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The PIPc Study—application of indicators of potentially inappropriate prescribing in children (PIPc) to a national prescribing database in Ireland: a cross-sectional prevalence study

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ABSTRACT

Objectives Evidence is limited regarding the quality of prescribing to children. The objective of this study was to apply a set of explicit prescribing indicators to a national pharmacy claims database (Primary Care Reimbursement Service) to determine the prevalence of potentially inappropriate prescribing in children (PIPc) in primary care.

Primary and secondary outcomes measures To determine the overall prevalence of potentially inappropriate prescribing (PIP) in children in primary care. To examine the prevalence of PIPc by gender.

Design and setting Cross-sectional study. Application of indicators of commission of PIP and omission of appropriate prescribing to a national prescribing database in Ireland.

Participants Eligible children <16 years of age who were prescribed medication in 2014.

Results Overall prevalence of PIPc by commission was 3.5% (95% CI 3.5% to 3.6%) of eligible children <16 years of age who were prescribed medication in 2014. Overall prevalence of PIPc by omission was 2.5% (95% CI 2.5% to 2.6%) which rose to 11.5% (95% CI 11.4% to 11.7%) when prescribing of spacer devices for children with asthma was included. The most common individual PIPc by commission was the prescribing of carbocisteine to children (3.3% of eligible children). The most common PIPc by omission (after excluding spacer devices) was failure to prescribe an emollient to children prescribed greater than one topical corticosteroid (54% of eligible children). PIPc by omission was significantly higher in males compared with females (relative risk (RR) 1.3; 95% CI 1.0 to 1.7) but no different for PIPc by commission (RR 1.0; 95% CI 0.7 to 1.6).

Conclusion This study shows that the overall prevalence of PIP in children is low, although results suggest room for improved adherence to asthma guidelines.

Strengths and limitations of this study

- This is the first study to examine potentially inappropriate prescribing in children using explicit criteria using a national dispensing database.
- The study focuses on commonly prescribed medications in general practice.
- National dispensing database lacks clinical information to confirm diagnoses.
- Study population limited to those eligible for publicly funded healthcare (approximately 40% of the population under 16 years).
- Some medications are available over the counter which may affect prevalence estimates.

INTRODUCTION

Recently, there has been concern over the quality of care that children receive in primary care in particular. The rational use of medicines in children has been inadequately studied.[1 2] Medicines are generally considered appropriate in an adult population when they have a clear evidence-based indication, are well tolerated in the majority of patients and are cost-effective. Medicines or prescribing patterns that do not fit this description can be considered inappropriate or potentially inappropriate.[3] These terms can include underprescribing, overprescribing and misprescribing where underprescribing refers to the omission of a prescription that is needed, overprescribing is the prescription of a medication that is unnecessary and misprescribing includes the incorrect prescription of an indicated medication.[4] The term 'potentially inappropriate prescribing' (PIP) acknowledges the reality of prescribing in clinical practice whereby the prescription of an inappropriate medication may be justified by the individual needs of a particular patient.[5] For example, sedating antihistamines may be considered inappropriate for young children because of the risk of side effects such as sedation, paradoxical excitation and potential cardiac toxicity. However, they may in some instances be considered

appropriate in the treatment of insomnia relating to itch caused by eczema. PIP in older adults has been shown to lead to increased morbidity, adverse drug events and hospitalisations.[6 7] In Ireland, 36% of those aged 70 years or over received at least one potentially inappropriate prescription in 2007, with an associated expenditure of over €45 million (9% of prescribing costs in this age group).[8] No comparable data are available on PIP in children (PIPc) in Ireland.

Research into PIP in adults has focused on the development of indicators or explicit criteria of prescribing which are measurable criteria against which quality standards can be set and audited.[9] Explicit indicators such as the Screening Tool to Alert doctors to the Right Treatment/Screening Tool of Older Peoples potentially inappropriate Prescriptions criteria were devised to identify PIP in older adults and have been found to be valid, reliable and generalisable across international primary care settings.[10]

Recent studies have highlighted that explicit prescribing indicators are not sufficient to assess whether prescribing is appropriate or not in the context of assessing daily prescribing practices.[11] Ideally, a prescribing indicator would be based on a thorough review of patient records with access to the full clinical and treatment history of the patient. Nonetheless, this process is time-consuming and can be extremely complex.[12 13] Although the evidence base for developing explicit prescribing indicators is limited, combining expert professional opinion with consensus methodology can create quality indicators in areas where it would not otherwise be possible.[14] Explicit indicators can be useful in assessing the quality of prescribing using large national prescribing databases without clinical information.[15]

We previously developed a set of 12 explicit indicators of PIPc in primary care using a modified Delphi technique.[16] These were conceptualised as indicators of omission or commission based on either the active prescribing of a potentially inappropriate medicine or apparent failure to prescribe appropriately based on clinical guidelines.

