Drug Saf (2014) 37:805–813
DOI 10.1007/s40264-014-0215-2

ORIGINAL RESEARCH ARTICLE

Comparison of Pregnancy and Lactation Labeling for Attention-Deficit Hyperactivity Disorder Drugs Marketed in Australia, the USA, Denmark, and the UK

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Published online: 12 August 2014

Abstract

Background Pregnancy and lactation labeling is presented in the officially recognized product information (PI) accompanying prescription drugs to ensure appropriate prescribing in pregnant and breastfeeding women.

Objective The aim of this study was to analyze pregnancy and lactation labeling in PI for attention-deficit hyperactivity disorder drugs marketed across countries and to compare this information with respect to consistency and discrepancy.

Methods We manually surveyed PI for atomoxetine, methylphenidate, and modafinil marketed by the same pharmaceutical companies in Australia, the USA, Denmark, and the UK. We extracted information regarding data sources (animal and human data), risk to the fetus or breastfed child, excretion in breast milk, and recommendations for use. The extracted information was then analyzed and compared with respect to consistency and discrepancy.

Results Inter-country discrepancies were identified with respect to both animal and human data sources presented, types of risks listed in association with exposure during pregnancy and lactation, information regarding excretion of the drug in breast milk, and recommendations for use. Consistency was identified between PI for drugs marketed in the EU.

Conclusion The study suggests that pregnancy and lactation labeling in PI for drugs marketed by the same pharmaceutical companies depend on the country of marketing; this raises concern about the reliability of PI documents as a useful source of information for appropriate prescribing during pregnancy and lactation. Discrepancies in this information can potentially lead to inappropriate prescribing in pregnant and breastfeeding women, who may expose their fetuses and breastfed children to unnecessary risks. At the same time, unjustified warnings against breastfeeding may result in children being unnecessarily weaned from being breastfed.

Key Points

This study revealed discrepancies in the pregnancy and lactation labeling provided in officially recognized product information (PI) documents for selected attention-deficit hyperactivity drugs marketed by the same pharmaceutical companies in Australia, the USA, and the EU.

Although no general assumptions can be made solely on the basis of these findings, they do call into question the reliability of PI as a useful source of information for appropriate prescribing during pregnancy and lactation.

Discrepant pregnancy and lactation labeling is likely to have clinical implications, as pregnant and breastfeeding women may be prescribed inappropriate and unsafe drugs and subsequently expose their fetuses and/or breastfed children to unnecessary risks. At the same time, unjustified warnings against breastfeeding may result in children being unnecessarily weaned from being breastfed.

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1 Introduction

The officially recognized product information (PI), also known as 'prescribing information' or 'summary of product characteristics', accompanying all prescription drugs, is considered a key source document oriented at healthcare professionals (HCPs), as it summarizes product-specific information essential for safe and effective prescribing. Risk assessments based on pre-clinical (i.e. animal data) and clinical data, along with recommendations for use during pregnancy and lactation, is an integral part of the PI and is intended to assist HCPs in choosing the most appropriate therapy under these circumstances [1]. However, research has shown that the safety information provided in PI documents may depend on the country in which a drug is marketed. A study by Aagaard and Hansen [2] compared adverse drug reaction (ADR) labeling for atomoxetine, methylphenidate, and modafinil marketed by the same pharmaceutical companies in Australia, Denmark, and the USA and found that only 60 % of listed ADRs were found in all three countries. Eriksson et al. [3] compared ADRs listed in PI for 40 separate drugs marketed in Denmark and the USA and found substantial inconsistencies both in types of listed ADRs and in frequency. Garbe and Andersohn [4] assessed whether contraindications added to US labeling between January 2003 and May 2005 had been added to the German PI and found that frequently this was not the case. Kesselheim et al. [5] compared PI for the same drugs approved in the USA, Canada, the UK, and Australia and found substantial variation in both the numbers of ADRs listed and the presence of qualitative content of boxed warnings. Although the results of these studies do not provide direct evidence of discrepancy in pregnancy and lactation labeling, we presume this may be the case. Therefore, with focus on three drugs (methylphenidate, atomoxetine, and modafinil) commonly used for the treatment of adult attention-deficit hyperactivity disorder (ADHD), we compared the pregnancy and lactation labeling provided in PI across countries with respect to consistency and discrepancy. ADHD drugs were selected in light of the increasing number of adults, including women of child-bearing age, being prescribed pharmacological treatment for the disorder in recent years [6, 7]. According to national and international ADHD treatment guidelines, there is generally consensus that pharmacotherapy should be initiated in adults presenting moderate to severe symptoms of ADHD [8–10]. Stimulants (methylphenidate and dexamphetamine) are considered first-line treatment based on extensive data concerning efficacy and safety. Atomoxetine is usually considered second-line treatment, while modafinil, along with several other non-stimulant drugs (e.g. buproprion, guanfacine, and tricyclic antidepressants), are considered third-line treatments [8, 10–13].

