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## Adverse Side Effects of Intranasal Detemir Insulin in the SNIFF Trial

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Insulin signaling is impaired in Alzheimer's disease [1]. In the SNIFF Trial, Claxton et al. have reported that long-acting intranasal insulin Detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease [2]. Adverse effects included mild rhinitis. In an earlier publication, Craft et al. note 8.3% nosebleeds and 16.7% rhinitis with a 20 IU intranasal insulin dose [3]. The SNIFF trial has been "temporarily suspended" (<http://www.nia.nih.gov/alzheimers/clinical-trials/study-nasal-insulin-fi...>). Insulin glulisine (Apidra) failed to have an acute impact on cognition in APOE4 carriers with mild-moderate Alzheimer's disease, but other intranasal insulin preparations were also ineffective in ApoE4 carriers [4,5].

Off the shelf injectable insulins, such as Detemir, Humalog, Apidra, etc., contain various excipients that may be responsible for rhinitis, nosebleeds, and allergic reactions [6]. Chief among these are cresol, meta-cresol, and phenol. These three compounds are added to injectable insulin to stabilize it and extend its shelf life. But their potential for causing severe allergic reactions is well documented [7].

Zinc, another component of Detemir and Humalog but not Apidra, has less potential for harm. Zinc is added to insulin preparations to prolong their action by causing the insulin monomers to form hexamers.

Zicam, a homeopathic nasal gel for the common cold containing 33 mM zinc, was ineffective [8] and was associated with anosmia [9]. However, the concentration of zinc in Detemir is 1 mM, or 3% of the zinc concentration in Zicam. Moreover, there were no reports of anosmia as an adverse effect in the SNIFF study.

In sum, an intranasal insulin preparation containing no cresol, metacresol, or phenol might be a better formulation for treatment of Alzheimer's disease than regular injectable insulins.

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**Disclosure:** Dr. Lehrer has filed a patent application on the use of preservative-free nasal insulin for the treatment of Alzheimer's disease.

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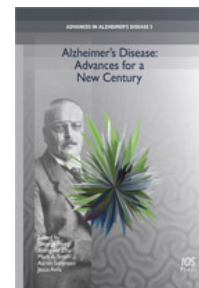
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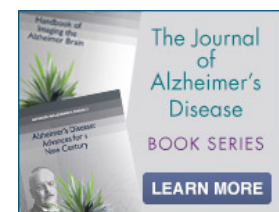
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