Citation for published version:
Parsons, RD, McParland, J & Jordan, A 2022, 'Commentary: Multimodal Assessment of Medication Adherence among Youth with Migraine: An Ancillary Study of the CHAMP Trial', *Journal of Pediatric Psychology*, vol. 47, no. 4, pp. 388-390. https://doi.org/10.1093/jpepsy/jsac009

DOI:
10.1093/jpepsy/jsac009

Publication date:
2022

Document Version
Peer reviewed version

Multimodal Assessment of Medication Adherence among Youth with Migraine: An Ancillary Study of the CHAMP Trial

Ryan D Parsons, MSc *[1, 2], Dr Joanna McParland, PhD [3], Dr Abbie Jordan, PhD [1,2]

[1]Department of Psychology, University of Bath, Claverton Down, Bath, UK, BA2 7AY

[2]Centre for Pain Research, University of Bath, Claverton Down, Bath, UK, BA2 7AY

[3]Department of Psychology, Glasgow Caledonian University, Cowcaddens Rd, Glasgow, UK, G4 0BA

*Correspondence to:
Ryan Parsons
Department of Psychology,
University of Bath,
Claverton Down,
Bath, UK
BA2 7AY
Email: rdp39@bath.ac.uk

Migraine headaches are experienced by approximately 6 million young people in the United States and often result in associated disability (Powers et al., 2021). While the management of migraine headaches regularly involves the use of medication (Silberstein & Goadsby, 2002), little is known about adherence to medication among young people (Ramsey et al., 2014). Responding to this knowledge gap, Reidy et al. (this issue) provide a US-based systematic, multi-modal investigation of adherence in a sample of 328 participants aged 8-17 years. Participants were recruited into the Child and Adolescent Migraine Prevention clinical trial. Adherence was measured over a six-month period, using subjective and objective monthly measures. Measures included pill counts, self-report daily diary data, and drug serum levels at months' 3 (end of titration period) and 6 (end of trial). Participants were required to take two pills daily and were randomly assigned either Topiramate, Amitriptyline or placebo pills. Relationships between medication adherence, self-reported headache frequency and functional disability were investigated, in addition to the influence of sociodemographic factors on adherence.

The findings of this study raise important issues concerning the measurement of adherence in clinical contexts. In this commentary, we consider (1) elevated adherence rates reported in this study, (2) discrepancies between adherence rates using subjective and objective measures, (3) the use of supplementary measures to more accurately measure consumption of medication, (4) the effect of placebo medication and the potential influence of suggestibility, and (5) the influence of sociodemographic factors on adherence.

Higher adherence rates were reported in Reidy et al. (this issue) (75%-95%) compared with rates presented in previous studies (Kroon Van Diest et al., 2016: 64%-75%; Van Diest et al., 2017: 79%). As Reidy et al. (this issue) acknowledge, these increased adherence rates may be due to the implementation of prompts (e.g. regular calls and meetings with study staff) to reinforce medication adherence during the data collection period. Use of prompts is a study strength and an important methodological consideration for future work and clinical practice. Existing research has highlighted the promise of provision of prompts via applications and call-center reminder systems to promote adherence in young people with migraine (Ramsey et al., 2018).

A second key finding concerns a discrepancy between adherence rates as reported by self-report, pill count measures, and blood serum levels. As expected, findings showed that self-reported medication adherence was higher than adherence measured via blood serum levels, indicating that young people may inflate their adherence levels. These findings are congruent with those of previous studies (Kroon Van Diest et al., 2016; Yang et al., 2018), highlighting the relevance of including subjective and objective measures. However, while self-report diary entries and pill counts remained stable across the trial period, blood serum levels decreased, suggesting further work is needed to examine the accuracy of such measurements. As reported by Reidy et al. (this issue), serum levels were only able to measure adherence for approximately five days before being drawn and could only provide a measure of zero or non-zero adherence. Consequently, it would be beneficial to increase the frequency of blood serum data collection (i.e., baseline, monthly) to further assess the accuracy of this method of measuring medication adherence. Such additional data combined with further qualitative work and daily questionnaires may more accurately capture adherence and account for inconsistencies in this data.

