Title
Treatment of Pediatric Migraine in the Emergency Room

Journal
Pediatric Neurology, 47(4)

ISSN
0887-8994

Authors
Gelfand, Amy A
Goadsby, Peter J

Publication Date
2012-10-01

DOI
10.1016/j.pediatrneurol.2012.06.001

Peer reviewed

Published in final edited form as:
Pediatr Neurol. 2012 October ; 47(4): 233–241. doi:10.1016/j.pediatrneurol.2012.06.001.

Treatment of Pediatric Migraine in the Emergency Room

Amy A. Gelfand, MD[1,2] and **Peter J. Goadsby, MD, PhD**[2]

[1]Department of Neurology, Division of Child Neurology, University of California, San Francisco, CA USA

[2]Department of Neurology, Headache Center, University of California, San Francisco, CA USA

Abstract

Migraine is a relatively common reason for pediatric emergency room visits. Given the paucity of randomized trials involving pediatric migraineurs in the emergency department setting compared to adults, recommendations for managing these children are largely extrapolated from adult migraine emergency room studies and trials involving outpatient home pediatric migraine therapy. This paper reviews what is known about pediatric migraineurs who present to the emergency room and how they are currently managed, then goes on to summarize the best evidence currently available to guide clinical decision making.

Keywords

migraine; primary headache disorders; pediatric

Introduction

Migraine is common in pediatrics, with a prevalence of 1.2-3.2% in 3-7 year-olds, 4-11% in 7-11 year-olds, and 8-23% by age fifteen(1). Headache is a frequent pediatric complaint in the emergency room, and migraine is the most common primary headache disorder in these children(2, 3). The purpose of this article is to review the epidemiology of pediatric migraine in the emergency room and how it is currently treated, and then to outline the evidence base for managing acute migraine in children and adolescents in the emergency room setting. The differential diagnosis of acute headache in a pediatric patient is beyond the scope of this paper, and has been recently reviewed elsewhere(4, 5).

As there is only one controlled trial of pediatric migraine patients in the emergency room, acute therapy trials in other clinical settings will be discussed. How these studies' findings compare to emergency room outcomes is not known. All pediatric migraine therapies described in this article refer to an off-label indication except when otherwise specified.

Correspondence: Amy Gelfand, MD UCSF Headache Center 1701 Divisadero St San Francisco CA 94115 (415) 353-8393 (Telephone) GelfandA@neuropeds.ucsf.edu.

Disclosures: AAG: Receives grant support from NIH/NINDS and the UCSF Center for Translational Science Institute; she has received compensation for medical legal consulting, and honoraria for Journal Watch Neurology.
PJG: Is on the board of Allergan, Colucid, MAP, MSD, Neuralieve, ATI, Boston Scientific, Coherex, Eli-Lilly, Medtronic, Linde gases, and BMS. He has consulted for Pfizer and Air Produces. He has received compensation for expert legal testimony. He has grant support from GlaxoSmithKline, MAP, MSD, Neuralive, and Amgen. He has received honoraria from Amgen, and compensation from the American Headache Society for developing educational materials.

Epidemiology of pediatric migraine in the emergency room

Adolescents are more likely than younger children to come to the emergency department for migraine. This is likely, at least in part, a reflection of the higher prevalence of migraine(1) in this older age group. Across several studies, the mean age of pediatric migraineurs presenting to the emergency room was 12.1-13.6 years(6-8), with a median age of 14.0 years (SD 2.4 years) reported in one study.

Girls predominate in some(6, 8, 9), but not all(3, 7), studies of pediatric migraine in the emergency room. In one study the ratio of children attending for status migrainosus was 64.2% female and 35.8% male(9). In another study 57.4% of children presenting to the emergency room for migraine were female(8). Given that migraine is more common in females from adolescence onwards,(1) this sex difference is likely explained by the underlying prevalence rates.

Typically the headache has been going on for a couple of days by the time the child or adolescent comes to the emergency room(7-9). In one study, children presented an average of 2.2 days after their migraine had started(8). In another study of pediatric “status migrainosus” in the emergency department, where “status” simply meant that abortive intravenous therapy was required, mean headache duration at presentation was 72 hours(9).

Only a minority of children who present to the emergency room for migraine have chronic migraine (migraine ≥15 days per month)(10); in one study these children constituted 14.5% of the group(8). However it is possible this is an under-representation as detailed headache histories may not always be taken in the emergency room setting, and most chronic migraineurs have exacerbations that seem no less troublesome in practice than those experienced by episodic migraineurs.

Most pediatric patients (62.6-71%) have already tried a migraine-abortive medication before presenting to the emergency room(7, 8). Most often they have used a non-specific oral analgesic such as acetaminophen or ibuprofen(7, 8). In one study 2.2% had used a triptan prior to presenting, while 4.7% had used an opioid, suggesting either that children may be more likely to be given an opioid for their outpatient migraine therapy than a migraine-specific triptan, or that those who treated home attacks with triptans were less likely to need to come into the ED(8).

Current Treatment of Pediatric Migraine in the Emergency Room

Being treated in a pediatric emergency room, as opposed to a mixed population emergency room, appears to influence the management of pediatric migraine. In one study pediatric emergency physicians were more likely to prescribe dopamine receptor antagonists and less likely to prescribe opioids than physicians practicing in a mixed environment. Of note, being treated in a pediatric emergency room was also predictive of complete headache resolution(3).

In pediatric emergency rooms in Canada, dopamine receptor antagonists are prescribed most commonly for pediatric migraine(8, 9), with metoclopramide being the most commonly used agent. Opioids are the second-most common, being prescribed in 5.5% of cases(8). Triptans are used only rarely, in 0.5% of cases(8). Providing an intravenous fluid bolus is relatively common(8).

Of note, in nearly a third of pediatric migraineurs no treatment may be given(3). It is possible that these patients’ visits were focused on diagnosis, as evidenced by the relatively high use of neuroimaging (16.3-20.9% CT scan rate) in the evaluation of pediatric patients

who are ultimately diagnosed as having migraine. Of note, serious intracranial pathology that altered management was not found in any of the children imaged in these two studies(8, 9). Brain imaging has not been found to decrease the likelihood of a return visit and in one pediatric study was actually a risk factor for further visits to the emergency room(9).

