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Drug therapy for migraine in children by paediatricians in Germany - what role do discount agreements play?

Migraine and other headaches are a significant health problem in children and adolescents and affect their quality of life. Although they are often associated with adults, headache disorders such as migraines and tension headaches often begin in childhood or adolescence (Blankenburg et al., 2019). The clinical picture of migraine in children and adolescents poses a particular diagnostic and therapeutic challenge, as young patients may describe their symptoms inadequately or show atypical symptoms (Silveira Bianchim et al., 2024). The guidelines of the German Migraine and Headache Society and the Society for Neuropaediatrics recommend ibuprofen in a single dose of 10 mg/kg body weight as the drug of first choice for the treatment of acute headaches in children that occur as part of a migraine or tension headache. Paracetamol in a single dose of 15 mg/kg body weight is recommended as a second choice. For migraine attacks that do not respond to analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), triptans should be used in adolescents (Diener et al., 2019). In rare exceptional cases or for individual indications, triptans are also used off-label in children under 12 years of age. Acetylsalicylic acid is generally not recommended in Germany for children under 12 years of age due to the risk of Reye's syndrome (Mund et al., 2015). There is a clear research gap in the knowledge of how acute migraine therapies are actually prescribed in children and adolescents.

>> Katsuki et al. investigated migraine treatment in children and adolescents in Japan and found that 99% of patients aged 6-11 years and 91% of adolescents aged 12-17 years received NSAIDs. In addition, 9% of adolescents received triptans, either as monotherapy or in addition to NSAIDs (Katsuki et al., 2024). In Germany, there have only been a few studies on the use and frequency of the various migraine medications in children and adolescents. Consequently, data on the actual use of these therapies in practice, including age-related differences in prescribing habits, are scarce.

The aim of the present study is to investigate the acute treatment of migraine in German paediatric practices, including the prescribed medications, dosages and dosage forms.

Drug treatment of migraine in children by pediatricians in Germany - What role do rebate contracts play?

Data on the real-world utilization of migraine therapies in children are limited. The aim of the present study is to evaluate the real-world patterns of acute migraine therapy in office-based pediatricians in Germany. The retrospective cross-sectional study included children aged 2-12 years with a migraine diagnosis made by one of 258 pediatricians between January 2015 and December 2023. 10.9% of children aged 2-5 years and 18.3% of children aged 6-12 years received a prescription for migraine medication.

The most frequently prescribed medication was ibuprofen (75.4% and 75.9%). Among children aged 2-5 years who received an ibuprofen prescription, 68.2% received ibuprofen as a suspension, 16.3% as rectal suppositories, and 15.5% as melting tablets. In the age group 6-12 years, the suspension (36.3%) was the most frequently prescribed dosage form, followed by melting tablets (31.8%) and regular tablets (29.9%).

The proportion of melting tablets was significantly higher in privately insured patients compared to statutory insured patients (53.7% vs. 31.0%) and higher in 2015 compared to 2024 (40.5% vs. 24.8%). Apparently, melting tablets are the preferred dosage form for children, but they cannot always be used due to rebate contracts.

Keywords

children, pediatricians, migraine, ibuprofen, rebate contracts

Methods

The present study used data from the IQVIA Disease Analyser database. This database has already been described in the literature and categorised as representative of care in the private practice sector in Germany (German private practices) (Rathmann et al., 2018). It contains data from around 3000 general and specialist practices in Germany, including basic demographic information, diagnoses and prescriptions.

The study included children aged 2-12 years who were diagnosed with migraine (ICD-10: G43) by one of 250 registered paediatricians in Germany between January 2015 and December 2024. The study endpoint was the proportion of children who received at least one prescription for migraine medication on the day of diagnosis. All medications prescribed with a migraine diagnosis were included in the analysis, including NSAIDs, acetylsalicylic acid, triptans and Mentha piperita for topical application.

For NSAIDs, the proportions of the different active ingredients (i.e. ibuprofen, metamizole, paracetamol), dosage forms (i.e. normal tablets, orodispersible tablets, suspensions and others) and dosages (i.e. <200 mg, 200 mg, 400 mg, >400 mg) were further analysed.

