

Coping with Migraine Headaches

The Promising Role of Digital Therapeutics for Mental Health

"...the first thing that I am aware of, it's like somebody's put a knife through my head. The pain is so intense that for several seconds I don't even open my eyes, in the hope that I'm just dreaming about it..."



Migraine patient in study conducted by Peters, Abu-Saad, Vydellingum, Dowson, and Murphy (2005) [1]

Approximately 1 in 6 Americans self-report experiencing migraines or severe headaches over a 3-month period [2], while almost 1 in every 4 households includes at least one household member suffering from migraines [3]. Relative to the general population, migraines are more prevalent among women, people between 25 and 55 years of age, and people from lower socioeconomic statuses [4,5]. While the causes of migraines remain unclear, migraine patients typically report multiple triggers; these commonly include [6,7]:

- Emotional stress
- Having too much or too little sleep
- Odors
- Missing meals
- Menstruation, for the majority of women

Worldwide, migraines also represent one of the primary causes of disability [8]. Among those between 15 and 49 years of age, for instance, headaches account for 9.5% of all years of healthy life lost to disability [9]. Migraines are commonly associated with [10,11]:

- Reduced vitality
- Fatigue
- Poorer physical and mental health
- Reduced social and occupational functioning
- Pain
- More than half of migraine patients report substantial impairment to daily activities or that their migraines require bed rest

Prevalence of Migraines



1 in 6

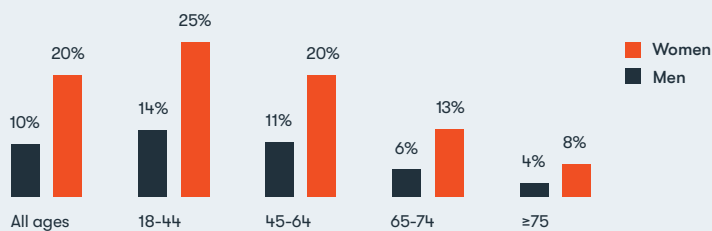
individuals experience migraines every 3 months



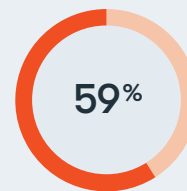
1 in 4

households have a migraine sufferer

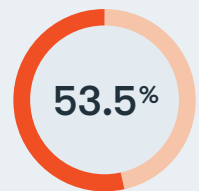
Women suffer more migraines than men across all ages



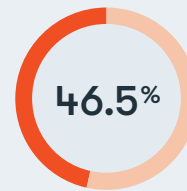
Common Migraine Triggers



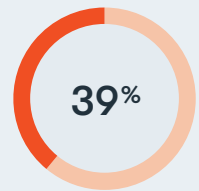
"Emotional stress"



"Too much or little sleep"



"Odors"



"Missing meals"

Source: https://www.cdc.gov/mmwr/volumes/69/wr/mm6912a8.htm?s_cid=mm6912a8_w

Episodic vs. Chronic Migraines

The International Classification of Headache Disorders (ICDH-3) distinguishes between episodic migraines, when patients have 14 or fewer migraines per month, and chronic migraines, when patients experience 15 or more headaches per month (of which 8 must meet criteria for migraines) for more than 3 months [12]. Although chronic migraines are less common than episodic migraines, affecting 1-2% of the general population [13], they are the most common reason for visits to headache centers [14, 15]. What's more, approximately 3-5% of cases of episodic migraines transform into chronic migraines [16,17]; early reports suggest this number may have been closer to 10% during the COVID-19 pandemic, when many migraine patients saw an increase in migraine frequency [18].

While a small proportion of migraine sufferers have chronic migraines, these individuals are more likely to suffer from comorbid conditions including depression, anxiety, and chronic pain [19]. Moreover, the rate of disability days among chronic migraine patients is 3.63 times higher than among those with episodic migraines [20]. However, research suggests that chronic migraines can be reversed with adequate treatment; as many as 26% of transformed migraines recover to episodic migraines within 2 years [21]. Indeed, many of the risk factors for chronic migraines are treatable, including obesity, depression, and stress [22], and thus present as important targets for chronic migraine intervention.

The Burden of Migraines

Migraines also present a high economic burden, with average medical costs 1.7x higher than in matched controls [23]. For example, headaches account for 3% of emergency department visits in the United States, making it the fourth or fifth leading cause of emergency department visits overall [24].

Some research suggests most of these costs are direct medical costs (60-64%), and primarily driven by pharmaceutical utilization [25]. Other research suggests that up to two-thirds of the economic costs associated with migraines may be indirect costs, such as lost productivity [26]. One study found that migraines were associated with 22% absenteeism, over 60% presenteeism, work productivity loss, and activity impairment [27]. On average, migraines are associated with 4.4 missed work days per year as well as an additional average of 11.4 days per year with reduced productivity [28]. People with chronic migraines are more likely to be occupationally disabled and less likely to be employed full-time than those with episodic migraines [29], suggesting their migraines may be sufficiently debilitating to interfere with full-time employment.

