Opinion / For Discussion

The claims of medical foods

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Abstract

Health claims for medical foods

Souvenaid (Nutricia, Zoetermeer, the Netherlands) is a medical food for the dietary management of early Alzheimer’s disease. The mix of nutrients in this drink is suggested to have a beneficial effect on cognitive function; such implicit health claims for medical foods are not checked by government agencies. Souvenaid has been investigated in three clinical trials. The first trial showed that Souvenaid produced a significant improvement in delayed verbal recall, but not in other psychological tests. The second and largest trial showed no effect on any outcome. The third trial showed no significant effect at 12 or 24 weeks, but a significant difference in the 24-week time course of the composite memory score. None of these outcomes was clearly specified as a primary outcome at trial registration. In conclusion, there is no convincing proof that Souvenaid benefits cognitive function. Better scrutiny of the efficacy of medical foods is warranted.
Dietary foods for special medical purposes, or medical foods in short, serve to provide nutrients to malnourished patients. Patients may become malnourished if they cannot eat properly or lack appetite. A drink with a pleasant taste and a high concentration of vitamins, protein and other nutrients might perhaps help in such a case.¹

There is little supervision over medical foods. The producer must submit the label and the composition of the product to the Dutch Food and Merchandise Authority (NVWA), but the NVWA only checks whether the product does no harm and that it meets human nutrient needs. However, producers suggest that some products do more than just providing nutrients. Thus, Cubitan is suggested to contribute to healing of pressure sores, and Souvenaid is suggested to reduce memory loss in patients with early Alzheimer’s dementia. Nutricia manufactures both products.

Patients can purchase products such as Souvenaid themselves, but that costs 1300 euros per year. If the patient’s physician fills out a ZN medical declaration, health insurance companies will reimburse the costs. A physician who receives such a request will want to know whether the product is effective. Nutricia says "nutrients can have a major influence on the pathophysiology and progression of Alzheimer's disease" (www.souvenaid.nl) and the company refers to a publication which states: "data from this study suggest that Souvenaid has a beneficial effect on cognitive function in mild Alzheimer's disease."² But Souvenaid is not authorized as a medicine. The suggestion that it counters decline of memory in early Alzheimer’s disease has not been evaluated by the European Food Safety Authority (EFSA), the agency which assesses health claims for foods. In the absence of government assessment the physician must decide for him- or herself whether the product works.

In my opinion, supervision over these quasi-drugs is deficient. The case of Souvenaid also illustrates problematic aspects of the cooperation between companies and researchers in the field of nutrition and health.

WHAT IS SOUENNAID?

Souvenaid is intended for ‘dietary management of the early stages of Alzheimer’s disease.’ The name appears to be a combination of 'souvenir' (memory) and 'aid' (help), and thus denotes ‘aiding memory’. Souvenaid is a milk drink. In addition to the usual nutrients it contains fish oil fatty acids, phospholipids, choline, uridine, selenium and 5 vitamins. Many of these components have been investigated previously and found to be ineffective against memory loss. Souvenaid investigators suggest that they are effective if they are given simultaneously in proper proportions.

It is remarkable that this specific blend of nutrients proved to be patentable. Mixtures of nutrients for the treatment or prevention of memory loss had been published or patented by others before, but apparently there was still room for a patent for Souvenaid. The research that led to the proportion of nutrients in the product has not been published. Was the composition motivated solely by research outcomes, or did considerations of what had already been patented also play a role?

We cannot tell. But the evidence that Souvenaid is effective in the management of patients in the early stages of Alzheimer's disease is open to scrutiny. Below I will discuss the results of three trials that examined the efficacy of Souvenaid (table).

