

Rejoinder to commentary by Drs. Boaz Musafia and Gilad Rosenberg




Invited Letter Rejoinder

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We appreciate the commentary by Drs. Boaz Musafia and Gilad Rosenberg on our systematic review and meta-analysis of headache in attention-deficit/hyperactivity disorder (ADHD) (Pan et al., 2021). In view of the high consumption of caffeinated beverages among youths (Babu, Church, & Lewander, 2008), the association between caffeine and paediatric headache is an issue which is potentially highly relevant. While we agree with the suggestion to consider caffeine withdrawal as a possible mechanism underlying headache among youths with ADHD, in our view additional evidence is needed on the links between caffeine withdrawal, administration of ADHD medications, and headache among children with ADHD. We provide here a concise overview of relevant literature to support our statement.

Caffeine consumption in youths with ADHD

Increased caffeine consumption has been indeed reported for adolescents with ADHD in some studies (Cusick, Langberg, Breaux, Green, & Becker, 2020; Walker, Abraham, & Tercyak, 2010), and it might be associated with ADHD symptom severity (Martin et al., 2008). This raises the possibility for an attempt of 'self-medication' owing to the positive effects of caffeine on arousal and physical performance (Torres-Ugalde, Romero-Palencia, Roman-Gutierrez, Ojeda-Ramirez, & Guzman-Saldana, 2020). Caffeine has also been considered an alternative treatment for ADHD symptoms, due to its decreasing effects on impulsivity, and improvement of executive performance (Leon, 2000).

Caffeine has been shown to produce reinforcing effects and addictive properties via the striatal adenosine A_{2A} -dopamine D_2 receptor heteromer (Ferré, 2016). In addition, secondary reinforcement effects might emerge by the favours of caffeinated beverages (Myers & Izbicki, 2006). Thus, another explanation for the higher consumption of caffeine in youths with ADHD might be dysregulation of reward pathways, which are associated with substance misuse (Grimm et al., 2021).

Caffeine withdrawal headache in children and adolescents

Although caffeine dependence in teenagers has been reported (Bernstein, Carroll, Thuras, Cosgrove, & Roth, 2002), the profile of withdrawal headache in youths is understudied. A small double-blind placebo-controlled trial of including nine caffeine consumers (≥ 37 mg/d, 109 ± 70 mg/d) investigated the symptoms after overnight caffeine abstinence among children with habitual caffeine consumption (Heatherley, Hancock, & Rogers, 2006). Following caffeine abstinence, the consumers reported an increase in headache severity with placebo (1.5 to 1.58 on a scale ranging from 1 to 5), but this did not occur with the administration of 50 mg of caffeine.

Research in adults has shown that subjective response to caffeine and the susceptibility to withdrawal symptoms could be variable across individuals and influenced by genetic variants (Rogers et al., 2010). For example, a large epidemiological study of adults revealed a low incidence of withdrawal headache even among those with high caffeine consumptions (Sjaastad & Bakketeig, 2004). Therefore, more studies are needed to enhance our knowledge on caffeine withdrawal headaches in youths, such as the frequency and risk factors.

The mechanisms of caffeine associated headache

Caffeine has several effects on headaches, including relieving acute pain, triggering chronic headaches in case of overuse, and withdrawal headaches (Alstadhaug & Andreou, 2019). It

has long been used as an adjuvant to commonly used analgesics to enhance pain relief in adults (Derry, Derry, & Moore, 2014), partly through a blockade of the A_{2A} receptor with central dopaminergic mechanisms involved (Ferré et al., 2007). However, caffeine-induced headache has also been reported among habitual consumers, both children and adults, and headache improves after caffeine discontinuation (Hering-Hanit & Gadoth, 2003; Lee, Choi, Choi, & Chung, 2016). The proposed pathophysiology involves several mechanisms (Alstadhaug & Andreou, 2019). Repetitive exposure to caffeine could lead to up-regulation of adenosine receptors and the compensatory increased levels of plasma adenosine, which has been reported to elicit headaches. In addition, caffeine might increase the predisposition to migraine via interfering the circadian system, sleep, and pain processing at the posterior hypothalamus. All these mechanisms remain speculative.

Taken together, we think it is relevant for clinicians working managing ADHD in youths to take caffeine consumption into consideration when addressing headaches, but there is insufficient evidence to inform specific clinical guidelines. We suggest further studies are needed to explore the profiles of caffeine withdrawal headaches among youths. From a clinical standpoint, as mechanisms underlying the effects of caffeine on headaches are complex, we suggest that gaining insight on the specific aetiology of caffeine associated headaches is crucial to inform management strategies.