Principles and Evidence Regarding Pediatric Migraine Therapy in the Emergency Room

Treatment environment

Once the diagnosis of migraine has been made, it is important to reassure the patient and family about the benign etiology of the headache, and that the pain and associated symptoms can be controlled. If possible, the patient should be put in a dark, quiet area of the emergency room. Sleep should be encouraged(11).

Imaging is generally not indicated in those with a normal neurologic examination(1) particularly when the child has a well established history of episodic headaches. In multiple studies of children presenting to the emergency room with headache, all who had serious intracranial pathology had red flags in their history or objective neurologic signs on examination, e.g. loss of consciousness, optic disc swelling, ataxia, hemiparesis, abnormal reflexes or abnormal eye movements(2, 12, 13). In addition, in a study of over 3000 children with brain tumors, of those that presented with headache, less than 1% had headache as their only symptom, and 97.7% had at least one objective abnormality on neurologic examination(14).

Hydration

Children with migraine may have been vomiting prior to emergency room presentation, and their oral intake may have been poor secondary to nausea. The main downside to intravenous rehydration is the need for catheter placement, although about half of pediatric migraineurs (48.4%) will be treated with intravenous therapy in the emergency room and hence will require IV insertion regardless(8). In these patients, fluid replacement is unlikely to be harmful and may be beneficial. Assuring good hydration can also provide renal protection before treating with an NSAID, such as ketorolac, which is important as higher dose ketorolac has been associated with acute renal failure(15). Fluids can also help prevent postural hypotension(16) after treatment with a phenothiazine, such as chlorpromazine.

Opioids

The American Academy of Neurology practice parameter for migraine treatment recommends against using opioids as first-line therapy for acute migraine in adults(17), although they are often prescribed for this purpose nonetheless(18).

In adults, opioids have limited efficacy for acute migraine compared to more specific agents(19-21), with more side effects(22, 23) and potential for dependence(24). Their use is associated with an increased risk of developing chronic migraine(25). Opioids also can precipitate medication overuse headache(26), and appear to decrease the efficacy of other acute rescue medications(27).

While there are no controlled trials comparing the efficacy of opioids to other agents for acute migraine in children, opioids are generally not favored in the treatment of acute migraine in children(11), and their use is considered to be out of keeping with the evidence-base(8). This message appears to be reaching pediatric emergency physicians as they are significantly less likely to prescribe opioids for pediatric migraine than physicians working in a mixed ED environment (6.8% vs 12.9%, p=0.044)(3).

Dopamine receptor antagonists

Dopamine receptor antagonists are useful in treating both migraine head pain and accompanying nausea. The most commonly used agents are chlorpromazine, prochlorperazine, and metoclopramide. Chlorpromazine and prochlorperazine are both phenothiazines, while metoclopramide is in its own class. Many dopamine receptor antagonists have other pharmacologic effects, i.e. anti-histaminic or anti-cholinergic, which may also play a role in their therapeutic effects.

The adult AAN practice parameter recommends treating significant nausea that accompanies migraine, even without vomiting(28). Dopamine receptor antagonists have been used extensively in children to treat nausea and vomiting from a variety of etiologies(29-33), and they are commonly used for this purpose in the emergency room setting(30, 31). Chlorpromazine has also been used to treat children with psychiatric disorders(34, 35) and even to provide systemic vasodilation in neonates undergoing cardiac surgery(36). With regards to pediatric migraine, intravenous dopamine receptor antagonists were the parenteral agents prescribed most frequently in pediatric emergency rooms(8).

While metoclopramide is used most frequently for pediatric migraine in the emergency room setting(8, 9), the evidence for prochlorperazine in children is somewhat stronger(7, 37, 38). In an adult migraine trial in the emergency room setting, prochlorperazine was superior to placebo while metoclopromide was not(39).

In the only randomized trial of treatment for pediatric migraine in the emergency department setting, intravenous prochlorperazine provided relief at one hour in 84.8% of children compared to only 55.2% of those treated with ketorolac(37).

Chlorpromazine has multiple placebo-controlled trials(40, 41) supporting its efficacy in adults, and has been used clinically in pediatric emergency rooms for migraine(8).

The main side effects of dopamine receptor antagonists are sedation and extrapyramidal symptoms, such as dystonia and akathisia. In adults, treatment with diphenhydramine decreases the likelihood of akathisia, but increases sedation(42). Even with diphenhydramine co-administration,at least five percent of children will experience akathisia after prochlorperazine administration(7). Slowing the infusion of metoclopramide to run over fifteen minutes decreases sedation(43) and akathisia(43-46), and does not influence the headache(45) or nausea benefits(45, 46). However, slowing the infusion does not appear to decrease akathisia from prochlorperazine(47). Phenothiazines can also prolong the QT interval, hence it may be prudent to perform a screening ECG prior to administration.

NSAIDs and other non-specific analgesics

Ibuprofen (7.5 mg/kg - 10mg/kg)(48, 49) and acetaminophen (15mg/kg)(49) have been shown in randomized, double-blind placebo controlled trials(49) to be effective in home treatment of acute migraine in studies including children as young as age four. However, the majority of pediatric migraineurs in the emergency room will have already taken one of these oral non-specific analgesics before presentation(9).

Ketorolac was evaluated in the one pediatric migraine trial done in an emergency room setting. Dosing was 0.5mg/kg intravenous to a maximum of 30 mg, and efficacy was 55.2% at one hour(37). Pretreatment with intravenous fluids can provide renal protection, particularly if the child is dehydrated on presentation.

A parenteral form of naproxen is available for pediatric use in Canada(8), while in the U.S. the oral formulation is available. Naproxen 500 mg is effective in treating headache

recurrence after emergency room discharge in adults(50). Diclofenac 75 mg by intramuscular injection was useful in the emergency room setting in adults(51). Intravenous aspirin has a placebo-controlled trial supporting its use in acute migraine in adults(52), however it is not easily obtained in the U.S. as it is not FDA approved. Aspirin is generally avoided in children under 15 years due to concern for Reye's syndrome(28).

