Unlicensed use of metformin in children and adolescents in the UK

Yingfen Hsia,1 Dalia Dawoud,1,2 Alastair G. Sutcliffe,3 Russell M. Viner,3 Sanjay Kinra4 & Ian C. K. Wong1,3,5

1Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London, London, UK, 2Clinical Pharmacy Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt, 3UCL Institute of Child Health, University College London, London, UK, 4Department of Non-communicable Disease Epidemiology, London School of Tropical Medicine and Hygiene, London, UK and 5Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Metformin is licensed for type 2 diabetes mellitus (DM) treatment in the UK.
• Evidence has shown the moderate efficacy of metformin treatment for polycystic ovarian syndrome (PCOS) and obesity.

WHAT THIS STUDY ADDS
• Metformin prescribing increased in children and adolescents between 2000 and 2010, in particular in girls aged 16–18 years.
• PCOS and obesity were the main, but unlicensed, indications for metformin prescribing amongst female adolescents.

AIM
Metformin is the most commonly prescribed oral anti-diabetic drug in young people. It is also prescribed for polycystic ovarian syndrome (PCOS) and obesity treatment in adults in an unlicensed fashion. Little is known as to the extent metformin has been used in young people. We investigated the use of metformin in children and adolescents aged 0–18 years in the UK.

METHODS
Population-based prescribing data were obtained from the UK IMS Disease Analyzer between January 2000 and December 2010.

RESULTS
A total of 2674 metformin prescriptions were issued to 337 patients (80% female) between 2000 and 2010. The prevalence of metformin prescribing increased from 0.03 per 1000 person-years [95% confidence interval (CI) 0.02, 0.05] to 0.16 per 1000 person-years (95% CI 0.12, 0.20) (P = 0.001). There was a steady increase in metformin prescribing in girls aged 16–18 years. There were 290 metformin treated patients (81% female; n = 235) who had at least one diagnosis of diabetes, PCOS or obesity. Among these patients, PCOS was the most common indication for metformin prescribing in girls (n = 120) followed by diabetes. There were 22 patients (7.6%) who received metformin for obesity treatment only.

CONCLUSIONS
Prescribing of metformin increased between 2000 and 2010, in particular amongst girls aged 16–18 years. The main indication for metformin prescribing was PCOS. At present, metformin is not licensed for PCOS and obesity treatment in adults or children. As there is a steady increase in the prescribing of metformin in young people, further studies are required to investigate the efficacy and safety of these prescriptions.
Introduction

Metformin is the most commonly prescribed oral anti-diabetic drug for diabetes mellitus (DM) in children and adolescents in the UK [1]. As metformin has been shown to be effective in reducing testosterone concentrations and improving irregular menstrual cycles [2], it has also been prescribed for the treatment of polycystic ovarian syndrome (PCOS) in women of reproductive age [3, 4]. However, there is still controversy regarding metformin use in PCOS. Two large randomized controlled trials (RCTs) did not show metformin to be more efficacious than placebo in adult women with PCOS [5, 6]. In adolescents, RCTs have shown the effectiveness of metformin treatment in girls with PCOS [7–9]. In contrast to these findings, a recent RCT did not show benefit from metformin treatment along with lifestyle modification in adolescents with PCOS [10]. Despite the controversy, metformin is still recommended as one of the therapeutic options for PCOS in teenage girls [2]. In addition to PCOS, metformin is also effective as an anti-obesity drug due to its effect on insulin resistance [11]. Metformin may also have other effects on weight loss, as it reduces hepatic glucose production, inhibits fat cell lipogenesis, increases peripheral insulin sensitivity and may reduce food intake [12]. Studies have shown metformin is associated with moderate BMI reduction in obese non-diabetic adolescents [13, 14]. In the UK, metformin is licensed for children over the age of 10 years with type 2 diabetes who have failed strict dieting [15]. At present, metformin is not licensed for the treatment of PCOS and obesity in adults or children in the UK [15, 16]. Little is known about the extent to which this drug has been used in young people in UK primary care. Therefore, this study was conducted to examine metformin prescribing patterns in children and adolescents in the UK primary care setting.

