Pharmacotherapy for treating chronic pain in children: A need for pragmatic idealism

Chronic pain, defined as persistent or recurrent pain lasting beyond 3 months, is a global health issue in children and adolescents associated with substantial levels of disability, mood disorder, school absenteeism, social isolation, and family disharmony. Studies from the United States and the UK also suggest that chronic pain in young people places a considerable economic burden on society with regard to healthcare expenditure and parental unemployment. Furthermore, inadequately treated pain in childhood is a known risk factor for chronic pain in adulthood.

The prevalence of chronic and recurrent pain in children and adolescents appears to be increasing in parallel with prevalence rates in adults. Recurrent pain refers to disabling pain flares with intervening pain-free periods usually associated with a return to normal levels of function, whereas chronic pain is characterized by continuous pain and pain-related disability. A recent epidemiological study that reviewed health survey data from over 200,000 adolescents across Europe and Canada found that 44.2% of adolescents aged 11-15 years had reported chronic weekly pain over the preceding 6 months. Another systematic review reported highly variable prevalence rates across different chronic pain conditions. Headache was reported in 8%-83%, abdominal pain in 4%-53%, back pain in 14%-24%, and musculoskeletal pain in 4%-40%. The variability in prevalence rates largely reflects differences in the time period of reporting across studies (ie, daily, weekly, and monthly prevalence rates). Female gender, increasing age, and lower socioeconomic status were associated with higher pain prevalence rates, similar to findings in adult studies of pain prevalence. Future studies looking at the prevalence of pain-related disability in children and adolescents are also needed to provide a better understanding of the impact and trajectory of recurrent and chronic pain across different pediatric age groups.

Evidence to support the pharmacological management of chronic pain in children and adolescents worldwide continues to lag behind that of adults. The overview of systematic reviews by Eccleston et al highlights the lack of high-quality evidence with regard to both the efficacy and safety of analgesics in the setting of both cancer and noncancer-related chronic pain. All of the 23 included reviews were classified as either Effective Practice and Organization of Care Class 1 or 2 (ie, very low-quality evidence) primarily related to the paucity of data. The primary outcomes used in the review by Eccleston et al were participant-reported pain relief of at least 30% or 50%, or observer-reported pain in the absence of self-reported pain, and improvement in patient global impression of change. While it is widely acknowledged that pain relief is an appropriate efficacy outcome measure in the acute pain setting, it has reduced weighting as an outcome measure in chronic pain. Many patients with chronic pain continue to report high levels of pain despite multiple analgesics and dose escalation.

The absence of good quality safety data is also an important issue that needs to be addressed. Eccleston et al also advocate for improved global monitoring of adverse events using existing or newly established pediatric analgesic prescription registers. Many patients with chronic pain who take regular analgesics, irrespective of age, experience adverse cognitive and gastrointestinal adverse effects with very little improvement in pain or functional status. Analgesic-related functional deterioration may occur due to daytime somnolence, impaired concentration, motivational apathy, and increased school absenteeism and social isolation. Another more serious area of concern is the use of prescription opioids combined with other sedative anxiolytics in children and adolescents with chronic noncancer pain. While the North American prescription opioid epidemic, and the associated morbidity and mortality, appears to be a problem primarily affecting the adult population, there is certainly a growing body of evidence demonstrating significant opioid-related harm in children and adolescents mostly due to diversion and unintentional administration.

There is no robust evidence of long-term benefit beyond 3 months in adults with chronic pain, and there is certainly good evidence of potential increasing disability and significant harm affecting not only the individual with chronic pain, but also the family, wider society, and the health system, which is tasked with managing the adverse effects of opioids and polypharmacy substance-use disorder. It is difficult to understand why clinicians would be prepared to prescribe long-term opioid therapy in children and adolescents with chronic noncancer pain when the significant risks may outweigh any benefit in this setting. What begins as appropriate prescribing of opioids and other sedative analgesics for acute perioperative pain in hospital may lead to continued prescribing in the community if we do not improve discharge communication, education, and support for primary care physicians responsible for looking after these children once they leave hospital. Multidisciplinary transitional pain services have been implemented in a number of Canadian adult and pediatric hospitals aimed at early identification and comprehensive multidisciplinary management of patients at high risk for chronic postsurgical pain to
try to prevent the transition to chronic pain and to facilitate earlier opioid weaning and improve pain self-management skills following hospital discharge.3

Eccleston et al3 comment on some of the factors contributing to this relative absence of high-quality evidence including the lack of testing of pharmaceuticals in children (despite FDA and EMA requirements to test all new drugs in children and adolescents), ethical issues around placebo-controlled studies and withholding analgesics, long-held acceptance of extrapolation of adult evidence to the pediatric population, and widespread prescribing of off-label or unlicensed medications. Conducting clinical research in children with chronic pain is also challenging due to limited numbers of pediatric chronic pain clinics from which to recruit patients, small and heterogeneous disease populations, the need to obtain both parental consent and child assent, difficulties with standardization of pain measurement tools across different pediatric age groups, and a relative lack of pediatric-specific analgesic formulations to facilitate weight-based dosing.

