

The Genetics and Neurobiology of Opioid Use Disorder

1. Approximately 70% of the risk of developing OUD upon exposure to opioids is determined by genetics. There are several genetic variants that predispose towards OUD.
 - a. Some of the genetic variations predisposing to OUD are the same as those predisposing towards alcohol misuse. Family history of alcohol misuse is a red flag for prescribing opioids.
2. Genetic variants result in a different neurobiological response in the brain when exposed to opioids. A clue that this is occurring, at least in some people, is that they feel energized by the opioid (often with as little as 5 mg hydrocodone).
 - a. Warn patients that feeling energized by an opioid is not normal and may indicate a genetic variant predisposing to OUD.
3. The specific genetic variant likely influences that rapidity and extent of the neurological changes that occur with exposure to opioids. OUD can occur within a week.
 - a. Willpower cannot prevent (or reverse) these changes.
 - b. Changes occur quickly, reversal of these changes does not.
 - c. The motivational systems in the brain that guide survival behaviors become “wired” and drive drug-seeking behaviors.
 - d. Drug cravings result from limbic/motivational system messages that the drug is needed for survival. This is different from “cortical” cravings for things like candy bars or ice cream. Instead, it is like craving water when you are dehydrated in the desert. The longer you ignore “survival” cravings, the stronger they become.
 - e. The rewired brain is not a logical brain.
4. Informed consent/opioid use agreements should include a careful family history regarding substance misuse and education about genetic contributions that increase the risk of OUD.
 - a. When people do not understand that genetic variants can cause their brain to change in ways they cannot control, they may believe that OUD will not happen to them because they “are stronger than that”. They are wrong.
5. Medication-Assisted Treatment (MAT) has been the medical standard of care for OUD since 1994. There is a large body of data showing that outcomes are better when methadone or buprenorphine are used in conjunction with counseling.
 - a. The long-acting nature of these medications quiets that brain areas that drive addictive behavior.
 - b. A quiet brain is more responsive to counseling. Counseling helps establish new neural pathways that increase the change of healthy responses to the environment.

- c. Research indicates that the epigenetic changes created by opioid exposure leading to OUD are very slow to reverse (years). It is not clear that the brain ever returns fully to its pre-exposure state.
- d. As with depression, some people can eventually taper off their medication and not relapse. Others may need a lifetime of medication to maintain brain health. This is not an indication of weakness, but of biology.

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