Methods

A retrospective cohort study was conducted using a primary care database, the IMS Disease Analyzer (IMS DA) database. This database contains approximately 2 million anonymous patient records and over 95 million prescriptions from about 125 general practices and more than 500 general practitioners (GPs) [17]. In the UK, virtually all patient care is managed by GPs in primary care. When patients are seen in secondary care (e.g. hospital), consultants or specialists will make the diagnosis and initiate treatment, and GPs will usually continue to monitor patients and issue prescriptions. Electronic medical records are routinely used in UK general practice. GPs usually enter diagnosis and prescription information into the electronic medical records to assist them in patient management [18].

Information held on the database includes patient demographics, indications for treatment and prescription details. Prescribed drugs are coded based on the Anatomical Therapeutic Chemical (ATC) classification issued by the European Pharmaceutical Market Research Association [19], and medical diagnoses are coded according to the International Classification of Disease (ICD) version 10 codes [20]. The database has been shown to be of high quality and is widely used in paediatric pharmacoepidemiological studies [21–23]. This study consisted of children and adolescents aged 0–18 years registered with a GP who contributed data to the IMS DA between January 2000 and December 2010. All subjects needed to have a minimum of 6 months valid data in the database. Age bands were based on the modification of the International Conference of Harmonization (ICH) as follows: <2, 2–11, 12–15 and 16–18 years [24]. Prevalence was calculated as the total number of subjects with at least one prescription of metformin during each year of investigation divided by the total number of study subjects registered on the database in the same year, stratified by age and gender. Annual prevalence of metformin prescribing was calculated using Poisson distribution with a 95% confidence interval (CI). A χ² test (Cochran-Armitage test for trend) was used to examine the yearly trend of metformin prescribing. As IMS DA directly links prescriptions to medical indications, the following indications were examined for metformin prescriptions: diabetes (ICD10 E10-E14), PCOS (E282) and obesity (E66). Analyses were carried out using Stata version 11.0 (Stata Corp., College Station, TX, USA).

This study protocol was approved by the IMS Independent Scientific and Ethical Advisory Committee.

Results

A total number of 2674 metformin prescriptions were issued to 337 children and adolescents between 2000 and 2010, 80% were female (n = 270). There were no metformin prescriptions issued to children aged under 2 years. The majority of children were taking metformin for diabetes treatment aged 2–11 years. The metformin prescribing started at age 5 years old for diabetes treatment. The number of female adolescents aged 12–18 years who received metformin treatment steadily increased over time (Table 1). The annual prevalence of metformin prescribing increased from 0.03 per 1000 person-years (95% CI 0.02, 0.05) to 0.16 per 1000 person-years (95% CI 0.12, 0.20) (P = 0.001) (Figure 1). There were a total of 290 patients with at least one diagnosis of DM, PCOS or obesity in their medical records, of whom 235 patients were female (81%) (Table 2). Of 290 patients, 120 female patients were prescribed metformin for the treatment of PCOS and obesity. There were 23 female patients with DM, PCOS and obesity diagnoses who received metformin treatment during the study.
period. There were 22 patients (7.6%, 22/290) who were prescribed metformin for obesity treatment alone. A total number of 47 patients were prescribed metformin without specific relevant diagnosis. After scrutinizing their medical records, the most common diagnosis for prescribing were ‘unknown and unspecified causes of morbidity’. As IMS DA only contains data from GPs, there is no hospital record in the database to verify diagnoses for these prescriptions.

**Discussion**

Our study showed that the use of metformin in the paediatric population has increased markedly between 2000 and 2010 in primary care, with prescribing prevalence increasing from 0.03 to 0.16 per 1000 person-years. This increase was particularly marked amongst girls aged 12–18 years.

