



Caffeine and Headache (2005)

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Many migraine patients report that their attacks can sometimes be aborted by a good cup of coffee. This is not surprising to hear. Caffeine is a key active ingredient in multiple combination medications marketed for headache including Excedrin(TM), Anacin(TM), Midol(TM), Darvon Compound(TM), Fioricet(TM), and Migranal(TM), to name a few. Is caffeine itself a remedy for headache? Remarkably few studies have examined this simple question, but the answer appears to be a qualified, yes; caffeine can provide some headache relief. For example in one small controlled study, caffeine was as effective as acetaminophen (Tylenol(TM)), and significantly better than placebo, at relieving tension-type headaches.

So why not treat every headache with coffee? Unfortunately, caffeine's effects on the brain and on migraine mechanisms can vary tremendously depending upon its frequency of use. With intermittent use, it may provide some acute headache relief. With daily or near daily exposure to caffeine, the brain may develop a tolerance for, and a dependency upon, the drug. In caffeine tolerance, a given dose becomes less potent following repetitive exposure, and in caffeine dependency, the brain develops an expectation that an additional dose of caffeine will be coming soon. There are major consequences if that caffeine expectation is unmet: a withdrawal syndrome may result which includes headache itself as a prominent symptom, along with fatigue, impaired concentration, nausea, and other symptoms suggestive of migraine. A good example of this is the "weekend migraine" pattern where individuals experience attacks on Saturdays or Sundays associated with sleeping later than usual, and delaying their morning cup of coffee.

The brain mechanisms underlying these differential effects of caffeine are incompletely understood. However, the molecular target of action of caffeine is known. Caffeine antagonizes the activity of the brain neuromodulator adenosine at particular receptor subtypes (e.g. A1 and A2A receptors). Adenosine is widely available in cerebral cortex and its actions are associated with a reduction in neural activity and with cerebral vasodilatation. In general, caffeine's blockade of adenosine results in an activation of cerebrocortical function and vasoconstriction. It is unclear which of these effects, or others, underlie caffeine's acute anti-migraine and analgesic actions, but it is known that endogenous adenosine is released in blood during migraine attacks and exogenous adenosine can precipitate migraine attacks. In habitual caffeine users, caffeine intake produces relatively less neural activation and vasoconstriction, and caffeine withdrawal is associated with a significant increase in cerebral blood flow consistent with vasodilatation. These chronic effects of caffeine are likely a consequence of adaptive changes in adenosine receptor expression and function which may contribute to the development of tolerance and dependency.

Caffeine dependency has some surprising features. It can occur after a relatively short period of caffeine exposure (as little as 7 days), and can be sustained by small doses of caffeine (100 mg per day). In fact, withdrawal symptoms may be thwarted in many individuals by as little as 25mg caffeine -- the equivalent of 2-3 tablespoons of most "gourmet" coffee.

Caffeine is the world's most widely used psychostimulant drug. More than 85% of Americans of all ages consume some caffeine daily, with a mean daily dosage of 200mg. Further studies of caffeine dependency and tolerance have shown that daily caffeine users are motivated to consume it more to avoid withdrawal symptoms, than to experience the lift that its stimulant properties can provide. This combination of a punishing syndrome of withdrawal with caffeine avoidance, versus a rewarding sense of well-being with caffeine consumption, has made coffee, tea, and chocolate, some of humanity's best-loved foods.

Not everyone consuming daily caffeine is equally susceptible to developing dependency and withdrawal syndrome. Epidemiological studies indicate that genetic contributions are important in rendering some people more vulnerable than others. It is not known whether the heritable causes of susceptibility to caffeine withdrawal syndrome are related to the genetic factors that predispose to migraine. However, it is clear from multiple studies that patients who experience chronic daily headaches are much more likely to use dietary caffeine on a daily basis and/or have a preference for caffeine-containing headache medications. Moreover, daily use of caffeine in patients who have episodic migraine attacks is associated with a higher risk of subsequent transformation of attacks to chronic daily headache. This association of habitual caffeine use with increased migraine frequency is particularly notable for

women under age 40 years – a group that is already at greater risk for the development of migraine.

In sum, caffeine can be considered a model agent for the development of analgesic-overuse headache. As such, it is reasonable to impose the same restrictions on the frequency of use of caffeine that are recommended for any other overused acute medication for migraine. For patients with a history of problematic migraine, it is appropriate to limit caffeine exposure to not more than two days per week. It is typically not the case that caffeine exposure is the only 'cause' of frequent headaches, but it is often a significant, but unappreciated, contributor to this problem. Most importantly it is a modifiable risk factor, unlike many other unavoidable migraine triggers.