Indeed, the cost associated with chronic migraines is even higher, at approximately 3x the costs associated with episodic migraines. Specifically, episodic migraines are associated with an average annual cost of \$2,649 USD, whereas chronic migraines are associated with an average annual cost of \$8,243 USD [30]. Similarly, people with transformed migraines have 4.4x higher annual per person costs relative to those who maintain episodic migraines [31]. The economic burden of chronic or transformed migraines is therefore substantially higher, highlighting the importance of preventing migraine progression or reversing the chronicity of transformed migraines.

Chronic Migraines:

When patients experience 15 or more headaches per month for more than 3 months

Episodic Migraines:

When patients have 14 or fewer migraines per month



The Economic Impact of Migraines

ER visits

3%



Migraines make up 3% of all ER visits

Average costs

+70%



Migraines contribute a 70% increase in average medical costs

Productivity costs

22% of absences

22% of absenteeism is due to migraines

-4.4 days

4.4 workdays missed on average due to Migraines

-11.4 days

11.4 Reduced Productivity Days due to Migraines

Managing Migraines by Addressing Mental Health

Given the high economic burden associated with migraines and the prevalence of the condition, some researchers have pointed to the need for new treatment modalities in migraines [32]. While many migraine treatments focus on addressing the physical condition, researchers are becoming increasingly aware of the role of mental health, particularly stress, in the migraine cycle. Emotional stress is one of the most commonly reported triggers for migraines [33], and research suggests higher levels of generalized anxiety, stress, and depression are also risk factors for migraines [34,35]. However, migraines also increase one's risk for stress and poor mental health. For example, people who experience more migraine symptoms per month and who have experienced migraines for a longer period of time reported higher levels of migraine-associated stress [36].



Migraine patients are more than 2x more likely to have major depressive disorder, bipolar disorder, panic disorder, and social phobia [37], and people with higher levels of migraine-related stress seem particularly at risk for elevated depression and anxiety [38].

Conceivably, then, helping migraine patients cope with stress and improve their mental health may reduce one of the primary triggers for migraines and result in corresponding improvements in migraine frequency or migraine-related disability. A growing body of research supports the use of **biobehavioral therapy**, such as cognitive behavioral therapy (CBT), in migraine patients [39], particularly for migraine prevention [40]. Research suggests that even as little as a one-day session of Acceptance and Commitment Therapy (ACT) coupled with Migraine Education may be sufficient to produce noticeable improvements in migraine frequency and severity, as well as medication usage and headache-related disability [41]. Evidence for the adjunctive benefits of biobehavioral therapy with preventative drug therapy is not as strong (Grade B) [42], though some research suggests it may augment the effects of pharmacologic treatments [43].

The U.S. Headache Consortium has suggested—

Non-pharmacologic treatments like biobehavioral therapy for migraine patients who prefer non-pharmacologic interventions, who have had an inadequate response, poor tolerance or have medical contraindications to pharmacologic treatments, who have a history of medication overuse, and/or experience high levels of stress or have poor stress-coping skills [44].

How can Happify help?

Happify is a global software-enabled healthcare platform designed to help improve mental and physical health that can be accessed via mobile app or the internet. The Happify program integrates various therapeutic approaches including CBT, mindfulness-based stress reduction (MBSR), positive psychology, and ACT. Activities inspired by these theoretical frameworks are organized into 'tracks' that are developed to help users focus on a specific area of concern, like coping better with stress or improving well-being while living with a chronic illness. Users may also access activities in an instant play format. Thus users have several avenues for personalizing their program.

This digital approach to behavioral interventions helps to reduce many of the barriers associated with treatment-seeking and adherence to traditional, in person interventions [45,46,47] and thus may engage migraine patients who would not otherwise consider biobehavioral therapy [48]. Our research has shown that completing approximately 16 activities over 8 weeks via Happify leads to significant improvements in subjective well-being [49,50], depressive symptoms, anxiety, and resilience [51]. More recently, we have shown that users with chronic illness report lower levels of subjective well-being compared to users with no self-reported chronic conditions, but improve at the same rate while using Happify as those without chronic illness [52]. Taken together, these data suggest that Happify may be a favorable method for improving mental health in migraine patients and, in turn, help to improve migraine-related outcomes as well.

Happify Effects on Migraine Patients: A Pilot Study

In late 2020, Happify Health ran a pilot study to explore the effects of Happify usage on mental health and migraine-related outcomes among adults with self-reported migraines. During the study, participants were asked to complete the Happify Happiness Assessment and a separate migraine-related assessment at two week intervals. We collected usage and assessment data from participants between October 27, 2020 and January 14, 2021, and new participants continued to enroll in the pilot throughout that period of time.

The results discussed here represent the changes observed between a user's first and last assessment, while controlling for the number of days between assessments, for users who had at least 2 assessments (users could choose to opt out of any assessment).

User demographics are represented in Table 1 and migraine-specific demographics are represented in Table 2.

Happiness Assessment

Starting their second day on Happify and every 2 weeks thereafter, users were prompted to complete our Happiness Assessment.

