

Short Communication

## Systematic Review of Drug Labeling Changes That Inform Pediatric Weight Gain

Ingrid Kohlstadt MD, MPH<sup>1\*</sup> and M. Dianne Murphy MD<sup>2</sup>

<sup>1</sup>*Johns Hopkins Bloomberg School of Public Health, Department of International Health, Baltimore, MD\**

<sup>2</sup>*The U.S. Food and Drug Administration, Office of Pediatric Therapeutics, Silver Spring, Maryland USA*

<sup>#</sup>*Research conducted at The U.S. Food and Drug Administration, Office of Pediatric Therapeutics, Silver Spring, Maryland USA*

<sup>\*</sup>*Corresponding author: Dr. Ingrid Kohlstadt, 198 Prince George St., Annapolis, MD 21401; Tel: 813.966.8746; Fax: 410.280.4886;*

*Email: Kohlstadt@outlook.com AND ikohlst2@jhu.edu*

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### Abstract

#### Background:

The FDA communicates what clinicians need to know about the drugs they prescribe through the information found in the medication's package insert and electronic sources collectively referred to as drug labeling. If a drug product has been studied in pediatrics and the trial submitted to the FDA, drug labeling will contain information specific to children, based on these research findings independent of what is reported in the medical literature.

#### Purpose:

This study systematically reviews the database of pediatric drug labeling changes for relevance to clinical decision-making around childhood weight gain. This review quantifies pediatric drug research's potential impact on the obesity epidemic using a metric distinct from the medical literature.

#### Methods:

The authors conducted a systematic review of the pediatric labeling changes incorporated into U.S. product information (2/10/98 thru 6/30/11) as a result of pediatric legislation.

#### Results:

Thirty-one percent (120) of the database's 385 product labeling changes are for drugs which can influence a child's weight. These drugs relate to obesity as follows: Treatment for childhood obesity (n=3); therapies for glycemic control which influence weight maintenance (n=11); products which act centrally where they may alter appetite (n=51); products which improve symptoms with the net effect of reducing exposure to corticosteroids (n=24); drugs prescribed concurrently with diet and exercise (n=30) or are contraindicated if obesity is present (n=1).

#### Conclusions:

Since almost 1/3 of the products studied in children could influence weight, pediatric drug research findings as communicated through drug labeling are relevant to childhood obesity. The FDA communiques address approaches to minimizing patient exposure to obesity-promoting medications, implementing lifestyle modification alongside medications, and managing medication-related changes in appetite. The largest percentage of products may act centrally to influence appetite and food selection in the developing brain.

#### Introduction:

Preventing undesired weight gain requires practitioner knowledge of pharmacology, not only for the few patients requiring pharmacotherapy, but also for any patients prescribed medications which may alter appetite and metabolism.

Children are receiving more medications to treat chronic diseases [1]. Some drug effects are unique to children [2]. Children are more vulnerable to central drug effects such as

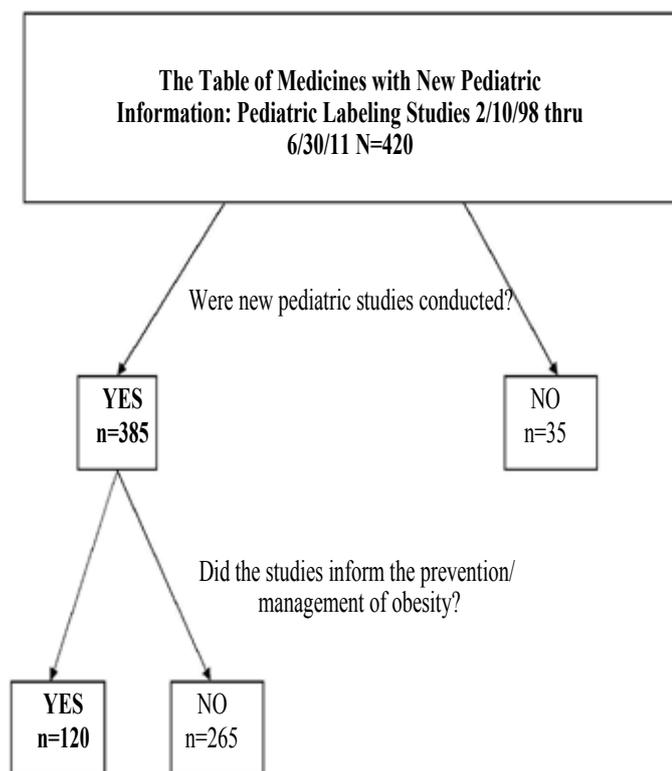
the effects on appetite and satiety [3]. Preexisting childhood obesity increases the vulnerability to adverse metabolic drug effects [3]. Taken together this information underscores the need to apply the advances in pediatric drug research [4] to preventing undesired weight gain among children.

