

Commentary

Ethical challenges in pediatric pain research

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The history of research involving children includes both atrocities and organized attempts to protect and maintain the rights of children (e.g. Nuremberg Code, Declaration of Helsinki, Belmont Report; Matutina, 2009). Although research has moved beyond blatant violations of the rights of children, many ethical controversies remain. Children, by their nature, are vulnerable. They are not able to legally consent, there are power imbalances inherent in their relationships with adults, and their cognitive and decision-making abilities are continually developing. As pediatric pain researchers, we strive to reduce the pain and suffering of children by conducting meaningful research with children in ethically appropriate ways. Given that we investigate pain and distress among this vulnerable population, the ethics of our research methodology is often closely scrutinized. The following sections highlight some current ethical controversies facing pediatric pain researchers, namely, the exclusion of children from research, the problem of defining minimal risk, and the therapeutic misconception. While these issues span other areas of research involving children, we will illustrate their unique application and the specific challenges they pose to pediatric pain research.

Exclusion of children from research

The International Association for the Study of Pain's (IASP) *Core Curriculum for Professional Education in Pain* states that individuals should "be aware that some groups, such as children...are vulnerable to unfair exclusion from pain research" (Charlton, 2005, Ch. 6, p. 3). The National Institutes of Health (NIH) in the United States released a

policy requiring researchers to (1) include children in all human research conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them; and (2) provide rationale specific to the exclusion of children in their research plans (NIH, 1998). Along with our responsibility to protect children, we have an ethical obligation to ensure that they receive optimal pain management as determined by empirical evidence. For all individuals, "preventing and alleviating [pain above moderate levels] is a matter of charity or doing good (beneficence), but carries a duty to prevent harm (nonmaleficence)" (Charlton, 2005, Ch. 6, p. 1).

Considerable controversy surrounds the inclusion of children in clinical trials. Whereas the ethical principle of nonmaleficence implies that children should not be harmed by their inclusion in randomized controlled trials, it is widely believed that it is unethical to exclude children from this research (Sammons, 2009). Despite this, children are often prescribed and administered medications that are unlicensed and off-label. For example, approved medications (including analgesics) were used in an off-label/unlicensed manner in 90% of infants in a neonatal setting and 36% of children in a general pediatric setting (Turner et al., 1998; Conroy et al., 1999). Medications used in this way place the already vulnerable child at increased risk for adverse drug reactions and complications (Choonara & Conroy, 2002). Children deserve the right to proper pain management; however, until they are included in clinical trials examining the effectiveness of medications specifically with children, they will either be denied the relief or

exposed to potentially unknown negative consequences. In this way, the principle of nonmaleficence implies that investigators have an ethical responsibility to include children in clinical trials of pain management medications when data on their efficacy and toxicity is lacking. However, this research is only appropriate when prior adult and animal studies suggest that pediatric studies are justified and likely to be safe. More generally, the inclusion of children in pediatric pain research is essential for understanding pain in children (e.g. developmental influences, issues in pain assessment, appropriateness of interventions); extrapolating knowledge from adult research is not sufficient and arguably unethical.

Children are identified as vulnerable, however, their exclusion from research unjustly denies them its potential benefits. The Declaration of Helsinki states that “medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research” (World Medical Association, 2008, p. 3). In Canada, the most recent edition of the Tri-Council Policy Statement currently in draft form (CIHR, NSERC, SSHRC, 2009) states that “children shall not be inappropriately excluded from research solely on the basis of age or development status” (p. 39). It also states that research involving those who lack the capacity to consent for themselves (i.e. children) is ethical if it (1) can only be addressed with those particular individuals, (2) involves minimal risk or justified minor increase above minimal risk; and (3) imposes risks which are appropriately balanced with the potential to provide direct benefits to the participants or the group to which they belong. In pediatric pain research, it is perhaps the younger, more ill and vulnerable child who has the greatest potential to benefit directly from participation in research given our empirical knowledge about the long-term consequences of early untreated painful experiences (Charlton, 2005). We argue that pediatric pain researchers should be striving for innovative ways to provide direct benefit to children, for example by using

empirically-validated ways of assessing and managing pain for common childhood pain experiences.

Minimal risk

As can be seen above, ethical consideration of inclusion of children in research is largely dictated by the degree of risk involved. These risks can be physical, psychological, or social in nature and either immediate or delayed. The assessment of risk becomes particularly important in the context of nonbeneficial pediatric research, that is, research that does not offer participating children any direct clinical benefit. Indeed, nonbeneficial pediatric research has been the subject of debate for over 25 years (Ackerman, 1994; Brock, 1994). Current guidelines exist which permit nonbeneficial pediatric research when it poses minimal risk and can be used to generate information that will improve children’s health and well-being. The controversy lies in how these guidelines interpret acceptable or minimal risk (Wendler & Glantz, 2007) and how this analysis can vary between Institutional Research Boards (IRBs) and pediatric pain researchers themselves.

