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Using Modern Neuroscience to Inform Opioid Use and Abuse Liability in Adolescents

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Opioid abuse and overdosing have reached epidemic status in the United States, and this epidemic has profound negative effects on the lives of adolescents and their families. A combination of readily available opioids (including illicit opioids, such as heroin, and overprescribed prescription opioid-based painkillers) and an abuse vulnerability inherent to adolescence drives the problem. The pharmacology of opioids in the context of adolescent brain neurobiology helps explain the enhanced vulnerability to drug abuse experienced by the young. This report overviews these topics as they relate to orthopaedic procedures employed for adolescent patients.

Introduction

Adolescents are a central demographic in the tragic increase in incidence of opioid use disorders (OUDs) and associated overdosing and deaths that afflict modern society. Several factors likely contribute to these statistics, including readily available potent and highly addictive black market opioids (e.g., heroin, fentanyl), the vulnerability of adolescents to initial experimentation and subsequent abuse of opioids, and the proclivity of practitioners to prescribe opioids to treat pain subsequent to medical procedures. This review focuses on the latter two factors. We overview opioid pharmacology in the context of both pain management and OUDs and discuss aspects of teenage neurobiology that augment vulnerability to develop OUDs. The relevance of this enhanced vulnerability to pain management of adolescents undergoing orthopaedic procedures is highlighted, and new empirical studies on nonopioid analgesics are presented. The review objective is to arm pediatric practitioners with modern neuroscience on OUDs with the hope that individualized pain management can be attained while keeping the risk for developing new or promoting ongoing OUDs.

Opioid Pharmacology

The term "opioid" includes natural (e.g., codeine, morphine), synthetic (e.g., heroin, fentanyl), and semisynthetic (e.g., oxycodone, hydrocodone) compounds that affect the nervous system by acting on the *mu* subtype of opioid receptors (MORs), which are expressed in neurons throughout the body. In the peripheral nervous system of the intestine, MOR opioids reduce transmission to inhibit peristalsis so that chronic use produces constipation. By activating MORs in the parasympathetic system (cranial nerve III), opioids constrict the pupil and pinpoint pupils are sensitive indicators of opioid use and overdose. Activation of MORs in the brainstem suppress breathing, and respiratory depression is a hallmark of opioid overdose.

MORs are expressed by particular spinal neurons, wherein they regulate aspects of pain *perception*. In the brain, MORs are highly expressed in the periaqueductal gray and thalamus, where they regulate pain perception, and in the amygdala and the frontal cortex, where they contribute to the emotional memory and the subjective valence of a pain experience, respectively. These affective aspects influence how significant the pain is to the individual. MORs are also widely distributed in the limbic reward system (e.g., the prefrontal cortex, nucleus accumbens, ventral pallidum, and ventral tegmental area), where they are responsible for the euphorigenic effects and abuse liability of the drugs. This anatomical distribution of MORs illustrates that all MOR opioids that are clinically approved to treat pain also carry the potential to be misused for the euphorigenic features.

Terminology Related to Opioid Use

Opioid misuse refers to taking prescribed (legal) opioids in an inappropriate manner (e.g., higher doses, taking in the absence of pain). *Opioid use disorder* is a diagnosis introduced in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). The

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diagnosis of OUD can be applied to an opioid-using individual who meets at least two of 11 criteria within a year (American Psychiatric Association, 2013). These criteria include (paraphrasing) taking more drug than intended, wanting to control drug use without success, craving opioids, spending a lot of time procuring and taking opioids despite knowing that use is causing physical or psychological problems, using opioids even when it is unsafe, failing to carry out normal life roles, tolerance for opioids, and exhibiting withdrawal symptoms when opioid taking is terminate. *Tolerance* is manifested when greater doses are needed to achieve the desired effect. Tolerance occurs for both the clinically desirable outcomes (e.g., pain management) and illicit effects (e.g., euphoria). *Dependence* reflects homeostatic compensation to chronic exposure to opioids. That is, the nervous system readjusts so that the more normal functional set point is now in the presence of the drug. Dependence is clearly manifested when the drug is removed, and the individual undergoes withdrawal. *Withdrawal* refers to negative physical (e.g., tremors, abdominal cramping, nausea and vomiting, chills) and psychological (e.g., agitation, anxiety, craving) consequences that occur after the opioid leaves the body. Thus, if a person is appropriately taking opioids for a medical condition, tolerance and withdrawal criteria are not used to diagnose OUDs.

