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Pro-kinetics prescribing in paediatrics: Evidence on cisapride, domperidone and metoclopramide from the UK primary care

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Corresponding Author:	Shahrul Mt-Isa Imperial College London London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Imperial College London
Corresponding Author's Secondary Institution:	
First Author:	Shahrul Mt-Isa
First Author Secondary Information:	
Order of Authors:	Shahrul Mt-Isa
	Stephen Tomlin
	Alastair Sutcliffe
	Martin Underwood
	Paula Williamson
	Nicholas M Croft
	Deborah Ashby
Order of Authors Secondary Information:	
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Abstract:	Objectives Domperidone and metoclopramide are pro-kinetics commonly prescribed off-label to infants and younger children in an attempt to treat gastro-oesophageal reflux symptoms. Another pro-kinetic drug, cisapride, was used but withdrawn in 2000 in the UK due to serious arrhythmic adverse events. MHRA issued safety warnings for domperidone in May 2012, and restricted its indications. We report here national primary care prescribing trends and safety signals of these drugs in children. Methods We used data from the General Practices Research Database between 1990 and 2006 for children <18 years. Descriptive statistics and Poisson regressions were performed to characterise prescribing trends. We examined safety signals in nested case-controls studies. Results The proportion of children <2 years old being precribed one of the medications doubled during the study period. Prescriptions of domperidone increased 10-fold, mainly following the withdrawal of cisapride in 2000. Prescriptions of metoclopramide did not significantly change. Despite the increase in prescriptions of domperidone no new

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	safety signals were identified. Conclusions These data showed dramatic changes in prescribing of cisapride and domperidone despite the lack of good quality supporting evidence. It is possible these prescribing trends were influenced by published guidelines. Even if produced without robust efficacy and safety evidence, published guidelines can influence clinicians and consequently impact prescribing. Therefore, improving the evidence base on pro-kinetics to inform future guidelines is vital. The lack of new safety signals over this period would support the development of suitable powered clinical studies.
Suggested Reviewers:	Nadeem Afzal, MB, BS, MD (Res), MRCP, MRCPCH (UK) University Hospital Southampton N.Afzal@soton.ac.uk
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Imperial College London

Imperial Clinical Trials Unit
Imperial College London

School of Public Health
St. Mary's Campus, Norfolk Place
London, W2 1PG.
Tel: +44 (0)2075941747 Fax: +44 (0) 2075940768

s.mt-isa@imperial.ac.uk
www.imperial.ac.uk/medicine/people/s.mtisa/

Shahrul Mt-Isa PhD

17th October 2014

Dear Editor,

Re: Pro-kinetics prescribing in paediatrics: Evidence on cisapride, domperidone and metoclopramide from the UK primary care

Off-label prescribing of drugs in children is a common practice in an attempt to treat very sick children. This practice may expose these children to unnecessary risks – in exchange of uncertain benefits.

We enclosed a manuscript for your review on the prescribing trends of three pro-kinetics: domperidone, cisapride and metoclopramide, based on analysis of routinely-collected data from primary care in the UK. Our analyses demonstrated remarkable increase in domperidone prescriptions in the absence of efficacy and safety evidence, despite withdrawal of a drug of similar class, cisapride, in July 2000. The observed trends suggest that published guidelines and consensus statements on the treatment of gastro-oesophageal reflux disease in children, when produced even without robust efficacy and safety evidence, can influence prescribing practice.

Recent warnings by the Medicines and Healthcare Products Regulatory Agency in the UK of small risks of serious ventricular arrhythmia and sudden cardiac death associated with domperidone (May 2012) and restricted indications (May 2014) escalate the importance of being earnest about the issue. In October 2014 significant changes in the BNFC also include revisions to domperidone as an off-label treatment for GORD in children, with multiple caveats on safety.

All authors have made substantial contribution in the preparation/approval of the manuscript as submitted. The authors confirm that the manuscript has not been published, is being submitted only to *JPGN* and will not be submitted elsewhere while under consideration, and should it be published in *JPGN*, it will not be published elsewhere. The authors take full responsibility of the content of the submitted manuscript and any impact it may have on public understanding. The study was funded in full by the MHRA Pharmacoepidemiology Research Programme, grant number SDS011. The writing and preparation of this paper received no additional funding.

We look forward to hearing good news from you, and we thank you in advance for your consideration.

Yours sincerely,

Shahrul Mt-Isa (Disclosure: none) and Nicholas M Croft (Disclosure: participated as an investigator in a trial of a treatment of reflux in infants funded by Johnson and Johnson)

On behalf of:
Stephen Tomlin (Disclosure: none)
Alastair Sutcliffe (Disclosure: none)
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Pro-kinetics prescribing in paediatrics: Evidence on cisapride, domperidone and metoclopramide from the UK primary care

Shahrul Mt-Isa[1], PhD, Stephen Tomlin[2], BPharm, FRPharmS, Alastair Sutcliffe[3], MD, PhD, Martin Underwood[4], FRCGP, MD, Paula Williamson[5], PhD, *Nicholas M Croft[6], MBBS, PhD, FRCPCH *Deborah Ashby[1], PhD, FMedSci

Address correspondence to: Dr Shahrul Mt-Isa. Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, United Kingdom. Fax: +44(0)2075940768. Telephone: +44(0)2075941747. E-mail: s.mt-isa@imperial.ac.uk.

