



# Current Perspectives on Consumer Use of Nonprescription Pain and Fever Products and Potential Unmet Needs: Epidemiology of Symptoms

Diane E. Hindman, MD PharmD FAAP  
FACMT

Board-Certified Pediatrician and Medical  
Toxicologist, Registered Pharmacist

Nonprescription Analgesic/Antipyretic Drug  
Development in Children 2 to <12 Years of Age  
FDA-University of Maryland CERSI Public  
Workshop

November 15, 2024

# Disclosures

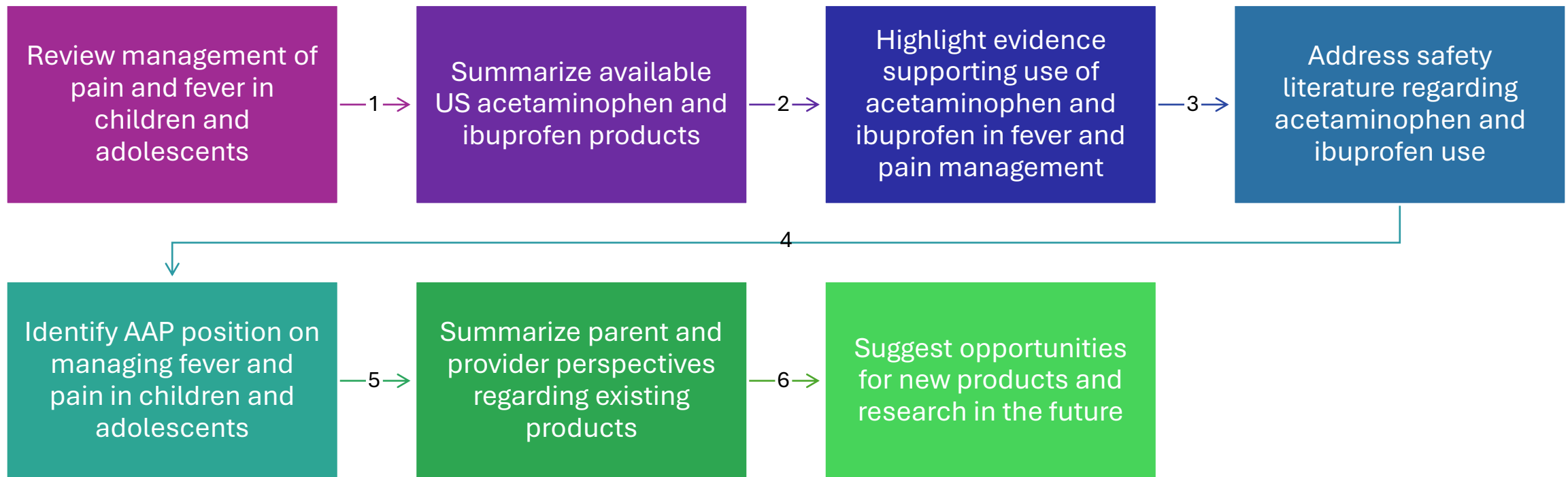


I have no financial relationship with companies and/or products that could affect the objectivity of this lecture.



Views and opinions expressed in this presentation are mine and do not necessarily reflect the policy of my employers or agencies for which I provide consultation.

# Objectives



# Pain and Fever in Children and Adolescents

- Common reasons medical care is sought and medications given<sup>1,2</sup>
  - Separately or in combination
  - Child may be miserable and not their usual self → leading to parental panic, fear and feeling helpless<sup>1,2,3</sup>
- Physiologic symptoms rather than illnesses<sup>1</sup>
  - Fever is beneficial in fighting infection<sup>1</sup>
- Fever ( $\geq 100.4^{\circ}\text{F} = 38.0^{\circ}\text{C}$ )<sup>1,4</sup>
  - Initial presentation in many childhood illnesses with generally a benign cause<sup>3</sup>
  - Degree doesn't always correlate with illness severity<sup>1</sup>
- Pain prevalence >50% in toothache, earache, headache, after vaccination, stomachache, respiratory infections, sore throat<sup>2</sup> and up to 80% of Emergency Department (ED) visits where MSK injury was most common<sup>5</sup>
- Self-care is generally appropriate, although not always necessary
- Self-care alone may not be appropriate if lasting >7 days or associated with other worrisome symptoms<sup>4</sup>