Adolescent Vulnerability to Opioid Use Disorder

The majority of drug users are teenagers and young adults, and age is a risk factor for substance use disorders. An OUD also follows this trajectory. For example, opioid use before or during high school is associated with a 33% increase in the risk for prescription opioid misuse by the age of 23 years compared with those without a history of opioid prescriptions (Miech, Johnston, O'Malley, Keyes, & Heard, 2015).

Adolescent introduction to opioids includes several avenues. One involves voluntary self-administration and not under the care of a physician. According to the National Institute on Drug Abuse (NIDA), individuals self-administer drugs either to feel good or to feel better (NIDA, 2018). The latter reflects self-medication for an underlying social or mental health problem, for example, to emotionally escape from a bad home or school context or to compensate for anxiety, depression, etc. "To feel good" refers to the desire to experience new pleasurable feelings and sensations. In adolescents, this often occurs in a social context and reflects a need for shared experiences with friends. The behavior is in keeping with the increased proclivity for risk-taking and impulsiveness that often characterizes youth. Another avenue for adolescents to be introduced to opioids is via prescriptions for treating pain, most typically following a surgical procedure. Prescriptions related to oral surgery (Baker, Avorn, Levin, & Bateman, 2016) and orthopaedic procedures (Monitto et al., 2017) are by far the most frequent clinical reasons for adolescents to be prescribed opioids.

The vulnerability of youth to the abuse liability of MOR opioids reflects, in part, the developing nature of the adolescent brain. In humans, there is a temporal unevenness in functional development across brain regions, with subcortical regions (e.g., nucleus accumbens) involved in reward-motivation maturing before puberty whereas frontal cortical regions involved in executive function and inhibitory control lagging behind by several years. Adult-like cortical connections are not achieved until early to mid-20s (Gogtay et al., 2004). As decision making reflects all of these systems, the imbalance in brain maturation between subcortical structures in the limbic system that drive reward-motivated behaviors and the prefrontal cortex, which is responsible for executive function and inhibitory control, impacts the neuronal processes engaged by teenagers to make choices. Thus, in teenagers, the reduced inhibitory control heightens risk-taking behavior, particularly when the behavior results in immediate rewards (Defoe, Dubas, Figner, & van Aken, 2015; van Duijvenvoorde, Jansen, Visser, & Huizenga, 2010). Another powerful influence on adolescent brain function is the salience of context, including the presence and importance of peers, which often impacts decision making. The complex interactions among reward-motivational processes, cognitive control, and social context are thought to drive decisions in adolescence, resulting in a tendency toward more risky behavior (Kilford, Garrett, & Blakemore, 2016) that promotes experimentation with abused drugs.