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References

- Alstadhaug, K. B., & Andreou, A. P. (2019). Caffeine and primary (Migraine) headaches-friend or Foe? *Frontiers in Neurology*, *10*, 1275. doi:10.3389/fneur.2019.01275
- Babu, K. M., Church, R. J., & Lewander, W. (2008). Energy drinks: The new eye-opener for adolescents. *Clinical Pediatric Emergency Medicine*, *9*(1), 35–42. doi:10.1016/j.cpeem.2007.12.002
- Bernstein, G. A., Carroll, M. E., Thuras, P. D., Cosgrove, K. P., & Roth, M. E. (2002). Caffeine dependence in teenagers. *Drug and Alcohol Dependence*, *66*(1), 1–6. doi:10.1016/s0376-8716(01)00181-8
- Cusick, C. N., Langberg, J. M., Breaux, R., Green, C. D., & Becker, S. P. (2020). Caffeine use and associations with sleep in adolescents with and without ADHD. *Journal of Pediatric Psychology*, *45*(6), 643–653. doi:10.1093/jpepsy/jsaa033
- Derry, C. J., Derry, S., & Moore, R. A. (2014). Caffeine as an analgesic adjuvant for acute pain in adults. *Cochrane Database of Systematic Reviews*, *2014*(12), Cd009281. doi:10.1002/14651858.CD009281.pub3
- Ferré, S. (2016). Mechanisms of the psychostimulant effects of caffeine: Implications for substance use disorders. *Psychopharmacology (Berl)*, *233*(10), 1963–1979. doi:10.1007/s00213-016-4212-2
- Ferré, S., Diamond, I., Goldberg, S. R., Yao, L., Hourani, S. M., Huang, Z. L., ... Kitchen, I. (2007). Adenosine A_{2A} receptors in ventral striatum, hypothalamus and nociceptive circuitry implications for drug addiction, sleep and pain. *Progress in Neurobiology*, *83*(5), 332–347. doi:10.1016/j.pneurobio.2007.04.002
- Grimm, O., van Rooij, D., Hoogman, M., Klein, M., Buitelaar, J., Franke, B., ... Plichta, M. M. (2021). Transdiagnostic neuroimaging of reward system phenotypes in ADHD and comorbid disorders. *Neuroscience & Biobehavioral Reviews*, *128*, 165–181. doi:10.1016/j.neubiorev.2021.06.025
- Heatherley, S. V., Hancock, K. M., & Rogers, P. J. (2006). Psychostimulant and other effects of caffeine in 9- to 11-year-old children. *Journal of Child Psychology and Psychiatry*, *47*(2), 135–142. doi:10.1111/j.1469-7610.2005.01457.x
- Hering-Hanit, R., & Gadoth, N. (2003). Caffeine-induced headache in children and adolescents. *Cephalalgia*, *23*(5), 332–335. doi:10.1046/j.1468-2982.2003.00576.x
- Lee, M. J., Choi, H. A., Choi, H., & Chung, C.-S. (2016). Caffeine discontinuation improves acute migraine treatment: A prospective clinic-based study. *The Journal of Headache and Pain*, *17*(1), 71. doi:10.1186/s10194-016-0662-5
- Leon, M. R. (2000). Effects of caffeine on cognitive, psychomotor, and affective performance of children with attention-deficit/hyperactivity disorder. *Journal of Attention Disorders*, *4*(1), 27–47. doi:10.1177/108705470000400103
- Martin, C. A., Cook, C., Woodring, J. H., Burkhardt, G., Guenther, G., Omar, H. A., & Kelly, T. H. (2008). Caffeine use: Association with nicotine use, aggression, and other psychopathology in psychiatric and pediatric outpatient adolescents. *The Scientific World Journal*, *8*, 512–516. doi:10.1100/tsw.2008.82
- Myers, K. P., & Izbicke, E. V. (2006). Reinforcing and aversive effects of caffeine measured by flavor preference conditioning in caffeine-naive and caffeine-acclimated rats. *Physiology & Behavior*, *88*(4-5), 585–596. doi:10.1016/j.physbeh.2006.05.010
- Pan, P. Y., Jonsson, U., Şahpazoğlu Çakmak, S. S., Häge, A., Hohmann, S., Nobel Norrman, H., ... Bölte, S. (2021). Headache in ADHD as comorbidity and a side effect of medications: A systematic review and meta-analysis. *Psychological Medicine*, 1–12. doi:10.1017/S0033291721004141
- Rogers, P. J., Hohoff, C., Heatherley, S. V., Mullings, E. L., Maxfield, P. J., Evershed, R. P., ... Nutt, D. J. (2010). Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. *Neuropsychopharmacology*, *35*(9), 1973–1983. doi:10.1038/npp.2010.71
- Sjaastad, O., & Bakketeig, L. S. (2004). Caffeine-withdrawal headache. The vågå study of headache epidemiology. *Cephalalgia*, *24*(4), 241–249. doi:10.1111/j.1468-2982.2003.00638.x
- Torres-Ugalde, Y. C., Romero-Palencia, A., Roman-Gutierrez, A. D., Ojeda-Ramirez, D., & Guzman-Saldana, R. M. E. (2020). Caffeine consumption in children: Innocuous or deleterious? A systematic review. *International Journal of Environmental Research and Public Health*, *17*(7), 2489. doi:10.3390/ijerph17072489
- Walker, L. R., Abraham, A. A., & Tercyak, K. P. (2010). Adolescent caffeine use, ADHD, and cigarette smoking. *Children's Health Care*, *39*(1), 73–90. doi:10.1080/02739610903455186