This assessment consists of our 9-item Happify Scale, a proprietary measure of subjective well-being (highly correlated with depression) with scores ranging from 0 to 100 (higher scores mean greater well-being), and the Generalized Anxiety Scale 2 [53], a widely used screening tool for generalized anxiety with scores ranging from 0 to 6 (higher scores mean greater anxiety).



Migraine Assessment

Starting one day after the happiness assessment, users were also prompted to complete a 7-item migraine assessment every 2 weeks.

This assessment asked users to rate their level of stress, fatigue, sleep quality, migraine frequency, migraine severity, as well as the extent to which migraines interfered with activities and the extent to which they felt helpless because of their migraines during the previous 7 days. On the second migraine assessment, and every migraine assessment that followed, participants were also asked how their quality of life changed since they started Happify.





	Sample 1: Changes in Mental Health (Completed 2+ Happiness Assessments)	Sample 2: Changes in Migraine- Related Outcomes (Completed 2+ Migraine Assessments)
n	694	652
Gender (%)		
Female	91.1%	90.2%
Male	7.8%	8.6%
Other	1.2%	1.2%
Age (%)		
18-24	12.2%	11.7%
25-34	30.1%	31%
35-44	28.1%	27.8%
45-54	21.2%	21%
55-64	7.8%	7.7%
65+	0.6%	0.9%
Race		
White	74.5%	74.7%
Black	3.3%	3.1%
Hispanic or Latino/a	4.9%	4.7%
Asian Pacific Islander	3.2%	3.4%
American Indian	0.6%	0.6%
Middle Eastern	0.3%	0.1%
Other	2.45%	2.45%
Mixed Race	7.35%	7.8%
Unreported	3.46%	3.1%
Employment Status (%)		
Employed	58.4%	57.8%
Self-Employed	5.5%	6.1%
Student	9.5%	8.9%
Homemaker	9.8%	10%
Retired	5.2%	5.8%
Unemployed	11.7%	11.3%

Table 1: User Demographics for Samples Used to Estimate Changes in Mental Health and Changes in Migraine-Related Outcomes.



	Sample 1: Changes in Mental Health (Completed 2+ Happiness Assessments)	Sample 2: Changes in Migraine-Related Outcomes (Completed 2+ Migraine Assessments)
Migraine Frequency (per month)		
Less than 4	41.4%	41.1%
4-14	45.2%	45.2%
More than 14	13.4%	13.7%
Migraine Pain		
None	0.6%	0.2%
Mild	6.9%	6.4%
Moderate	45.8%	44.9%
Severe	40.3%	41.9%
Extremely Severe	6.3%	6.6%
Migraine Duration		
Less than 4 hours	19.2%	19.2%
4-12 hours	44.2%	43.3%
13-24 hours	21.2%	20.6%
More than 24 hours	15.4%	17.0%
Years Since Onset		
Less than 1	6.3%	6.9%
1-10	43.1%	42.5%
11-20	24.9%	24.5%
More than 20	25.7%	26.1%
Migraine Treatment		
Any Treatment	86.7%	87.3%
Over the Counter Pain Relief	62.5%	62.9%
Prescription Pain Relief	30.4%	30.5%
Preventative Self-Injection	3.2%	3.5%
Other Preventative	11.4%	13.7%
Other	12.5%	12.3%

Table 2: Migraine-Specific Demographics for Samples Used to Estimate Changes in Mental Health and Changes in Migraine-Related Outcomes.

Migraines Are Associated with Poorer Mental Health

Among users who completed at least two happiness or migraine assessments, 70.2% of those users reported initial anxiety scores that met screening criteria for a clinically relevant anxiety disorder [54,55]. The mean score on the Happify scale was 37.47 (SD = 18.22) and 88% of our participants had scores below 61, which marks the 50th percentile for the scale in the general population.

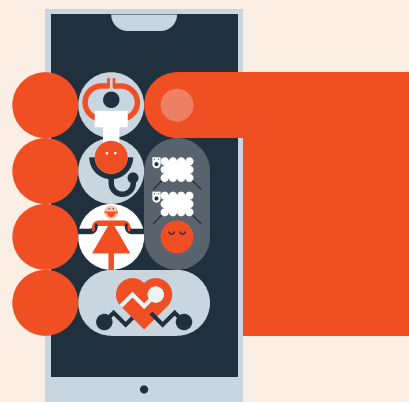
Within the sample, users with more frequent migraines reported significantly lower levels of subjective well-being ($p = .002$) and significantly higher levels of anxiety ($p = .005$). Compared to users who reported fewer than 4 migraines per month, well-being scores were 10% lower among those with 4 to 14 migraines per month and 16.16% lower among those with more than 14 migraines per month. Anxiety scores were 8.25% higher among users with 4 to 14 migraines per month, and 15.15% higher among those with more than 14 migraines per month.

Additionally, both migraine pain severity and migraine duration were significantly associated with poorer mental health. Users who reported longer and more painful migraines reported lower levels of subjective well-being ($r_s = -0.14$ - -0.16 , $p_s < .001$) and higher levels of anxiety ($r_s = 0.16$, $p < .001$) when they started using Happify.

