such as mood and emotional problems were reported 4-fold more frequently using the tick-list approach than using free-text reporting.

Discussion

The results of this study confirm that at-risk patient populations and medicines of interest can be identified and targeted for the purposes of pharmacovigilance and ADR detection using specialist medical clinics. Our approach to ADR monitoring proved easy to establish and inexpensive to run, while achieving relatively high parental return rates for ADR questionnaires. We have also demonstrated the feasibility of using parental reporting as a method for monitoring paediatric ADRs, achieving a parental return rate of 36%. Submitted ADR reports were clear, concise and described both common and less common ADRs relevant to the medicines of interest. Two different mechanisms for identifying potential ADRs, free-text reporting and a tick list to identify possible symptoms associated with medication, were used. Parents used both methods to describe possible ADRs; however, the symptom tick list elicited a greater number and nature of possible ADRs. Although it has been suggested that the tick-list approach to identifying ADRs lacks specificity,[17] this did not appear to be the case in this study where the majority of free-text ADR reports were also reported by the respondents using the symptom tick-list approach.

While the majority of reports were for common and well recognized ADRs, such as lack of appetite,[5,18] a significant number of parents also reported issues such as hyperactivity, depression and nervousness, which have been previously attributed to the disease, co-morbidities or failure of treatment, but which have only recently been highlighted by the US FDA[11] as possible uncommon paediatric ADRs associated with ADHD medicines.

Although ADRs associated with mood and psychotic symptoms in children prescribed ADHD stimulants have been described as rare,[19,20] a small retrospective chart review study of 98 children prescribed ADHD stimulant medications has reported that 6% of children develop psychotic symptoms such as depression, hallucination and paranoia months or years after the stimulant treatment.[21] In general, there is a lack of data concerning the long-term potential adverse effects of ADHD medications.[22-25]

Of note, parental reports also highlighted a high incidence of rash (5.2% of reports) associated with methylphenidate monotherapy, an ADR that is generally considered uncommon or rare.[26] During the 2-month data collection period, a total of 437 possible ADRs and symptoms linked to the administration of methylphenidate as monotherapy were reported by parents. In contrast, the YCS received a total of 906 ADR and 13 fatal ADR reports concerning methylphenidate for all age ranges between 1964 and 2009.[27] Unlike our initial study performed in community pharmacies, which required face-to-face recruitment of parents in the pharmacy,[12,13] the approach we used in this study required an invitation letter from the child's

Table III. Comparison between free text and symptom tick-list reporting of adverse drug reactions linked to study medicines

Medicine(s)	Headache		Lack of appetite and feeding problems		Insomnia, nightmares, sleeping problems		Stomach upset, nausea, constipation, mouth ulcers		Mood change, depression, anxiety irritability, hyperactivity		Skin problems (rash, spots, dry skin)		Muscular and joint pains		Weight change		Cough and breathing problems		Hearing problems		Blurred vision		Poor concentration, schooling problems	
	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list	free text	tick list
Methylphenidate	24	43	46	42	14	39	20	43	20	82	7	15	2	13	1	10		4		2		4		8
Methylphenidate + melatonin	2	3	6	5	4	6	3	6	6	22	1	2			1	3				1				9
Atomoxetine	2	5	4	2	2	3		6	5	7		2	1	1	2	2								
Methylphenidate + atomoxetine	3	1	5	4	5	8	4	4	6	4	2	1			1	1								4
Dexamfetamine	2	3	1	2	1	2	1	1		3						1								1
Dexamfetamine + melatonin	1	2		1	1	2		3	2	10		1				1		1		2				3
Risperidone	1														1									
Dexamfetamine + atomoxetine		1	1	1						1		1		1		1								
Dexamfetamine + methylphenidate			1								1													
Atomoxetine + melatonion				1				1		1														1
Dexamfetamine + lorazepam				1				2		1				1										
Total	**35**	**58**	**64**	**59**	**27**	**60**	**28**	**62**	**39**	**131**	**11**	**22**	**3**	**16**	**6**	**19**	**0**	**5**	**0**	**5**	**0**	**4**	**0**	**26**

consultant only, and thus minimized the time and effort required for recruitment. Despite half of the parents taking part in our community pharmacy-based study expressing a preference for telephone rather than postal reporting of ADRs,[14] and unlike the Australian experience of telephone ADR reporting,[28] <3% of parents in this study made use of this facility.

As with most spontaneous reporting systems such as the YCS, our study has several limitations, including recall and respondent bias, together with the confounding factors such as coexisting morbidities.[9] Although we cannot be certain of any link between reported ADRs or symptoms and a child's medication, it is clear that such a link has been made by the child's parents.

Further research is required to demonstrate transferability of this system of monitoring ADRs to other settings, patient groups and target medicines.

Conclusions

The results of our study demonstrate the feasibility of using specialist clinics to target both at-risk patient populations and/or medicines of interest. We have also clearly demonstrated the practicality and feasibility of parental reporting. Parents reported common and less common ADRs such as suicidal ideation, using both free text and symptom tick-list approaches.

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