Typically, “minimal risk” is defined as the probability of harm or discomfort that is no more than what children encounter in their daily lives or during routine physical examinations or tests (Sammons, 2009). This definition has provoked controversy and confusion over whether it refers to the daily risks encountered by the specific study sample (i.e. relative interpretation) or the average healthy child (i.e. absolute interpretation; Wendler, 2009). Consider a research study involving children with chronic pain completing a laboratory pain induction technique that does not provide direct clinical benefit to the children. Using the relative interpretation of minimal risk, the degree of pain induced in these children would be considered within the realm of their daily experiences and therefore deemed minimal. Conversely, interpreted in an absolute way, it could be argued that this degree of pain or risk exceeds that which is encountered in the daily life of the average healthy child.

Given the degree of impairment experienced across academic, emotional and social domains

(Palermo, 2000), children with chronic pain are arguably more vulnerable than average healthy children. Is it more acceptable to induce pain in children already experiencing chronic pain as compared to healthy children who rarely experience pain of this degree? The relative interpretation of minimal risk implies that it is and is the definition that is currently adopted in Canada (CIHR, NSERC, SSHRC, 1998). Furthermore, IRBs tend to agree with this interpretation. In a survey examining how IRBs apply risk and benefit categories for pediatric research, IRB chairpersons were more likely to consider a lumbar puncture without sedation as minimal risk among children with illness who had previously undergone lumbar punctures as compared to the same lumbar puncture in healthy children (Shah et al., 2004).

Interpretation of minimal risk is largely left in the hands of individual IRBs. As a result, it is not surprising to find considerable variability between IRB chairpersons in their assessment of benefits and risks in pediatric research. Furthermore, their application often contradicts empirical evidence on risk (Shah et al., 2004). Citing the same survey, a single 10 mL blood draw by venipuncture was considered minimal risk by 81% of IRB chairpersons whereas a confidential survey of sexual activity was categorized as minimal risk by only 44% of chairpersons. It is surprising that a painful procedure to collect biological data was considered lower risk than completion of a survey. Researchers should be aware that the approval of study protocols is intrinsically tied to the interpretations of minimal risk being applied.

Pediatric pain researchers might also assess risk differently than IRBs. As noted in a best practices document for research with children and adolescents (Samuël et al., 2010), defining minimal risk as the risk comparable to that of a medical exam is subjective and requires separate analysis for each individual child. Indeed, our field has documented how invasive and painful routine medical procedures can be for children. We are also acutely aware of the deleterious outcomes associated with even one poorly managed painful procedure (Charlton, 2005). Take for example a highly anxious child who undergoes a venipuncture without pharmacological or psychological

intervention. We know that this child is at risk for developing negatively exaggerated pain memories (Rocha et al., 2009; Noel et al., 2010), heightened distress at subsequent procedures (Chen et al., 2000), and possibly even avoidance of medical care into adulthood (Pate et al., 1996). We also know that one poorly managed venipuncture might be riskier to a child than several well-managed procedures. Clearly, our analysis of risk as pediatric pain researchers might contradict that of IRBs. We argue that our knowledge translation activities should extend to our IRBs, particularly when they are responsible for defining categories of minimal risk. Perhaps most importantly, it is our responsibility as researchers to ensure that participants understand the risks inherent in our research.

Therapeutic misconception

First described in the context of psychiatric research over 25 years ago, the therapeutic misconception refers to the research participant's assumption that decisions being made about their personal care are always made with their individual benefit in mind (Appelbaum et al., 1982). In other words, participants are likely to believe that they will receive treatment as opposed to placebo even after the concepts of randomization and double-blind techniques are explained. Appelbaum and colleagues (1982) demonstrated that research participants often adopt an entirely therapeutic understanding of treatment studies and interpret experimental methodology as relating to their individual needs. Researchers should be aware of the subtlety of this phenomenon and its presence even when participants appear to understand the methodological aspects of the research (Appelbaum et al., 1982).

Children may be even more likely to adopt a therapeutic misconception by believing that both their doctor (or the researcher) and their parents will always act in their best interests. In pediatric pain research, the researcher is sometimes the patient's clinician thereby facilitating the risk of both parents and children adopting the therapeutic misconception. This is further complicated by the debate surrounding the purpose of child assent as either a developmentally appropriate engagement in the

decision-making process (Miller & Nelson, 2006) or a true cognitive understanding of the research (Wendler, 2006). This is relevant for pediatric pain researchers as pain management is among the top priorities of parents regarding their child's inpatient care (Ammentorp et al., 2005) potentially increasing their expectancies for therapeutic gain from research participation. Children and parents in palliative care are particularly at risk for believing that research will always be therapeutic and offer a chance of survival (Samuël et al., 2010). It is within our responsibility as pain researchers to understand the unique ethical issues in palliative and intensive care (Charlton, 2005) and we argue that the therapeutic misconception constitutes an important, and often overlooked, ethical issue in our field. Although there is debate about the scope of the therapeutic misconception and how to ameliorate or minimize it (Kimmelman, 2007), it is a real phenomenon and one that pediatric pain researchers should be aware of.