Engagement

Across the 789 users in both samples, participants in the pilot did an average of 20.65 activities (SD = 34.62), ranging from 0 to 330 activities, and were active on the Happify platform an average of 10.90 days (SD = 10.23), ranging from 1 to 69 days.

Engagement with the program was not significantly related to migraine severity or duration of migraine headaches, though we observed a trend ($p = .067$) that participants with more than 14 migraines per month completed more activities than those with fewer migraines.



Migraine Sufferers and Anxiety Levels

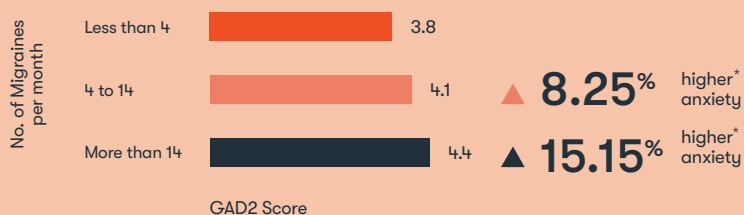


Figure 1. Initial Levels of Anxiety from Happify Users (n = 694) based on Migraine Frequency.
*based on users that had less than four migraines a month

Migraine Sufferers and Subjective Well-Being

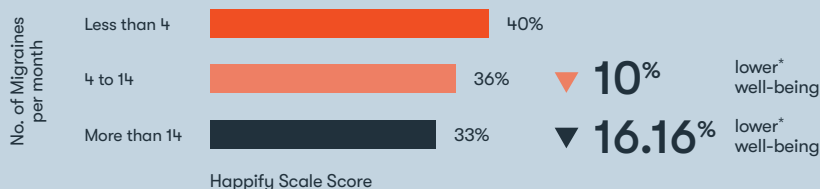
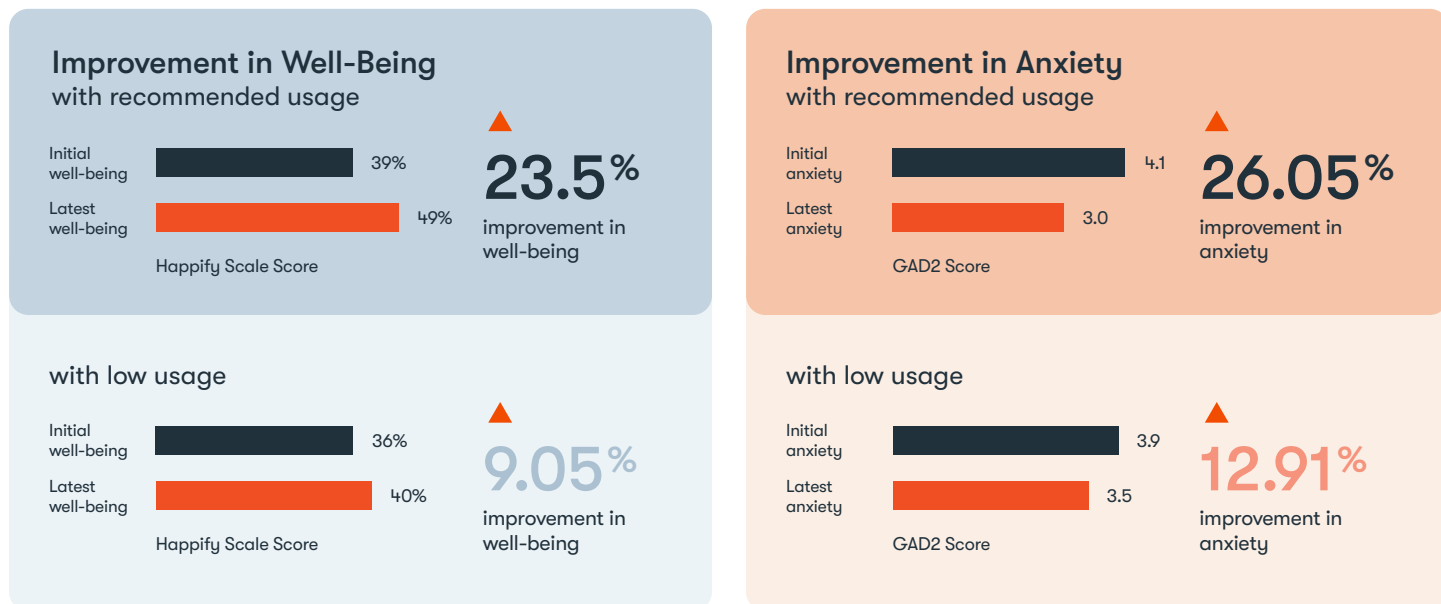


Figure 2. Initial Levels of Subjective Well-Being from Happify Users (n = 694) based on Migraine Frequency.
*based on users that had less than four migraines a month