A number of other tools have been developed to assess the quality of prescribing in children sometimes in combination with other elements of care,[17–19] however to date none have been applied to assess the prevalence of PIP in children.[20]

The aim of the current study was to apply the PIPc indicators to a national pharmacy claims database in 2014 to determine the prevalence of PIPc in primary care. Secondary objectives were to explore the association between PIP and gender.

METHODS

Study design and setting

This was a cross-sectional study using national pharmacy claims data for 2014 from the Health Services Executive-Primary Care Reimbursement Service (HSE-PCRS) database in Ireland. Specifically, data were used from the General Medical Services (GMS) scheme, a form of public health cover funded by the Irish state.

Patient and public involvement

Patients were not involved in the conception, design or conduct of this research. We will disseminate findings from this study to the wider public via web-links on the research team's departmental/institutional website.

HSE-PCRS database

The HSE-PCRS database records pharmacy claims for dispensed medicines prescribed to patients by their general practitioner (GP) or prescribed by a hospital specialist and subsequently transcribed by their GP. Drug information on strength, quantity dispensed and dosage form is included. Limited patient demographic data recorded includes age, gender and region but there is no clinical or diagnostic information. Approximately 39% (414 856) of the total population (1 072 220) of children aged <16 years in Ireland were eligible for the scheme in 2014.[21] The population of GMS eligible patients is changeable from month to month as patients join and leave the scheme; therefore, the average population over a 12-month period was used in this study. Eligibility to 'free' medical care under this scheme is based on age and household means testing. A prescription charge of €2.50/item to a maximum of €25 per month applies to all prescriptions dispensed under this scheme. Due to the eligibility criteria, based on household income and age, the GMS scheme over-represents children from socioeconomically deprived families.

Study population

The study population included all children under 16 years of age eligible for the HSE-PCRS GMS scheme, who were dispensed a prescription during the study period (January-December 2014). The data were anonymised, and access to patient identifiable information such as coded diagnoses was not possible.

Data extraction

Data were extracted for the study period between 1 January 2014 and 31 December 2014. For some indicators, prescribing data from 1 January to 31 December 2013 were required to establish a diagnosis For example, a diagnosis of asthma was determined by the use of two or more inhaled corticosteroids (ICS). Each medication was identified using WHO Anatomical Therapeutic Chemical classification codes.[22]

PIPc indicators

The previously published PIPc indicators were divided in two categories, those that described the commission of PIP and those that highlighted omissions. Where age is not referred to, the indicator applies to all children aged under 16 years.

Outcomes

Children were categorised as having received, or not having received, any of the PIPc indicators. The primary

Table 1 Patient demographics

Age group (years)	Total	Female	% Female
0–4	116093	56465	48.6
4–11	196478	95579	48.6
12–15	102285	49504	48.4

outcomes included the overall prevalence of commission of PIPc, defined as the occurrence of at least one of the indicators of commission, and the overall prevalence of omission of appropriate prescribing, defined as the occurrence of at least one of the indicators of omission. The secondary outcomes were the prevalence of each individual PIPc indicator within the relevant age category, the association between the presence of any PIPc (binary variable) and gender (male/female).

Statistical analysis

Overall prevalence of PIP by commission and omission was calculated as a percentage of GMS eligible children with 95% CIs. The prevalence of each individual PIPc indicator was also calculated. These estimates represent the number of individuals exposed to a PIP as a proportion of all the eligible individuals within the particular age category detailed in the indicator (ie, all those dispensed a prescription during 2014). Eligible GMS population data are recorded in age bands in the HSE-PCRS database (eg, 0–4 years, 5–11 years and 12–15 years). Where age limits of PIPc indicators overlapped with these age bands, it was necessary to calculate an average of the number of children within certain age limits (eg, the number of children under 2 years was calculated as the number of children in the 0–4 years band divided by 5 and multiplied by 2). The relative risk (RR) of exposure to PIP by commission and PIP by omission in males compared with females was calculated with 95% CIs. Analyses were performed using SAS V.9.2 (SAS Institute).

RESULTS

Population

This study includes 414856 children aged <16 years who received at least one dispensed prescription in 2014. Table 1 describes the population.