Affiliations:
[1]Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, United Kingdom;
[2]Evelina Children Hospital, Pharmacy Department, King's Health Partners, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom;
[3]General and Adolescent Paediatrics Unit, Institute of Child Health, University College London, London, United Kingdom;
[4]Warwick Medical School, University of Warwick, Coventry, United Kingdom;
[5]Centre for Medical Statistics and Health Evaluation, University of Liverpool, Liverpool, United Kingdom;
[6]Centre for Digestive Diseases, Blizard Institute, Barts and the London School of Medicine, Queen Mary University of London, London, United Kingdom.

*NMC and DA are joint senior authors.

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ABSTRACT

Objectives

Domperidone and metoclopramide are pro-kinetics commonly prescribed off-label to infants and younger children in an attempt to treat gastro-oesophageal reflux symptoms. Another pro-kinetic drug, cisapride, was used but withdrawn in 2000 in the UK due to serious arrhythmic adverse events. MHRA issued safety warnings for domperidone in May 2012, and restricted its indications. We report here national primary care prescribing trends and safety signals of these drugs in children.

Methods

We used data from the General Practices Research Database between 1990 and 2006 for children <18 years. Descriptive statistics and Poisson regressions were performed to characterise prescribing trends. We examined safety signals in nested case–controls studies.

Results

The proportion of children <2 years old being precribed one of the medications doubled during the study period. Prescriptions of domperidone increased 10-fold, mainly following the withdrawal of cisapride in 2000. Prescriptions of metoclopramide did not significantly change. Despite the increase in prescriptions of domperidone no new safety signals were identified.

Conclusions

These data showed dramatic changes in prescribing of cisapride and domperidone despite the lack of good quality supporting evidence. It is possible these prescribing trends were influenced by published guidelines. Even if produced without robust efficacy and safety evidence, published guidelines can influence clinicians and consequently impact prescribing. Therefore, improving the evidence base on pro-kinetics to inform future guidelines is vital. The lack of new safety signals over this period would support the development of suitable powered clinical studies.

Keywords: clinical practice guideline, gastro oesophageal reflux, paediatrics, cisapride, domperidone

INTRODUCTION

It is a common practice to prescribe off-label drugs to children.(1) This is neither promoted nor prohibited by the Medicines Act (1968) as informed use of off-label drugs is often necessary to treat sick children.(2) In many cases, there is little evidence for efficacy or safety of the drugs when used in this population. Over 50% of medicines used in children in the European Union have never been studied in this population.(3)

An example of this is the use of pro-kinetic drugs in children with gastro-oesophageal reflux disease (GORD). GORD is an involuntary passage of gastric contents into the oesophagus and is a common problem in infants.(4) GORD is generally benign and resolves between 12-24 months old, but in some cases a drug treatment is used in an attempt to control worsening or persistence of the symptoms. Pro-kinetics such as cisapride, domperidone and metoclopramide have been used to treat GORD symptoms in children, but their licensing indications in children are restricted to nausea and vomiting. Cisapride was withdrawn in July 2000 following cardiac adverse reactions in adults. A drug of similar class, domperidone, emerged as an alternative following the withdrawal. However, in May 2012 the UK Medicines and Healthcare Products Regulatory Agency (MHRA) warned of the small risk of serious ventricular arrhythmia and sudden cardiac death associated with domperidone, with elevated risk in those consuming daily doses of more than 30mg.(5) The MHRA subsequently revised the contraindications of domperidone and enforced restricted use in May 2014 for adults, while acknowledging further research is needed in children;(6) and later placed it under additional monitoring (Black Triangle) in July 2014.(7) These changes triggered a revision to the off-label use of domperidone for GORD in the UK British National Formulary for Children (BNFC) in October 2014.(8) Other treatment options are available, all with limited evidence of efficacy.(4;9-13)

A Cochrane systematic review on cisapride after its withdrawal concluded that there was no clear evidence that cisapride reduces GORD symptoms and suggested substantial publication bias towards studies showing positive effect of cisapride.(14) A systematic review of domperidone concluded that there is a minimal evidence for efficacy of domperidone in reducing GORD symptoms but very few trials were available.(15) Systematic reviews of metoclopramide concluded that there may be some benefit against placebo,(12) but there is insufficient evidence to support or oppose its use for GORD in infants since very few trials were available and mostly were of short duration.(16)

GORMET (Gastro-Oesophageal Reflux Medicines – Evidence for Trials) was a study designed to explore the potential of the General Practice Research Database (GPRD) for informing clinical trial design on safety of medicines used off-label in primary care for the treatment of GORD symptoms in children.(17) The study population was extracted from approximately 3.6 million active patients from around 433 practices participating in GPRD, covering 5.5% of the UK population (http://www.gprd.com in April 2008; http://www.cprd.com from 29/03/2012).(18)

We address chronological changes in prescribing trends of cisapride, domperidone and metoclopramide in children, as explored in GORMET.(17) We consider external factors that may have influenced the trends observed, particularly the emergence of paediatric guidelines on the management of GORD during this critical period. The side-effects of these drugs are well-documented for adult use but not in children. Therefore, we also looked for signs of any increased clinical events associated with these drugs that may be causally-related

(safety signals) with their use in children to identify potential safety issues, particularly for younger children where the indications were likely to be for GORD.