2 Methods

2.1 Data Sources

Data analyzed in this study included pregnancy and lactation labeling provided in PI for the ADHD drugs atomoxetine, methylphenidate, and modafinil marketed by the same pharmaceutical companies in Australia, the USA, Denmark, and the UK. These countries were chosen as they represent three different regulatory systems: the Australian, the US, and the European regulatory system. The PI documents were accessed in March 2014 through the websites of the national regulatory agencies in each country: Australia (The Therapeutic Goods Administration) [14], the USA (The US Food and Drug Administration) [15], Denmark (the Danish Health and Medicines Authorities) [16], and the UK (the Medicines and Healthcare Products Regulatory Agency) [17]. If more than one PI was identified per drug, the PI for the highest strength marketed was selected (Table 1).

2.2 Data Extraction

Relevant sections of the PI documents were manually surveyed, and information pertaining to drug exposure during pregnancy and lactation were extracted using a data extraction form (one per drug and country). We extracted information regarding data sources (animal vs. human data), risks to the fetus or breastfed child, excretion in breast milk, and recommendations for use. Risk in the current study is defined as a potential hazardous effect associated with maternal drug exposure during pregnancy or lactation in either animals or humans and was chosen to avoid confusion with the term ADR, which is used to describe all noxious and unintended reactions following the administration of a drug [18]. As a result of PI being prepared according to national guidelines and hence presenting different structures, information was extracted from different sections depending on the country of marketing. In the Australian and US PI, pregnancy and lactation labeling information was available in two separate sections (one for pregnancy and one for lactation), both summarizing animal data along with human data. In the Danish and UK PI, the same information was available in one overall pregnancy and lactation section. This section did not present animal data but provided an interpretation of these with reference to a section summarizing preclinical data.

Table 1 Licensing information for investigated attention-deficit hyperactivity drugs, by country

Country	Drug	Dosage form; route	Strength (mg)	Year of approval	Company	Product information version
Australia	Atomoxetine (Strattera®)	Capsules; oral	10, 18, 25, 40, 60, 80, 100	2004	Eli Lilly	21 Aug 2013
	Methylphenidate (Ritalin 10®/ Ritalin LA®)	Tablets; oral/modified-release capsules; oral	10/10, 20, 30, 40	1991	Novartis	13 Jan 2013
	Modafinil (Modavigil®)	Tablets; oral	100	2007	Cephalon	May 2011
USA	Atomoxetine (Strattera®)	Capsules; oral	10, 18, 25, 40, 60, 80, 100	2002	Eli Lilly	20 Feb 2014
	Methylphenidate (Ritalin-SR®)	Tablets; oral/modified-release tablets; oral	5, 10, 20/20	1995	Novartis	13 Dec 2013
	Modafinil (Provigil®)	Tablets; oral	100, 200	1998	Cephalon	21 Oct 2010
Denmark	Atomoxetine (Strattera®)	Capsules; oral	10, 18, 25, 40, 60, 80, 100	2006	Eli Lilly	2 Jul 2013
	Methylphenidate (Ritalin Uno®)	Modified-release capsules; oral	10, 20, 30, 40	1956	Novartis	5 Dec 2013
	Modafinil (Modiodal®)	Tablets; oral	100	1997	Cephalon	18 Sep 2012
UK	Atomoxetine (Strattera®)	Capsules; oral	100	2009	Eli Lilly	13 Dec 2013
	Methylphenidate (Ritalin®)	Tablets; oral	10	1999	Novartis	20 May 2013
	Modafinil (Provilgil®)	Tablets; oral	200	2002	Cephalon	24 Jun 2012

Source Product information documents available through the websites of the national regulatory agencies in Australia [14], the USA [15], Denmark [16], and the UK [17]

ADHD attention-deficit hyperactivity disorder, *LA* long acting, *SR* sustained release

