Sumatriptan for Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with refractory migraine is sumatriptan an effective treatment for refractory migraine in the ED?

Question Originator:

Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Based on very low quality evidence, the Migraine in the ED CPG team makes a conditional recommendation that sumatriptan may be considered to treat a patient who presents with a refractory migraine. The AAN Practice Parameter (Lewis et al., 2004) states sumatriptan is effective for acute migraine. However, (Hamalainen, Hoppu, & Santavuori, 1997) reported no difference in pain at 2 hours between children treated with sumatriptan (PO) or placebo (N= 46) OR = 0.09, 95% CI [0.17, 0.34]. (Winner, Rothner, Wooten, Webster, & Ames, 2006) compared sumatriptan nasal spray at two doses to placebo. They report pain relief at two hours was significantly better at 2 hours with 20mG of sumatriptan (nasal spray).There is reporting and attrition bias in this report. Although they report ITT analysis, per protocol analysis was used in the report, and the denominator of included subjects varies. (McDonald et al., 2011) reported the results of a long term cohort study on use of sumatriptan (PO) on migraine. Ninety-one percent (7791/8517) migraines were treated with sumatriptan/naproxen alone and rescue medications were not needed. Forty-two percent of the migraines were pain free within two hours of administration, and rescue medications were not required. This study is indirect evidence to the question, as treatment was started at home, at first sign of a migraine, not in the ED. It is recommended that sumatriptan be taken when migraine symptoms are first noticed (Scholpp, Schellenberg, Moeckesch, & Banik, 2004). Patients who present to the ED for the management of their migraine pain have usually had a migraine for a longer time.

Dihydroergotamine should not be administered if sumatriptan has been taken within the past 24 hours. (Lexicomp Online, 2013)

EBP Scholar's responsible for analyzing the literature:

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Search Strategy and Results:

Studies included in this review:

Hamalainen 1997

McDonald 2011

Winner 2006

Studies <u>not</u> included in this review with rationale for exclusion:

Author	Reason for Exclusion
Ahonen 2004	Home treatment with sumatriptan spray

(Berenson et al., 2010)	Not acute treatment in an ED or UCC
(Bhattacharyya, Laha, & Gangopadhyay, 2012)	Did not randomize; this is a case series
(Boureau, Chazot, Emile, Bertin, & d'Allens, 1995)	Did not blind subjects or providers
(Burstein, Collins, & Jakubowski, 2004)	Not blinded, allocation was not concealed
(Derosier et al., 2012)	Adult subjects, study of the efficacy of butalbital containing products
(Dodick, Brandes, Elkind, Mathew, & Rodichok, 2005)	Adult subjects, and treatment to begin at home, not the ED
(Hewitt et al., 2013)	Home treatment with rizatriptan orally disintegrating tablet
(Ho et al., 2012)	Did not include sumatriptan
(Kelly, Ardagh, Curry, D'Antonio, & Zebic, 1997)	Adult subjects; poor randomization- by date of presentation; non-inferiority study of sumatriptan vs. chlorpromazine
(Lampl, Huber, Haas, Rittberger, & Diener, 2008)	Subjects were randomized after self-selection by asking if they wanted to in re-evaluate their migraine attacks
(Linder et al., 2008)	Did not include sumatriptan
(Meredith, Wait, & Brewer, 2003)	Adult subjects, included in the ketorolac CAT
(Rahimdel, Mellat, Zeinali, Jafari, & Ayatollahi, 2014)	Adult subjects, included in the valproic acid CAT
(Rothner, Wasiewski, Winner, Lewis, & Stankowski, 2006)	Adult subjects, zolmitriptan study
	Adult subjects, answers the question abo
(Tfelt-Hansen, Bach, Daugaard, Tsiropoulos, & Riddersholm, 2006)	Adult subjects
(Winner et al., 2002)	Did not include sumatriptan
(Winner, Adelman, Aurora, Lener, & Ames, 2006)	Adult subjects

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5) (Higgins & Green, 2011),

Tables:

Characteristics of included study:

Hamalainen 1997

Methods	Randomized placebo-controlled, double-blind, crossover

Participants	**Setting:** Helsinki, Finland in 3 Pediatric Hospitals between February 1994 and October 1995 **Randomized:**31 -crossover study- all received both medications-study does not give info for who got what first **Completed:** 23-crossover study- all received both medications-study does not give info for who got what first **Gender:** 48% male **Age:** Children age 8.3-16.4 years **Inclusion:** Children over 8 years who suffered at least two migraine attacks per month, Meeting IHS criteria, had not benefitted from previous meds **Exclusion:** Children with renal, hepatic, or cardiovascular disease, who needed other treatment for their headache, on any continuous daily oral drug therapy, prophylactic drug therapy for migraine **Power analysis:** 11 to 20 children were required for 80% power and 5% significant level
Interventions	50mG Sumatriptan tablet for body surface area of 0.75 to 1.5m² (corresponding to approx. 6 to 12 yrs of age), and 100mG Sumatriptan for a body surface area of 1.5m² or more (approximate age over 12 years) Each patient received two identical packages, both containing either one or two 50mG capsules of sumatriptan or placebo
Outcomes	**Primary outcome**: reduction of pain intensity by at least 50% after 2 hours, 100 pt VAS **Secondary:** Headache severity using visual analog scale (VAS) at time points before treatment, at 30 min, at 60 min, and continuing hourly for 5 hours, Parents report-nausea, mobility, and expressions of pain, grading of headache, and choosing which treatment worked best at end of study
Notes	Pain Intensity Difference- (PID) is an estimate of pain relief at each time point Summed Pain Intensity Difference (SPID) gives an estimate of overall pain relief during a time period