The brain processes that evolve as one shifts from experimentation to chronic/habitual use in addiction are exceedingly complex, especially in the context of a developing brain (for review, see Koob & Volkow, 2016). In brief, subcortical limbic brain regions involve emotionally laden factors that motivate drug experimentation (e.g., to feel good, to feel better, the desire to conform to peers) and are fully developed in the adolescent. Adolescents are particularly sensitive to rewards. These drives exert a heavy influence on decision making, which proceeds relatively unchecked as inhibitory control is not fully developed in the adolescent frontal cortex. Decision making in teenagers reflects preferences for immediate, positive rewards, and less so the capacity to inhibit actions, in order to weigh the long-term benefits of a choice does not weight on decision making to the same extend as does immediate positive rewards. The continual positive reinforcement provided by repeated exposures to rewarding drugs such as opioids engages more and more those brain regions that govern habits (e.g., the dorsal striatum). Once drug taking becomes habitual, it no longer is sustained by "good feelings" but rather by the need to sustain the habit itself. Conscious, cognitive control over the behavior is diminished and the capacity to terminate drug taking is compromised. Associated with the neurobiological processes that underpin drug-related habits are tolerance and dependence, as well as withdrawal upon termination of the drug. The negative emotional memories of withdrawal involve another early development, subcortical limbic structure, called the amygdala. This region promotes decision making that avoids the painful consequences of withdrawal and, in so doing, supports drug taking.

The enhanced vulnerability for developing OUDs by adolescents deserves consideration during scenarios that indicate pain management. For adolescents, these scenarios frequently involve orthopaedic procedures. In the next sections, we overview pain management in the context of adolescent orthopaedic procedures, including current patterns of opioid prescriptions for certain procedures and describe nonopioid alternatives.

Current Opioid Prescription Patterns

Historically, pain was often undertreated (or not treated at all) in many patients (Apfelbaum, Chen, Mehta, & Gan, 2003). In 2001, pain was introduced as the "fifth vital sign" and it became a qualitative indicator of healthcare. This led to a significant increase in the amount of opioids being prescribed for patients. Yet, the risks associated with opioid use (i.e., misuse and abuse) were often downplayed (Monitto et al., 2017). To help curtail the burgeoning opioid epidemic, in 2016, the Centers for Disease Control and Prevention (CDC) published guidelines for opioid prescribing that focus on the management of chronic nonmalignant pain for adults (Dowell, Haegerich, & Chou, 2016) but do not include recommendations for pain management in children. The World Health Organization (2012) issued recommendations for prescribing opioids to children younger than 12 years with the disclaimer that the evidence supporting the recommendations was weak. Despite the efforts of the CDC and the WHO to provide guidelines on opioid prescribing, there remain significant gaps in the recommendations for the age group at highest risk for prescription opioid abuse—adolescents and young adults.

Few studies have investigated the potential impact of acute pain management in adolescents on the opioid epidemic. Postoperative pain is a type of acute pain for which management involves a multimodal approach, including opioids for the treatment of moderate-severe pain. An analysis of Medicaid insurance claims for opioids after surgical tooth extraction in adolescent patients aged 14–17 years filled more opioid prescriptions than in older age groups (Baker et al., 2016). A recent study by Monitto et al. (2017) assessed opioid prescribing for acute postoperative pain after hospital discharge in pediatric patients (younger than 21 years). They demonstrated that across all surgical services, immediate-release oxycodone was most commonly prescribed and the number of opioid doses dispensed was significantly greater than the number of opioid doses consumed. This resulted in approximately 58% of opioid doses (40,000 morphine mg equivalents) that were not consumed after opioid therapy was discontinued, and only 4% of families in the study reported proper disposal of unused drug (Monitto et al., 2017). These results are similar to those reported by Bicket, Long, Pronovost, Alexander, and Wu (2017) in adult patients, wherein a systematic review of postsurgical opioid use revealed that up to 71% of prescribed opioids went unconsumed, and these were associated with low rates of disposal of leftover drugs. These studies indicate that a disproportionately large number of opioids are prescribed for postsurgical pain, and these unused opioid doses likely remain in the home, providing a significant pool of drug that can be diverted for nonmedical use.

Opioid Prescribing for Orthopaedic Injuries in Adolescents

As recently reviewed by Dautremont, Ebramzadeh, Beck, Bowen, and Sangiorgio (2017), there is a significant gap in our knowledge of postoperative pain management following orthopaedic procedures in adolescents. Although the clinical literature on this topic is sparse, Monitto et al. (2017) reported that in children and adolescents at The Johns Hopkins Hospital, nonspine orthopaedic surgical procedures result in the third largest opioid consumption among the analyzed surgical services (orthopaedics [spine and nonspine], cardiothoracic, general pediatric surgery, genitourological surgery, neurosurgery, plastic surgery, and Nuss procedure).