Pediatric legislation [5] has prompted pediatric drug research resulting in products with new pediatric information in the labeling [6, 7]. Since the U.S. Food and Drug Administration often communicates clinical findings in product labeling, drug labeling can be evaluated to gauge the extent to which pediatric drug research also addresses the effects of therapies used by children that may contribute to the nation's epidemic of childhood obesity.

## Methods:

A systematic review of The Table of Medicines with New Pediatric Information (Database) was conducted, to include pediatric product labeling changes occurring from the Database's February 1998 inception through June 30, 2011. (Figure 1).

Figure 1. Diagram of the systematic review of pediatric labeling studies



Both the Database [8] and the revised drug labels [9-11] are publicly accessible. The Database is maintained by The U.S. Food and Drug Administration, Office of Pediatric Therapeutics. Each Database entry represents a product labeling revision stemming from research conducted in

children or where information directly affecting children is identified. Children are defined as those in the age range of birth to 17 years.

The research prompting the labeling changes is primarily through The Best Pharmaceuticals for Children Act (BPCA) (n=148), The Pediatric Research Equity Act (PREA) (n=175), BPCA and PREA (n=50) and The Pediatric Rule [12] which preceded PREA (n=47). The Pediatric Exclusivity provision is an incentive program originally created in the Food and Drug Administration Modernization Act of 1997 [13], and reauthorized in January 2002, as the BPCA [14]. PREA was signed into law in December 2003 and is a requirement which allows the FDA to require pediatric studies for certain applications [15]. BPCA and PREA were reauthorized in September 2007 and made permanent in 2012 [16].

Labeling changes which did not arise from research involving children were excluded, in order for the analysis to most closely reflect actual research involving children (Figure 1). Most excluded labeling changes involved either formulation bioavailability studies in adults or labeling resulting from additional safety signals.

A Database entry was classified as relevant if it facilitated the practice of medicine in one or more of the following ways:

- Treat obesity.
- Utilize new routes of administration, formulations, and dosing regimens to reduce medications' potential adverse effects on body weight.
- Expand therapeutic options to include medications with fewer adverse metabolic effects.
- Avoid concurrent medications which may synergistically increase appetite.
- Counsel patients on a drug's anticipated effects on appetite.
- Prescribe medication in conjunction with diet and exercise.
- Recognize when preexisting obesity is a drug contraindication.
- Detect, monitor and treat drug-related nutrient deficiencies and adverse metabolic effects.
- Consider effects on metabolism and appetite which may extend beyond the use of the drug or become apparent upon discontinuation.

Not related to weight were: Otic, ophthalmic, nasal and topical medications since systemic absorption associated

with these routes of administration is minimal; monoclonal antibodies and co-stimulation modulators since their corticosteroid-sparing potential is limited; antihypertensives for in-hospital, short-term use; and medications to treat gastroesophageal reflux in infants.

**Results:**

As of 2014 over 500 products have had pediatric studies which resulted in pediatric information being placed in product labeling. This analysis was restricted to pediatric labeling as of June 30, 2011. As of that time 385 product labeling changes to include pediatric information had occurred and 120 (31%) were for drugs which can influence a child’s weight (Figure 1). The products and their labeling include new insulin dosing regimens for children with type I diabetes; oral agents in type II diabetes to accompany diet and exercise; pediatric indications for monoclonal antibodies; antiepileptic agents which reduce appetite; weight considerations with attention-deficit hyperactivity disorder and expanded options for managing hypertension (Table 1).

**Table 1.** Pediatric drug labeling of products potentially influencing unintended weight gain or relevant to childhood obesity

Obesity application	Drugs by indication studied (updates, if more than one)	Additional information
Treat obesity	Orlistat Sibutramine Octreotide	Evidence did not support octreotide as a treatment for hypothalamic obesity from cranial insult.
Maintain glycemic control	Insulin preparations (7) Glimepiride Rosiglitazone Glyburide/metformin Metformin	Insulin stimulates appetite. Oral agents for type 2 diabetes differ in their effects on fat metabolism.
Anticipate alterations in appetite based on central nervous system effects	<b>Bipolar disorder and schizoprenia:</b> Paliperidone Risperidone (2) Aripiprazole (3) Olanzapine Quetiapine Divalproex <b>Epilepsy and migraine:</b> Topiramate (5) Gabapentin Lamotrigine (6) Levetiracetam (2) Oxcarbazepine <b>Depression and anxiety:</b> Buspirone Nefazodone Mirtazapine Paroxetine Sertraline Fluoxetine Fluvoxamine Citalopram Venlafaxine (2) Escitalopram	Some antipsychotic medications are less obesogenic than others, based on comparative effectiveness trials, data which is communicated in the drug labeling.  Antiepileptic agents vary in their effects on appetite with some promoting weight loss and others weight gain. These agents can also be combined with a ketogenic diet which tends to be associated with weight loss.