MATERIALS AND METHODS

We used GORMET data from the GPRD for children aged under 18 years old between 1990 and 2006 who were prescribed cisapride (N=1,497), domperidone (N=9,319), or metoclopramide (N=17,985), and had at least three months of follow-up data recorded.(17) Each child was matched by age and sex to four children without any prescription of the three drugs. The number of all children in GPRD under 18 years old, by year, during the same time period were used as denominators.

We used Poisson regression adjusted for the size of the underlying child population in the GPRD by year to calculate incidence rates (number of new children per million starting prescription in a particular year). We calculated these rates for all children initially, and then for the subset of children under two years old (<2) and for those two years old and older (≥2) because the likely different indications in these two age groups. The prescribing would be expected to be somewhat different between these groups of children. We discuss the trends of prescriptions, and the influence of paediatric guidelines on GORD.

We hypothesised that side-effects listed in the British National Formulary(19;20) for all three drugs were known safety signals for children. We calculated the proportional reporting ratios of other drug-event pairs to generate hypotheses of unknown safety signals.(21;22) We conducted nested case-control studies for the unknown safety signals, and argued the drug-event causality according to Bradford-Hill.(23)

Ethical approval for this study was obtained from the Independent Scientific Advisory Committee for MHRA database research (project number SDS011).

RESULTS

Data

Table 1 shows the number of children whose data were used in the analyses. Because GPRD does not record clear diagnosis of GORD, the data extracted contain children prescribed with cisapride, domperidone, and metoclopramide for any indication. The prescription of these drugs is most likely for the treatment of recurrent vomiting due to GORD in children <2. In children ≥2, GORD indication is less common; and these drugs may be prescribed for the licensed indications of nausea and vomiting from various causes including chemotherapy and migraine.

Incidence rates of prescribing

There was a small increase in the percentage of all children being prescribed one of these three medications from 0.09% (1990) to 0.11% (2006). Use in <2's increased markedly from 0.4% to 0.75% whereas use in those ≥2 decreased from 0.5% to 0.35%.

The annual incidence rates of cisapride (1990-2000) and domperidone (1990-2006) prescription in all children increased by 24.6% (95% CI 10.7%-38.6%) and 7.5% (95% CI 6.8%-8.1%), respectively. That of metoclopramide (1990-2006) in all children declined by 4.3% (95% CI 3.4%-5.3%).

Figure 1 shows the incidence rates per million children by age group and year. There was a dramatic increase in incidence rates in children < 2 years old being prescribed domperidone following the withdrawal of cisapride in July 2000. A much smaller increase was observed in those ≥2 years old. The incidence rates in those prescribed with metoclopramide were similar across age groups, with some evidence of a decline.

Age at start of therapy

The median starting ages in children <2 years old were 6 (inter-quartile range, IQR 4-10), 5 (IQR 3-10), 14 (IQR 9-19) months old for cisapride, domperidone and metoclopramide, respectively. The starting age decreased over time in children <2 years old among those on cisapride and domperidone, whilst those on metoclopramide did not significantly vary.

The median starting ages in children ≥2 years old were 10 (IQR 5-15), 15 (IQR 11-17), and 14 (IQR 9-16) years old for cisapride, domperidone and metoclopramide, respectively. There were no marked variations in starting age over time for all three drugs in this group.

Therapy amount and duration

The mean number of prescriptions issued per child <2 years old were generally greater than those issued to children ≥2 years old (Figure 2). Not only there were more prescriptions, the mean therapy duration were generally longer in the younger group of children than the older one (Figure 3). Both trends fit with the indications for chronic GORD symptoms in younger children and the short-term prescribing for licensed indications such as nausea, migraines and following a chemotherapy in older children. Additionally, increasing trends of therapy amount and duration were most pronounced in the domperidone cohorts.

Emergence of guidelines and prescribing trends

Several guidelines supporting the prescribing of cisapride,(24-27) domperidone (24-26) and metoclopramide (24-26) to children <2 years old emerged over the years and may be accountable for some of these dramatic changes. The greatest increased number of cisapride prescriptions was observed between 1994 and 1998. A steady increase of domperidone prescriptions in <2 years was also observed particularly after the year 2000. The prescribing of metoclopramide decreased over the same time period. Figure 4 demonstrates a possible temporal effect in response to these best known guidelines.

Safety signals

The results from these analyses were presented in full in GORMET report.(17) Following the systematic approach, we did not uncover any new causally-related safety issues in children prescribed with these drugs. Only diarrhoea was associated with domperidone prescription in children <2 years old with incidence rates ratio of 1.26 (95% CI 1.08-1.47). However, the unknown safety signals were, in general, associated with concomitant medications and illnesses, and increased dose or duration of pro-kinetics use.