Combining an NSAID with a triptan has greater efficacy than either agent alone in adults(53), and the safety of this combination has been studied in adolescents(54). Using an NSAID in conjunction with a dopamine receptor antagonist may also be a useful strategy, particularly for those with significant nausea.

Triptans

Triptans are most efficacious when taken while the head pain is still mild, which tends to be early on in the attack(55, 56). Given that the average duration of pediatric migraine exceeds twenty-four hours by the time they are presenting to the emergency room, and the fact that they have come to the emergency room makes it less likely that their pain is only mild, the response rate of triptans when used in the emergency room is likely to be decreased in the emergency room setting. Indeed, when used within six hours of migraine onset, subcutaneous sumatriptan has 91.2% efficacy in adults(52), while in the emergency room setting it has 75% efficacy(57). Nonetheless, there are multiple trials in adults(57, 58) supporting the use of triptans in the emergency room setting for acute migraine, and while no pediatric specific trials have been done in this setting, triptans remain a potentially useful option. The choice of which route of administration to use (injection, oral or nasal spray triptan) often depends on how severe the child's nausea is and how willing the child is to try an injection or nasal spray medication.

Table 1 summarizes the results of positive randomized acute migraine treatment trials in pediatric patients, including randomized pediatric triptan trials.

Oral triptans—Several oral triptans, including almotriptan, rizatriptan, and zolmitriptan, have positive, placebo-controlled, randomized, double-blind trials supporting their efficacy in pediatric migraineurs. Almotriptan is FDA approved for acute migraine therapy in 12-17 year olds, making it the only triptan with an FDA indication in the pediatric age group(59). In a placebo-controlled parallel group study of almotriptan in adolescents, the two hour pain relief rate was 71.8% with 6.25 mg and 72.9% with 12.5 mg.(59)

Rizatriptan has been studied in younger children, ages 6 to 17(60), and oral zolmitriptan has been studied in children ages 6-18. In the placebo-controlled crossover-design rizatriptan trial, the two-hour pain relief rate was 73-74%.(60). For the three-way crossover-design oral zolmitriptan study, the pain relief rate at two hours was 62% for zolmitriptan, 69% for ibuprofen, and 28% for placebo ($p<0.05$ for the difference between zolmitriptan and placebo)(61). The zolmitriptan study included a *post-hoc* analysis of children under age thirteen that showed the two-hour pain relief rate with zolmitriptan was 64% in this age group, indicating that it was similarly effective for younger children as it was for adolescents(61).

Oral sumatriptan was not different from placebo in a pediatric crossover study(62). A second pediatric oral zolmitriptan study was negative; this was thought to be due to the very high placebo response rate (58%) in the adolescents in this parallel-group study(63).

Nasal spray triptans—Sumatriptan nasal spray is the best-studied triptan in children, with three positive randomized placebo-controlled trials. In two of the studies, children were selected for their "treatment resistance to commonly used antimigraine drugs"(64) such as

acetaminophen (paracetamol) or NSAIDs(65). This is pertinent to treating children in the emergency room setting as many of them have presented because their headache is refractory to an over-the-counter analgesic. In a small randomized, double-blind, placebo controlled study of pre-pubertal children (6.4-9.8 years) improvement of two grades in pain intensity was seen in 86% at two hours compared to 43% in the placebo group (p=0.031), and total headache relief was seen in 64% vs. 14% (p=0.016)(64). In a somewhat larger study in 8-17 year-olds nasal spray sumatriptan had a two-hour efficacy of 64% vs. 39% (p=0.003)(65). In a much larger trial involving adolescents, 56% of those receiving 10 mg or 20 mg sumatriptan nasal spray had headache relief at one hour compared to 41% in the placebo group ($p<0.05$). At two-hours, complete relief was significantly greater in the 20 mg dose group than placebo (36% vs. 25%). In all three trials there were no serious adverse events and the most common side effect was taste disturbance(64-66).

Intranasal sumatriptan is approved for use in adolescents in Europe(67) The joint AAN/ Child Neurology Society 2004 practice parameter regarding treatment of migraine in children states, “sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine in adolescents”(28). Zolmitriptan nasal spray has superior absorption compared to sumatriptan(68, 69). In a double-blind randomized placebo-controlled study of adolescents (ages 12-17) the zolmitriptan treated group (5 mg dose) had a higher one-hour response rate than placebo (58.1% vs. 43.3%, $p<0.05$)(70).

Injectable triptan—Sumatriptan is the only triptan available in an injectable form. It is also the oldest triptan, having been in clinical use in the US since 1993. Subcutaneous sumatriptan has been studied in an open-label fashion in children. In the office setting, 78% of children (ages 6-18) responded within two hours to a dose of 0.06mg/kg(71). A second small open-label study (ages 6-16) used doses of 3 to 6 mg subcutaneously(72). The two smaller children who had received 3 mg were headache free at two hours, and eight of fifteen who received 6 mg experienced headache relief by two hours. There were no major adverse events, and side effects such as unusual sensation in the neck, were brief and mild.

Triptans combined with NSAIDs—In adults, the efficacy of sumatriptan 85 mg/ naproxen 500 mg in combination for home treatment of acute migraine attacks is higher than with either agent alone(53). Such comparative efficacy has not been studied in the pediatric population. However, in open-label home use of sumatriptan 85 mg/naproxen 500 mg over twelve-months, 622 adolescents (ages 12-17) treated over 12,000 migraine attacks without any serious adverse events related to study drug. The overall two-hour pain free rate was 42%(54). This provides a reassuring safety assessment for the use of this combination in the adolescent age group. The synergistic effect is thought to be a triptan/NSAID class effect(73), and hence other triptans, such as almotriptan could be substituted for providers who prefer to prescribe the FDA approved triptan to adolescents. In fact, there is some evidential basis for using an NSAID/almotriptan combination in adults(74).