# Available US OTC Pain/Fever Products

- Acetaminophen (APAP)
  - Oral Liquid: 160 mg/5 mL
  - Chewable Tablet: 80, 120 mg
  - Tablet/Capsule: 325, 500\* mg
  - Gummy: 80, 500\* mg
  - Dissolvable Packet: 160, 500\* mg
  - Suppository: 80, 120, 325 mg
  - Adult Formulations\*:
    - Extended-release tablet: 650 mg
    - Oral liquid: 500 mg/15 mL
    - Suppository: 650 mg
- Ibuprofen (IBUP)
  - Oral Liquid: 50 mg/1.25 mL, 100 mg/5 mL
  - Chewable Tablet: 100 mg
  - Tablet/Capsule: 200 mg\*
- Naproxen (sodium)
  - Tablet/Capsule: 220 mg\*
- Acetaminophen/Ibuprofen
  - Adult Formulations\*:
    - Tablet: 250/125 mg

\*Ask a doctor labelling for <12 yo

Other product strengths, formulations and strengths may be available in other countries

Ref: 6

# Acetaminophen and Ibuprofen Dosing for Children and Adolescents

Variable	Acetaminophen	Ibuprofen
Decline in temperature, °C	1–2	1–2
Time to onset, h	<1	<1
Time to peak effect, h	3–4	3–4
Duration of effect, h	4–6	6–8
Dose, mg/kg	10–15 every 4 h	10 every 6 h
Maximum daily dose, mg/kg	90 mg/kg <sup>a</sup>	40 mg/kg
Maximum daily adult dose, g/d	4	2.4
Lower age limit, mo <sup>b</sup>	3	6

Data represent approximate averages from referenced sources.<sup>46,47,56,58,76,87</sup>

a Label is for 75 mg/kg; 90 mg/kg per day should be limited to less than 3 consecutive days.<sup>88–90</sup>

b Unless specifically recommended by a health care provider for the younger patient and, then, only after the infant has been examined by a health care provider.

Single doses not exceeding adult maximum doses: APAP 500–1000 mg / IBUP 600–800 mg  
 Rectal APAP doses 10–20 mg/kg Q4H to 75 mg/kg/day<sup>7,8</sup>

# Efficacy/Effectiveness of OTC Pain/Fever Products for Children and Adolescents

- APAP and IBUP generally well-tolerated for mild–moderate pain and fever if dosing is appropriate
- Unlikely to prevent febrile seizures
- APAP PO vs. PR antipyresis equally effective at t=1, 3 h<sup>7</sup>
- Multiple studies (short-term mono, dual, alternating, combined therapy) for fever<sup>9,10,11,12</sup>
  - Combined and alternating may be superior to APAP but IBUP (7.5–10 mg/kg) may be comparable at t=4, 6 h<sup>13</sup>
  - APAP 10–15 mg/kg was not different from IBUP 5–7.5 mg/kg<sup>13</sup>