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	randomized, double-blind, placebo-controlled, crossover trial
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Investigators were blinded as well as participants.
Blinding of outcome assessment (detection bias)	Low risk	Treatment was recorded as a success or a failure before the blind was broken.

Incomplete outcome data (attrition bias)	High risk	8 of 31 did not complete the study, the study reports on the 23 completers (74% of those recruited), Reasons for non-participation may affect results, tablet too large to swallow, inappropriate recruiting- not enough headaches in the study period
Selective reporting (reporting bias)	Low risk	primary and secondary outcomes are reported
Other bias	Unclear risk	Although randomized, initial pain score was higher in the placebo group, and remained higher throughout the study.

McDonald 2011

Methods	Open-Label Cohort
Participants	**Setting:** This study was an open-label, uncontrolled, long-term (12 months), multi-center (70) study (USA) of adolescents, from July 2007 to August 2009. **Participants:** N = 656 subjects enrolled, N = 622 (95%) treated at least 1 migraine with sumatriptan/naproxen sodium. **Age (mean):** N = 14.7 (1.68) **Completed:** Of the 656 subjects in the enrolled population, 78% (511/656), 66% (435/656), 59% (390/656), and 55% (363/656) completed the study visits at 3, 6, 9, and 12 months respectively. **Gender:** Male = 255 (41%) Female = 367 (59%) Race: 85% White (Caucasian); 12% African American; 2% Native American; 1% Other **Inclusion Criteria:** Subjects were to be 12-17 years old and were to have had an average of 2-8 migraines per month meeting the International Classification of Headache Disorders (ICHD-II) which typically lasted 2 hours, if untreated, for >6 months. **Exclusion Criteria:** Uncontrolled hypertension; 3 cardiovascular or any cerebrovascular risk factors; contraindications or hypersensitivities to sumatriptan or naproxen; weighed <75 pounds (33.3 kg); history of epilepsy or structural brain lesions; use of methysergide or dihydroergotamine in the past 3 months; use of daily medications that were not stabilized (dose changes in the past 2 months) or had taken or were planning to take monoamime oxidase inhibitor, preparations containing St. John's Wort (Hypericum perforatum) within 2 weeks of screening through 2 weeks after last treatment; 15 headache days per month; retinal, basilar, or hemiplegic migraine, as well as secondary headaches; positive pregnancy test or the presence of substances on toxicology screen that could not be attributed to treatment of an underlying medical condition. In addition, female adolescents of childbearing potential were required to perform urine pregnancy tests at all study visits and every 6 weeks.
Interventions	All subjects were instructed to treat migraines with a single fixed-dose tablet of sumatriptan and naproxen sodium (sumatriptan 85 mG and naproxen sodium 500 mG) and beginning 2 hours post dose, they were allowed to rescue with a single dose of a naproxen containing product, over-the-counter pain reliever

	(not to exceed the daily recommended dose), or anti-emetics; repeat doses of sumatriptan/naproxen sodium were required to be separated by a 24-hour pain-free period.
Outcomes	Evaluate the long-term safety, tolerability, effectiveness, impact on quality of life, and medication satisfaction of sumatriptan/naproxen sodium in the acute treatment of migraine headache in adolescents.
Notes	**Baseline Symptoms and Pain Freedom Post Treatment:** • 602 subjects recorded data in the electronic diary, of which 591 provided post-baseline data. • On average, subjects treated 86% (8517) of their migraines with sumatriptan/naproxen sodium during the study. **Rescue Medication:** • Of the 8517 migraine attacks, 91% (7791) were not associated with rescue medication use. • Of the 8517 migraine attacks, 90% (7657) were not associated with rescue medication use or prohibited medication use. **2-hour pain Free:** • 42% (3596) of attacks were migraine pain-free within 2hours of administration of sumatriptan/naproxen sodium, without rescue or prohibited medication use. **Adverse Events:** • Of subjects who took at least 1 dose of sumatriptan/naproxen sodium, at least 1 adverse event was reported: of any severity (63%; 393/622); of moderate-to-severe intensity (42%; 264/622); potentially related to study drug (27%; 170/622); or that met criteria for serious (<1%; 4/622). • Within 3 days of taking sumatriptan/naproxen sodium, at least 1 adverse event was reported: of any severity (11%; 1116/9989); of moderate-to-severe intensity (5%; 492/9989); potentially related to study drug (9%; 906/9989); • The most commonly reported adverse events across both age groups (4%) were nausea (9%), upper respiratory tract infection (9%), nasopharyngitis (8%), sinusitis (6%), and dizziness (4%). Nausea (44/622; 7%) remained the most common adverse event deemed treatment-related by investigators, followed by dizziness (20/622; 3%), muscle tightness (18/622; 3%), and chest discomfort (16/622; 3%). • There were minor differences (<5%) between the age groups in the incidence of the most commonly reported adverse events.