Dihydroergotamine (DHE)

Dihydroergotamine, an ergot alkaloid or tetracylic ergolene derivative, is effective for acute migraine in adults in intravenous, intramuscular, and intranasal formulations(75). While there are multiple placebo-controlled trials involving dihydroergotamine use in adults, most were performed in the outpatient setting(75). In the emergency room setting, 0.75 mg DHE IV was effective at one hour in 60% of adult patients in a placebo-controlled study(76).

In pediatric migraineurs, repetitive dosing of intravenous DHE has been used on an inpatient basis to treat “status migraine”(77, 78). In one study, on discharge 74.4% of children were headache free, and the majority of those who responded began to improve within the first

five doses. However, it is important to note that the patients were also being treated with IV hydration and dopamine receptor antagonists before the first three doses, hence these other measures may account for some of the benefit seen with the first few doses(78). Nonetheless, this strategy of giving a dopamine-receptor antagonist followed by several doses of intravenous DHE could easily be adapted to treat pediatric migraine in the emergency room setting. The dosage given in the study was 1 mg intravenously every eight hours, with children under 25 kg or under age 10 receiving 0.5 mg(78); weight-based dosing has also been used(79). In an emergency room setting, a second dose could be given an hour after the first if needed(75).

Oral dihydroergotamine, which has very poor bioavailability, was not more effective than placebo at two hours in a small (n=12) pediatric double-blind placebo-controlled cross-over home treatment trial(80).

While DHE does have vasoconstrictive effects, at recommended doses in appropriate patients, serious cardiovascular adverse events in adults are not commonly seen. Nonetheless, uncontrolled hypertension, cardiovascular disease, stroke, and pregnancy are contraindications. Nausea is the most common side effect. While intravenous DHE requires pre-treatment with an anti-emetic, almost certainly because of an emetogenic activation of the dopamine D_2 receptor(81), intramuscular administration is notably less nauseating(75), likely due to its lower C_{max}.

Sodium Valproate

In an open-label retrospective study performed in the clinic setting, 78% of pediatric migraineurs (mean age 15±2 years) achieved desired pain relief after a 1000 mg infusion of sodium valproate at approximately one hour(82). While these results are encouraging, it has to be noted that sodium valproate has never been studied in a placebo controlled trial for acute migraine in adults or children, and the results of randomized studies(83, 84) have efficacy rates notably lower than in open-label series(85-88). Hence the role of sodium valproate in the treatment of acute migraine remains unclear.

Summary treatment recommendations for pediatric migraine patients in the emergency room

Once the diagnosis of migraine has been established, adequate hydration should be provided, either orally or intravenously, if needed. Stimulation, i.e. sounds and light, in the child's treatment environment should be minimized. If there is substantial nausea accompanying the head pain, a dopamine receptor antagonist would be the most useful as these agents treat both pain and nausea. Prochlorperazine is the best-studied agent in this class. If nausea is not a significant component, then triptans, DHE or dopamine receptor antagonists are all reasonable first-line options to consider. Ketorolac and sodium valproate represent additional options. Opioids should be avoided if at all possible. The clinician's choice will be guided by the patient's comorbidities, e.g. hypertension, or pregnancy in adolescent girls, which classes of treatments the patient had already taken before emergency room presentation, and side effect profile.

Strategies for Managing the Patient at ED Discharge

If the child is headache free at emergency room discharge, the therapeutic focus shifts to ensuring the family has the tools they need to treat their next migraine attack effectively at home, thus preventing a repeat emergency room visit. One aspect of this is ensuring that the patient has a follow-up visit in place, ideally with a provider experienced in pediatric

headache. Observational data suggests that pediatric patients who are followed in a headache center are unlikely to come to the ED for an acute attack, though this remains to be studied in a prospective fashion(13).

At discharge the patient must be provided with at least one rescue treatment option that is appropriate for their level of migraine severity. By virtue of having presented to the emergency room, these children have usually demonstrated that they are capable of having at least moderately severe migraine attacks, and hence it may not be appropriate for them to have only non-specific analgesics for home rescue options. The AAN and Child Neurology Society practice parameter recommends the use of “migraine-specific agents in patients whose headaches respond poorly” to NSAIDs or acetaminophen(28). Triptans are migraine-specific therapies that are appropriate for the treatment of moderate and severe migraine attacks. It is possible that clinicians are still uncomfortable prescribing triptans to children, as evidenced by the fact that pediatric migraineurs leaving pediatric emergency rooms received opioids 5.4% of the time but triptans only 1% of the time(8). However, the medical-literature evidence base supporting the use of triptans in children has grown and their treatment should reflect this. For adolescents, almotriptan is FDA approved for acute migraine and should not be withheld in the absence of a medical contraindication. For younger children, or for those whom nausea makes an oral medication untenable, nasal spray sumatriptan and zolmitriptan have been proven efficacious and safe in randomized, placebo-controlled trials. Sumatriptan is available as a generic and some insurance carriers may require a trial of this medication before granting approval of newer triptans. Combining triptans with NSAIDs improves efficacy and reduces rebound headache after ED discharge in adults(89). The efficacy and safety of the combination of sumatriptan and naproxen in adolescents has been established(54). DHE is also a migraine-specific therapy that can be administered at home via nasal spray or injection.

Dopamine receptor antagonists represent another option for home use, particularly with those children who have significant nausea or vomiting. If the clinician has any concerns regarding possible cardiac effects at home, checking an ECG to rule-out long-QT syndrome would be non-invasive and reassuring. Prochlorperazine can be administered at home orally, by injection, or per rectum.

Recurrent emergency room visits for pediatric migraine are not uncommon. In one study, 12% of pediatric migraineurs returned to the ED within seven days(7) and in another 11.2% returned within a month of their initial visit(9); nearly half (42.9%) of this latter group ultimately returned for a third visit(9). Clearly strategies for preventing emergency room bounce back are needed, though no such strategies have been specifically studied in children.