The self-report diary entries recorded whether participants had taken their medication twice daily but did not investigate any further aspects of adherence around consumption. This is important as it was impossible to determine how much medication was ingested using pill counts alone. Inclusion of supplementary measures may help to explain the discrepancies between self-reported measures and drug serum levels. Suggestions include the adapted version of the Medication Adherence Report Scale (MARS) previously used with adults (Linde et al., 2008), the mHealth management system (Cushing et al., 2016) and the Morisky 8-Item Medication Adherence Scale (MMAS-8) (Morisky et al., 2008). Future research should also include qualitative investigation of adherence behavior to elucidate a more detailed understanding around reasons for non-consumption and contextual factors concerning how many, when and where pills were consumed each day.

Findings in this study indicated that while adherence measures did not predict headache days at the end of the trial, mid-point trial serum drug levels predicted headache-related disability. Although not a focus of this paper, the similar effect of medication and the placebo on headache days and disability should be noted. The finding contradicts other work where the same medications were significantly more effective than placebo in migraine prevention in adults (Gonçalves et al., 2016; Silberstein et al., 2007; Storey et al., 2001) and children (Winner et al., 2005), but supports other headache and pain studies which have noted high placebo response rates (Powers et al., 2017). It is not reported whether reinforcement of the effectiveness of pills was included during monthly communication with staff. Suggestions are known to be an important component of placebo responsiveness (Wager & Atlas, 2015) and may have affected results if implemented.

The findings should be interpreted in the context of the predominantly white, female sample with an average age of 13.75 years reported in the study. A novel aspect of this research is the consideration of sociodemographic variation in adherence. Age was positively associated with self-report adherence, which may be due to the influence of caregivers, although as reported, parental monitoring was not assessed. Findings related to ethnicity and socioeconomic status were mixed. Further studies would benefit from inclusion of a more diverse sample to expand on these mixed findings, particularly with regards to correlations between ethnicity and medication adherence. Barriers to adherence in other pediatric long term conditions include familial, developmental and socioeconomic factors including financial and minority status (Divertie, 2002: asthma; Yang et al., 2018: epilepsy). These barriers may also apply to young people living with migraine, as Kroon Van Diest et al. (2016) observed increased nonadherence among minority youth in this group. Limited financial resources may affect the use of electronic equipment to promote adherence and so should be considered in the design of future studies to increase medication adherence in young people with migraine.

In conclusion, this study provides a novel development in the field of pediatric migraine medication adherence and highlights a range of methodological considerations that could direct future research to develop this important field of investigation. In particular, the use of prompts to promote adherence, the inclusion of both qualitative and quantitative measures to measure subjective and objective adherence more precisely, and more detailed investigations of sociodemographic factors with diverse participant samples would assist to identify optimal methods to promote adherence in young people living with migraine.

References

Cushing, A., Manice, M. P., Ting, A., & Parides, M. K. (2016). Feasibility of a novel mHealth management system to capture and improve medication adherence among adolescents with asthma. *Patient preference and adherence, 10*, 2271.

Divertie, V. (2002). Strategies to promote medication adherence in children with asthma. *MCN: The American Journal of Maternal/Child Nursing, 27*(1), 10-18.

Gonçalves, A. L., Ferreira, A. M., Ribeiro, R. T., Zukerman, E., Cipolla-Neto, J., & Peres, M. F. P. (2016). Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *Journal of Neurology, Neurosurgery and Psychiatry, 87*(10), 1127-1132.