Sports-related injuries are emerging as a significant point of entry to orthopaedics, by adolescents, and in recent years these procedures have increased steadily (Dodwell et al., 2014; Shea, Grimm, Ewing, & Aoki, 2011; von Rosen, Heijne, Frohm, Friden, & Kottorp, 2018). Between 2007 and 2011, surgical reconstruction for anterior cruciate ligament surgery increased by 27.6% in patients 10–14 years of age and 15.7% in patients 15–19 years of age (Werner, Yang, Looney, & Gwathmey, 2016). These numbers may continue to increase, for example, the National Federation of State High School Associations recently reported that participation in high school sports has increased for 29 consecutive years (National Federation of State High School Associations, 2018). This is a significant concern because student athletes are at increased risk for injury and therefore may be at a higher risk for nonmedical use of opioids (Veliz et al., 2014). Moreover, medical exposure to opioids as an adolescent increases the likelihood to develop OUDs as an adult, even if an adolescent disapproves of using illegal drugs (Miech et al., 2015).

Optimizing pain management in this vulnerable population is critically needed, and there is a significant interest in utilizing nonopioid medications in lieu of, or as adjunct therapy for, acute pain. Yet, the literature is sparse on this topic for the nonadult population. In a small pilot study (n = 82), Reynolds et al. (2017) compared the efficacy of intranasal ketamine with intranasal fentanyl on pain relief in pediatric patients with suspected extremity fracture. Results indicated that the magnitude of pain relief was similar between the two groups, but ketamine was associated with more, albeit minor, side effects (Reynolds et al., 2017). Similarly, a prospective study on postoperative pain management following minor outpatient orthopaedic procedures in children (5–17 years old) revealed no difference in efficacy between oral morphine and ibuprofen (Poonai et al., 2017). Nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen) provide excellent relief for mild to moderate pain. However, these drugs may negatively affect bone and/or soft-tissue healing (e.g., Cohen, Kawamura, Ehteshami, & Rodeo, 2006; Dahners & Mullis, 2004); accordingly, their use may be limited by the severity of the orthopaedic procedure. Adjunct therapy to opioids is also of interest. Studies on posterior spinal fusion in patients with adolescent idiopathic scoliosis revealed that adjunct therapy with bupivacaine (Wade Shrader et al., 2015) or ketorolac (Munro et al., 2002; Reuben, Connelly, Lurie, Klatt, & Gibson, 1998) improved analgesia with lower pain scores and lower opioid postoperative requirements (but see, Wade Shrader et al., 2015). In contrast, administration of postsurgery acetaminophen had no effect on postsurgical opioid consumption (Hiller et al., 2012). Although these studies indicate that there may be effective alternatives or adjuncts to opioid for postoperative management of acute pain in adolescents, additional research is needed to fill the gap in our knowledge of pain management in this population.

Potential Solutions

The dearth of biomedical and clinical research on pain management in adolescents makes devising safe, yet efficacious, programs for this demographic a significant challenge to the medical profession. But an emerging literature is identifying paradigms that hold promise for encouraging outcomes. Examples are overviewed as follows.