# Efficacy/Effectiveness of OTC Pain/Fever Products for Children and Adolescents (cont'd)

- Rigorous, randomized controlled trials comparing analgesia
  - APAP lacks anti-inflammatory properties of IBUP<sup>14</sup>
  - Comparisons more often with opioids, various NSAIDs<sup>14</sup>
  - Recommended dosing is comparable to use in fever<sup>14,15,16</sup>
- IBUP 4–10 mg/kg comparable pain relief to APAP 7–15 mg/kg at t=2, 4 h<sup>16</sup>
- IBUP 10 mg/kg better than ketorolac 0.5 mg/kg for severe traumatic pain; no difference for moderate<sup>17</sup>
- IBUP better than placebo for migraine<sup>18</sup>
- APAP and IBUP alone better analgesia than placebo for dental pain; combination better than monotherapy<sup>19</sup>
- APAP and IBUP alone probably better analgesic than placebo for acute otitis media; unclear if IBUP or IBUP+APAP are more effective than APAP alone<sup>20</sup>
- 3.3:1 APAP:IBUP fixed combination product consensus by a 10-clinician board for mild-to-moderate pain in children if monotherapy ineffective<sup>21</sup>
  - Excluded recommendation in post-tonsillectomy and abdominal surgery<sup>21</sup>
  - US adult formulation is 2:1 APAP:IBUP combination product<sup>6</sup>



# Adverse Effects of OTC Pain/Fever Products for Children and Adolescents

- No significant difference in systemic adverse events(AE)<sup>16,18,19,22,23,24</sup>
- FAERS data (2003–2021): APAP- and IBUP-associated renal injury reported in patients <18 yo but unable to clearly discern risks in this group<sup>25`</sup>
  - Impacts of intentional overdose, deliberate poisoning and suicide attempt noted but not delineated
- No increased RR of any AE in infants <6 mo prescribed IBUP<sup>26</sup>
  - Most also prescribed APAP
  - No significant difference in severe GI or renal AE for IBUP +/- APAP vs. APAP only groups, although GI AE were more common in infants <6 mo given IBUP vs APAP alone
- No significant increase in severe bleeding s/p tonsillectomy +/- adenoidectomy with IBUP vs. APAP<sup>27</sup>
  - No significant AE or deaths reported

# AAP Statements Related to Management of Pain/Fever in Children and Adolescents

- Fever
  - Fever and Antipyretic Use in Children – Clinical Report<sup>1</sup>
    - Originally published in 2011 → reaffirmed in 2022
  - Fever Without Fear: Information for Parents<sup>28</sup>
  - Wade and Mathis Commentary<sup>29</sup>
    - Has raised the issue of dual therapy and its appropriateness for fever
  - No consensus on alternating or combined dosing
- Pain
  - No current publication or guideline regarding non-opioid pain management but AAP Committee on Drugs (COD) is putting forth an intent to publish a Clinical Report

# Parent Perspectives

- Fever definition and phobia
- Some parents have a drug preference
  - Flavor, formulation
  - One product works better
  - Autism or other sensitivities
- Lack of awareness of products available
  - APAP suppositories when child is vomiting or refuses PO
  - Availability of more than one drug option
  - Benefit of NSAID if inflammation
  - Precautions regarding the use of a specific drug, e.g., bleeding risk
  - Multiple component products containing APAP or ibuprofen
- Ability to assess child's other clinical features
  - Often won't give medication until provider assesses
- Confusion regarding
  - Actual drug names (generic/brand)
  - Strength of product
  - Dose to give
  - Dose given (mg, mL, spoon vs. oral syringe)
  - Administration (PO, PR)
  - Alternating doses relative to drug pharmacokinetics
  - Recurrence of fever or pain when the drug wears off
- Desires
  - Something their child will take, e.g., gummies
  - Natural flavors/colors
  - Longer-acting, fewer daily doses

# Provider Perspectives

- Not all provider definitions of alternating doses are the same
- Most common reason drugs don't work is related to dose or frequency given
- Packaging instructions often confusing
  - Age vs. weight-based dosing
- Dangers of large package sizes, candy-appearing dosage forms
  - Intentional or unintentional overdose
  - Need for safe storage awareness
- Pain or fever only products would increase confusion
- Uncertainty of safety with APAP/IBUP combination products
- Desires
  - Ibuprofen suppositories, powders
  - Remove infant ibuprofen strength to avoid dosing errors
  - Additional strengths of existing products
  - Naproxen for younger children and oral liquid OTC access
  - New formulations
    - Intranasal
    - Oral dissolving tablets (ODTs)
  - Nipple container for easier administration in infants/toddlers
  - Effective standardized teaching materials

