Dihydroergotamine, Then and Now
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Background
• Migraine is common, affecting 10% of women and 6% of men worldwide, with a lifetime prevalence of 31% in the US.
• Migraine is associated with disability, decreased work productivity, and increased healthcare costs.

Figure 1. Historical Timeline of Development of Ergot alkaloids for Medical Use (Then and Now)

Objective
• We provide a history of DHE from its synthesis in 1943 to modern day formulations and routes of administration.
• This review highlights existing evidence for the effectiveness of DHE for acute migraine with a focus on some routes of administration for DHE.

Figure 2. Dihydroergotamine (mesylate) – the Molecules

Table 1: Comparison of PK Parameters for Different Formulations of DHE and Reconstituted formulations

Table 2: Rates of Pain Relief, Pain Freedom, and Treatment Effects (Active Maximal Pain Relief Time) at 3 Hours for Different Doses 

Figure 3. Relative Strength of DHE – Then and Now

DHE – Then
• DHE was approved for migraine in 1946.
• DHE is recommended as an alternative to triptans for treating acute migraine.
• DHE is available for intravenous, subcutaneous (SC), intramuscular (IM), and nasal administration.
• DHE is approved for IV, IM, and SC administration but not for nasal administration.

Migraine
• The worldwide prevalence of migraine is 14.6% and along with tension headache is estimated to affect 1 in 10 adult Americans.
• Migraine represents one of the leading causes of disability worldwide.
• In the U.S., annual costs for healthcare and productivity lost from migraine are estimated at $27 billion. In Europe, annual costs are estimated at €7 billion.

Figure 4. Intravenous Delivery of MAG-3 (Technology* - Labeled Peptide) by POD Versus a Nasal Pump (SPECT Imaging) in 7 Healthy Subjects

Pharmacology of Nasal Drug Delivery
• DHE solution has low bioavailability and large inter- and intra-subject variability and a long terminal phase constant (T1/2) that limits efficacy.
• Drug delivery via the highly vascularized epithelial surface of the upper nasal cavity leads to more consistent and predictable systemic absorption.
• Delivery to the olfactory epithelium decreases the likelihood of drug exiting the orbit of the nose, where it may be caught by the oral and nasal cavities or reduced by mucociliary clearance.

Figure 5. Contrasting Plumes of DHE Propelled From POD (left panel) and Magistral Nasal Spray (right panel)

Figure 6. Plasma DHE Concentrations: Following Administration of Single Doses of IMP104, IV DHE, and DHE Nasal Spray

Summary
• DHE has a valuable role in the treatment of migraine.
• In spite of recent injectable DHE shortages, the US physicians are writing approximately 50,000 prescriptions for DHE a year (all formats combined), showing that there is still a demand for the drug.

References
• Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine.
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