Eccleston et al3 suggest that there is a need to consider alternative trial designs to facilitate comparative analgesic efficacy research including micro-randomized trials, enriched enrolment randomized withdrawal trials, and single-case designs. Optimizing analgesic trial design in children is exceedingly difficult due to differences in cognitive maturity and understanding of numerical concepts that are crucial to pain intensity reporting, limited previous pain experience, and underlying psychosocial factors that have a major influence on how children and adolescents experience and report pain. Perhaps continuing to undertake more pediatric comparative analgesic efficacy trials is not the answer. If we assume that analgesics that are effective in adults with chronic pain are likely to be similarly effective in children and adolescents with chronic pain, then perhaps we should instead focus our limited research funding and resources on PK-PD modeling and simulation techniques to optimize pediatric dosing regimens for antineuropathic agents and other analgesics that are commonly prescribed in patients with chronic pain.

The biomedical approach to chronic pain management has been replaced by a biopsychosocial approach that recognizes the complex biopsychosocial interactions that contribute to an individual's chronic pain experience. This approach focuses instead on education around chronic pain mechanisms and symptom validation, functional reactivation, cognitive-behavioral therapies, parental education and support, and healthy lifestyle training (eg, sleep hygiene, relaxation, exercise, and nutrition), with prescribing of analgesics to facilitate rehabilitation, improve sleep patterns, and moderate pain-related anxiety or other significant mood disorders. However, a respectful body of evidence in support of this approach in children and adolescents is also lacking. A recently published systematic review and subset meta-analysis that examined the effectiveness of inpatient and outpatient interdisciplinary interventions in the setting of pediatric chronic pain reported short-term improvements in pain intensity and functional disability.6 However, heterogeneity with regard to the type of interventions administered, reported outcome variables, duration of treatment, and chronic pain conditions, along with small sample sizes meant that conclusions and recommendations regarding key components of interdisciplinary approaches could not be made.

Unfortunately, government-funded healthcare agencies and health insurers are generally focused on getting adults with chronic pain back into the workforce, rather than creating pediatric and adolescent-specific programs that facilitate getting children and adolescents back to school and young adults back into tertiary education. This significant global healthcare disparity between children and adolescents with chronic pain compared with adults needs to be addressed. Increasing the availability of pediatric and adolescent-focused multidisciplinary outpatient pain clinics and intensive pain management programs will not only facilitate more research to be undertaken, but will more importantly provide the necessary resources to enable young people to learn pain self-management strategies that aim to improve physical and psychological function, reduce pain-related disability, build resilience to pain in the future, and perhaps even prevent chronic pain in adulthood. The important role of parents in helping to manage children with chronic pain is well recognized; however, family-centric multidisciplinary programs, which can also support and teach parents the necessary skills to facilitate their children’s rehabilitation, are relatively scarce. The transition of children and adolescents with chronic pain into adult services is still suboptimal and better communication, collaboration, and integration of services across this vulnerable time in a young person’s life needs to be encouraged.

The lack of high-quality evidence makes it impossible to formulate evidence-based guidelines and policies to guide clinicians involved in prescribing analgesics to children and adolescents with chronic pain. The unfortunate reality of this situation is that clinicians must instead rely on adult evidence-based guidelines, such as the Neuropathic Pain Guidelines (NeuPSIG) recommendations for neuropathic pain in adults,7 and expert opinion-based clinical recommendations for children (https://www.gov.scot/publications/management-chronic-pain-children-young-people/pages/14/) to guide management. Children are disadvantaged further by a relative global shortage of pain specialists and allied healthcare professionals with specific training and expertise in pediatric chronic pain, and significant limitations in research funding and resource allocation. While this is far from ideal, we need to be pragmatic in our approach and continue to utilize monitored analgesic trials to help inform us of the risk-benefit profile of these agents, while having clear and transparent discussions with patients and their families around analgesic efficacy and potential adverse effects all within the context of a multidisciplinary team approach to chronic pain management.

**KEYWORDS**
adolescent, child, chronic pain, drugs
CONFLICT OF INTEREST
No conflicts of interest declared.

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REFERENCES