Primary outcomes: prevalence of overall PIPc

The overall prevalence of PIPc by commission was 3.5% (95% CI 3.5% to 3.6%) of the eligible GMS population. The overall prevalence of PIPc by omission was 2.5% (95% CI 2.5% to 2.6%) though this rose to 11.5% (95% CI 11.4% to 11.7%) when the spacer device indicator was included in the prevalence calculation. In the commission category, the carbocisteine indicator heavily influenced the results and when this was removed, the overall prevalence of PIPc by commission was 0.29% (95% CI 0.27% to 0.30%) (see table 2 and table 3, respectively).

Secondary outcomes: prevalence of specific indicators of PIPc

The most prevalent indicator of PIPc by commission was the prescription of carbocisteine to children (3.3% in children aged <16 years) followed by prescription of intranasal beclometasone to children under 6 years of age (0.25%) (table 2).

The most prevalent PIPc by omission (70%) was the failure to prescribe a spacer device at least annually to children aged <12 years who were prescribed a pressurised metered-dose inhaler (pMDI), and the second most prevalent drug PIPc by omission (54%) was the failure to prescribe an emollient to children who were prescribed greater than one topical corticosteroid (table 3).

The remaining PIPc indicators of omission relate to the failure to prescribe appropriate inhalers in the

Table 2 Prevalence of PIPc by commission

Indicator	No of children with at least one PIP	No of eligible children	Children prescribed at least one PIP (%)	95% CI
Carbocisteine should not be prescribed to children	13546	414856	3.27	3.21 to 3.32
Intranasal beclometasone should not be prescribed to children under 6 years of age	358	144161	0.25	0.22 to 0.27
Sedating antihistamines should not be prescribed to children under 2 years of age	86	46437	0.19	0.15 to 0.22
Codeine/dihydrocodeine medications should not be prescribed to children under 12 years of age	414	312571	0.13	0.12 to 0.15
Loperamide should not be prescribed to children under 4 years of age	89	92874	0.10	0.08 to 0.11
Tetracyclines should not be prescribed to children under 12 years of age	182	312571	0.06	0.05 to 0.07
Domperidone should not be prescribed concomitantly with erythromycin	86	414856	0.02	0.02 to 0.03

PIP, potentially inappropriate prescribing; PIPc, PIP in children.

Table 3 Prevalence of PIPc by indicators of omission of appropriate dispensing

Indicator	No of children who were *not* prescribed appropriate medication	No of children eligible to be prescribed appropriate medication	Children who were *not* prescribed appropriate prescription (%)	95% CI
A spacer device should be prescribed at least every 12 months to children under 12 years of age who are prescribed a pressurised metered-dose inhaler	39 945	57 010	70.1	69.4 to 70.8
An emollient should be prescribed to children prescribed greater than one topical corticosteroid in a year	7479	13 953	53.6	52.4 to 54.8
An inhaled corticosteroid should be prescribed to children aged 5–15 years who are prescribed a long-acting beta-2 agonist	18	45	40.0	21.5 to 58.7
An inhaled short-acting beta-2 agonist should be prescribed to children under 5 years of age who are prescribed a leukotriene receptor antagonist	1914	5146	37.2	35.5 to 38.9
An inhaled short-acting beta-2 agonist should be prescribed to all children who are prescribed two or more inhaled corticosteroids	1410	22 492	6.3	5.9 to 6.5

management of asthma in accordance with international guidelines; 37.2% of children prescribed a leukotriene receptor antagonist (LTRA) were not prescribed a short-acting beta agonist (SABA), 6.3% of children prescribed two or more ICS were not prescribed a SABA. Forty per cent of children who were prescribed a long-acting beta agonist (LABA) were not prescribed an ICS (table 3).

Association of PIP and gender

There was a significantly higher risk of PIP by omission in males compared with females (RR 1.3; 95% CI 1.0 to 1.7 p<0.05); however, there was no gender difference for PIPc by commission between males and females (RR 1.0; 95% CI 0.7 to 1.6 p>0.05). Removal of outlier indicators in both categories (carbocisteine and spacer indicators) did not alter these findings.

DISCUSSION

Summary of results

Using the PIPc indicators previously developed using a consensus approach,[16] this study has shown that prescribing potentially inappropriate medicines in children is uncommon in Ireland with an annual prevalence of PIPc by commission of 3.5% which reduced to 0.29% when the most prevalent indicator (prescribing of carbocisteine) is removed. The overall prevalence of PIP by omission was 2.5% when the indicator relating to annual prescribing of a spacer device for children with asthma is removed. Our aim was to examine prevalence at a population level but for some specific indicators the prevalence within children with potential exposure to the indication would be significantly higher. Approximately a third of children with asthma were not prescribed medications in line with current asthma guidelines.