2.3 Data Analysis

The extracted information was compared and analyzed with respect to consistency and discrepancy. Consistency was defined as inter-country agreement in the information provided regarding data sources (animal vs. human data), risks associated with exposure during pregnancy and lactation, excretion in breast milk, and recommendations for use. Discrepancy was defined as disagreement in this information between countries. Pre-approval data provided for all of the three drugs, irrespective of country of marketing, originated solely from animal studies. Human data per definition derived from post-approval surveillance (primarily from spontaneous reports), which is explained by the fact that pregnant and breastfeeding women are generally excluded from well controlled clinical trials, due to ethical considerations [19]. For the majority of drugs, human data regarding pregnancy and lactation therefore generally do not emerge until after approval. We did not consider the pregnancy risk classification systems adopted by the Australian [20] and US [21] regulatory agencies, as similar systems are not used in the EU [22, 23].[1] However, Australian and US drugs investigated in this study were classified according to pregnancy category B3 and C, respectively, both of which refer to evidence of harm identified in animal studies but inadequate data regarding exposure in pregnant women [20, 21]. All data extraction and analyses were conducted by the first author and validated by the second and third author (50 % each).

3 Results

3.1 Pregnancy Labeling

3.1.1 Data Sources

Teratology data from animal studies conducted in rabbits and/or rats were presented in all PI documents irrespective of drug and country (data not shown). Inter-country consistency was found between PI documents for atomoxetine and modafinil, as they all presented data from the same studies conducted in both rabbits and rats. However, inter-country discrepancy was identified between the PI documents for methylphenidate; the Australian PI presented data from rabbits, while the Danish and UK PI presented data from rats only. The US PI, in contrast, presented data from both rabbits and rats. Pregnancy data related to human exposure were only presented in three of the 12 PIs surveyed, namely in the Danish and UK PI for methylphenidate and in the US PI for modafinil, indicating inter-country discrepancy.

[1] The Australian Therapeutic Goods Administration and the US Food and Drug Administration classify risk associated with medication exposure during pregnancy into seven (A, B1, B2, B3, C, D, X) and five (A, B, C, D, X) categories, respectively, based on the availability of human and animal data. A is considered the safest category while the category X is completely contraindicated.

3.1.2 Fetal Risks

Fetal risks associated with maternal drug exposure in pregnant animals and humans are summarized in Table 2. Discrepancy was identified with respect to types of fetal risks associated with exposure in pregnant animals; for atomoxetine, the Australian and US PI both listed a number of non-identical fetal risks associated with studies conducted in rats, while the Danish and UK PI stated that "no effects on fertility or reproductive performance was observed." For methylphenidate, the US PI stated 'fetal spina bifida' associated with exposure in rabbits, whereas the Australian PI stated that "oral administration of methylphenidate to rabbits during the period of organogenesis has produced teratogenic effects." However, these effects were not further specified. The Danish and UK PI for methylphenidate described no risks. Also for methylphenidate, 'fetal toxicity (i.e. litter loss)' identified in rats was only stated in the Danish and UK PI, while 'fetal skeleton variation' and 'decreased offspring body weight' was only mentioned in the US PI. The Australian PI mentioned no teratogenic effects. For modafinil, 'hydronephrosis' was only stated in the Australian PI, while 'stillbirths' were only mentioned in the Danish and UK PI. Information regarding fetal risks associated with human exposure during pregnancy was provided in the Danish and UK PI for methylphenidate and in the US PI for modafinil only. The Danish and UK PI documents provided consistent information, as they both stated that "cases of neonatal cardiorespiratory toxicity, specifically fetal tachycardia and respiratory distress have been reported in spontaneous reports." The US PI for modafinil stated that "two cases of intrauterine growth retardation and one case of spontaneous abortion have been reported in association with armodafinil and modafinil."

3.1.3 Recommendations for Use

The recommendations provided in the PI regarding drug use during pregnancy were found to be consistent for atomoxetine, as the exact same wording was used across all four countries (Table 3). However, for methylphenidate and modafinil, there appeared to be discrepancies, although different wording made it difficult to make a direct comparison of the meaning. The discrepancy identified in PI for methylphenidate may be a matter of different emphasis put into the wording, e.g. the Australian PI stated "should not be prescribed for women of childbearing age" as opposed to "is not recommended for use during pregnancy" stated in the Danish and UK PI. However, for modafinil, the intercountry discrepancy was more evident; the Australian PI described modafinil as contraindicated during pregnancy, while the Danish and UK PI described it as "not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception." The US PI stated that modafinil "should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

3.2 Lactation Labeling

3.2.1 Data Sources

Inter-country consistency was identified in the PI documents for atomoxetine and modafinil, as they all stated that the drug is excreted in the milk of rats, while no data regarding excretion in human breast milk were presented (data not shown). Inter-country discrepancy was found in the PI for methylphenidate: the Australian, Danish, and UK PI stated that methylphenidate has been found in the breast milk of lactating women. The US PI for methylphenidate stated that "it is not known whether methylphenidate is excreted in human milk." None of the PI documents for methylphenidate provided animal data regarding excretion in breast milk.

