Opioids: A Look at Their Side Effects

By Alexander Tran

We all feel pain sometime in our life. Whether it is a small cut, a slight bruise or even a broken bone, pain is a natural phenomenon. There are people; however, that experience pain every day. Pain that will last their entire lives. Chronic pain is the most clinically widespread problem affecting over 1.2 billion people worldwide. Opioids, natural or synthetic drugs used to reduce pain, are the most effective treatment for this pain. Although opioids are the most effective treatment for pain, its use is often hindered by the development of tolerance, dependence, and respiratory depression (Benyamin et al., 2008). What are these side effects? Tolerance is essentially the reduction in drug potency when using the same amount of drug dosage, thus requiring a higher dosage to achieve the same effect (Benyamin et al., 2008; Berger et al., 2014). Dependence, also known as addiction, is the strong urge to use the drug with the inability to stop (Benyamin et al., 2008; Berger et al., 2014). Respiratory depression is essentially decreased breathing rate. There are many other side effects with opioid use but how do they arise? What underlies the cause of tolerance, dependence and these other side effects?

Tolerance is an extremely common side effect with opioids. Using opioids as short term pain medication can induce acute tolerance; a tolerance effect that lasts over a short period of time. Rats injected with 1 injection of morphine, an opioid, into the brain had shown to develop acute tolerance to the morphine (Bobeck et al., 2012). How does this happen? Although there is no current agreed mechanism for the induction of tolerance, there are many hypotheses on what is happening on a cellular level when people become tolerant to drugs. One hypothesis is that receptors that are activated by opioids are downregulated (Allouche et al., 2014). Downregulation means that the body reduces the number of receptors that are present so that

more drug is needed to gain the same effectiveness. This can be a problem as increasing drug administration can cause many adverse effects. When an opioid enters the body, it binds to an opioid receptor which causes the analgesic and euphoric effects that people experience. Acute or chronic exposure to these opioids causes the body to downregulate the receptors that the opioid is binding to. This downregulation contributes to the development of tolerance. Studies in live animals have shown that chronic treatment with opioids induced opioid receptor down-regulation (Bernstein et al., 1998; Stafford et al., 2001; Fabian et al., 2002). Other studies, however, have also shown that down-regulation of opioid receptors did not occur when tolerance to opioids developed (Polastron et al., 1994). This suggests that there are other factors that contribute to the development of tolerance to opioids. Another contributing factor to the development of tolerance is receptor desensitization. When a receptor is "desensitized" it essentially stops working as efficiently as it did before. If an opioid is used, a receptor can signal many times. Desensitization would be if an opioid is used and the receptor signals significantly less. Similarly to a decreased number of receptors; when receptors become desensitized, more drug administration is needed in order to achieve the full effect. Desensitization can lead to many adverse effects such as dependency or respiratory depression. There are many cellular methods as to how receptor desensitization may occur. It is thought that when a receptor is signaling excessively then the receptor is taken in by the body thus preventing it from continuing to signal i.e. desensitization (Finn and Whistler, 2001). This can occur only if the receptor is signaling more than necessary. If excess signaling does not happen then receptor desensitization may not occur. Studies in rats have shown that rats pretreated with 1 injection of morphine into the periaqueductal gray; an important brain region in the modulation of pain, developed tolerance; however, rats pretreated with only 1 injection of fentanyl; another opioid, did not develop tolerance (Bobeck et al., 2012).

Due to the short acting duration of fentanyl and the long acting duration of morphine, these results suggest that excessive opioid receptor signaling contributes to the development of tolerance. Tolerance is one of the many side effects of opioid use. Opioid dependence is another drawback to opioid use in clinical medicine.

Opioid dependence or addiction is the strong urge to use the drug without the ability to stop (Benyamin et al., 2008; Berger et al., 2014). Studies in rats have shown that the locus coeruleus is an important brain region that contributes to physical aspects of opioid addiction (Nestler, 1992). Neurons in the locus coeruleus has shown to contribute to opioid addiction and withdrawal (Nestler, 1992). A remarkable finding within the locus coeruleus shows that the concentration of cyclic adenosine monophosphate (cAMP); an important chemical in neurons that helps tell neurons what to do, is increased (Duman et al., 1988), assumingly as a compensatory mechanism because opioids; in general, inhibit the signaling of neurons by preventing the production of cAMP in the body (Clark et al., 2003). This increase of cAMP changes the activity of neurons causing them to send more or less messages. It was found that these neurons were sending more messages. This increase in cAMP is what causes opioid addiction and withdrawal symptoms (Nestler, 1992). When opioids are introduced into the body at the time cAMP levels are elevated, the signaling rate of neurons within the locus coeruleus returns to normal, eliminating the effects of dependence and withdrawal (Nestler, 1992). This means that people who have opioid dependency have elevated cAMP levels. These elevated cAMP levels cause the locus coeruleus to be more active causing withdrawal within opioid addicts. If these opioid dependent people use opioids, their cAMP levels are lowered and they will not suffer from withdrawal. Continually using opioids in order to avoid withdrawal may seem like a reasonable response but is it really solving the problem? This is why scientists are

researching the mechanisms behind drug dependency in order to find a method that allows people to be weaned off drugs without continuing to use them. Many mechanisms behind drug dependence are being studied especially mechanisms behind addiction to drugs that stimulate dopamine; an important chemical in reward systems. It is believed that opioid addiction is related to reward pathways as relieving pain can be considered to be a reward (Navratilova et al., 2012); however, such mechanisms are not well understood nor documented. While these are the two side effects that effect surrounding family and friends, there are many personal side effects.

There are many other side effects to opioid use aside from tolerance, dependency and withdrawal. Abusing opioids can lead to respiratory depression which can be fatal. Simply using opioids can also lead to constipation, nausea, vomiting, sedation and dizziness (Benyamin et al., 2008). Respiratory depression comes from the activation of opioid receptors within the brain, specifically the pre-Bötzinger complex; an important region in the brain that modulates breathing rhythm (Boom et al., 2012). Similarly, the other side effects can be attributed to the activation of opioid receptors throughout the body such as in the chemoreceptor trigger zone, a region in the brain that sends information to the vomiting center in the brain to initiate vomiting, for nausea and the gastrointestinal tract for constipation (Swegle and Logemann, 2006).

Opioid prescription can potentially be dangerous as there are many consequences to improper opioid use, opioid abuse and even proper opioid use. Tolerance, dependence, withdrawal, as well as all the other adverse effects can occur in people who use opioids. While some mechanisms of these adverse effects are published, they are still not completely understood. Research is currently underway in order to solidify a mechanism for these adverse effects in order to develop better medications; opioids still and will continue to be used for as long as people suffer from pain. This pushes scientists to search for methods around these

adverse effects while maintaining the potency of opioids. In the meantime; however, avoidable adverse effects from opioid use can be controlled through careful use and regulation of opioid prescriptions, allowing many people to continue their lives; to an extent, pain free. The responsibility, though, lies not on the doctor prescribing the medicine but the human using it.

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