Conclusion

Inclusion of children in research is an ethical responsibility given its potential benefits to children and the groups to which they belong. Research with children requires greater attention to the purpose of the research, research methodology, and assessment of the harms/benefits ratio. It also requires careful analysis of risk at the level of the individual child, paying careful attention to groups of children most vulnerable to negative pain-related outcomes (e.g.

children with developmental disabilities, chronic pain, high anxiety/catastrophizing). It is our responsibility to educate IRBs through empirical evidence on the likelihood of, and outcomes associated with, risk. Finally, we should attempt to address the therapeutic misconception with parents and children through assessment, avoidance of treatment-related language, and education about the differences between treatment and research.

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References

Ackerman TF. Nontherapeutic research procedures involving children with cancer. *J Pediatr Oncol Nurs* 1994;11:134-136.

Ammentorp J, Mainz J, Sabroe S. Parents' priorities and satisfaction with acute pediatric care. *Arch Pediatr Adolesc Med* 2005;159:127-131.
www.pubmed.gov/15699305

Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: informed consent in psychiatric research. *Int J Law Psychiatry* 1982;5:319-329.

Brock DW. Ethical issues in exposing children to risks in research. In: Grodin MA, Glantz LH, editors. *Children as research subjects: science, ethics and law*. New York: Oxford University Press, 1994. pp. 81-101.

www.worldcat.org/oclc/27854169

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Tri-council policy statement: ethical conduct for research involving humans, 1998 (with 2000, 2002 and 2005 amendments).

www.pre.ethics.gc.ca/eng/policy-politique/tcps-epct

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Tri-council policy statement: ethical conduct for research involving humans, 2009 (Revised Draft 2nd ed.). www.pre.ethics.gc.ca/eng/policy-politique/initiatives/draft-preliminaire

Charlton, JE, editor. Core curriculum for professional education in pain (3rd ed.). Seattle: IASP Press, 2005. www.iasp-pain.org/AM/Template.cfm?Section=Home&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=10731

Chen E, Zeltzer LK, Craske MG, Katz ER. Children's memories for painful cancer treatment procedures: implications for distress. *Child Dev* 2000;71:933-947. www.pubmed.gov/11016557

Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. *Drug Saf* 2002;25:1-5. www.pubmed.gov/11820908

Conroy S, McIntre J, Choonara I. Unlicensed and off label drug use in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;80:142-144. www.pubmed.gov/10325794

Kimmelman J. The therapeutic misconception at 25: treatment, research, and confusion. *Hastings Cent Rep* 2007;37:36-42. www.pubmed.gov/18179103

Matutina RE. Ethical issues in research with children and young people. *Paediatr Nurs* 2009;21:38-44. www.pubmed.gov/19886567

Miller VA, Nelson RM. A developmental approach to child assent for nontherapeutic research. *J Pediatr* 2006;149(1 Suppl):25-30. www.pubmed.gov/16829238

NIH policy and guidelines on the inclusion of children as participants in research involving human subjects (NIH Guide Notice). National Institutes of Health. March 6, 1998. <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

Noel M, McMurtry CM, Chambers CT, McGrath PJ. Children's memory for painful procedures: the relationship of pain intensity, anxiety, and adult behaviors to subsequent recall. *J Pediatr Psychol* 2010;35:626-636. www.pubmed.gov/19889718

Palermo TM. Impact of recurrent and chronic pain on child and family daily functioning: a critical review of the literature. *J Dev Behav Pediatr* 2000;21:58-69. www.pubmed.gov/10706352

Pate JT, Blount RL, Cohen LL, Smith AJ. Childhood medical experience and temperament as predictors of adult functioning in medical situations. *Child Health Care* 1996;25:281-298.

Rocha EM, Marche TA, von Baeyer CL. Anxiety influences children's memory for procedural pain. *Pain Res Manag* 2009;14:233-237. www.pubmed.gov/19547763

Sammons H. Ethical issues of clinical trials with children: a European perspective. *Arch Dis Child* 2009;94:474-477. www.pubmed.gov/19208673

Samuël J, Black L, Avard D, Knoppers BM. Best practices for research involving children and adolescents: genetic, pharmaceutical, longitudinal and palliative care research. Centre de recherche en droit public (CRDP), Université de Montréal, September 10, 2009. www.pediagen.org/ressources/Best_Practices.pdf

Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA* 2004;291:476-482. www.pubmed.gov/14747505

Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* 1998;316:343-345. www.pubmed.gov/9487167

Wendler DS. Assent in paediatric research: theoretical and practical considerations. *J Med Ethics* 2006;32:229-234. www.pubmed.gov/16574878

Wendler D. Minimal risk in pediatric research as a function of age. *Arch Pediatr Adolesc Med* 2009;163:115-118. www.pubmed.gov/19188642

Wendler D, Glantz L. A standard for assessing the risks of pediatric research: pro and con. *J Pediatr* 2007;150:579-582.

World Medical Association Declaration of Helsinki - Ethical principles for medical research involving human subjects. October 2008. www.wma.net/en/30publications/10policies/b3/17c.pdf

Wilder RT. Management of pediatric pain patients with complex regional pain syndrome. *Clin J Pain* 2006;22:443-448. www.pubmed.gov/16772799