3.2.2 Risks Associated with Breastfeeding

Limited information was generally available in the PI regarding risks associated with animal and human exposure during lactation (Table 4). With respect to animal data (primarily rats), discrepancy was found between the Australian and US PI for atomoxetine in the types of risks listed: both PI documents stated decreased 'pup body weight' and 'pup survival', while 'incisor overgrowth' and 'maternal toxicity' was only stated in the Australian PI. In contrast, no risks were reported in the Danish and UK PI for atomoxetine in relation to lactation. For methylphenidate and modafinil, 'decreased offspring body weight gain' and 'decreased viability in offspring', respectively, were stated in the US PI, while no risks were presented in the Australian, Danish, and UK PI. Information regarding risks to the breastfed child associated with human exposure during lactation was only provided in the Danish and UK PI for methylphenidate, both stating that "there is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate."

3.2.3 Recommendations for Use

Breastfeeding was not recommended in any of the PI documents (Table 5). However, discrepancy was found in the emphasis put into the wording of the recommendations for use during lactation. For atomoxetine, the Danish and

Table 2 Country-specific information provided in product information for atomoxetine, methylphenidate, and modafinil regarding fetal risks associated with exposure in pregnancy, by data source

Drug	Country	Fetal risk[a]		
		Animals		Humans
		Rabbits	Rats	
Atomoxetine	Australia	↓ Live fetuses, early resorption, maternal toxicity, major blood vessel variations	↓ Fetal and pup weight, fetal skeletal anomalies, maternal toxicity, ↓ pup survival	NA
	USA	↓ Live fetuses, early resorption, atypical origin of carotid artery, absent subclavian artery	↓ Pup weight, ↓ pup survival, incomplete ossification of vertebral arch in fetuses	NA
	Denmark	↓ Live fetuses, early resorption, atypical origin of carotid artery, absent subclavian artery, maternal toxicity	No effects on fertility or reproductive performance observed	NA
	UK	↓ Live fetuses, early resorption, atypical origin of carotid artery, absent subclavian artery, maternal toxicity	No effects on fertility or reproductive performance observed	NA
Methylphenidate	Australia	Teratogenic effects[b]	NA	NA
	USA	Fetal spina bifida	Fetal skeleton variations, maternal toxicity, ↓ offspring body weight	NA
	Denmark	NA	Fetal toxicity (i.e. litter loss), maternal toxicity	Cases of neonatal cardiorespiratory toxicity (fetal tachycardia and respiratory distress)
	UK	NA	Fetal toxicity (i.e. litter loss), maternal toxicity	Cases of neonatal cardiorespiratory toxicity (fetal tachycardia and respiratory distress)
Modafinil	Australia	No embryotoxicity observed	Embryotoxicity, ↑ resorption, hydronephrosis, skeletal variations	NA
	USA	Fetal structural alterations, embryofetal death, visceral and skeletal variations, decreased fetal body weight, ↓ viability of off-spring	↑ Time to mate, resorptions, visceral and skeletal variations, ↓ fetal body weight, ↓ viability of off-spring	Two cases of intrauterine growth retardation and one case of spontaneous abortion reported in association with armodafinil and modafinil
	Denmark	Skeletal variation (changes in the numbers of ribs), delayed ossification, embryo-fetal lethality (peri-implantation loss and resorptions)	Skeletal variation (changes in the numbers of ribs), delayed ossification, embryo-fetal lethality (peri-implantation loss and resorptions), stillbirths	NA
	UK	Skeletal variation (changes in the numbers of ribs), delayed ossification, embryo-fetal lethality (peri-implantation loss and resorptions)	Skeletal variation (changes in the numbers of ribs), delayed ossification, embryo-fetal lethality (peri-implantation loss and resorptions), stillbirths	NA

Source Product information documents available through the websites of the national regulatory agencies in Australia [14], the USA [15], Denmark [16] and the UK [17]

NA not available

[a] Associated with maternal exposure during pregnancy

[b] These teratogenic effects were not further specified

Table 3 Country-specific recommendations provided in product information for atomoxetine, methylphenidate, and modafinil regarding use during pregnancy