There are some data in adults to suggest that a single parenteral dose of corticosteroids at ED discharge, while not helpful in treating migraine acutely, may decrease the likelihood of headache recurrence at twenty-four hours. Some clinicians have adopted this practice in children, and it appears 2.4%-10% of children with migraine are prescribed corticosteroids on discharge from the emergency room(8, 9). It is important to remember however that many return ED visits for migraine take place after the initial twenty-four hours, and there are no data to suggest that corticosteroids prevent these visits. In fact, corticosteroids did not decrease the likelihood that a child would have a return ED visit within a month(9). Additionally, if the practice were to become widespread, some children could accumulate a significant exposure to corticosteroids with their repeated emergency room visits. While rare, cases of avascular necrosis of the bone have been reported after relatively short courses of oral corticosteroids(90-93).

If the child is not headache free at discharge, a course of standing naproxen may be useful. While naproxen is most often used as an acute migraine therapy, there are several positive trials demonstrating its efficacy as a preventive(94-97), including a positive trend in a small adolescent study wherein patients were treated with 250 mg naproxen twice daily for six weeks (98). One pediatric emergency room incorporates standing naproxen for seven days after discharge as part of their treatment protocol(7). The potential for NSAIDs to cause medication overuse headache is unresolved(26), and in moderate use they protect against conversion to chronic migraine in adults(25). Suitable gastric protection, i.e. a proton-pump inhibitor or H_2 blocker, can be added if necessary.

Admission to the hospital for acute migraine has many downsides, including significant sleep disruption and likely exacerbation of photophobia and phonophobia. Furthermore, admitting the patient provides no guarantee that the headache will break in the hospital, as evidenced by the fact that 25.6% of pediatric patients admitted acutely for “status migraine” were still not headache free after twenty doses of DHE, a treatment course which would have taken nearly seven inpatient days to administer(78). Evidence from adults informs us that the benefit of an inpatient course of intravenous DHE is cumulative through the first month after discharge, with headache freedom obtained in the first few weeks after discharge rather than during the admission in a significant subset of patients(79). Therefore the goal for any admission for migraine should be to provide an adequate dose of DHE, safely and with good nausea control, with the clearly set expectation that the headache will not necessarily abate during the admission.

Conclusions

Migraine is a common pediatric problem in the emergency room. Direct trial evidence for treatment of pediatric migraine in the emergency room is quite limited, therefore clinical decision making is largely guided by adult data and pediatric data collected in the outpatient setting. More pediatric migraine treatment trials in the emergency department setting are clearly needed.

References

1. Lewis DW. Pediatric migraine. Pediatr Rev. 2007; 28:43–53. [PubMed: 17272520]
2. Conicella E, Raucci U, Vanacore N, et al. The child with headache in a pediatric emergency department. Headache. 2008; 48:1005–1011. [PubMed: 18705026]
3. Richer L, Graham L, Klassen T, Rowe B. Emergency department management of acute migraine in children in Canada: a practice variation study. Headache. 2007; 47:703–710. [PubMed: 17501852]
4. Kabbouche MA, Cleves C. Evaluation and management of children and adolescents presenting with an acute setting. Semin Pediatr Neurol. 2010; 17:105–108. [PubMed: 20541102]
5. Abend NS, Younkin D, Lewis DW. Secondary headaches in children and adolescents. Semin Pediatr Neurol. 2010; 17:123–133. [PubMed: 20541105]
6. Trottier ED, Bailey B, Dauphin-Pierre S, Gravel J. Clinical outcomes of children treated with intravenous prochlorperazine for migraine in a pediatric emergency department. J Emerg Med. 2010; 39:166–173. [PubMed: 19150192]
7. Trottier ED, Bailey B, Lucas N, Lortie A. Prochlorperazine in children with migraine: a look at its effectiveness and rate of akathisia. Am J Emerg Med. 2011
8. Richer LP, Laycock K, Millar K, et al. Treatment of children with migraine in emergency departments: national practice variation study. Pediatrics. 2010; 126:e150–155. [PubMed: 20530076]
9. Legault G, Eisman H, Shevell MI. Treatment of pediatric status migrainosus: can we prevent the “bounce back”? J Child Neurol. 2011; 26:949–955. [PubMed: 21555778]
10. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004; 24(Suppl 1):9–160. [PubMed: 14979299]

11. Bulloch B, Tenenbein M. Emergency department management of pediatric migraine. Pediatr Emerg Care. 2000; 16:196–201. [PubMed: 10888462]
12. Lewis DW, Qureshi F. Acute headache in children and adolescents presenting to the emergency department. Headache. 2000; 40:200–203. [PubMed: 10759922]
13. Scagni P, Pagliero R. Headache in an Italian pediatric emergency department. J Headache Pain. 2008; 9:83–87. [PubMed: 18250964]
14. The epidemiology of headache among children with brain tumor. Headache in children with brain tumors. The Childhood Brain Tumor Consortium. J Neurooncol. 1991; 10:31–46. [PubMed: 2022972]
15. Arora S, Wagner JG, Herbert M. Myth: parenteral ketorolac provides more effective analgesia than oral ibuprofen. CJEM. 2007; 9:30–32. [PubMed: 17391598]
16. Loga P, Lewis D. Compazine in Migraine. Emergency Medicine Journal (BMJ). 2007:297–298.
17. Silberstein SD. 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. 2000; 55:754–762. [PubMed: 10993991]
18. Colman I, Rothney A, Wright SC, Zilkalns B, Rowe BH. Use of narcotic analgesics in the emergency department treatment of migraine headache. Neurology. 2004; 62:1695–1700. [PubMed: 15159464]
19. Belgrade MJ, Ling LJ, Schleevogt MB, Ettinger MG, Ruiz E. Comparison of single-dose meperidine, butorphanol, and dihydroergotamine in the treatment of vascular headache. Neurology. 1989; 39:590–592. [PubMed: 2648190]
20. Klapper JA, Stanton J. Current emergency treatment of severe migraine headaches. Headache. 1993; 33:560–562. [PubMed: 8294195]
21. Lane PL, McLellan BA, Baggoley CJ. Comparative efficacy of chlorpromazine and meperidine with dimenhydrinate in migraine headache. Ann Emerg Med. 1989; 18:360–365. [PubMed: 2705667]
22. Carleton SC, Shesser RF, Pietrzak MP, et al. Double-blind, multicenter trial to compare the efficacy of intramuscular dihydroergotamine plus hydroxyzine versus intramuscular meperidine plus hydroxyzine for the emergency department treatment of acute migraine headache. Ann Emerg Med. 1998; 32:129–138. [PubMed: 9701293]
23. Scherl ER, Wilson JF. Comparison of dihydroergotamine with metoclopramide versus meperidine with promethazine in the treatment of acute migraine. Headache. 1995; 35:256–259. [PubMed: 7775186]
24. Buse DC, Pearlman SH, Reed ML, Serrano D, Ng-Mak DS, Lipton RB. Opioid Use and Dependence Among Persons With Migraine: Results of the AMPP Study. Headache. 2012; 52:18–36. [PubMed: 22268775]
25. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache. 2008; 48:1157–1168. [PubMed: 18808500]
26. Dodick D, Freitag F. Evidence-based understanding of medication-overuse headache: clinical implications. Headache. 2006; 46(Suppl 4):S202–211. [PubMed: 17078852]
27. Ho TW, Rodgers A, Bigal ME. Impact of recent prior opioid use on rizatriptan efficacy. A post hoc pooled analysis. Headache. 2009; 49:395–403. [PubMed: 19222588]
28. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004; 63:2215–2224. [PubMed: 15623677]
29. Nahata MC, Ford C, Ruymann FB. Pharmacokinetics and safety of prochlorperazine in paediatric patients receiving cancer chemotherapy. J Clin Pharm Ther. 1992; 17:121–123. [PubMed: 1583079]
30. Mee MJ, Egerton-Warburton D, Meek R. Treatment and assessment of emergency department nausea and vomiting in Australasia: a survey of anti-emetic management. Emerg Med Australas. 2011; 23:162–168. [PubMed: 21489163]