DISCUSSION

These data show marked changes in the prescription of cisapride, and then domperidone in children <2 years old despite the lack of marketing authorisation for use in this population or good quality published evidence of efficacy and safety to support these changes. The drivers for these changes are likely to have been a combination of marketing from the companies, publication of papers and publication of guidelines by professional societies. A New Zealand study showed similar trends of prescribing for cisapride; and suggests delayed response to safety alerts by the general practitioners (GPs) – 'this delay was more pronounced with paediatricians when the prescribing practice is already embedded in their routine care'.(28) There is also a suggestion that clinicians adhere to guidelines poorly,(29) but there is no research attempting to link prescription rates to clinical guidelines in the literature.

The main limitations of this study are biases and underestimation. The GPRD only records drug prescription, but it is unknown whether the drugs were actually consumed by the patients as prescribed. Many prescriptions of these drugs may have been initated in the hospitals by paediatricians, neonatologists or specialist paediatric gastroenterologists, therefore some early prescriptions would not have been captured in the GPRD. Consequently, the prescribing rates are likely to be an underestimate of the true prescribing. Another limitation of this article is that it presents somewhat older prescribing data (1990 – 2006). We believe, however, these periods cover the critical time points of the changing guidelines and evidence of pro-kinetics in children. Moreover, any recent data would not change the temporal trends of the prescribing of cisapride, domperidone and metoclopramide that we observed in the general practices. This historical evidence may be used to guide future learning and continuing debates in this area.

Cisapride was licensed in the UK in 1988 for the treatment of GORD in patients over 12 years old. Cisapride suspension, which would be the form of choice in the prescribing for younger children, became available in the UK in mid-1992 when we also observed an initial increase in the rates of cisapride prescribing in children. In 1993, a working group of the the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended cisapride as the first drug treatment in children and infants with GORD following 'failed lifestyle changes over 1-2 weeks'.(25;30) Despite acknowledging limited data were available, domperidone and metoclopramide were listed as alternatives in the face of no response to cisapride.

The ESPGHAN guidelines and the introduction of cisapride suspension in 1992 in the UK were followed by the observed steep increase in the prescribing of cisapride between 1994 and 1998 when the medication became widely available. However, reports of prolonged QT intervals and fatal cardiac arrhythmias events among adults on cisapride treatment soon emerged around 1997.

The profusion of publications and practice guidelines suggesting a benefit from cisapride may have influenced clinicians' decisions to prescribe cisapride.(31) The guidelines on treating reflux with cisapride were based on small, mostly unblinded, clinical trials which were evaluated qualitatively by a working group within the ESPGHAN.(25) The process of drawing up the guidelines, and conflicts of interest were not clearly defined in the published document. There was no evidence of systematic critical evaluation as would be expected now in the UK in the development of NICE or SIGN guidelines.(32;33) Another factor that may bias decisions and which was not openly addressed in many publications of that period was the disclosure of industry support for individuals in the working group who could influence

the final document. Therefore, in retrospect, for paediatricians and GPs to react positively to these guidelines was not fully warranted; instead the guidelines should have been challenged for the lack of evidence.

As part of post-marketing safety monitoring, Janssen Pharmaceutica, who manufactured cisapride and domperidone, issued safety warnings on cisapride in June 1998. This was followed by a reduction in cisapride prescribing rate, suggesting that GPs became more cautious when prescribing cisapride to children. Nevertheless, ESPGHAN and NASPGHAN (North American Society of Paediatric Gastroenterology Hepatology and Nutrition) remained openly and largely supportive of the efficacy and safety of cisapride.(26;27) However, the updated 2009 guideline on GORD in infants developed between ESPGHAN and NASPGHAN warns that 'potential adverse effects of currently available pro-kinetic agents outweight the potential benefits of these medications for the treatment of GORD'.(34) It emphasises there is insufficient evidence of clinical efficacy to justify routine use of bethanecol, metoclopramide, cisapride or domperidone.(34) Unlike the initial ESPGHAN guideline, this report was developed systematically with full disclosure of conflicts of interest.

Accumulating safety evidence from the UK Yellow Card Scheme and other worldwide reports finally prompted the MHRA and the Committee on Safety of Medicines to take action. Marketing authorisation of cisapride in the UK was suspended on 28 July 2000, and subsequently withdrawn.

Since the withdrawal of cisapride, with less evidence of efficacy and safety, domperidone has become widely prescribed to children for the treatment of GORD symptoms despite the fact that the BNFC does not and never did recommend the use of domperidone in children with GORD symptoms. Over fourteen years later, the Paediatric Formulary Committee continues to recognise that domperidone may be used when other interventions have been tried; despite unconvincing evidence of efficacy.(8) The data suggest that domperidone prescribing in children rapidly increased in primary care. Prescribing in North America did not go down this route; possibly because the NASPGHAN guidelines never had mentioned domperidone as an alternative.(27)

It is possible that the influx in domperidone prescription was initiated at first as a replacement for cisapride where there had been a large increase previously. This would fit with the ESPGHAN guidelines in 1993 and the report published in 1997, which advised domperidone and metoclopramide might be considered as alternatives to cisapride if there was no response to it.(24;25) However, the perceived safety of domperidone with presumed efficacy for the treatment of GORD symptoms in children was most likely the reason for the subsequent rise over the following years. A study in Belgium also observed increasing trend of acid suppressants use in children that could as well be partly contributed by the withdrawal of cisapride.(35)

Metoclopramide has lost popularity, possibly because of the known extrapyramidal adverse reactions, alongside several early studies showing the superiority of domperidone to metoclopramide.(36-39) It is primarily used in older children with nausea and sickness rather than infants with reflux. Metoclopramide prescriptions may continue to decline in response to a 'black box' warning for tardive dyskinesia adverse reactions issued by the FDA on 29 February 2009.(40) However, the concerns on long-term adverse reactions in children who were affected by the drugs still remain and need further investigation.

