Paediatrics & Child Health, 2019, 303–305
doi: 10.1093/pch/pxy188
Commentary
Advance Access publication 5 January 2019

Commentary

Choosing medications wisely: Is it time to address paediatric polypharmacy?

Orly Bogler[1], Daniel Roth MD MSc PhD[2,3,4], James Feinstein MD MPH[5,6], Marina Strzelecki BScPhm ACPR RPh[7,8], Winnie Seto BScPhm PharmD MSc ACPR RPh[3,4,7,8], Eyal Cohen MD MSc FRCP(C)[2,3,4]

[1]Faculty of Medicine, University of Toronto, Toronto, Ontario; [2]Division of Paediatric Medicine, Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario; [3]Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, Ontario; [4]Institute of Health Policy, Management & Evaluation, University of Toronto, Toronto, Ontario; [5]Adult and Child Consortium for Health Outcomes Research and Delivery Science (ACCORDS), Aurora, CO, USA; [6]Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA; [7]Department of Pharmacy, The Hospital for Sick Children, Toronto, Ontario; [8]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario

Correspondence: Eyal Cohen, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8. Telephone 416-813-5795, fax 416-813-5663. E-mail eyal.cohen@sickkids.ca

Abstract

There is a growing focus in the medical community on de-escalating medical treatments where appropriate; however, specific efforts to reduce medication burden in patients with polypharmacy has largely been targeted toward adult populations. Polypharmacy increases the risk of adverse drug reactions in children, and that risk may be further increased by the use of off-label drugs. The paediatric prescribing community should explore pharmacovigilance strategies and deprescription initiatives that prioritize patients with polypharmacy. Currently, best practices may be extrapolated from the adult literature, including medication review algorithms and patient education tools. Enhancing access to nonpharmacological modalities to address child and youth mental health may mitigate psychotropic polypharmacy. The aim of these initiatives should be to improve patient outcomes and experiences by avoiding adverse drug events and drug–drug interactions.

Keywords: *Deprescriptions; Drug-related side effects and adverse reactions; Polypharmacy; Prescription drug overuse.*

With the current focus on 'Choosing Wisely' in contemporary medicine, providers are encouraged to refrain from using unnecessary treatments. Included in this 'less-is-more' approach is an awareness of medication overuse and its consequences. Polypharmacy (i.e., the concurrent use of multiple prescribed medications by one patient) is associated with adverse drug reactions and potential patient morbidity (1,2). Concerns about polypharmacy have led to initiatives aimed at preventing overprescribing and increasing deprescribing (i.e., safe discontinuation of a prescribed drug). However, attention has been almost exclusively on adult populations, especially older adults among whom rates of polypharmacy are higher. To date, there has been minimal focus on potential harms associated with polypharmacy in paediatrics. We propose that increased pharmacovigilance is also needed for children with polypharmacy, providing examples and future directions for how this can be achieved.

Paediatric polypharmacy is prevalent in both inpatient and outpatient settings. A large proportion of hospitalized children experience polypharmacy (3). Children in an intensive care setting are exposed to an average of 10 drugs each day and 20 drugs by the time of discharge, and 69% of such patients are at risk of at least one major potential drug–drug interaction (1). Data from outpatient settings are more limited, but polypharmacy

Received: September 25, 2018; Accepted: November 26, 2018

is prevalent in children with neuropsychiatric conditions like attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (4) as well as in patients with complex medical conditions (5). About 7.5% of the general paediatric population is exposed to polypharmacy (6). However, 35% of fee-for-service Medicaid patients (a population with a high proportion of patients with medical complexity) are exposed to some degree of polypharmacy (5).

Polypharmacy increases the risk of drug-related adverse events. The use of five or more low-risk drugs or three or more high-risk drugs (high-risk was defined as analgesics, antiepileptics, antibacterials, systemic antimycotics and corticosteroids, and immunosuppressants) is associated with adverse drug reactions in children (2). Being on four or more home medications is also a risk factor for a medication discrepancy on admission to hospital (7). Off-label drug use is common in paediatrics and is problematic when there is limited paediatric evidence on drug efficacy, safety, and drug interactions (8,9). Exposure to off-label medications is associated with polypharmacy (8) and multiple off-label medication use increases the risk for an adverse drug event. Polypharmacy can also lead to unintended consequences beyond conventional drug–drug interactions. For example, among children with neurologic impairments like cerebral palsy who are at risk of frequent aspiration from gastroesophageal reflux, the addition of a proton-pump inhibitor (PPI) may alter the intestinal microflora and potential pathogens, possibly affecting the efficacy of antibiotics targeted at common causes of aspiration (10).