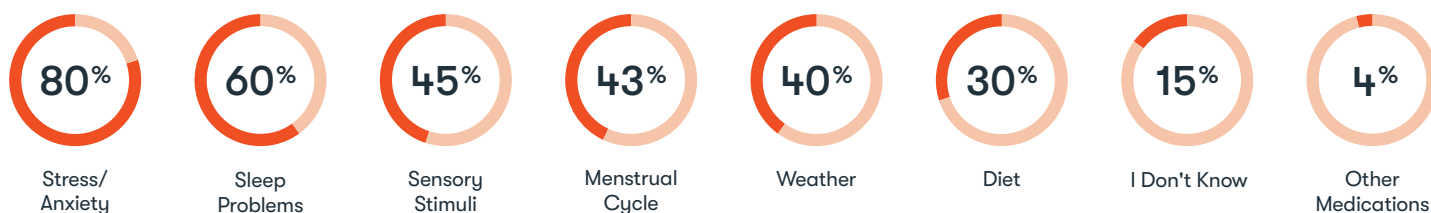
Happify Helps Improve Mental Health in Migraine Patients

Our pilot data show that people with self-reported migraines report significant improvements in subjective well-being ($p = .001$) and anxiety ($p = .002$) after using Happify. What's more, users who complete the recommended number of activities (16) report significantly more improvement in these outcomes than those with low levels of engagement ($ps < .001$). Users who completed fewer than 16 activities saw an average improvement of 9.05% in their Happify Scale scores and 12.91% in their anxiety scores, whereas users who completed 16 activities or more saw an improvement of 23.5% in Happify Scale scores and 26.05% in anxiety scores. And we observed these effects regardless of a user's migraine frequency, migraine severity, the duration of their migraines, or how many years they'd suffered from migraines.



Figures 3 (top) and 4 (bottom). Changes in Subjective Well-Being and Anxiety as Measured by the Happify Scale and the Generalized Anxiety Disorder 2-item (GAD2) Scale Between First and Last Assessment by Recommended Usage (Fig. 3) and Low Usage (Fig. 4).

Common Migraine Triggers



Stress and Sleep are Important Migraine Triggers

When we asked participants to identify what their migraine triggers were, the most commonly reported trigger was stress and anxiety, reported by 82.7% of our participants. The second most commonly reported trigger was sleep problems (58.5%), followed by sensory stimuli (45%). This is consistent with other research and further supports the argument that interventions that help to reduce stress and anxiety may ultimately help to reduce the actual frequency of one's migraines. Indeed, although we did not find overall improvements in stress ($p = .357$), migraine frequency ($p = .353$), or migraine severity ($p = .056$), we did find that when users experienced better than average improvement in stress (i.e., more than a 0.42 point improvement in stress ratings), they reported significant decreases in migraine frequency ($p < .001$). When users experienced minimal improvements in stress, their migraine frequency increased by 2.89%, but when users experienced greater than average improvements in stress, their migraine frequency decreased by 18.78%. Similarly, we saw a trend that when users experienced higher than average levels of improvement in anxiety (i.e., more than a 0.66 point improvement in GAD-2 ratings), they reported decreases in migraine frequency ($p = .054$). Users who had minimal improvements in anxiety had just a 0.59% improvement in migraine frequency, whereas users who had greater than average improvements in anxiety had a 12.80% improvement in migraine frequency.

The Happify Impact on Migraines:

Summary of Findings

Completing activities as part of the Happify program did not just help to improve mental health outcomes, we also found evidence that engaging with Happify may help people manage the negative effects of their migraines.

For example, participants in our pilot study reported significantly less interference from migraines on their day-to-day activities ($p = .009$), particularly when they completed the recommended dosage ($p = .002$). That is, users with low levels of engagement reported an improvement of just 3% in migraine interference, whereas users who completed at least 16 activities reported an 18.4% improvement in migraine interference.

Similarly, although we did not see a significant improvement in how frustrated or helpless users felt due to their migraines overall ($p = .125$), users who completed at least 16 activities during the study did report feeling significantly less frustrated and helpless due to their migraines ($p = .039$), with scores improving by 19.13%.



Overall, 71.9% of users also reported noticeable changes in their quality of life since joining Happify.

Summary

Migraines, particularly chronic migraines, are a debilitating and costly condition. Given the key role of stress and anxiety in the migraine cycle, biobehavioral therapies that can target these mental health outcomes are an important treatment modality as a preventative tool as well as to enhance the benefits of pharmacologic treatments. As the need for digital interventions increase due to the barriers associated with in-person treatment, there is a pressing need to explore whether biobehavioral therapies for migraines can be effectively delivered digitally. Our pilot study provides some promising preliminary results for effects of engaging with a general mental health platform that is not even optimized for migraine among people with self-reported migraines. Our data suggests that a digital biobehavioral approach can help to improve subjective well-being and anxiety, and to reduce perceived migraine interference with daily activities and feelings of frustration and helplessness related to migraines. Particularly noteworthy is that this pilot data suggests that users who successfully reduced their stress and/or anxiety reported corresponding decreases in migraine frequency. Digital programs, like Happify, may then provide a cost-effective and scalable means of offering support to migraine patients who might not otherwise pursue biobehavioral therapy.