The present cross-sectional study included descriptive analyses to present the proportions without performing hypothesis tests.

Results

A total of 21,315 children (1,539 aged 2-5 years and 19,776 aged 6-12 years) were diagnosed with migraine for the first time between 2015 and 2024. 168 (10.9%) of children aged 2-5 years and 4,620 (18.3%) of children aged 6-12 years received a prescription for migraine medication. The most commonly prescribed drug was ibuprofen (75.4% in the age group 2-5 years and 75.9% in the age group 6-12 years), followed by paracetamol (19.8% in the age group 2-5 years and 11.2% in the age group 6-12 years). Other

therapies were rarely prescribed (Fig. 1).

Figure 2 shows the distribution of ibuprofen doses. In the age group 2-5 years, only doses of <200 mg (36.0%) and 200 mg (64.0%) were prescribed. The 200 mg dose was also the most common in the 6-12 age group (66.7%), followed by 400 mg (20.5%) and <200 mg (9.2%). Higher doses (>400 mg) were rarely prescribed (3.6%).

Among children aged 2-5 years who received an ibuprofen prescription, 68.2% received ibuprofen as a suspension, 16.3% as rectal suppositories and 15.5% as orodispersible tablets. In the 6-12 age group, suspension (36.3%) was the most commonly prescribed dosage form, followed by orodispersible tablets (31.8%) and regular tablets (29.9%) (Fig. 3).

Discussion

This study provides insights into the care management of migraine in paediatric patients in Germany based on real-world data collected between 2019 and 2023. The treatment concept for acute migraine attacks in children includes general measures such as local cooling, rest, shielding from stimuli and, if possible, sleep. These measures are often sufficient so that drug therapy is not even necessary (Baglioni et al., 2024). This concept of non-pharmacological treatment could not be considered in the present study, as it focuses on pharmacotherapy.

Pharmacological therapies were prescribed more frequently for older children aged 6-12 years than for young children aged 2-5 years of age. This discrepancy may reflect the reluctance of paediatricians to prescribe medication to very young children. In addition, pain attacks in this age group are often shorter and can often be controlled by parental care and the general measures mentioned above.

Among the prescribed active ingredients, ibuprofen was the most frequently used therapy in both age groups, followed by paracetamol. This corresponds to the current German guidelines.

The preference for ibuprofen in our study is consistent with its established

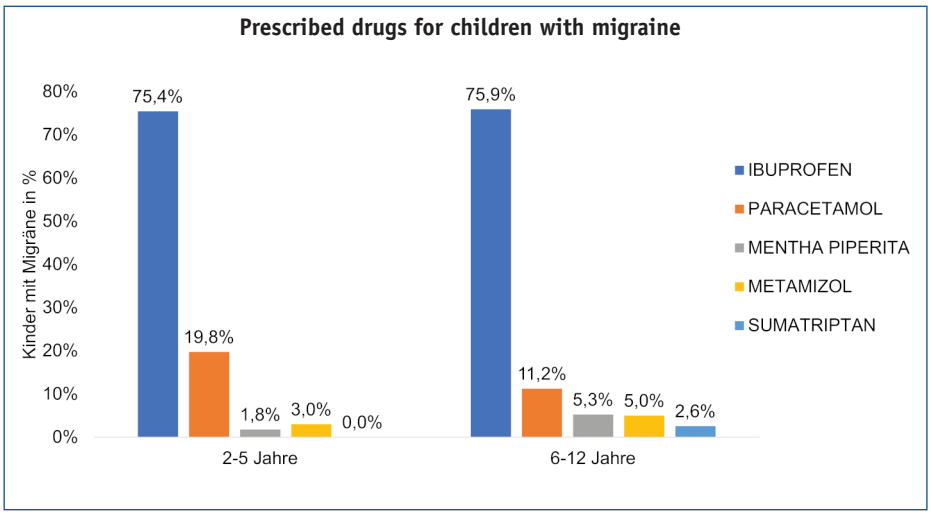


Fig. 1: Drugs prescribed by paediatricians in Germany for children with migraine.