31. Kwon KT, Rudkin SE, Langdorf MI. Antiemetic use in pediatric gastroenteritis: a national survey of emergency physicians, pediatricians, and pediatric emergency physicians. Clin Pediatr (Phila). 2002; 41:641–652. [PubMed: 12462313]
32. Al-Ansari K, Alomary S, Abdulateef H, Alshawagfa M, Kamal K. Metoclopramide versus ondansetron for the treatment of vomiting in children with acute gastroenteritis. J Pediatr Gastroenterol Nutr. 2011; 53:156–160. [PubMed: 21788756]
33. Fujii Y. Clinical management of postoperative vomiting after strabismus surgery in children. Curr Drug Saf. 2010; 5:132–148. [PubMed: 19814703]
34. Correll CU, Harris J, Figen V, Kane JM, Manu P. Antipsychotic drug administration does not correlate with prolonged rate-corrected QT interval in children and adolescents: results from a nested case-control study. J Child Adolesc Psychopharmacol. 2011; 21:365–368. [PubMed: 21823910]
35. Pejovic-Milovancevic M, Miletic V, Popovic-Deusic S, Draganic-Gajic S, Lecic-Tosevski D, Marotic V. Psychotropic medication use in children and adolescents in an inpatient setting. Psychiatrike. 2011; 22:314–319. [PubMed: 22271844]
36. Imoto Y, Kado H, Masuda M, Yasui H. Effects of chlorpromazine as a systemic vasodilator during cardiopulmonary bypass in neonates. Jpn J Thorac Cardiovasc Surg. 2002; 50:241–245. [PubMed: 12073600]
37. Brousseau DC, Duffy SJ, Anderson AC, Linakis JG. Treatment of pediatric migraine headaches: a randomized, double-blind trial of prochlorperazine versus ketorolac. Ann Emerg Med. 2004; 43:256–262. [PubMed: 14747817]
38. Kabbouche MA, Vockell AL, LeCates SL, Powers SW, Hershey AD. Tolerability and effectiveness of prochlorperazine for intractable migraine in children. Pediatrics. 2001; 107:E62. [PubMed: 11335783]
39. Coppola M, Yealy DM, Leibold RA. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. Ann Emerg Med. 1995; 26:541–546. [PubMed: 7486359]
40. McEwen JI, O'Connor HM, Dinsdale HB. Treatment of migraine with intramuscular chlorpromazine. Ann Emerg Med. 1987; 16:758–763. [PubMed: 3592329]
41. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. J Emerg Med. 2002; 23:141–148. [PubMed: 12359281]
42. Vinson DR, Drotts DL. Diphenhydramine for the prevention of akathisia induced by prochlorperazine: a randomized, controlled trial. Ann Emerg Med. 2001; 37:125–131. [PubMed: 11174228]
43. Tura P, Erdur B, Aydin B, Turkcuer I, Parlak I. Slow infusion metoclopramide does not affect the improvement rate of nausea while reducing akathisia and sedation incidence. Emerg Med J. 2012; 29:108–112. [PubMed: 21292793]
44. Regan LA, Hoffman RS, Nelson LS. Slower infusion of metoclopramide decreases the rate of akathisia. Am J Emerg Med. 2009; 27:475–480. [PubMed: 19555621]
45. Parlak I, Erdur B, Parlak M, et al. Intravenous administration of metoclopramide by 2 min bolus vs 15 min infusion: does it affect the improvement of headache while reducing the side effects? Postgrad Med J. 2007; 83:664–668. [PubMed: 17916877]
46. Parlak I, Atilla R, Cicek M, et al. Rate of metoclopramide infusion affects the severity and incidence of akathisia. Emerg Med J. 2005; 22:621–624. [PubMed: 16113179]
47. Vinson DR, Migala AF, Quesenberry CP Jr. Slow infusion for the prevention of akathisia induced by prochlorperazine: a randomized controlled trial. J Emerg Med. 2001; 20:113–119. [PubMed: 11207403]
48. Lewis DW, Kellstein D, Dahl G, et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine. Headache. 2002; 42:780–786. [PubMed: 12390641]
49. Hamalainen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology. 1997; 48:103–107. [PubMed: 9008503]