Drug	Country			
	Australia	USA	Denmark	UK
Atomoxetine	Should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus	Should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus	Should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus	Should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus
Methylphenidate	Should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks	Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	Not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy	Not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy
Modafinil	Should be contraindicated during pregnancy; sexually active women of child-bearing potential should be established on a contraceptive program before taking modafinil	Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	Not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception	Not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception

Source Product information documents available through the websites of the national regulatory agencies in Australia [14], the USA [15], Denmark [16] and the UK [17]

Table 4 Country-specific information provided in product information for atomoxetine, methylphenidate, and modafinil regarding potential risks to breastfed animal or child associated with maternal exposure

Drug	Country	Risk associated with breastfeeding	
		Animal data[a]	Human data
Atomoxetine	Australia	Incisor overgrowth, ↓ pup body weight, ↓ Pup survival, maternal toxicity	NA
	USA	↓ Pup body weight, ↓ pup survival	NA
	Denmark	NA	NA
	UK	NA	NA
Methylphenidate	Australia	NA	NA
	USA	↓ Offspring body weight gain	NA
	Denmark	NA	↓ Weight in infant[b]
	UK	NA	↓ Weight in infant[b]
Modafinil	Australia	NA	NA
	USA	↓ Viability in offspring	NA
	Denmark	NA	NA
	UK	NA	NA

Source Product information documents available through the websites of the national regulatory agencies in Australia [14], the USA [15], Denmark [16], and the UK [17]

NA not available

[a] Risk observed in the fetuses of rats treated with atomoxetine, methylphenidate or modafinil prior to mating through the periods of organogenesis and lactation

[b] Based on one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate

UK PI both stated that "because of the lack of data, atomoxetine should be avoided during breastfeeding," while the Australian and US PI both stated that "caution should be exercised if atomoxetine is administered to a nursing woman." While these recommendations are clear and concise, the Australian PI for methylphenidate was found

to give a rather long and incoherent recommendation. First, it was stated that "for safety reasons, mothers taking methylphenidate should refrain from breastfeeding their infants" after which it was stated "a decision should be made by the prescriber whether the mother must abstain from breastfeeding or abstain from methylphenidate therapy, taking into account the benefit of breastfeeding to the child and the benefit of therapy to the mother." The first part of this recommendation does not consider the benefit of breastfeeding to the child but only considers potential risks associated with drug exposure, although these seem unjustified given the lack of human data (see Sect. 3.2.2). The recommendations provided in the Danish and UK PI for methylphenidate were identical and resembled the second part of the recommendation provided in the Australian PI. The recommendation provided in the US PI, on the other hand, resembled a general opinion regarding prescribing during lactation rather than a product-specific recommendation, since it was stated that "because many drugs are excreted in human milk, caution should be exercised if methylphenidate is administered to a nursing woman." For modafinil, the Australian, Danish, and UK PI were almost identical, the Australian PI stating "not recommended" as opposed to the "should not be used" stated in the Danish and UK PI. The US PI, like for methylphenidate, resembled a general opinion rather than a product-specific recommendation.