The decline in age over time when children were started on cisapride and domperidone therapy indicates that paediatricians and/or GPs did react positively to these guidelines. The increasing number of prescriptions per child and longer therapy duration over time suggest GPs were getting more comfortable prescribing these drugs to children; although this may be a sign that these drugs were not very effective and there were continuing symptoms, or that may be the children were suffering a chronic disease and did receive some clinical benefit. For infants with reflux, the reality is no-one knows if these drugs are of any use and importance. It is quite possible that they may have a role, but the evidence is currently simply not there.(14;15)

The guidelines may not be all that have contributed to these changes – societal factors such as anxious and more inexperienced parents could be less accepting of having infants with, what is for the majority a benign and self-limiting disorder, and chose to turn to drugs treatment for help. The increase in the proportion of infants being treated over the course of the study would be consistent with this. These are only speculations and cannot be explored using these data. Despite these changes in off-label prescribing of pro-kinetics in children, extensive analyses in GORMET did not reveal any safety signal that may be causally related to the use of cisapride, domperidone or metoclopramide.(17) Our results on safety are also consistent with MHRA's recommendation of reduced dose and duration of domperidone use in adults.(6) Our analyses support the development of new well-designed clinical studies to further investigate the efficacy and safety of domperidone use in children <2 for the treatment of GORD.

Off-label drugs prescribing may lead to many unknown complications when the efficacy and safety have never been formally assessed in the intended population. Vulnerable populations like children are affected by this trade, and require more regulated and transparent intervention. More importantly, the efficacy and safety of the drugs that are widely used off-label, such as domperidone in children, need to be formally assessed in the representative population in a controlled environment to make its use safer.

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Figure 1 Mean incidence rates per million children by year and age group

Figure 2 Mean number of prescriptions per child by year and age group
Data for cisapride after year 2000 was truncated.

Figure 3 Mean therapy duration per prescription by year and age group
Data for cisapride after year 2000 was truncated.

Figure 4 Number of prescriptions of cisapride, domperidone and metoclopramide prescribed per 10,000 children below two years old by year and temporal events

Figure 1
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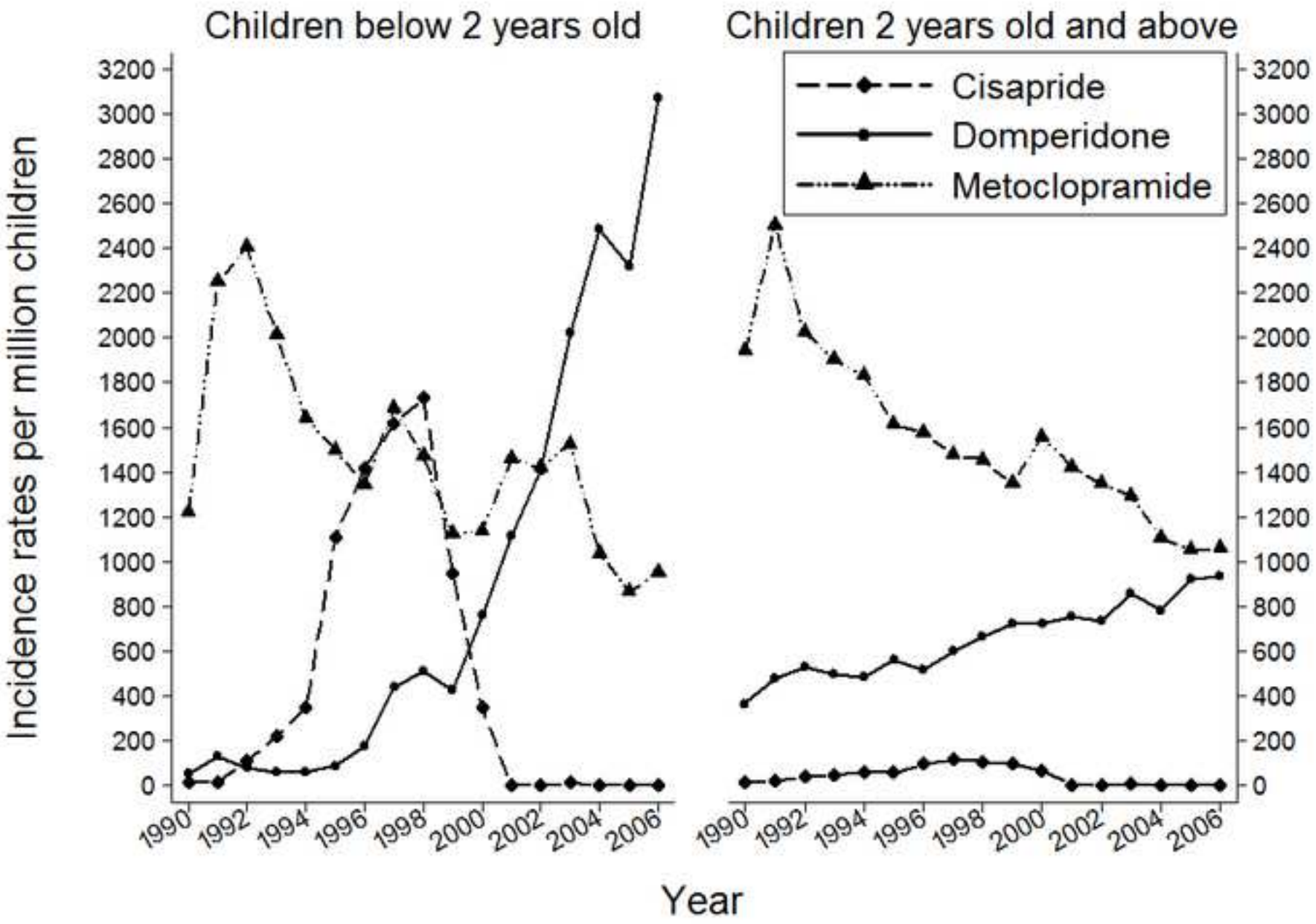