The Impact Happify has on Migraines

Interference



18.4% improvement

Users who completed 16 activities

3% improvement

Users who completed less than 16 activities

Feeling Frustrated and Helpless



-19.13% reduction

Users who completed 16 activities

Quality of Life



71.9% noticeable improvement

Improvements in Well-Being and Anxiety

23.5% improvement in well-being

26.1% improvement in anxiety

References

1. Peters, M., Huijjer Abu-Saad, H., Vydelingum, V., Dowson, A., & Murphy, M. (2005). The patients' perceptions of migraine and chronic daily headache: a qualitative study. *The journal of headache and pain*, 6(1), 40–47. <https://doi.org/10.1007/s10194-005-0144-7>
2. Burch, R., Rizzoli, P., & Loder, E. (2018). The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache*, 58(4), 496–505. <https://doi.org/10.1111/head.13281>
3. Lipton, R. B., Stewart, W. F., Diamond, S., Diamond, M. L., & Reed, M. (2001). Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*, 41(7), 646–657. <https://doi.org/10.1046/j.1526-4610.2001.041007646.x>
4. Percentage of Adults Who Had a Severe Headache or Migraine in the Past 3 Months, by Sex and Age Group – National Health Interview Survey, United States, 2018. *MMWR Morb Mortal Wkly Rep* 2020;69:359. DOI: <http://dx.doi.org/10.15585/mmwr.mm6912a8>
5. Lipton, R. B., & Bigal, M. E. (2005). Migraine: epidemiology, impact, and risk factors for progression. *Headache: The Journal of Head and Face Pain*, 45, S3-S13.
6. Andress-Rothrock, D., King, W., & Rothrock, J. (2010). An analysis of migraine triggers in a clinic-based population. *Headache*, 50(8), 1366–1370. <https://doi.org/10.1111/j.1526-4610.2010.01753.x>
7. Andress-Rothrock, D., King, W., & Rothrock, J. (2010). An analysis of migraine triggers in a clinic-based population. *Headache*, 50(8), 1366–1370. <https://doi.org/10.1111/j.1526-4610.2010.01753.x>
8. Stovner, L. j., Hagen, K., Jensen, R., Katsarava, Z., Lipton, R., Scher, A., Steiner, T., & Zwart, J. A. (2007). The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia : an international journal of headache*, 27(3), 193–210. <https://doi.org/10.1111/j.1468-2982.2007.01288.x>
9. GBD 2016 Headache Collaborators (2018). Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology*, 17(11), 954–976. [https://doi.org/10.1016/S1474-4422\(18\)30322-3](https://doi.org/10.1016/S1474-4422(18)30322-3)
10. Raggi, A., Giovannetti, A. M., Quintas, R., D'Amico, D., Cieza, A., Sabariego, C., Bickenbach, J. E., & Leonardi, M. (2012). A systematic review of the psychosocial difficulties relevant to patients with migraine. *The journal of headache and pain*, 13(8), 595–606. <https://doi.org/10.1007/s10194-012-0482-1>
11. Lipton, R. B., Stewart, W. F., Diamond, S., Diamond, M. L., & Reed, M. (2001). Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*, 41(7), 646–657. <https://doi.org/10.1046/j.1526-4610.2001.041007646.x>
12. The International Classification of Headache Disorders - ICHD-3. ICHD. (2021, January 12). <https://ichd-3.org/>.
13. May, A., & Schulte, L. H. (2016). Chronic migraine: risk factors, mechanisms and treatment. *Nature reviews. Neurology*, 12(8), 455–464. <https://doi.org/10.1038/nrneurol.2016.93>
14. Pascual, J., Colás, R., & Castillo, J. (2001). Epidemiology of chronic daily headache. *Current pain and headache reports*, 5(6), 529–536. <https://doi.org/10.1007/s11916-001-0070-6>
15. Diener, H. C., Solbach, K., Holle, D., & Gaul, C. (2015). Integrated care for chronic migraine patients: epidemiology, burden, diagnosis and treatment options. *Clinical medicine (London, England)*, 15(4), 344–350. <https://doi.org/10.7861/clinmedicine.15-4-344>
16. Munakata, J., Hazard, E., Serrano, D., Klingman, D., Rupnow, M. F., Tierce, J., Reed, M., & Lipton, R. B. (2009). Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*, 49(4), 498–508. <https://doi.org/10.1111/j.1526-4610.2009.01369.x>
17. May, A., & Schulte, L. H. (2016). Chronic migraine: risk factors, mechanisms and treatment. *Nature reviews. Neurology*, 12(8), 455–464. <https://doi.org/10.1038/nrneurol.2016.93>
18. Al-Hashel, J. Y., & Ismail, I. I. (2020). Impact of coronavirus disease 2019 (COVID-19) pandemic on patients with migraine: a web-based survey study. *The journal of headache and pain*, 21(1), 115. <https://doi.org/10.1186/s10194-020-01183-6>
19. Buse, D. C., Manack, A., Serrano, D., Turkel, C., & Lipton, R. B. (2010). Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *Journal of neurology, neurosurgery, and psychiatry*, 81(4), 428–432. <https://doi.org/10.1136/jnnp.2009.192492>
20. Adams, A. M., Serrano, D., Buse, D. C., Reed, M. L., Marske, V., Fanning, K. M., & Lipton, R. B. (2015). The impact of chronic migraine: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. *Cephalalgia : an international journal of headache*, 35(7), 563–578. <https://doi.org/10.1177/0333102414552532>
21. May, A., & Schulte, L. H. (2016). Chronic migraine: risk factors, mechanisms and treatment. *Nature reviews. Neurology*, 12(8), 455–464. <https://doi.org/10.1038/nrneurol.2016.93>
22. May, A., & Schulte, L. H. (2016). Chronic migraine: risk factors, mechanisms and treatment. *Nature reviews. Neurology*, 12(8),