50. Friedman BW, Solorzano C, Esses D, et al. Treating headache recurrence after emergency department discharge: a randomized controlled trial of naproxen versus sumatriptan. Ann Emerg Med. 2010; 56:7–17. [PubMed: 20303198]
51. Engindeniz Z, Demircan C, Karli N, et al. Intramuscular tramadol vs. diclofenac sodium for the treatment of acute migraine attacks in emergency department: a prospective, randomised, double-blind study. J Headache Pain. 2005; 6:143–148. [PubMed: 16355295]
52. Diener HC, The ASASUMAMIG Study Group. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. Cephalalgia. 1999; 19:581–588. discussion 542. [PubMed: 10448545]
53. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. JAMA. 2007; 297:1443–1454. [PubMed: 17405970]
54. McDonald SA, Hershey AD, Pearlman E, et al. Long-term evaluation of sumatriptan and naproxen sodium for the acute treatment of migraine in adolescents. Headache. 2011; 51:1374–1387. [PubMed: 21797863]
55. Goadsby PJ, Zanchin G, Geraud G, et al. Early vs. non-early intervention in acute migraine-'Act when Mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan. Cephalalgia. 2008; 28:383–391. [PubMed: 18294251]
56. Diaz-Insa S, Goadsby PJ, Zanchin G, Fortea J, Falques M, Vila C. The impact of allodynia on the efficacy of almotriptan when given early in migraine: data from the "act when mild" study. Int J Neurosci. 2011; 121:655–661. [PubMed: 21777163]
57. Akpunonu BE, Mutgi AB, Federman DJ, et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study. Ann Emerg Med. 1995; 25:464–469. [PubMed: 7710149]
58. Meredith JT, Wait S, Brewer KL. A prospective double-blind study of nasal sumatriptan versus IV ketorolac in migraine. Am J Emerg Med. 2003; 21:173–175. [PubMed: 12811706]
59. Linder SL, Mathew NT, Cady RK, Finlayson G, Ishkanian G, Lewis DW. Efficacy and tolerability of almotriptan in adolescents: a randomized, double-blind, placebo-controlled trial. Headache. 2008; 48:1326–1336. [PubMed: 18484981]
60. Ahonen K, Hamalainen ML, Eerola M, Hoppu K. A randomized trial of rizatriptan in migraine attacks in children. Neurology. 2006; 67:1135–1140. [PubMed: 16943370]
61. Evers S, Rahmann A, Kraemer C, et al. Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. Neurology. 2006; 67:497–499. [PubMed: 16775229]
62. Hamalainen ML, Hoppu K, Santavuori P. Sumatriptan for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine respond to oral sumatriptan differently from adults? Neurology. 1997; 48:1100–1103. [PubMed: 9109909]
63. Rothner AD, Wasiewski W, Winner P, Lewis D, Stankowski J. Zolmitriptan oral tablet in migraine treatment: high placebo responses in adolescents. Headache. 2006; 46:101–109. [PubMed: 16412157]
64. Ueberall MA, Wenzel D. Intranasal sumatriptan for the acute treatment of migraine in children. Neurology. 1999; 52:1507–1510. [PubMed: 10227648]
65. Ahonen K, Hamalainen ML, Rantala H, Hoppu K. Nasal sumatriptan is effective in treatment of migraine attacks in children: A randomized trial. Neurology. 2004; 62:883–887. [PubMed: 15037686]
66. Winner P, Rothner AD, Saper J, et al. A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. Pediatrics. 2000; 106:989–997. [PubMed: 11061765]
67. Agency, EM. [Accessed March 12, 2012] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004039.pdf
68. Duquesnoy C, Mamet JP, Sumner D, Fuseau E. Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. Eur J Pharm Sci. 1998; 6:99–104. [PubMed: 9795022]

69. Yates R, Nairn K, Dixon R, Kemp JV, Dane AL. Pharmacokinetics, dose proportionality, and tolerability of single and repeat doses of a nasal spray formulation of zolmitriptan in healthy volunteers. J Clin Pharmacol. 2002; 42:1244–1250. [PubMed: 12412823]
70. Lewis DW, Winner P, Hershey AD, Wasiewski WW. Efficacy of zolmitriptan nasal spray in adolescent migraine. Pediatrics. 2007; 120:390–396. [PubMed: 17671066]
71. Linder SL. Subcutaneous sumatriptan in the clinical setting: the first 50 consecutive patients with acute migraine in a pediatric neurology office practice. Headache. 1996; 36:419–422. [PubMed: 8783473]
72. MacDonald JT. Treatment of juvenile migraine with subcutaneous sumatriptan. Headache. 1994; 34:581–582. [PubMed: 7843952]
73. Cleves C, Tepper SJ. Sumatriptan/naproxen sodium combination for the treatment of migraine. Expert Rev Neurother. 2008; 8:1289–1297. [PubMed: 18759540]
74. Schoenen J, De Klippel N, Giurgea S, et al. Almotriptan and its combination with aceclofenac for migraine attacks: a study of efficacy and the influence of auto-evaluated brush allodynia. Cephalalgia. 2008; 28:1095–1105. [PubMed: 18644036]
75. Saper JR, Silberstein S. Pharmacology of dihydroergotamine and evidence for efficacy and safety in migraine. Headache. 2006; 46(Suppl 4):S171–181. [PubMed: 17078849]
76. Callaham M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. Headache. 1986; 26:168–171. [PubMed: 3519528]
77. Linder SL. Treatment of childhood headache with dihydroergotamine mesylate. Headache. 1994; 34:578–580. [PubMed: 7843951]
78. Kabbouche MA, Powers SW, Segers A, et al. Inpatient treatment of status migraine with dihydroergotamine in children and adolescents. Headache. 2009; 49:106–109. [PubMed: 19125879]
79. Nagy AJ, Gandhi S, Bhola R, Goadsby PJ. Intravenous dihydroergotamine for inpatient management of refractory primary headaches. Neurology. 2011; 77:1827–1832. [PubMed: 22049203]
80. Hamalainen ML, Hoppu K, Santavuori PR. Oral dihydroergotamine for therapy-resistant migraine attacks in children. Pediatr Neurol. 1997; 16:114–117. [PubMed: 9090684]
81. Cook RO, Armer TA. Precise pulmonary delivery of dihydroergotamine and exploration of reduce adverse effect profile. Cephalalgia. 2009; 29:107.
82. Reiter PD, Nickisch J, Merritt G. Efficacy and tolerability of intravenous valproic acid in acute adolescent migraine. Headache. 2005; 45:899–903. [PubMed: 15985107]
83. Leniger T, Pageler L, Stude P, Diener HC, Limmroth V. Comparison of intravenous valproate with intravenous lysine-acetylsalicylic acid in acute migraine attacks. Headache. 2005; 45:42–46. [PubMed: 15663612]
84. Tanen DA, Miller S, French T, Riffenburgh RH. Intravenous sodium valproate versus prochlorperazine for the emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial. Ann Emerg Med. 2003; 41:847–853. [PubMed: 12764341]
85. Shahien R, Saleh SA, Bowirrat A. Intravenous sodium valproate aborts migraine headaches rapidly. Acta Neurol Scand. 2011; 123:257–265. [PubMed: 20569223]
86. Mathew NT, Kailasam J, Meadors L, Chernyschev O, Gentry P. Intravenous valproate sodium (depacon) aborts migraine rapidly: a preliminary report. Headache. 2000; 40:720–723. [PubMed: 11091289]
87. Hering R, Steiner TJ. Sodium valproate for acute migraine attacks. Cephalalgia. 1994; 14:305–306. [PubMed: 7954764]
88. Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. Headache. 2001; 41:976–980. [PubMed: 11903525]
89. Krymchantowski AV. Naproxen sodium decreases migraine recurrence when administered with sumatriptan. Arq Neuropsiquiatr. 2000; 58:428–430. [PubMed: 10920403]