There are limited data on paediatric metformin prescribing patterns in the UK. As some prescribing databases do not have links with indications for prescribing, an added strength of this study was that we were able to identify the disease indication for metformin therapy. However, our findings are subject to some limitations. First, the IMS DA only records prescriptions issued in primary care, excluding prescriptions dispensed from hospitals. It is possible that our data did not include a small number of initial hospital prescriptions. While the great majority of these would have been continued in primary care, unfortunately there are no data to investigate the extent of metformin prescribing in hospitals. Second, we were unable to identify whether subjects were treated with lifestyle modification along with metformin, as healthy diet and exercise are mainstays of the treatment for obesity, PCOS and type 2 diabetes [2, 4]. Third, we have no information on diagnostic criteria used for any of the conditions under study as diagnoses are often made in secondary care and as the dataset does not record criteria for those made in primary care. While diagnostic criteria for type 2 diabetes are internationally accepted, a number of different definitions exist for obesity and PCOS. Fourth, the IMS DA does not contain data on ethnicity and socioeconomic status and thus their impact on prescribing patterns remains unstudied.

### Table 1

Characteristics of study subjects between 2000 and 2010 by age and calendar year

<table>
<thead>
<tr>
<th>Year</th>
<th>Aged &lt;2 years</th>
<th>Aged 2–11 years</th>
<th>Aged 12–15 years</th>
<th>Aged 16–18 years</th>
<th>Total</th>
<th>Person-time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
</tr>
<tr>
<td>2000</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2001</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2002</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>2003</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>2004</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>2005</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>2006</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>2007</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>2008</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2009</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>2010</td>
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<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>13</td>
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</tbody>
</table>

### Table 2

Metformin prescriptions for diabetes, polycystic ovarian syndrome (PCOS) and obesity between 2000 and 2010

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
<td>Girls</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Diabetes only</td>
<td>48</td>
<td>66</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>Obesity only</td>
<td>4</td>
<td>18</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>PCOS and obesity</td>
<td>NA</td>
<td>120</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Diabetes and obesity</td>
<td>3</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Diabetes, PCOS and obesity</td>
<td>NA</td>
<td>23</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

NA, not applicable.
Our finding that PCOS was the main indication for metformin prescribing in female adolescents was unexpected. This indicates that the use of metformin for PCOS in teenage girls is increasing in general practice. It has been well documented that adolescent obesity is increasing in population-based studies in the US [25] and UK [26]. In addition, a previous study has shown an increased prevalence of type 2 diabetes in adolescents aged 12–18 years in the UK [1]. Therefore, it is possible that the prevalence of PCOS in adolescents may also have increased. Although metformin has been shown to be of benefit in teenage girls with PCOS in a number of studies [7–9], the current evidence is limited and inconsistent. The efficacy of metformin treatment in adolescents with PCOS remains to be confirmed by well designed randomized controlled studies. In addition, to extrapolate treatment from adults to adolescents with PCOS is questionable since the risks and benefits are unclear.

There were a small number of patients who received metformin for obesity treatment in our study. This prescribing trend may increase in the next few years. In January 2010, the European Medicines Agency (EMA) recommended removing sibutramine from all markets in the European Union (EU) due to the risk of developing cardiovascular events in adults [27]. Consequently orlistat is the only licensed anti-obesity drug in the EU. As there is limited drug choice for obesity treatment, metformin is likely to gain its popularity for obesity treatment. In addition, a systematic review on economic consequences of obesity treatments has shown that metformin appeared to be a cost-saving treatment for obese patients with type 2 diabetes [28]. At present, metformin has not yet received a paediatric licence for PCOS or obesity treatment. As it is mainly prescribed for these unlicensed indications in the paediatric population, more studies are needed to demonstrate its efficacy and safety in this population.

In conclusion, metformin prescribing in children and adolescents has increased substantially in the past decade. There is an increased number of teenage girls receiving metformin for PCOS treatment in general practice. As metformin is not licensed for PCOS and obesity treatment in the paediatric population, further studies are required to investigate its long-term efficacy and safety for these conditions.

Competing Interests

There are no competing interests to declare.

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REFERENCES