455–464. <https://doi.org/10.1038/nrneurol.2016.93>

23. Polson, M., Williams, T. D., Speicher, L. C., Mwamburi, M., Staats, P. S., & Tenaglia, A. T. (2020). Concomitant medical conditions and total cost of care in patients with migraine: a real-world claims analysis. *The American journal of managed care*, 26(1 Suppl), S3–S7. <https://doi.org/10.37765/ajmc.2020.42543>
24. Burch, R., Rizzoli, P., & Loder, E. (2018). The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache*, 58(4), 496–505. <https://doi.org/10.1111/head.13281>
25. Messali, A., Sanderson, J. C., Blumenfeld, A. M., Goadsby, P. J., Buse, D. C., Varon, S. F., Stokes, M., & Lipton, R. B. (2016). Direct and Indirect Costs of Chronic and Episodic Migraine in the United States: A Web-Based Survey. *Headache*, 56(2), 306–322. <https://doi.org/10.1111/head.12755>
26. Edmeads, J., & Mackell, J. A. (2002). The economic impact of migraine: an analysis of direct and indirect costs. *Headache*, 42(6), 501–509. <https://doi.org/10.1046/j.1526-4610.2002.04262.x>
27. Gibbs, S. N., Shah, S., Deshpande, C. G., Bensink, M. E., Broder, M. S., Dumas, P. K., Buse, D. C., Vo, P., & Schwedt, T. J. (2020). United States Patients' Perspective of Living With Migraine: Country-Specific Results From the Global "My Migraine Voice" Survey. *Headache*, 60(7), 1351–1364. <https://doi.org/10.1111/head.13829>
28. Leonardi, M., & Raggi, A. (2019). A narrative review on the burden of migraine: when the burden is the impact on people's life. *The journal of headache and pain*, 20(1), 41. <https://doi.org/10.1186/s10194-019-0993-0>
29. Buse, D. C., Manack, A., Serrano, D., Turkel, C., & Lipton, R. B. (2010). Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *Journal of neurology, neurosurgery, and psychiatry*, 81(4), 428–432. <https://doi.org/10.1136/jnnp.2009.192492>
30. Messali, A., Sanderson, J. C., Blumenfeld, A. M., Goadsby, P. J., Buse, D. C., Varon, S. F., Stokes, M., & Lipton, R. B. (2016). Direct and Indirect Costs of Chronic and Episodic Migraine in the United States: A Web-Based Survey. *Headache*, 56(2), 306–322. <https://doi.org/10.1111/head.12755>
31. Munakata, J., Hazard, E., Serrano, D., Klingman, D., Rupnow, M. F., Tierce, J., Reed, M., & Lipton, R. B. (2009). Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*, 49(4), 498–508. <https://doi.org/10.1111/j.1526-4610.2009.01369.x>
32. Polson, M., Williams, T. D., Speicher, L. C., Mwamburi, M., Staats, P. S., & Tenaglia, A. T. (2020). Concomitant medical conditions and total cost of care in patients with migraine: a real-world claims analysis. *The American journal of managed care*, 26(1 Suppl), S3–S7. <https://doi.org/10.37765/ajmc.2020.42543>
33. Andress-Rothrock, D., King, W., & Rothrock, J. (2010). An analysis of migraine triggers in a clinic-based population. *Headache*, 50(8), 1366–1370. <https://doi.org/10.1111/j.1526-4610.2010.01753.x>
34. Peres, M., Mercante, J., Tobo, P. R., Kamei, H., & Bigal, M. E. (2017). Anxiety and depression symptoms and migraine: a symptom-based approach research. *The journal of headache and pain*, 18(1), 37. <https://doi.org/10.1186/s10194-017-0742-1>
35. May, A., & Schulte, L. H. (2016). Chronic migraine: risk factors, mechanisms and treatment. *Nature reviews. Neurology*, 12(8), 455–464. <https://doi.org/10.1038/nrneurol.2016.93>
36. Malone, C. D., Bhowmick, A., & Wachholtz, A. B. (2015). Migraine: treatments, comorbidities, and quality of life, in the USA. *Journal of pain research*, 8, 537–547. <https://doi.org/10.2147/JPR.S88207>
37. Jette, N., Patten, S., Williams, J., Becker, W., & Wiebe, S. (2008). Comorbidity of migraine and psychiatric disorders--a national population-based study. *Headache*, 48(4), 501–516. <https://doi.org/10.1111/j.1526-4610.2007.00993.x>
38. Malone, C. D., Bhowmick, A., & Wachholtz, A. B. (2015). Migraine: treatments, comorbidities, and quality of life, in the USA. *Journal of pain research*, 8, 537–547. <https://doi.org/10.2147/JPR.S88207>
39. Harris, P., Loveman, E., Clegg, A., Easton, S., & Berry, N. (2015). Systematic review of cognitive behavioural therapy for the management of headaches and migraines in adults. *British journal of pain*, 9(4), 213–224. <https://doi.org/10.1177/2049463715578291>
40. Silberstein S. D. (2000). Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 55(6), 754–762. <https://doi.org/10.1212/wnl.55.6.754>
41. Dindo, L., Recober, A., Marchman, J., O'Hara, M. W., & Turvey, C. (2014). One-day behavioral intervention in depressed migraine patients: effects on headache. *Headache*, 54(3), 528–538. <https://doi.org/10.1111/head.12258>
42. Silberstein S. D. (2000). Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 55(6), 754–762. <https://doi.org/10.1212/wnl.55.6.754>