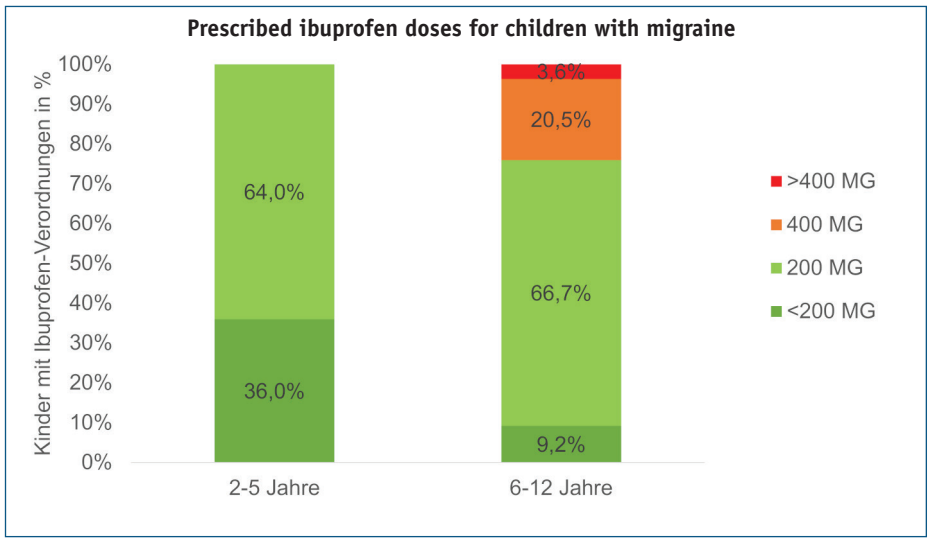


Fig. 2: Doses of ibuprofen prescribed by paediatricians in Germany for children with migraine,

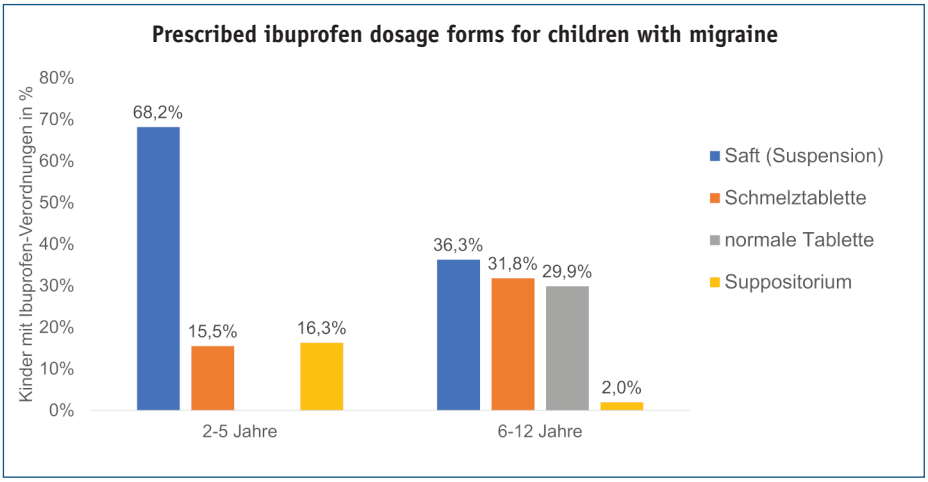


Fig. 3: Ibuprofen dosage forms prescribed by paediatricians in Germany for children with migraine.

efficacy and safety profile in paediatric migraine treatment (Jeric et al., 2018).

In both age groups, the 200 mg dose was most commonly prescribed. Higher doses (400 mg) were more commonly prescribed in older children, likely reflecting differences in body weight and tolerability. Importantly, doses above 400 mg were rarely prescribed, which is consistent with guidelines that recommend cautious dosing in paediatric populations to minimise side effects.