Why is polypharmacy so common and why is deprescribing challenging? It may be easier to prescribe a medication than to remove one. Often the decision about medication renewal is not made by the original prescribing physician. Subsequent physicians, who may not have ordered a medication originally, may also not want to question the clinical judgement of the original prescriber. Additionally, children and their caregivers may be reluctant to withdraw medications, particularly if the therapeutic goals were never clearly communicated or understood at the time of the original prescription.

So what should the paediatric community do to reduce the risks associated with polypharmacy? At a minimum, paediatric healthcare providers should be aware of the risks of paediatric polypharmacy and be vigilant when it occurs. Paediatric providers should also consider extrapolating initiatives from the adult literature on deprescription and apply them to paediatric settings. These initiatives include formal medication review programs and quality improvement initiatives to promote deprescription.

In adult settings, there has been a focus on formal deprescription initiatives to mitigate polypharmacy. In general, deprescription can be applied through a five-step protocol:

1. Ascertain all drugs the patient is currently taking and their indication;
2. Consider overall risk of drug-induced harm in determining the required intensity of deprescribing intervention;
3. Assess each drug in regard to its potential current or future benefit compared with current or future harm/burden;
4. Prioritize drugs for discontinuation that have the lowest benefit-harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes; and
5. Implement a discontinuation regimen and monitor patients closely for outcomes (11).

Interventions, such as medication review programs, have been developed to reduce polypharmacy in adults. These interventions are reported to be most effective when tailored to be patient-specific (12). However, while medication review has improved some outcomes (e.g., emergency room contact), it has not been shown to significantly improve morbidity and mortality (13).

Educational interventions have been implemented in adult settings with more success. Among long-term users of benzodiazepines, over 25% of the participants who read patient-empowering brochures stopped medications with help from their primary care physician (14). Other interventions include patient and physician education programs and 'Choosing Wisely' campaigns, which encourage patients to contribute to the decision-making process and feel empowered to discontinue medications. The Canadian Paediatric Society (CPS) has endorsed two Choosing Wisely recommendations focused on not initiating medications unnecessarily (for gastroesophageal reflux in infants and for ADHD in preschoolers), but these same concepts can be adapted to deprescribing as well (15).

Organizations that raise awareness about drug safety and the implications of polypharmacy, like the Institute for Safe Medication Practices Canada and the Canadian Deprescribing Network (deprescribing.org), provide evidence-based tools for providers and patients to deprescribe some commonly overused medications such as benzodiazepines, PPIs, and cholinesterase inhibitors. Such initiatives may be modified and applied to address paediatric polypharmacy and deprescription.

Psychotropic medications comprise a large proportion of outpatient polypharmacy (5), and may be a specific target for deprescribing initiatives. The alarming rise in off-label antipsychotic use in children, often as an adjunctive therapy for comorbidities of common behavioural conditions like aggression in children with ADHD, may be partially a response to a lack of psychosocial supports for affected children (16). Paediatricians can play an important role in advocating for funding and access to appropriate nonpharmacological interventions in order to mitigate the potential harm of psychotropic polypharmacy.

At the time of prescription, paediatric prescribers, in partnership with their patients and their caregivers, should establish clear expectations about the length, goals, and risks of pharmacotherapy, and refrain from automatic renewals of medications without establishing clear ongoing need. In our experience, many children with polypharmacy have underlying complex chronic conditions, for which medications are added by a variety of prescribers to

manage a symptom rather than an underlying condition (PPIs for feeding intolerance, anticholinergic for sialorrhea, sedatives for sleep, etc.). Given the lack of evidence, unknown risks of long-term use, and potential risk of polypharmacy, indication for ongoing need for symptom-control drugs should be reviewed with a high level of scrutiny at regular intervals. For many medications, there is often no immediate harm with trialling patients off the medications. Hospital admission and discharge reconciliation programs can be modified to flag patients at risk for polypharmacy and in whom deprescription efforts might be directed. Providers should aim to ensure that medication review is completed in an interprofessional setting, and optimize the various skills of physicians, pharmacists, nurse practitioners, and other allied healthcare professionals caring for complex children.

The CPS's 2017–2022 Strategic Framework targets paediatric medications and therapeutics as a priority. It suggests increased medication regulatory frameworks and further research to promote evidence-based prescribing and argues that paediatricians have a role to ensure safe, effective, and appropriate therapeutics in children. Recently, the Canadian Paediatric Surveillance Program, a joint project of the Public Health Agency of Canada and the CPS, published an Adverse Drug Reaction 'Tip of the Month' about the importance of deprescribing.