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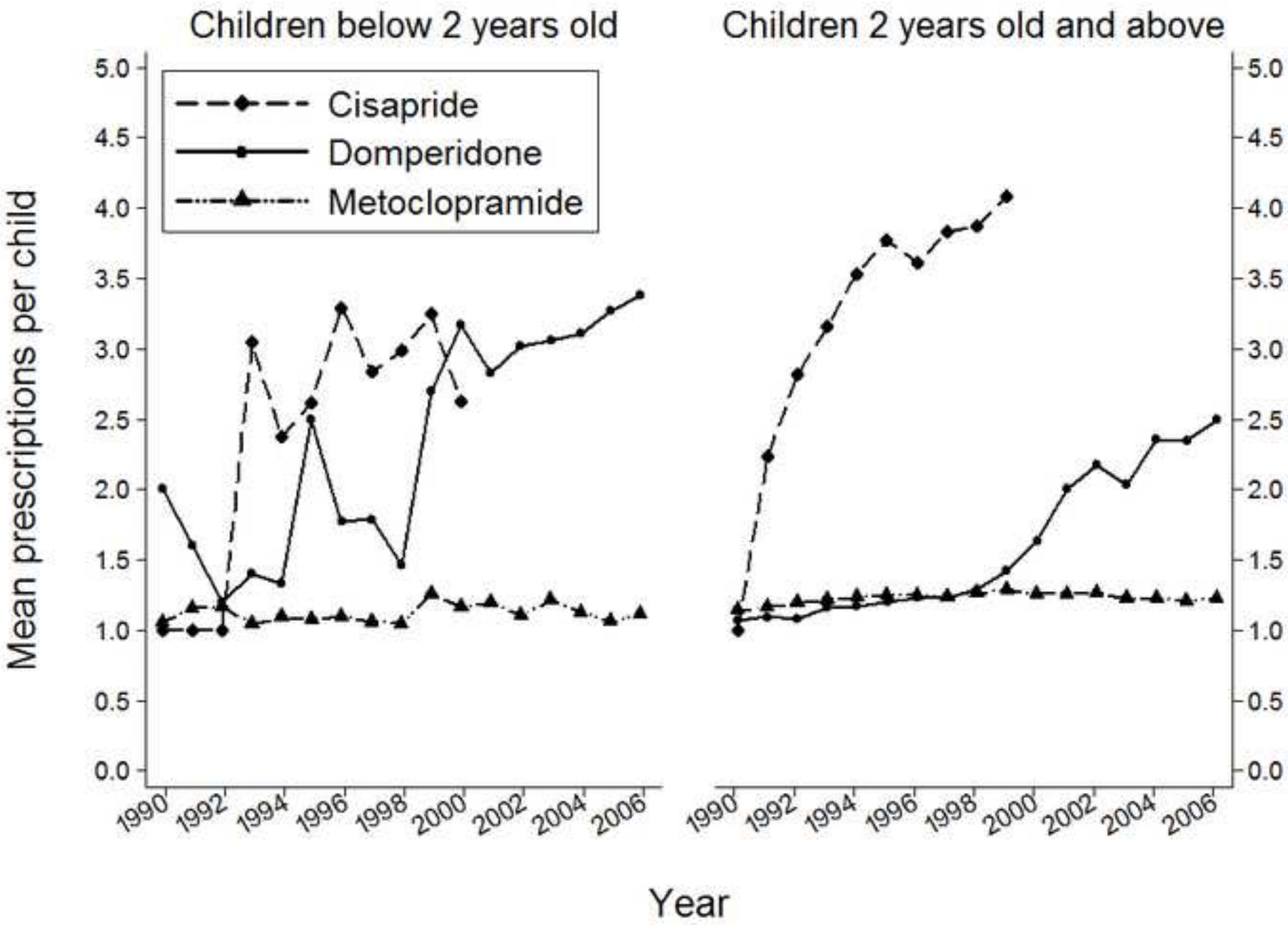