4 Discussion

To our knowledge, this is the first study to compare pregnancy and lactation labeling specifically, provided in officially recognized PI across countries. The study revealed discrepancies in both pregnancy and lactation labeling for identical ADHD drugs marketed in Australia, the USA, Denmark, and the UK, with respect to data sources presented (animal vs. human data), types of risks to the fetus or breastfed child associated with maternal exposure, excretion of the drug in breast milk, and recommendations for use. However, it should be noted that consistency was found between the pregnancy and lactation labeling provided in Danish and UK PI for all three drugs investigated (atomoxetine, methylphenidate, and modafinil), which is a result of these being prepared according to European regulations and standards [22, 23]. In the EU, drugs can be approved according to three different types of marketing authorizations (MAs): a 'national only MA' (i.e. a drug approved on a national basis only), a 'mutually recognized MA' (i.e. a drug approved at a European level involving at least two member states), or a 'central MA' (i.e. a drug approved on a community level involving all EU member states). To obtain a mutually recognized MA or a central MA, pharmaceutical companies are allowed to submit a single application to the European Medicines Agency. PI for drugs approved according to these procedures are obviously more likely to have identical labeling in the various countries than PI for drugs with a national only MA [24]. MA information is not publicly available and therefore was not investigated in the current study. However, it would be interesting to investigate the degree to which PI for drugs with a national only MA differ from PI for drugs with a mutually recognized or central MA, since, from a pharmaceutical and clinical point of view, discrepancies seem unjustified. Although our findings should be interpreted with caution given the limited number of PI documents and drugs investigated, they do call into question how pregnancy and lactation labeling provided in PI for the same drugs marketed by the same pharmaceutical companies can differ depending on the country of marketing. However, it should be recognized that, even if labeling for the investigated drugs had been found to be consistent, the advice provided would not necessarily have been more correct, as pharmaceutical companies are generally unnecessarily cautious in their recommendations provided regarding use, hence their recommendations regarding pregnancy and lactation is generally based upon legal rather than medical considerations [5]. Part of the discrepancies identified in this study is probably explained by differences in national regulatory requirements for providing pregnancy and lactation labeling in PI. However, this does not justify that safety data or recommendations regarding use during pregnancy and lactation, based on data from the same animal studies or case reports from human exposure, depend on the country in which a drug is marketed. Given the demographic similarities of the four countries from which we compared PI, there is no clinical explanation for why specific safety data should only be presented in PI in some countries and not in others. Our study is limited in that it considers PI for ADHD medication only, which limits the generalizability of the findings to other drug classes. However, other studies have also highlighted that safety information provided in PI may in some instances depend on the country in which a drug is marketed [2–6]. Although these studies focused on ADRs, and hence do not compare directly to our study, their findings do lead us to hypothesize that the discrepancy identified in the pregnancy and lactation labeling in this study is generalizable to drugs other than those investigated. Future studies investigating drugs other than ADHD drugs are required to confirm this hypothesis. Another limitation associated with the drugs investigated in this study is that ADHD was previously considered a childhood disorder that would resolve during adolescence or early adulthood [25, 26]. Consequently, the majority of available ADHD drugs have been developed for use in

Table 5 Country-specific recommendations provided in product information for atomoxetine, methylphenidate, and modafinil regarding use during lactation

Drug	Country			
	Australia	USA	Denmark	UK
Atomoxetine	Caution should be exercised if atomoxetine is administered to a nursing woman	Caution should be exercised if atomoxetine is administered to a nursing woman	Because of the lack of data, atomoxetine should be avoided during breastfeeding	Because of the lack of data, atomoxetine should be avoided during breastfeeding
Methylphenidate	For safety reasons, mothers taking methylphenidate should refrain from breastfeeding their infants. A decision should be made by the prescriber whether the mother must abstain from breastfeeding or abstain from methylphenidate therapy, taking into account the benefit of breastfeeding to the child and the benefit of therapy to the mother	Because many drugs are excreted in human milk, caution should be exercised if methylphenidate is administered to a nursing woman	A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman	A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman
Modafinil	Breastfeeding is not recommended during administration of modafinil	Because many drugs are excreted in human milk, caution should be exercised when modafinil is administered to a nursing woman	Should not be used during breastfeeding	Should not be used during breastfeeding

Source Product information documents available through the websites of the national regulatory agencies in Australia [14], the USA [15], Denmark [16] and the UK [17]

children and adolescents and not for women of childbearing age. This may explain the limited amount of human data presented in the PI investigated in this study. PI for other drug classes used in adults is likely to include more human data.

5 Conclusion

The findings of this study suggest that pregnancy and lactation labeling presented in PI for drugs marketed by the same pharmaceutical companies may to some extent depend on the country of marketing. This raises concerns about the reliability of PI documents as a useful source of information for appropriate prescribing in pregnant and breastfeeding women. Discrepancy in this information is a source of confusion for HCPs and can potentially lead to inappropriate prescribing in pregnant and breastfeeding women, who then may expose their fetuses and breastfed children to unnecessary risks. At the same time, unjustified warnings regarding breastfeeding may result in children being unnecessarily weaned from being breastfed. As a result of the wide use and recognition of the PI by HCPs, along with its legal status in prescribing, we encourage pharmaceutical companies and regulatory agencies to ensure consistency in the information provided, irrespective of country of marketing.

Author Contribution All authors were involved in the conception and design of this study; PW manually extracted pregnancy and lactation labeling information from the PIs investigated in this study, conducted the analysis, and wrote the first version of the manuscript; LA and EHH validated the extracted data; LA and EHH provided critical revision of the content and approved the final version of the manuscript.

Conflict of interests Pernille Warrer, Lise Aagaard, and Ebba Holme Hansen have no conflicts of interest that are directly relevant to the content of this study.

Funding This study was conducted as part of a PhD project financed by the PharmaSchool, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

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