CLINICAL TRIALS WITH SOUENNAID

Souvenir I study The Souvenir I study is the earliest of the three studies. The study was properly registered in a trial registry, the Dutch Trial Register (NTR 702), 'Cognitive performance at 12 weeks' was listed as primary
outcome measure. But that is not very specific; it was not indicated which of the planned psychological tests was considered decisive. The results were published in 2010. The abstract states: '... significant improvement in the delayed verbal recall task was noted in the active group compared with control (P = .021). However, this was not the outcome of the statistical test as planned. The authors stated without further explanation that after 12 weeks 40% of patients scored '0' on the memory test in question, and that as a consequence the planned statistical analysis was replaced by a different one. Souvenaid had no effect on the 'delayed verbal recall' score was increased in the control group over the 24-week intervention period (p = 0.023...'). In reality there was no significant effect of treatment, neither after 12 nor after 24 weeks. The significant p-value referred to a difference in the time course of the memory measure; the Souvenaid group did slightly worse than the control group after 12 weeks and slightly better after 24 weeks, although both differences were not significant. It is questionable how relevant this difference in the course of memory outcome with time is, given that the end result after 24 weeks was not clearly different. The authors did not report whether the effect on 'delayed verbal recall' seen in the Souvenir I study could be reproduced.

**CONCLUSIONS**

**Quality of the evidence** In the two 'successful' studies the primary outcome measure was not concretely specified beforehand. The significant outcome in the Souvenir I study was not confirmed in the Souvenir II study; the statistical significance in Souvenir II referred to an effect that may be of interest to statisticians but that is irrelevant for patients and practitioners. It remains conceivable that nutrients or mixtures of nutrients enhance memory. However, the results of the trials of Souvenaid do not justify marketing it as beneficial for cognitive function in Alzheimer's dementia. Reimbursement by the health insurance system is even less justified. That would generate needless expenses as well as premature hope for a cure.
**Influence of the company** The Souvenaid studies combined a number of problematic issues in the collaboration between scientists and industry. The studies were funded by Nutricia, and many of the authors were employed by that company or acted as an advisor or consultant. The data analysis of the Souvenir I study was supervised by Nutricia and the company hired a ghostwriter to write the article. The titles of the publications display the brand name of the product. Each study included a large number of clinical centers each of which contributed a small number of patients, even though there are many patients with incipient Alzheimer’s dementia and consuming a milk drink is not a burden. The studies could have been carried out more simply and cheaply with fewer centers each contributing more patients. Such a 'fragmenting' strategy resembles 'seeding', where a pharmaceutical company tries to familiarize as many doctors as possible with a new drug. The S-Connect study did not yield a positive outcome, but the Souvenir II study did; the S-Connect study was completed in 2010 but has not been published yet, while the Souvenir II study was completed in 2011 and published in 2012. There appears to be a publication bias here.

**WHAT SHOULD BE DONE?**

Current legislation for medical foods is tailored to patients who cannot or will not eat normal foods. There is nothing wrong with such products. But when a company suggests that a medical food prevents or cures Alzheimer’s dementia, pressure ulcers, or other illnesses, then the NVWA and the health insurers should characterize the product as a medicine. There should be no reimbursement for such a product without prior marketing authorization as a medicine. This resolves the dilemma of the prescribing physician. If the Medicines Evaluation Board concludes that the product is effective then many patients can benefit from it. If it does not work then the health insurers would do better to save their and our money.

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Literature


Table Results of randomized studies in which the efficacy of Souvenaid was investigated as dietary therapy in patients with mild or moderate Alzheimer's disease

<table>
<thead>
<tr>
<th>Study</th>
<th>number of patients who completed the study</th>
<th>duration (weeks)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Souvenir I</td>
<td>99</td>
<td>100</td>
<td>Souvenaid had a significant effect on 1 memory test ('delayed verbal recall'), but no significant effect on other psychological tests.</td>
</tr>
<tr>
<td>S-Connect</td>
<td>228</td>
<td>223</td>
<td>The primary (ADAS-cog) and secondary outcomes did not differ between the two groups.</td>
</tr>
<tr>
<td>Souvenir II</td>
<td>103</td>
<td>103</td>
<td>There was a significant difference in the time course of the memory function between the two groups. However, Souvenaid had no significant effect on memory after 12 or 24 weeks, or on other outcome measures.</td>
</tr>
</tbody>
</table>

ADAS-cog = "Alzheimer's Disease Assessment Scale-cognitive subscale."