Winner 2006

Methods	Randomized, placebo-controlled, double-blind, parallel-group, multi-center, single-attack, out-patient study
Participants	**Setting**: Multi-site: Palm Beach Headache Center, The Cleveland Clinic, Raleigh Neurology Associates, GlaxoSmithKline, Research Triangle Park, **Randomized:** Intent to treat=888 subjects • Per protocol=738

	• Placebo=245 • Sumatriptan NS 5mG=255 • Sumatriptan NS 20mG=238 **Completed:** • Placebo- (ITT=244, PP=233) • Sumatriptan NS 5mG-(ITT=250,PP=239) • Sumatriptan 20mG-(IT=237, PP=222) **Gender:** Majority was female **Inclusion criteria**: 12 to 17yrs of age, history of migraine of at least 6 months, IHS criteria **Exclusion criteria:** Ischemic or vasospastic coronary artery disease, confirmed or suspected cardiovascular disease, Prinzmetal's angina, systemic lupus erythematosus, Kawasaki disease, homozygous sickle cell anemia, recurrent syncope, cardiac arrhythmias requiring medication, atherosclerotic disease (including ischemic bowel disease) uncontrolled hypertension for age, Raynaud's syndrome, or epilepsy or chronic daily headaches. **Power analysis:** 232 subjects per treatment group were needed to detect a statistically significant difference (with a power analysis of 0.90 at a significance level of 0.50)
Interventions	**Intervention 1:** Sumatriptan Nasal Spray 5mG -up to 2 doses prn N=239 **Intervention 2:** Sumatriptan Nasal Spray 20mG-up to 2 doses prn N=222 **Placebo Nasal Spray:** up to 2 doses prn N=233
Outcomes	1hour headache relief, sustained relief from 1 to 24 hours,
Notes	There is a discrepancy here between the Scholar's use of the terms Per Protocol and Intent to treat and my understanding. They dropped subjects from the study if they did not get a complete data set from them, and thereby reducing both the per protocol and the intent to treat numbers. I am reporting the full numbers in the table here which are not fully disclosed on Fig. 1 in the article.

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	computer generated randomization sequence in blocks of 6
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	identical NS devices for all groups

Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	

Figures:

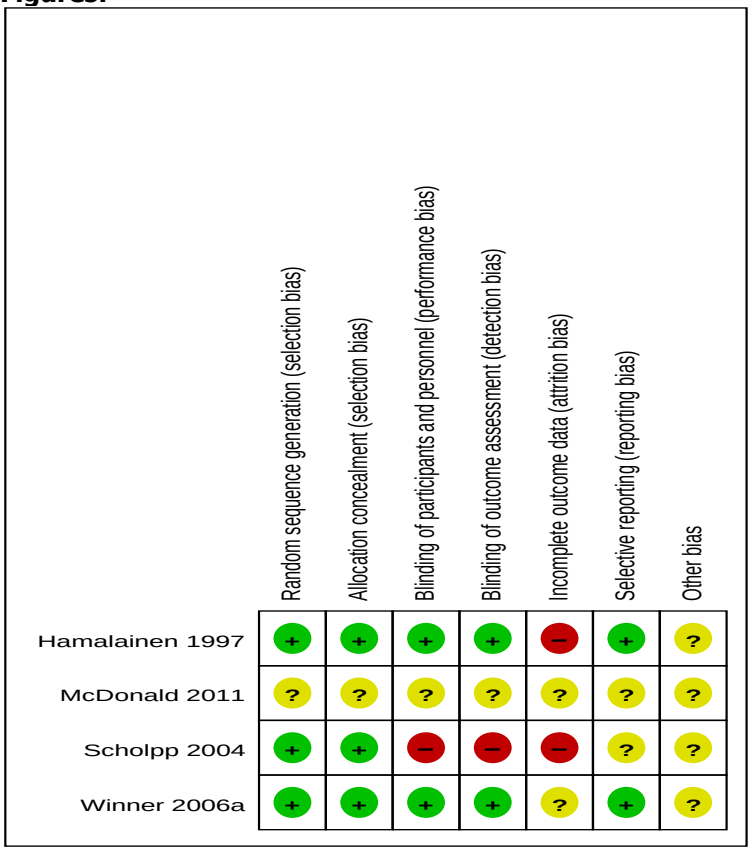

Figure 1. Risk of bias in included studies