	<b>ADHD:</b> Atomoxetine Amphetamine mixed salts Dexmethylphenidate (2) Methylphenidate (7) Clonidine Lisdexamfetamine (2) Guanfacine (2)	One psychostimulant which is not in the Database, metamphetamine, is indicated for the treatment of obesity among adolescents.
Minimize corticosteroid exposure in asthma by optimizing dosing	<b>Asthma:</b> Fluticasone/salmeterol (2) Fluticasone (3) Budesonide Formoterol/budesonide Mometasone furoate(2)	Simultaneously improving host factors including diet, nutrients and avoidance of food allergens [20] may potentially minimize corticosteroid dosing requirements.
Identify corticosteroid-alternatives	<b>Asthma/ bronchospasm:</b> Zafirlukast Levalbuterol (2) Montelukast Albuterol (2) Zileuton Ciclesonide <b>Ulcerative colitis:</b> balsalazide <b>Juvenile arthritis:</b> Etodolac Oxaprozin Leflunomide Rofecoxib Meloxicam Celecoxib	Additionally, adequate control of asthma allows patients with exercise-induced bronchospasm to continue fitness activities consistent with maintaining healthful weight.
Administer concurrent lifestyle and diet recommendations	<b>Hypertension:</b> Enalapril Fosinopril Lisinopril (2) Amlodipine Benazepril Losartan Irbesartan Metoprolol Valsartan Eplerenone Candesartan Olmesartan <b>Elevated cholesterol:</b> Lovastatin Simvastatin Atorvastatin Pravastatin Fluvastatin Ezetimibe/simvastatin Colesevelam Rosuvastatin <b>Gastroesophageal reflux:</b> Cimetidine Omeprazole Nizatidine Esomeprazole (3) Rabeprazole Lansoprazole Pantoprazole	Beta blockers and thiazide diuretics may interfere with lifestyle weight management, while ACE inhibitors and sartans may be insulin sensitizing.  Statin drugs may cause muscle pain to a degree which reduces adherence to an exercise program.  Physiologic reduction in stomach acid reduces absorption of protein, minerals and vitamin B12 and may be proinflammatory. By reducing heartburn a medication may be permissive, removing the discomfort otherwise associated with a high fat diet.
Identify obesity as contraindication	<b>Short stature in prader-willi:</b> Somatropin	

Within each indication, the drugs are listed in chronologic order of labeling changes.

Three medications in the Database were considered for treating childhood obesity. Octreotide did not receive an indication. Sibutramine's October 2010 removal from the U.S. market over concerns of increased cardiovascular risk [17] left orlistat as the only product in the Database (through June 2011) indicated for the treatment of childhood obesity. Methamphetamine which is approved for the treatment of obesity in adolescents was not among the psychostimulants in the Database.

### Discussion:

Three in ten pediatric labeling changes involved products potentially influencing weight gain among children. Relative to the few medications studied to treat childhood obesity, a large number can inform the prevention and management of weight gain among children. Approximately half of these medications act centrally, through often poorly elucidated mechanisms, to influence appetite, satiety and food selection in the developing brain.

Effects on weight gain represent an important area for drug product development and safety, in addition to the comparably well-studied effects on growth. Minimal risk to children and minor enhancements to study protocols could enhance approaches to study how a drug changes a child's nutrient requirements [18-20], its effects on a child's appetite long-term [21], and optimal drug dosing among severely obese children [22, 23].

Labeling changes were chosen as the outcome measure because of their perceived clinical usefulness and less reporting bias than sometimes seen in the literature. However, clinicians might not be obtaining the practice-relevant information from the drug label or other sources [24-27]. Pediatrician participation in overall weight-related care is low [28, 29].

Future efforts to enhance clinical prevention and management of childhood obesity should include potential pharmacologic effects, as practiced in geriatrics to avoid drug-induced weight gain among the elderly [30]. Given the unique vulnerabilities of the brain which is developing even through adolescence, this study's findings highlight the potential for pharmacologic influences on appetite, satiety and food selection among children.

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### REFERENCES:

1. Medco. 2010 Drug Trend Report. Drugtrend.com. Accessed 9/25/14.

2. Smith PB, Benjamin DK Jr, Murphy MD, Johann-Liang R, Iyasu S, et al. Safety monitoring of drugs receiving pediatric marketing exclusivity. *Pediatrics*. 2008, 122(3): 628-633.