90. Fast A, Alon M, Weiss S, Zer-Aviv FR. Avascular necrosis of bone following short-term dexamethasone therapy for brain edema. Case report. J Neurosurg. 1984; 61:983–985. [PubMed: 6491744]
91. Watkins S, Williams JR. Avascular necrosis of bone after high doses of dexamethasone during neurosurgery. Br Med J (Clin Res Ed). 1982; 284:742.
92. McCluskey J, Gutteridge DH. Avascular necrosis of bone after high doses of dexamethasone during neurosurgery. Br Med J (Clin Res Ed). 1982; 284:333–334.
93. Anderton JM, Helm R. Multiple joint osteonecrosis following short-term steroid therapy. Case report. J Bone Joint Surg Am. 1982; 64:139–141. [PubMed: 7054196]
94. Sargent J, Solbach P, Damasio H, et al. A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. Headache. 1985; 25:320–324. [PubMed: 3902723]
95. Welch KM, Ellis DJ, Keenan PA. Successful migraine prophylaxis with naproxen sodium. Neurology. 1985; 35:1304–1310. [PubMed: 4022376]
96. Bellavance AJ, Meloche JP. A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. Headache. 1990; 30:710–715. [PubMed: 2074163]
97. Ziegler DK, Ellis DJ. Naproxen in prophylaxis of migraine. Arch Neurol. 1985; 42:582–584. [PubMed: 4004602]
98. Lewis D, Middlebrook MT, Deline C. Naproxen sodium for chemophrophylaxis of adolescent migraine. Ann Neurol. 1994; 36:542.

Table 1

Positive Randomized Trials of Acute Therapies in Pediatric Migraineurs

Agent:	Trial design:	Clinical setting:	Ages studied (years):	Dosing:	Pain relief:	Contra-indications:
Non-specific analgesics						
Acetaminophen(49)	Double-blind, placebo-controlled, crossover	Home	4-15	15mg/kg PO	54% at 2 hours	•Liver failure
NSAIDs						
Ibuprofen(48, 49)	Double-blind, placebo-controlled, crossover(49)	Home	4-15	10mg/kg PO	68% at 2 hours	•Active GI bleeding •Significant renal impairment
	Double-blind, parallel group(48)	Home	6-12	7.5mg/kg	76% at 2 hours	
Ketorolac(37)	Double-blind; no placebo	Emergency department	7-18	0.5mg/kg IV; max 30 mg	55.2 % at 1 hour	
Dopamine receptor antagonists						
Prochlorperazine (37)	Double-blind; no placebo	Emergency department	7-18	0.15mg/kg IV; max 10 mg	84.8 % at 1 hour	•Long QT syndrome •Movement disorder
Triptans:						
Almotriptan*	Double-blind, placebo-controlled, parallel-group	Home	12-17	6.25 or 12.5 mg PO	71.8-72.9 % at 2 hours	•History of stroke or cardiovascular disease •Uncontrolled hypertension •Pregnancy(?) •Hemiplegic migraine
Rizatriptan(60)	Double-blind, placebo-controlled	Home	6-17	20-39kg→ 5mg PO ≥40 kg→10 mg	73-74% at 2 hours	
Zolmitriptan(61, 70)	Double-blind, placebo-controlled, crossover(61)	Home	6-18	2.5 mg PO	62% at 2 hours, 64% in those <13	
	Double-blind, placebo-controlled, crossover(70)	Home	12-17	5 mg NS	58.1 % at 1 hour	
Sumatriptan(64-66) **	Double-blind, placebo-controlled(64)	Home	6-9	20 mg NS	86% at 2 hours	
	Double-blind, placebo-controlled(66)	Home	12-17	5-20 mg NS	66% at 2 hours	

Agent:	Trial design:	Clinical setting:	Ages studied (years):	Dosing:	Pain relief:	Contra-indications:
	Double-blind, placebo-controlled, crossover(65)	Home	8-17	20-39kg→10 mg ≥40 kg→ 20 mg	64% at 2 hours	

*Almotriptan is FDA-approved for acute migraine treatment in 12-17 year olds

**2004 AAN practice parameter recommends consideration of nasal spray sumatriptan for acute migraine in pediatric patients, and it is approved in Europe for adolescents.

NS=nasal spray, PO=per os, IV=intravenous