These initiatives are a great start to build upon. Further action is needed to describe, understand, quantify, and improve polypharmacy and deprescription in the paediatric population. Initiatives should include:

1. Advocating for increased funding to conduct paediatric drug research in order to reduce off-label medication use, and to better understand potential drug–drug interactions, and potentially unsafe polypharmacy.
2. Improving and standardizing the training of prescribers and pharmacists to detect, track, recognize, and report adverse drug reactions through educational interventions, mobile applications and web-based notifications, and incentive programs.
3. Advocating for increased quality improvement programs focused on paediatric polypharmacy, medication utilization review, and validating deprescription tools in a paediatric setting.
4. Extrapolating proven medication review programs or quality improvement approaches used in the adult settings to paediatrics. Existing tools may be incorporated into clinical practice, all while adopting a patient-centred approach and including caregivers in the conversation about deprescribing. A helpful start is to implement a patient-provider discussion guided by the '5 questions to ask about your medications' pamphlet created by several patient-safety organizations. The pamphlet encourages patients and providers to address medication changes, continuation, proper use, monitoring, and appropriate follow-up planning (17).

By prioritizing evaluation of these interventions and processes in the paediatric setting, paediatric providers can work together to reduce unnecessary polypharmacy and associated adverse effects, thereby improving paediatric medication use, patient outcomes, and quality of care.

Funding information: Dr. Feinstein was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number K23HD091295.

Potential Conflicts of Interest: EC is a member of the Committee to Evaluate Drugs which provides advice to Ontario's Ministry of Health and Long-term Care on public drug policy. The views herein are solely those of the authors. There are no other disclosures. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Dai D, Feinstein JA, Morrison W, Zuppa AF, Feudtner C. Epidemiology of polypharmacy and potential drug-drug interactions among pediatric patients in ICUs of U.S. Children's hospitals. Pediatr Crit Care Med 2016;17(5):e218–28.
2. Rashed AN, Wong IC, Cranswick N, Tomlin S, Rascher W, Neubert A. Risk factors associated with adverse drug reactions in hospitalised children: International multicentre study. Eur J Clin Pharmacol 2012;68(5):801–10.
3. Feudtner C, Dai D, Hexem KR, Luan X, Metjian TA. Prevalence of polypharmacy exposure among hospitalized children in the United States. Arch Pediatr Adolesc Med 2012;166(1):9–16.
4. Horace AE, Ahmed F. Polypharmacy in pediatric patients and opportunities for pharmacists' involvement. Integr Pharm Res Pract 2015;4:113–26.
5. Feinstein JA, Feudtner C, Valuck RJ, Kempe A. The depth, duration, and degree of outpatient pediatric polypharmacy in Colorado fee-for-service medicaid patients. Pharmacoepidemiol Drug Saf 2015;24(10):1049–57.
6. Qato DM, Alexander GC, Guadamuz JS, Lindau ST. Prescription medication use among children and adolescents in the United States. Pediatrics 2018;142(3):e20181042.
7. Coffey M, Mack L, Streitenberger K, Bishara T, De Faveri L, Matlow A. Prevalence and clinical significance of medication discrepancies at pediatric hospital admission. Acad Pediatr 2009;9(5):360–365.e1.
8. Moulis F, Durrieu G, Lapeyre-Mestre M. Off-label and unlicensed drug use in children population. Therapie 2018;73(2):135–49.
9. Neville KA, Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Paul IM, Van Den Anker JN. Off-label use of drugs in children. Pediatrics 2014;133(3):563–567.
10. Rosen R, Amirault J, Liu H, et al. Changes in gastric and lung microflora with acid suppression: Acid suppression and bacterial growth. JAMA Pediatr 2014;168(10):932–7.
11. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Intern Med 2015;175(5):827–34.
12. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: A systematic review and meta-analysis. Br J Clin Pharmacol 2016;82(3):583–623.
13. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev 2016;2:CD008986.
14. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: The EMPOWER cluster randomized trial. JAMA Intern Med 2014;174(6):890–8.
15. Society CP. Five Things Physicians and Patients Should Question (updated November 2016). Available from: https://choosingwiselycanada.org/paediatrics/ (Accessed December 13, 2018).
16. Harrison JN, Cluxton-Keller F, Gross D. Antipsychotic medication prescribing trends in children and adolescents. J Pediatr Health Care. 2012;26(2):139–45.
17. 5 Questions to Ask About Your Medications: Institute for Safe Medication Practices Canada; 2016. Available from: https://www.ismp-canada.org/medrec/5questions.htm (Accessed December 13, 2018).