# Managing Benefits and Risks of Opioids in Paediatric Populations: A Review of FDA Paediatric Advisory Committee on Opioid Studies


This is a follow-up to an earlier Watch article regarding the FDA's Action Plan to Proactively Reduce Prescription Opioid Abuse[1]. This action plan consists of several wide-ranging strategies, the successful implementation of which will greatly impact pharmaceutical companies attempting to gain approval for opioid analgesic medications. These strategies include a reexamination of opioid labelling and monitoring; the prioritisation of abuse-deterrent formulations and non-opioids; the expansion of reversal medications; and importantly a more comprehensive assessment of paediatric issues. The recent labelling changes for OxyContin for use in patients aged 11 and older have generated substantial controversy both from lawmakers and patient advocacy groups. For many years, opioids such as this were prescribed off-label to children in severe pain and fears stemming from practice deviations anticipated after this approval have emerged. Of note, this approval came without convening an advisory committee and although arguable, several prominent lawmakers and pain researchers have lamented that had there been an advisory committee meeting there probably would not have been an approval. To help address issues such as this, the FDA assembled a Paediatric Advisory Committee to deliberate on the use of opioids in children and adolescents with the goal of providing further guidance for labelling, the development of high-quality evidence to guide treatment, as well as methods to improve practice patterns in order to reduce opioid abuse and diversion[2]. The purpose of this CNS Watch article is to review the discourse and conclusions from this meeting and highlight strategies designed to optimise the development and approval of paediatric analgesic medications.

The scourge of opioid abuse in the United States has received much publicity in recent years and appropriately so; it is estimated that over 2 million people in the United States suffer from substance use disorders related to prescription opioid use, with another 467,000 suffering heroin use disorders. Of note, many of those addicted to prescription opioids later "transfer" their addiction to heroin as this is often less expensive and easier to obtain. As a result of this opioid epidemic, there have been calls for policy-makers to stem the tide of opioid over-prescription through the introduction of regulations regarding the prescribing (particularly for refills) of opioids and increased funding and support of non-addictive analgesics[1]. In addition, many physician prescribers have begun to self-regulate, and indeed, current data substantiates a recent decline in the number of opioid prescriptions written in the United States since 2013[3].

However, despite this positive development, concerns remain regarding the potential of an overcorrection in the prescription of opioids and what this could mean to the millions of people who suffer from debilitating pain by potentially limiting their access to much needed treatment4. This is especially the case for our most vulnerable populations, such as children and adolescents, where the options for treatment are already restricted and where the regulatory process for making novel treatments available is relatively poorly demarcated. To help remedy this, the FDA recently convened a meeting to discuss opioid use in the paediatric populations with the purpose of ensuring a balance between the exuberance to control the spread of opioid use disorders whilst a guaranteeing that patients continue to have access to the appropriate treatments for their pain and, importantly, to address ways to incorporate paediatric populations into future clinical studies of opioids.

This two-day gathering of the Joint Meeting of the Anaesthetic and Analgesic Drug Products Advisory Committee [AADPAC], the Drug Safety and Risk Management Advisory Committee [DSaRM], and the Paediatric Advisory Committee [PAC], was held on 15-16 September 2016 in Silver Spring, MD and included members of the FDA and paediatricians from across the United States, all of whom are charged with managing chronic pain in this vulnerable population, including pain secondary to post-operative treatment, cancer, sickle cell and other critical illnesses.

The session began with a broad overview of the regulatory considerations for drug development in paediatrics, including an appraisal of the current approach for studying opioid analgesics in paediatrics from both pharmacological and clinical perspectives. Passage of the Best Pharmaceuticals for Children Act (BPCA) and the Paediatric Research Equity Act (PREA) in 2002 and 2003, respectively (both made permanent in 2012) were watershed events in the development of paediatric therapeutics. Together, these acts have led to at least 637 paediatric label changes and have ensured that paediatric populations are carefully considered in the development of all drugs. However, these laws have also made clear that many drugs previously thought to be safe in children are not; and that drugs without paediatric labelling represent a clear barrier to access for children, as up to 50% of drugs for children are still used off-label (albeit down from 80% pre-BPCA/PREA). Unfortunately, these acts have not had a real impact in regard to opioids as some of the most commonly used opioids (including oxycodone IR, methadone and morphine ER) still have no paediatric labelling, while many others (including buprenorphine, codeine, hydrocodone, etc.) are pending. Previous FDA guidance acknowledged the difficulty of conducting pain studies in children and permitted an extrapolation of clinical data from adults to children, as long as pharmacokinetic (PK) data was available and sufficient. However, extrapolation proved inadequate for drugs with a novel mechanism of action and this approach was reconsidered with updated guidance provided in 2012. This updated guidance contained requirements for the approval of both immediate-release (IR) and extended-release (ER) opioids in paediatrics with specific guidelines for both children and adolescents in each category.