In terms of dosage forms, suspensions were most commonly prescribed for younger children, presumably due to the ease of administration in this age group. In contrast, children aged 6-12 years were more likely to receive orodispersible tablets, but also regular tablets, reflecting their greater ability to take solid dosage forms. Melting tablets offer several advantages for children, particularly in the treatment of conditions such as migraine. They dissolve quickly on the tongue without the need for water, making them ideal for children who have difficulty swallowing traditional tablets or capsules, or who are reluctant to take medication. This form is particularly beneficial in situations where water is not readily available. Due to their ease of use and often pleasant taste, they are generally a popular dosage form in paediatric medicine. There is no need to swallow large tablets and anxiety can be reduced, which also improves adherence to treatment.

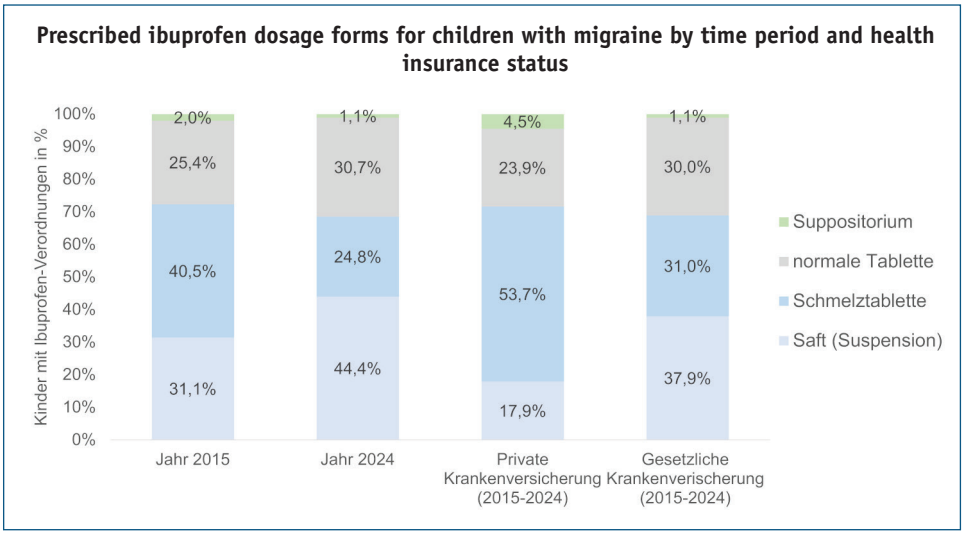


Fig. 4: Ibuprofen dosage forms prescribed by paediatricians in Germany for children with migraine by time period and health insurance status.

In addition, their compact form makes melting tablets easy to transport and administer in a variety of settings - such as at school, when travelling or during outdoor activities. For younger children or those with swallowing difficulties, orodispersible tablets eliminate the risk of choking or aspiration associated with swallowing whole tablets or capsules. Flavour masking technologies are also often used to make the bitter taste of active ingredients such as ibuprofen more pleasant. By addressing common challenges in childhood medication administration, orodispersible tablets improve the overall experience for children and carers and promote effective and consistent treatment adherence (Price 2015; Alyami et al., 2018; Comoglu & Dilek Ozyilmaz, 2019; Chinwala, 2020).

In the present study, many children aged 6-12 years received ibuprofen as an oral suspension. This can be associated with some challenges. For example, it can be difficult for parents to measure the exact dose with a dosing cup. Dosing is often based on the child's weight and age, which can lead to uncertainty if these factors are not accurately taken into account. Some children do not like the taste of the ibuprofen suspension, which can lead to resistance or refusal to take the medication. Older children need to take a larger amount of the suspension, which can be uncomfortable, especially in migraine-related nausea (Yin et al., 2014; Barnett & Bhatt, 2020). Finally, there is a risk of gagging or swallowing if the medication is administered too quickly, especially in infants or young children. Suppositories are a suitable alternative for these children.

When comparing the prescription frequency of ibuprofen suspension and orodispersible tablets, it is important to consider the health policy situation. In Germany, rebates from pharmaceutical companies to the statutory health insurance funds (rebate contracts) are a common strategy for controlling pharmaceutical expenditure. These contracts serve as a complementary measure to price regulation, especially if the latter does not sufficiently reduce drug costs (Vogler et al., 2012; Rodwin, 2021).