Kroon Van Diest, A. M., Ramsey, R., Aylward, B., Kroner, J. W., Sullivan, S. M., Nause, K., Allen, J. R., Chamberlin, L. A., Slater, S., & Hommel, K. (2016). Adherence to biobehavioral recommendations in pediatric migraine as measured by electronic monitoring: the Adherence in Migraine (AIM) study. *Headache: The Journal of Head and Face Pain, 56*(7), 1137-1146.

Linde, M., Jonsson, P., & Hedenrud, T. (2008). Influence of disease features on adherence to prophylactic migraine medication. *Acta Neurologica Scandinavica, 118*(6), 367-372.

Morisky, D. E., Ang, A., Krousel-Wood, M., & Ward, H. J. (2008). Predictive validity of a medication adherence measure in an outpatient setting. *The journal of clinical hypertension, 10*(5), 348-354.

Powers, S. W., Coffey, C. S., Chamberlin, L. A., Ecklund, D. J., Klingner, E. A., Yankey, J. W., Korbee, L. L., Porter, L. L., & Hershey, A. D. (2017). Trial of amitriptyline, topiramate, and placebo for pediatric migraine. *New England Journal of Medicine, 376*(2), 115-124.

Powers, S. W., Coffey, C. S., Chamberlin, L. A., Ecklund, D. J., Klingner, E. A., Yankey, J. W., Peugh, J. L., Korbee, L. L., Simmons, K., & Sullivan, S. M. (2021). Prevalence of headache days and disability 3 years after participation in the childhood and adolescent migraine prevention medication trial. *JAMA Network Open, 4*(7), e2114712-e2114712.

Ramsey, R. R., Holbein, C. E., Powers, S. W., Hershey, A. D., Kabbouche, M. A., O'Brien, H. L., Kacperski, J., Shepard, J., & Hommel, K. A. (2018). A pilot investigation of a mobile phone application and progressive reminder system to improve adherence to daily prevention treatment in adolescents and young adults with migraine. *Cephalalgia, 38*(14), 2035-2044.

Ramsey, R. R., Ryan, J. L., Hershey, A. D., Powers, S. W., Aylward, B. S., & Hommel, K. A. (2014). Treatment adherence in patients with headache: a systematic review. *Headache: The Journal of Head and Face Pain, 54*(5), 795-816.

Silberstein, S., & Goadsby, P. (2002). Migraine: preventive treatment. *Cephalalgia, 22*(7), 491-512.

Silberstein, S. D., Lipton, R. B., Dodick, D. W., Freitag, F. G., Ramadan, N., Mathew, N., Brandes, J. L., Bigal, M., Saper, J., & Ascher, S. (2007). Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. *Headache: The Journal of Head and Face Pain, 47*(2), 170-180.

Storey, J., Calder, C., Hart, D., & Potter, D. (2001). Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache: The Journal of Head and Face Pain, 41*(10), 968-975.

Van Diest, A. M. K., Ramsey, R., Kashikar-Zuck, S., Slater, S., Hommel, K., Kroner, J. W., LeCates, S., Kabbouche, M. A., O'Brien, H. L., & Kacperski, J. (2017). Treatment adherence in child and adolescent chronic migraine patients: Results from the Cognitive Behavioral Therapy and Amitriptyline Trial. *The Clinical Journal of Pain, 33*(10), 892.

Wager, T. D., & Atlas, L. Y. (2015, Jul). The neuroscience of placebo effects: Connecting context, learning and health. *Nature reviews. Neuroscience, 16*(7), 403-418. https://doi.org/10.1038/nrn3976

Winner, P., Pearlman, E. M., Linder, S. L., Jordan, D. M., Fisher, A. C., Hulihan, J., & Investigators, T. P. M. S. (2005). Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. *Headache: The Journal of Head and Face Pain, 45*(10), 1304-1312.

Yang, C., Hao, Z., Yu, D., Xu, Q., & Zhang, L. (2018). The prevalence rates of medication adherence and factors influencing adherence to antiepileptic drugs in children with epilepsy: a systematic review and meta analysis. *Epilepsy Research, 142*, 88-99.