A significantly higher rate of PIPc by omission was found in males compared with females but there was no gender difference for PIPc by commission.

Comparison with existing literature

The overall prevalence of PIP is substantially lower than that found in studies of middle-aged adults (43%) and older populations (36%) in Ireland using explicit criteria applied to the HSE-PCRS pharmacy claims database.[8 23] The primary drivers of PIP in older populations are polypharmacy and multimorbidity, both of which are uncommon in children. It was not possible to compare prevalence of PIPc in Ireland to that internationally as no studies that directly examine the prevalence of PIPc in primary care have been published. Recently developed prescribing tools from the UK and France have yet to be applied to determine the prevalence of PIP in children in those countries.[17 18 20]

The most prevalent PIPc by commission was the prescription of carbocisteine to children. This finding is in keeping with studies in Europe that demonstrate that carbocisteine is one of the 20 drugs most prescribed by family paediatricians in Italy.[24] In Spain, the prescription rate for mucolytics is 23.4/100 person years with the highest rate in those aged under 2 years.[25] Two recent Cochrane reviews found limited evidence of benefit of mucolytics in the treatment of respiratory tract infections.[26 27] In addition, there are concerns regarding the safety of carbocisteine in children relating to respiratory side effects such as bronchorrhoea, prolonged cough and mucous vomiting particularly in children under 2 years of age.[28] Dose-related effects might explain the adverse effects on children under 2 years of age, as the recommended doses of the marketing authorisation is unsupported by clinical research.[27] From April 2010, French and

Italian authorities withdrew the licence for carbocisteine and acetylcysteine in children younger than 2 years of age.[29] Carbocisteine is also unlicenced for use in Ireland in children under 2 years of age. Concerns around the safety of over-the-counter cough medicines persist. Some argue that differential age restrictions could lead to the sale and use of medicines for older children inadvertently being younger children. This is a concern given the lack of evidence of effectiveness for all ages of children.[27]

Asthma indicators

This study identifies significant omissions of appropriate prescribing in asthma; 70% of children who were prescribed a pMDI were not prescribed a spacer in the year of the study, and approximately 40% of children were prescribed potentially inappropriate combinations of inhaler medications. The PIPc indicator relating to prescribing of spacer devices is difficult to interpret. The over-the-counter cost of these devices is approximately €35 but they would only attract a €2.50 prescription copayment if prescribed. The National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network/British Thoracic Society (SIGN/BTS) 2016 guidelines recommend a new spacer device yearly as detachable plastic spacers are prone to developing an electrostatic charge. This charge causes adhesion of the drug to their surface, so reducing drug delivery and thus the effectiveness of inhaler treatments.[30–32] Metered-dose inhalers with spacers increase the lung deposition and clinical effectiveness of inhaled treatments during asthma exacerbations.[33] There is evidence of the effectiveness of spacer devices versus nebulisers for beta agonists in the management of mild to moderate acute asthma.[34] However, the clinical significance and impact of failure to adhere to the annual renewal of spacer devices is unclear.

SIGN/BTS guidelines recommend a SABA as a first-line treatment for asthma in children, and clinicians are advised to monitor the frequency of use of SABA as an indicator of need to increase or step up treatment.[32] SABAs should be continued when treatment is escalated, and two of the PIPc indicators relate to the omission of the appropriate prescription of SABA in this context.First, 6% of children under 16 years of age who were prescribed two or more ICS did not receive a SABA. The omission of SABA in this context may suggest a lack of preparedness for acute asthma where immediate reliever therapy is necessary. A Scottish study which analysed the changes in primary care prescribing patterns for paediatric asthma using a prescription database in 2012 found that 91% of children aged 0–4 years with at least one prescription for any asthma medication in the study year received a SABA indicating similar room for improvement in adherence to the initial steps of asthma guidelines.[35]

Second, 37% of children under 5 years of age who were prescribed a LTRA did not receive a SABA. The absence of clinical information in the HSE-PCRS database means that we do not know why prescribing is not in accordance with asthma guidelines. It may be that LTRAs are used for indications other than asthma, namely allergic rhinitis and episodic viral wheeze. However, the evidence to support LRTA prescribing for these conditions is weak and would also be considered potentially inappropriate.[36] A large Swedish study that looked at adherence to guidelines in primary care found that only 2 of 530 children under 6 years of age were prescribed a LTRA without a SABA.[37]