In our study, it was observed that the ibuprofen suspension was prescribed more frequently than the orodispersible tablet. A significant factor behind this prescription trend could be the existence of discount agreements, especially as the manufacturers of ibuprofen suspensions are in discount agreements and doctors and pharmacists are encouraged to prescribe and dispense cheaper preparations due to the generally tense economic situation of the healthcare system. The frequent use of suspensions could therefore be due to cost efficiency. This illustrates how financial incentives and agreements between manufacturers and payers can influence prescribing behaviour.

Further evidence for this hypothesis is the fact that in 2015, orodispersible tablets were the most commonly prescribed form for the treatment of paediatric migraine, although suspensions were also available at that time. In addition, orodispersible tablets remain the most common form of ibuprofen for privately insured patients in 2024. The reason for this could be that both doctors and parents prefer the orodispersible tablets if they can decide without the influence of discount agreements.

Oral suspensions are more suitable for children under 5 years of age, as the 200 mg orodispersible tablets cannot be divided into equivalent doses and smaller children would otherwise exceed the weight-based ibuprofen dose of 10 mg/kg. In addition, for young children, paracetamol and ibuprofen are available as rectal suppositories and are commonly used in this age group.

Although both paracetamol and ibuprofen are effective and well-tolerated treatment options (Pavithra et al., 2020), ibupro-

fen has sometimes been considered a better overall alternative for migraine pain relief (Teleanu et al., 2016). Physicians' professional experience could play an important role in their decision to prescribe paracetamol or ibuprofen.

With regard to other therapies observed in the present study, the low prescription rates of metamizole and Mentha piperita suggest that their use remains limited - possibly due to regulatory or practice restrictions as well as limited evidence in the paediatric population (Ruiz et al., 2007; Murtey et al., 2024).

The strengths of this study include the large sample size and comprehensive database. These results could have significant implications for clinical practice and research.

However, some limitations need to be considered. First, the study does not take into account non-pharmacological treatment approaches, which play an essential role in the management of paediatric migraine. Secondly, the lack of data on the severity and impact of migraine limits the ability to fully contextualise treatment decisions. Thirdly, no information was available on the methods used to diagnose migraine, so it is possible that the diagnoses documented by the paediatricians had already been made by a specialist without the paediatrician being involved in the diagnostic process. Finally, other types of headache such as tension headaches were not investigated in this study.

Conclusion

It appears that orodispersible tablets are the preferred dosage form for children, but they cannot always be prescribed due to discount contracts. Study results highlight the need to develop age-appropriate therapeutic strategies to improve migraine care in the paediatric population. <<

Literature

Alyami H, Koner J, Huynh C, Terry D, Mohammed AR. Current opinions and recommendations of paediatric healthcare professionals - The importance of tablets: Emerging orally disintegrating versus traditional tablets. PLoS One. 2018 Feb 28;13(2):e0193292. doi: 10.1371/journal.pone.0193292

Baglioni V, Bozza F, Beatrice A, Cameli N, Colacino Cinnante EM, Lentini G, Faedda N, Natalucci G, Guidetti V. Non-Pharmacological Treatments in Paediatric Migraine. J Clin Med. 2024 Feb 23;13(5):1278. doi: 10.3390/jcm13051278

Barnett S, Bhatt A. A chewable pediatric preparation of ibuprofen is palatable and acceptable to children. Paediatr Neonatal Pain. 2020 Feb 10;2(1):2-6. doi: 10.1002/pne2.12013

Blankenburg M, Schroth M, Braun S. Chronische Kopfschmerzen bei Kindern und Jugendlichen [Chronic Headache in Children and Adolescents]. Klin Padiatr. 2019 Jan;231(1):14-20. German. doi: 10.1055/a-0710-5014

Chinwala M. Recent Formulation Advances and Therapeutic Usefulness of Orally Disintegrating Tablets (ODTs). Pharmacy (Basel). 2020 Oct 10;8(4):186. doi: 10.3390/pharmacy8040186