Despite this explication, numerous challenges in study design and enrolment in paediatric pain trials remain for sponsors developing paediatric analgesics. Perhaps the most obvious challenge is overcoming apprehension on the part of parents to enroll their

children into *any* clinical study (whether opioid or not) due to the uncertainty regarding relative benefits and the risk for additional harm. Many institutional review boards (IRBs) are now requiring language specific to opioid dependency that may cause concern for the parents deciding whether to enroll their child in a pain study. In this case, supplemental informed consent materials such as booklets and flip charts that are easy to read and bright in color may prove beneficial. In addition, the involvement of the investigator in study-related discussions can help to alleviate parental concerns when opioids are being tested.

It is also the case that the representative placebo-controlled studies may not have the same practicality or utility as in the adult population both from an ethical perspective and due to the fact that children, especially younger ones, cannot express pain intensity nor relief in a consistent and reliable manner adequate for valid measurement purposes. Therefore, the use of an open label model in paediatrics may need to be considered. Both of these concerns can result in insufficient enrolment and inadequate statistical power. There is also consternation on the part of study investigators and/or their institutions that often view these studies adversely, which creates a general reluctance to take part in the first place. Finally, as with the investigation of opioids in any population, there is the potential for diversion and abuse. Adolescent patients may be particularly vulnerable to this risk, but also parents must be carefully scrutinised for diversion. All of these factors make investigators relatively reluctant to participate in these much needed trials.

Recommendations for overcoming the aforementioned challenges, all of which have implications for future clinical work, were also provided by the FDA. The first recommendations involve the robust use of adequate and properly designed clinical pharmacology studies in paediatrics, in order to improve both the extrapolation and dose selection processes for both IR and ER analgesic formulations. For early phase investigations, the use of PK modelling prior to the actual paediatric PK study through the use of adult data can aid in this process, particularly when physiological parameters such as weight, age and gender are taken into account. This modelling may be of particular benefit when deciding upon the initial dose in a paediatric (single ascending dose) SAD or (multiple ascending dose) MAD trial or when PK data from the IR or ER formulation is already published, as is the case for the majority of opioid medications. Additionally, the number and timing of blood samples collected during a paediatric PK programme should take into account the differences in absorption between adults and paediatric populations.

Suggestions for overcoming the challenges in conducting later phase efficacy studies were also discussed. For example, patient/nurse-controlled analgesia (PNCA) is one recommended tool for use in immediate release opioid studies, with NCA being more prevalent than PCA with relatively younger patients. Utilisation of the PNCA method may also

help to overcome some of the issues regarding overall exposure and placebo in paediatric studies. In these studies, all patients receive standard of care (SOC) PNCA with either study drug or placebo added to this. If the study drug is effective, there should be less SOC drug utilised and the primary efficacy endpoint is represented as the delta in the amount of SOC between the two treatment groups.

Finally, in order to guard against the potential for abuse in adolescents, the FDA recommendations are similar to studies of adults; namely look for signs of diversion, minimise the amount of drug distributed at any given time and assess risk on a patient-by-patient basis. In terms of post-approval commitments, the FDA will require sponsors to conduct several studies as well as mandate an annual reporting of adverse events, including accidental exposures and overdoses in children and adolescents. This will be done in an attempt to provide a more comprehensive analysis of side-effects, medication errors and prescribing patterns (including the types of prescribing physicians as well as the various types of treatment indications), and help to identify factors important in creating and maintaining adolescent opioid use disorders so that these can be successfully addressed in future clinical development programmes[1].

References


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