Prescribing of an LABA without an ICS, referred to as LABA monotherapy, has been used as an indicator of the quality of asthma care in adults in a number of studies.[15 38] A recent Cochrane review found that LABA monotherapy in children was associated with an increased risk of serious non-fatal adverse events which were statistically significant for formoterol but not for salmeterol.[39] In clinical practice, ICS/LABA combination inhalers are widely prescribed reducing the risk of inadvertent prescribing of LABA monotherapy, and these combination inhalers were not included in the PIPc indicator list. Similar low rates of LABA monotherapy have been found in other European studies.[35]

Other European studies have also reported suboptimal treatment of asthma. In Sweden, 45% of children over 7 years in the study had one prescription of ICS, and only 10% had more than four prescriptions over a 2-year period.[37] Similarly, in a Dutch study, 20% of children receiving continuous asthma medication were prescribed bronchodilators alone, indicating room for improvement in prescribing ICS.[40] Studies of adherence to asthma guidelines in primary care in the USA have also identified the failure to prescribe daily maintenance medication (eg, LTRA and ICS) in up to one-third of patients with persistent asthma.[41] In a previous study of Medicaid-insured children with asthma, 73% were underusers of controller therapy with 49% reporting no controller use and 24% less than daily use.[42]

The clinical significance of poor adherence to guidelines in asthma is highlighted in a US study in which an organised disease-management programme delivered to patients in primary care resulted in an increased adherence to guidelines in addition to a 35% reduction in hospitalisation rates, a 27% decrease in emergency department presentations and a 19% decrease in outpatient visits.[43]

Strengths and limitations

This is the first study to examine PIP in children in Ireland using explicit criteria applied to a national dispensing database. The HSE-PCRS claims database contains information on prescriptions dispensed to approximately 40% of the population of children under 16 years of age. Due to the income-based eligibility criteria, the GMS scheme over-represents children from socioeconomically deprived families, so is not generalisable to the full population. Although this study is only concerned with medications prescribed by a GP, lack of available information on over-the-counter medication use in the dataset could affect the accuracy of some prevalence estimates. This would specifically apply to the most common indicators (carbocisteine

and spacer devices) which are available to buy over the counter though would be available much more cheaply if prescribed by the GP. Furthermore, as this study is based on a dispensed prescription database, it is not possible to determine whether patients adhere to medications that are dispensed. A further limitation is that population data in the HSE-PCRS database is recorded in age categories of 0–4 years, 5–11 years and 12–15 years. In the case of four indicators with age limits that do not fit into these categories (carbocisteine, beclomethasone, sedating antihistamines and loperamide), an average of the number of children within specific age groups (the denominator) was calculated to determine the prevalence. Additionally, although the PIPc indicators were designed for use in dispensing databases without clinical information, some assumptions were made in relation to clinical diagnosis, for example, two or more ICS during the study period was used as a proxy for the diagnosis of asthma. Prescribing asthma medication is a widely used surrogate to identify children with asthma in research studies.[35 44] Finally, it should be acknowledged that some prescribing will not fall within the guidelines but remain clinically appropriate in certain circumstances, for example, the use of codeine in paediatric palliative care.

Implications for further research

This study has found low prevalence of inappropriate prescribing for children but has identified a lack of adherence in prescribing to asthma guidelines in primary care. Further studies are required to investigate guideline adherence in more depth. Studies investigating health outcomes (hospital admissions, adverse events) are also required to identify the clinical impact of PIP in children over time, and there is a need for studies that examine the factors influencing prescribing practices resulting in PIP in children.

Identification and quantification of PIP in older populations has led to the development of interventions that improve prescribing. For example, a randomised controlled trial of a multifaceted intervention, which included pharmacist academic detailing, web-based pharmaceutical treatment algorithms and tailored patient information leaflets, had positive results on PIP in older populations.[45] Integrating some of these supports into clinical decision support systems may prove to be a practical method of improving prescribing in children. Determination of the economic impact of inappropriate prescribing will also be important. For example, the cost-savings due to omissions of medicines may be outweighed by the higher complications and potential hospitalisations due to inadequate preventive treatment for conditions like asthma.

CONCLUSION

The application of the PIPc indicators to a national pharmacy claims database in Ireland has found that the use of potentially inappropriate medications in children is uncommon. However, the study suggests that there is an opportunity to improve adherence to asthma prescribing guidelines. These PIPc indicators could be used in other settings to investigate adherence to guidelines which may help to inform interventions designed to improve prescribing in children.

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Contributors EB analysed the prevalence data and drafted the manuscript. SMS conceived and supervised the study. KB extracted the prevalence data. FB provided statistical support and FM provided pharmaceutical and academic expertise. All authors reviewed the manuscript.

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