The 2016 American Pain Society guidelines for the management of postoperative pain (Chou et al., 2016) strongly recommend pre- and postoperative education for patients and responsible caregivers, a preoperative evaluation, and access to pain specialists. Preoperative education should include information on treatment options and documentation of plan and goals for postoperative pain management. In children and adolescents, parents should be educated on how to assess pain using developmentally appropriate methods. For postoperative education, patients and caregivers should be counseled on harmful drug interactions (e.g., alcohol or other illicit substances) that increase the risk for accidental overdose and death when combined with opioid analgesics. As severe postsurgical pain is often short-term, patients and caregivers should be educated on how to taper the opioid dose as pain subsides. The preoperative evaluation should assess current medications, pain history, prior treatment regimens for postoperative pain management and how well the patient responded, and medical and psychiatric comorbidities. The latter may be particularly relevant, for, in adolescents, impairments in emotion regulation are associated with a vulnerability to progress to OUDs (Wilson et al., 2017) and depression increases the risk of abuse prescription opioids (Sullivan, 2018). Finally, for patients who are opioid-tolerant or have a history of substance abuse, the opportunity to consult a specialist on pain management strategies should be provided, as these patients are at a higher risk for having poorly controlled pain postoperatively. Augmenting the American Pain Society recommendations, postoperative follow-up should also include assessment of opioid consumption. A recent study revealed that 25% of patients prescribed opioids more than 90 days postsurgery reported taking the opioids for a different indication than that for which the opioids were initially prescribed (Callinan, Neuman, Lacy, Gabison, & Ashburn, 2017).

Education of adolescent patients and their parents/caretakers regarding the proper use, risks, and benefits of opioids can serve as a cornerstone to prevention strategies once the patients are discharged from the hospital. The construct is that enhanced understanding of opioid-related neurobiology will promote healthier oversight by caregivers and aid in preventing adolescents from abusing the drugs. Other important topics for caregiver education include proper pain management for adolescents following surgery, what behavioral signs may indicate that adolescents are misusing prescription opioid pain medications, how to dispose of unconsumed opioids, and offer alternative, nonopioid means of pain control, if appropriate. The NIDA maintains exceptionally useful, informational websites targeted specifically for teens (https://teens.drugabuse.gov/) and parents (https://teens.drugabuse.gov/parents). Here, adolescents can find teen-friendly information on drug use and how it affects the brain, health blogs, and various educational activities and games to teach about drug abuse, including prescription drug abuse. Parents can find information on a number of topics, including talking to teens about drugs, learning about basic drug facts, and strategies to prevent teen drug use. Curriculum on substance use in the schools can also enhance adolescent understanding of addictions. For example, a substance use curriculum implemented in 969 Rhode Island ninth graders shows increased knowledge of opioid misuse, overdose response, and recovery resources (Patry et al., 2018). The Robert Crown Center for Health Education (RCC) is a nonprofit organization that has delivered science-based education to area schools in Chicago, IL, for more than 40 years. In response to the opioid epidemic, the RCC developed and implemented a drug education curriculum for elementary and high school students (https://www.robertcrown.org/). Indicating the utility of the program, pre- and post-curriculum assessment of opioid-relate knowledge by fourth/fifth-grade students increased by 70% (RCC, personal communication, 2018).

When an OUD is diagnosed for an adolescent, proper professional care is critical. Successful medication-assisted treatment (MAT) for OUDs is well documented for adults, and positive reports are emerging where MAT is being employed for adolescents. Significant reductions in heroin use by dependent adolescent patients are achieved within 3 months of starting opioid substitution treatment (Smyth, Elmusharaf, & Cullen, 2018). Adolescents who receive drug counseling during outpatient therapy with buprenorphine-naloxone (Suboxone) show less use of drugs at 1-year follow-up than those who only received counseling (Woody et al., 2008).

Conclusion

The developing adolescent brain provides a vulnerable backdrop for opioids to be abused. We hold that the current epidemic of OUDs in our youth needs a multi-pronged approach that involves all sectors of biomedical and health professional fields. Targets should include better understanding of how MOR activation uniquely engages the adolescent brain, reducing the opportunities for opioid exposure, better understanding of pain management in adolescents, increased education of both young patients and their caregivers of the proper use and the signs/symptoms of miss use, and developing OUD therapies that are tailored for adolescents. As recently concluded by Dautremont et al. (2017), clearly more research on adolescent pain management is needed to optimize therapy and to determine long-term consequences of the various treatment regimens.

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