Comoglu T, Dilek Ozyilmaz E. Orally disintegrating tablets and orally disintegrating mini tablets - novel dosage forms for pediatric use. Pharm Dev Technol. 2019 Sep;24(7):902-914. doi: 10.1080/10837450.2019.1615090

Jeric M, Surjan N, Jelicic Kadic A, Riva N, Puljak L. Treatment of acute migraine attacks in children with analgesics on the World Health Organization Essential Medicines List: A systematic review and GRADE evidence synthesis. Cephalalgia. 2018 Aug;38(9):1592-1607. doi: 10.1177/0333102417736902

Katsuki M, Matsumori Y, Ichihara T, Yamada Y, Kawamura S, Kashiwagi K, Koh A, Goto T, Kaneko K, Wada N, Yamagishi F. Treatment Patterns for and Characteristics of Headache in Children and Adolescents Aged 6-17 Years in Japan: A Retrospective Cross-Sectional and Longitudinal Analysis of Health Insurance Claims Data. Life (Basel). 2024 Jan 8;14(1):96. doi: 10.3390/life14010096

Mund ME, Gyo C, Brüggmann D, Quarcoo D, Groneberg DA. Acetylsalicylic acid as a potential pediatric health hazard: legislative aspects concerning accidental intoxications in the European Union. J Occup Med Toxicol. 2016 Jul 13;11:32. doi: 10.1186/s12995-016-0118-5

Murtey P, Noor NM, Ishak A, Idris NS. Essential Oils as an Alternative Treatment for Migraine Headache: A Systematic Review and Meta-Analysis. Korean J Fam Med. 2024 Jan;45(1):18-26. doi: 10.4082/kjfm.23.0106

Pavithra V, Mishra D, Behera S, Juneja M. Paracetamol versus Ibuprofen for the Acute Treatment of Migraine Headache in Children: A Blinded Randomized Controlled Trial. Indian J Pediatr. 2020 Oct;87(10):781-786. doi: 10.1007/s12098-020-03315-x

Preis M. Orally disintegrating films and mini-tablets-innovative dosage forms of choice for pediatric use. AAPS PharmSciTech. 2015 Apr;16(2):234-41. doi: 10.1208/s12249-015-0313-1

Rathmann W, Bongaerts B, Carius H-J, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. Int J Clin Pharmacol Ther 2018;56:459–66. doi: 10.5414/CP203320 .

Rodwin MA. Common Pharmaceutical Price and Cost Controls in the United Kingdom, France, and Ger-many: Lessons for the United States. Int J Health Serv. 2021 Jul;51(3):379-391. doi: 10.1177/0020731421996168.

Ruiz FB Jr, Santos MS, Siqueira HS, Cotta UC. Clinical features, diagnosis and treatment of acute primary headaches at an emergency center: why are we still neglecting the evidence? Arq Neuropsiquiatr. 2007 Dec;65(4B):1130-3. doi: 10.1590/s0004-282x2007000700007

Silveira Bianchim M, Caes L, Forbat L, Jordan A, Noyes J, Thomson K, Turley R, Uny I, France EF. Understanding how children and young people with chronic non-cancer pain and their families experience living with pain, pain management and services: a meta-ethnography. Health Soc Care Deliv Res. 2024 Jul;12(17):1-218. doi: 10.3310/UTPM7986

Teleanu RI, Vladacenco O, Teleanu DM, Epure DA. Treatment of Pediatric Migraine: a Review. Maedica (Bucur). 2016 Jun;11(2):136-143

Yin HS, Dreyer BP, Moreira HA, van Schaick L, Rodriguez L, Boettger S, Mendelsohn AL. Liquid medication dosing errors in children: role of provider counseling strategies. Acad Pediatr. 2014 May-Jun;14(3):262-70. doi: 10.1016/j.acap.2014.01.003

Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. South Med Rev. 2012 Jul;5(1):38-46

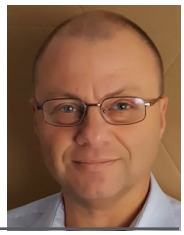
Author statement

The authors declare that there are no conflicts of interests.

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