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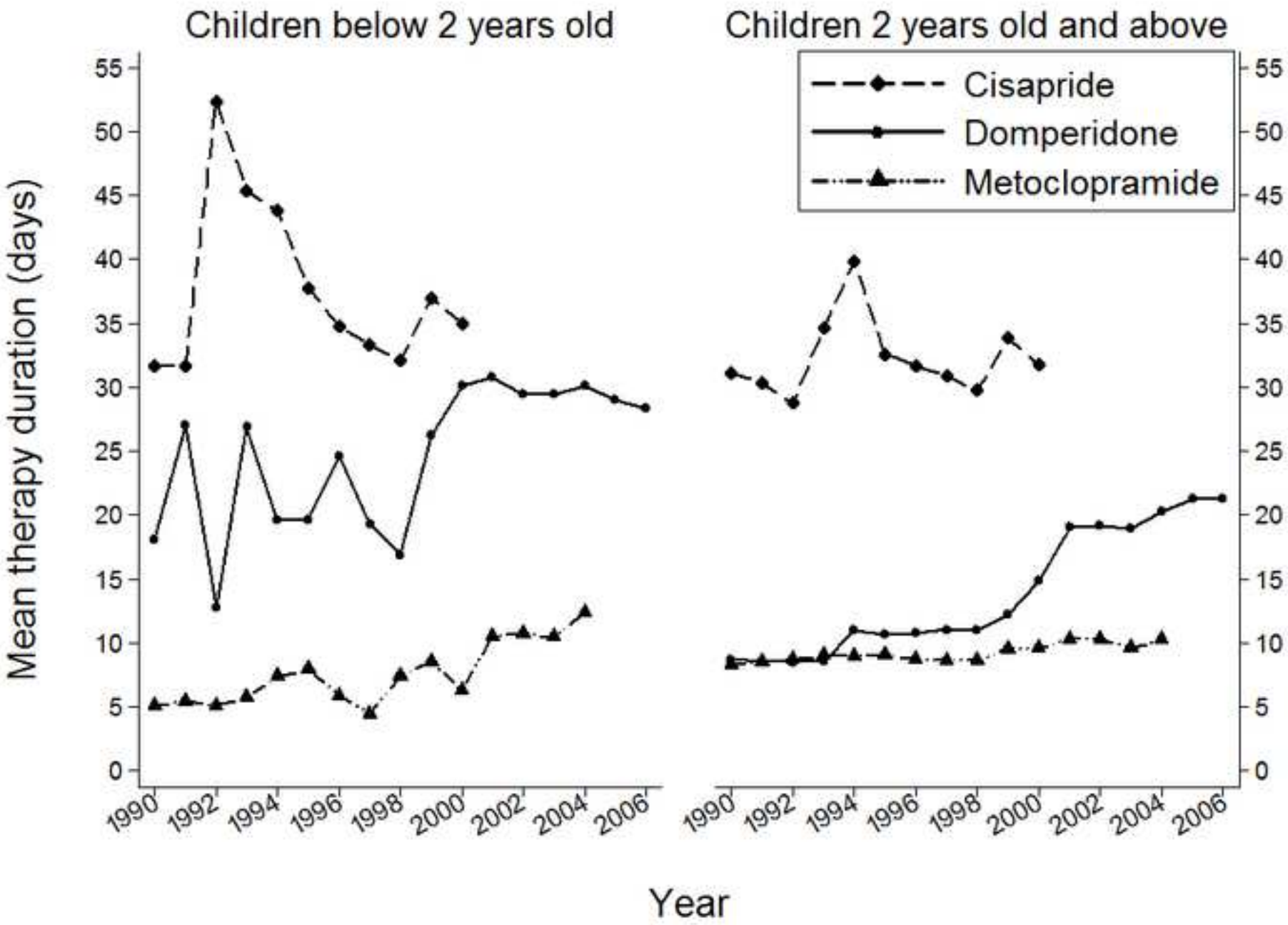