3. Correll CU, Manu P, Olshansky V, Napolitano B, Kane JM, et al. *Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents*. *Jama*. 2009, 302(16): 1765-1773.

4. Roberts R, Rodriguez W, Murphy D, Crescenzi T. *Pediatric drug labeling: improving the safety and efficacy of pediatric therapies*. *Jama*. 2003, 290(7): 905-911.

5. 21 United States Code, 2006 Edition Supplement 4, Title 21 - FOOD AND DRUGS CHAPTER 9 - FEDERAL FOOD, DRUG, AND COSMETIC ACT contained within SUBCHAPTER V - DRUGS AND DEVICES Part A - Drugs and Devices Sections 355a and c. [www.gpo.gov] Accessed September 30, 2014.

6. *Pediatric Research Equity Act*. *J Natl Cancer Inst*. 2004, 96(24): 1810.

7. Mathis, L.L. and S. Iyasu, *Safety monitoring of drugs granted exclusivity under the Best Pharmaceuticals for Children Act: what the FDA has learned*. *Clin Pharmacol Ther*. 2007, 82(2): 133-134.

8. U.S. Food and Drug Administration. *New Pediatric Labeling Information Database*. [http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase] Accessed 9/30/14.

9. Drugs@FDA. [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/] Accessed 9/30/14.

10. Physicians' desk reference: PDR. Medical Economics Co.: Oradell, N.J. and online at PDR.net. Accessed 9/30/14.

11. DailyMed. [http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm] Accessed 9/30/14.

12. 21 Code of Federal Regulations Sections 314.55 and 601.27. [www.gpo.gov] Accessed 9/30/14.

13. *Food and Drug Administration Modernization Act of 1997*. 111 Stat 2296, 105th Congress; 1997:107-109.

14. *Best Pharmaceuticals for Children Act of 2002*. Pub L No. 107-109, 115 Stat 1408.

15. *Pediatric Research Equity Act of 2003* Pub L No. 108-155, 117 Stat. 1936-1943.

16. Christensen, M.L. *Best Pharmaceuticals for Children Act and Pediatric Research Equity Act: time for permanent status*. *J Pediatr Pharmacol Ther*. 2012, 17(2): 140-141.

17. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, et al. *Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects*. N Engl J Med. 2010, 363(10): 905-917.
18. Offermann, G., V. Pinto, R. Kruse, *Antiepileptic drugs and vitamin D supplementation*. Epilepsia. 1979, 20(1): 3-15.
19. Komaroff, A.L. *By the way, doctor, I take a statin. Should I be taking coenzyme Q(10) to protect myself against the muscle pain that statins can cause?* Harv Health Lett. 2010, 35(4): 8.
20. Elliott, W.J, P.M. Meyer, *Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis*. Lancet. 2007, 369(9557): 201-207.
21. Kohlstadt, I, B. Vitiello, *Use of atypical antipsychotics in children: balancing safety and effectiveness*. Am Fam Physician. 2010, 81(5): 585.
22. Hanley, M.J., D.R. Abernethy, D.J. Greenblatt, *Effect of obesity on the pharmacokinetics of drugs in humans*. Clin Pharmacokinet. 2010, 49(2): 71-87.
23. Livingston, E.H, I. Kohlstadt, *Simplified resting metabolic rate-predicting formulas for normal-sized and obese individuals*. Obes Res. 2005, 13(7): 1255-1262.
24. The Media Network. *Focus groups with parents and physicians: Pediatric medication labeling*, Report HHSF223200930340P. April 21, 2010.
25. Kohlstadt, I., M.D. Murphy, L. Osmond. *Continuing education programs can assess practitioner knowledge of drug labeling*. The 11th International Congress on Obesity. 2010. Stockholm, Sweden: Wiley-Blackwell.
26. Schwartz, L.M, S. Woloshin, *Lost in transmission--FDA drug information that never reaches clinicians*. N Engl J Med. 2009, 361(18): 1717-1720.
27. Kohlstadt, I, G. Wharton, *Clinician uptake of obesity-related drug information: a qualitative assessment using continuing medical education activities*. Nutr J. 2013, 12: 44.
28. Young, P.C., et al. *Improving the prevention, early recognition, and treatment of pediatric obesity by primary care physicians*. Clin Pediatr (Phila). 2010, 49(10): 964-969.
29. Huang TT, Borowski LA, Liu B, Galuska DA, Ballard-Barbash R, et al., *Pediatricians' and family physicians' weight-related care of children in the U.S*. Am J Prev Med. 2011, 41(1):24-32.
30. Mathus-Vliegen, E.M, O. *Obesity Management Task Force of the European Association for the Study of, Prevalence, pathophysiology, health consequences and treatment options of obesity in the elderly: a guideline*. Obes Facts. 2012, 5(3): 460-483.