43. Ng, Q. X., Venkatanarayanan, N., & Kumar, L. (2017). A Systematic Review and Meta-Analysis of the Efficacy of Cognitive Behavioral Therapy for the Management of Pediatric Migraine. *Headache*, 57(3), 349–362. <https://doi.org/10.1111/head.13016>
44. American Headache Society (2019). The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache*, 59(1), 1–18. <https://doi.org/10.1111/head.13456>
45. Warmerdam, L., Smit, F., van Straten, A., Riper, H., & Cuijpers, P. (2010). Cost-utility and cost-effectiveness of internet-based treatment for adults with depressive symptoms: randomized trial. *Journal of medical Internet research*, 12(5), e53. <https://doi.org/10.2196/jmir.1436>
46. Ferwerda, M., van Beugen, S., van Burik, A., van Middendorp, H., de Jong, E. M., van de Kerkhof, P. C., van Riel, P. L., & Evers, A. W. (2013). What patients think about E-health: patients' perspective on internet-based cognitive behavioral treatment for patients with rheumatoid arthritis and psoriasis. *Clinical rheumatology*, 32(6), 869–873. <https://doi.org/10.1007/s10067-013-2175-9>
47. Gerhards, S. A., Abma, T. A., Arntz, A., de Graaf, L. E., Evers, S. M., Huibers, M. J., & Widdershoven, G. A. (2011). Improving adherence and effectiveness of computerised cognitive behavioural therapy without support for depression: a qualitative study on patient experiences. *Journal of affective disorders*, 129(1-3), 117–125. <https://doi.org/10.1016/j.jad.2010.09.012>
48. Minen, M., & Corner, S. (2020). Are People with Migraine Willing to Engage in Digitally Based Behavioral Therapies: A look at recruitment statistics for a mobile health study (2580). https://n.neurology.org/content/94/15_Supplement/2580.abstract.
49. Carpenter, J., Crutchley, P., Zilca, R. D., Schwartz, H. A., Smith, L. K., Cobb, A. M., & Parks, A. C. (2016). Seeing the “big” picture: big data methods for exploring relationships between usage, language, and outcome in internet intervention data. *Journal of medical Internet research*, 18(8), e241.
50. Carpenter, J., Crutchley, P., Zilca, R. D., Schwartz, H. A., Smith, L. K., Cobb, A. M., & Parks, A. C. (2017). Correction: Seeing the “Big” Picture: Big Data Methods for Exploring Relationships Between Usage, Language, and Outcome in Internet Intervention Data. *Journal of medical Internet research*, 19(12), e347. <https://doi.org/10.2196/jmir.8099>
51. Parks, A. C., Williams, A. L., Tugade, M. M., Hokes, K. E., Honomichl, R. D., & Zilca, R. D. (2018). Testing a scalable web and smart-phone based intervention to improve depression, anxiety, and resilience: A randomized controlled trial. *International Journal of Wellbeing*, 8(2). <https://doi.org/10.5502/ijw.v8i2.745>
52. Parks, A. C., Williams, A. L., Kackloudis, G. M., Stafford, J. L., Boucher, E. M., & Honomichl, R. D. (2020). The Effects of a Digital Well-Being Intervention on Patients With Chronic Conditions: Observational Study. *Journal of medical Internet research*, 22(1), e16211. <https://doi.org/10.2196/16211>
53. Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O., & Löwe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Annals of internal medicine*, 146(5), 317–325. <https://doi.org/10.7326/0003-4819-146-5-200703060-00004>
54. Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O., & Löwe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Annals of internal medicine*, 146(5), 317–325. <https://doi.org/10.7326/0003-4819-146-5-200703060-00004>
55. Staples, L. G., Dear, B. F., Gandy, M., Fogliati, V., Fogliati, R., Karin, E., Nielssen, O., & Titov, N. (2019). Psychometric properties and clinical utility of brief measures of depression, anxiety, and general distress: The PHQ-2, GAD-2, and K-6. *General hospital psychiatry*, 56, 13–18. <https://doi.org/10.1016/j.genhosppsych.2018.11.003>