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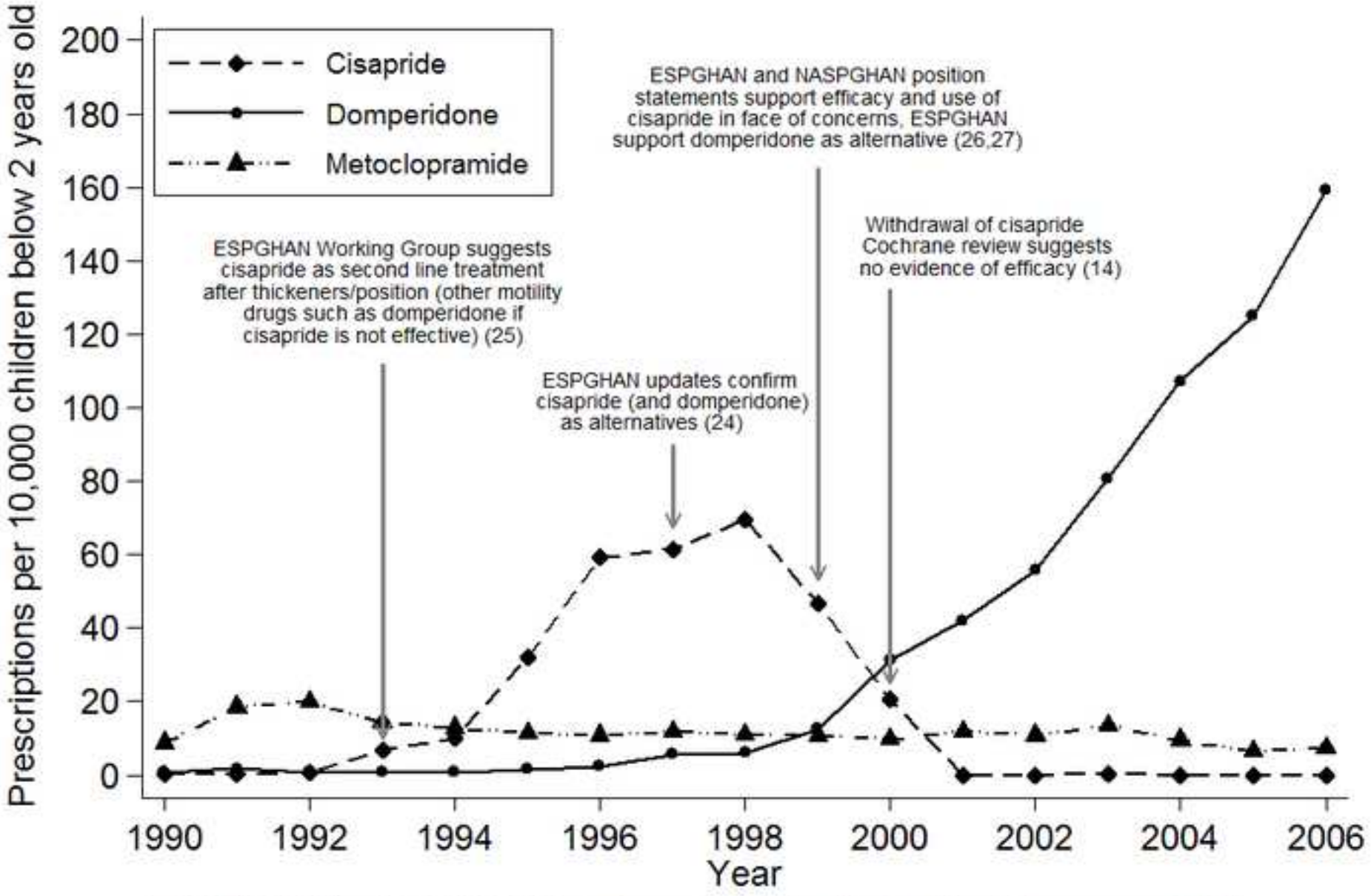

In 2009, NASPGHAN and ESPGHAN Pediatric Gastroesophageal Reflux clinical practice guidelines come up with joint recommendations concluding that there is insufficient evidence to justify the routine use of motility agents including cisapride, metoclopramide, the treatment of GERD.(34)

Table 1 Summary data, number of children whose prescription data were analysed in that year (% of whom were under 2 years old) unless otherwise specified

	Denominator[a]	**Cisapride**	**Domperidone**	**Metoclopramide**
1990-2006[b]	n/a	1497 (n/a)	9319 (n/a)	17985 (n/a)
1990	461712 (18%)	7 (14%)	171 (4%)	1030 (7%)
1991	497281 (18%)	30 (3%)	259 (6%)	1620 (10%)
1992	532257 (18%)	101 (8%)	302 (2%)	1642 (12%)
1993	566534 (17%)	225 (30%)	336 (2%)	1660 (8%)
1994	604001 (17%)	353 (29%)	359 (2%)	1789 (7%)
1995	640503 (16%)	734 (45%)	457 (3%)	1732 (7%)
1996	672740 (15%)	1208 (51%)	476 (5%)	1748 (6%)
1997	695884 (15%)	1406 (46%)	590 (10%)	1692 (7%)
1998	708868 (15%)	1540 (48%)	692 (9%)	1711 (7%)
1999	720343 (15%)	1290 (38%)	962 (14%)	1683 (7%)
2000	728945 (14%)	678 (31%)	1364 (23%)	1802 (5%)
2001	732916 (14%)	9 (0%)	1786 (23%)	1705 (7%)
2002	738181 (13%)	24 (0%)	2068 (26%)	1643 (6%)
2003	750996 (13%)	28 (4%)	2480 (32%)	1559 (8%)
2004	762111 (13%)	5 (0%)	3049 (36%)	1316 (7%)
2005	774650 (14%)	0 (0%)	3614 (37%)	1207 (6%)
2006	781167 (14%)	0 (0%)	4329 (40%)	1232 (6%)

[a] Only the count data of number of children were extracted and used in analyses.

[b] Total number of unique child, among whom may have multiple prescriptions and/or prescriptions spanning over one year.

n/a = not applicable

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