# Evidence and Future Opportunities

- Quality clinical trials on new formulations from the outset
- Clarify terminologies/definitions and encourage use in future studies
  - Pain and fever
  - Outcomes
  - Adverse effects
- Address research gaps
  - Fixed dose combination
  - Alternating and combination doses
  - Post-marketing (e.g., FAERS) data summary by pediatric age categories



# Summary

APAP and IBUP are effective in children and adolescents

Unclear which drug and dosing format are best in all situations

Definitive research is lacking

Opportunities for new products

New routes, formulations, additional strengths

Unclear if APAP/IBUP combination product is effective, safe and offers correct ratio of drugs

Research to support new products will be important

Clear labelling and education are essential to ensure parent and patient understanding, and safe and appropriate use

# References

1. Sullivan JE, Farrar HC, et al; Section on Clinical Pharmacology and Therapeutics. Fever and antipyretic use in children. *Pediatrics*. 2011;127(3):e20103852. Doi: 10.1542/peds.2010-382
2. Zempsky W, Bell J, Mossali VM, Kachroo R, Siddiqui K. Common selfcare indications of pain medications in children. *Pediatric Drugs*. 2023;25:321–341. Doi: 10.1007/s40272-023-00562-1
3. Kanabar D. A practical approach to the treatment of low-risk childhood fever. *Drugs R D*. 2014;14:45–55. Doi: 10.1007/s40268-014-0052-x
4. Adam HM. Commentary: Fever is your Friend. *Pediatr Rev*. 2023;44:120:701. Doi: 10.1542/pir.4412commentary
5. Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet*. 2016;387:83–92. Doi: 10.1016/S0140-6736(14)61686-X.
6. National Institutes of Health (NIH) National Library of Medicine (NLM). DailyMed. Available at <https://dailymed.nlm.nih.gov/dailymed/index.cfm>. Accessed October 27, 2024.
7. Tantivit N, Thangjui D, Trongtorsak A. Antipyretic effectiveness of oral acetaminophen versus rectal acetaminophen in pediatric patients with fever. *Hosp Pediatr*. 2022;12(6):e201. Doi: 10.1542/hpeds.2021-006377
8. Acetaminophen (paracetamol): Drug information. UptoDate® Lexidrug™. Available at [https://www.uptodate.com/contents/acetaminophen-paracetamol-drug-information?search=acetaminophen&source=panel\\_search\\_result&selectedTitle=1%7E150&usage\\_type=panel&kp\\_tab=drug\\_general&display\\_rank=1](https://www.uptodate.com/contents/acetaminophen-paracetamol-drug-information?search=acetaminophen&source=panel_search_result&selectedTitle=1%7E150&usage_type=panel&kp_tab=drug_general&display_rank=1). Accessed October 27, 2024.

# References

9. Hay AD, Costelloe C, Redmond NM, Montgomery AA, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): Randomized controlled trial. *BMJ*. 2008;337(7672):729–773
10. Allan GM, Ivers N, Shevchuk. Treatment of pediatric fever. Are acetaminophen and ibuprofen equivalent? *CFP*. 2010 AUG;56:773.
11. Paul IM, Sturgis SA, Yang C, Engle L, et al. Efficacy of standard doses of ibuprofen alone, alternating, and combined with acetaminophen for the treatment of febrile children. *Clin Ther*. 2010;32(14):2433–2440. Doi: 10.1016/j.clinthera.2011.01.006
12. Kuo n, Su N-Y, Hou S-K, Kang Y-N. Effects of acetaminophen and ibuprofen monotherapy in febrile children: a meta-analysis of randomized controlled trials. *Arch Med Sci*. 2022;18(4):965–981. Doi: 10.5114.aoms/140875
13. De la Cruz-Mena JE, Veroniki A-A, Acosta-Reyes J, Estupinan-Bohorques A, et al. Short-term dual therapy or monotherapy with acetaminophen for fever: A network meta-analysis. *Pediatrics*. 2024;154(4):e2023065390. Doi: 10.1542/peds.2023-065390
14. Chumpitazi CE, Chang C, Atanelov Z, Dietrich AM. Managing acute pain in children presenting to the emergency department without opioids. *JACEP Open* 2022;3:e12664. Doi: 10.1002/emp2.12664
15. Sansone L, Gentile. C, Grasso EA, Di Ludovico A, et al. Pain evaluation and treatment in children: A practical approach. *Children*. 2023;10:1212. Doi: 10.3390/children10071212
16. Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen versus ibuprofen for treating children's pain or fever: A meta-analysis. *Arch Pediatr Adolesc Med*. 2004;158:521–526.
17. Ghirado S, Trevisan M, Ronfani L, Zanon D, et al. Oral ibuprofen versus oral ketorolac for children with moderate and severe acute traumatic pain: a randomized comparative study. *Eur J Pediatr*. 2023;182:929–935. Doi: 10.1007/s00431-022-04759-3



# References

18. Richer L, Billinghamurst L Linsdell MA, Russell K, et al. Drugs for the acute treatment of migraine in children and adolescents. *Cochrane Database Syst Rev*. 2016;4:CD005220. Doi: 10.1002/14651858.CD005220.pub2
19. Miroshnychenko A, Azab M, Ibrahim S, Roldan, et al. Analgesics for the management of acute dental pain in the pediatric population. A systemic review and meta-analysis. *JADA*. 2023;154(5):403–416. Doi: 10.1016/j.adaj.2023.02.013
20. de Sevaux JLH, Damoiseaux RAMJ, van de Pol AC, Hay AD, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database Syst Rev*. 2023;8:CD011534. Doi: 10.1002/14651858.CD011534.pub3
21. Parri N, Silvagni D, Chiarugi A, Cortis E, et al. Paracetamol and ibuprofen combination for the management of acute mild-to-moderate pain in children: expert consensus using the Nominal Group Technique (NGT). *Ital J Pediatr*. 2023;49:36. Doi: 10.1186/s13052-023-01445-4
22. Southey ER, Soares-Weiser K, Kleijnen J. Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. *Curr Med Res Opin*. 2009;25(9):2207–2222. Doi: 10.1185/03007990903116255
23. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: A meta-analysis and qualitative review. *Ann Pharmacother*. 2010;44:489–506.
24. Kanabar DJ. A clinical and safety review of paracetamol and ibuprofen in children. *Inflammopharmacol*. 2017;25:1–9. Doi: 10.1007/s10787-016-0302-3
25. Shao Q-h, Yin X-d, Liu H-x, Zhao B, et al. Kidney injury following ibuprofen and acetaminophen: A real-world analysis of post-marketing surveillance data. *Front Pharmacol*. 2021;12:750108. Doi: 10.3389/fphar.2021.750108

# References

26. Walsh P, Rothenberg SY, Bang H. Safety of ibuprofen in infants younger than six months; A retrospective cohort study. *PLoS One*. 2018;13(6):e0199493. Doi: 10.1371/journal.pone.0199483
27. Diercks GR, Comins J, Bennett K, Gallagher TQ, et al. Comparison of ibuprofen vs acetaminophen and severe bleeding risk after pediatric tonsillectomy. A noninferiority randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2019;145(6):494–500. Doi: 10.1001/jamaoto.2019.0269
28. Fever without Fear: Information for parents. Available at [healthychildren.org](https://www.healthychildren.org). Accessed October 27, 2024.
29. Wade KC, Mathis C. Antipyretic strategies: Is fever clearance enough to justify dual therapy? *Pediatrics*. 2024;154(4):e2024067408 Doi: 10.1542/peds.2024-067408