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# **Efficacy of acetylleucine in vertigo and dizziness: a systematic review of randomised controlled trials**

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## ABSTRACT

**Purpose :** To assess the efficacy of acetylleucine to improve or stop an attack of vertigo and dizziness (vertigo/dizziness).

**Methods :** Systematic review by 2 independent reviewers. Consultation of the Medline, Cochrane and ClinicalTrials.gov databases until September 2018. Key words: Acetylleucine, Tanganil<sup>®</sup>, Acetyl-DL-leucine, Acetyl-leucine were used. Trial selection: Randomised controlled trials (RCTs) comparing Acetylleucine against placebo.

**Results :** Up till 2018, no RCTs have been published on the efficacy of acetylleucine in vertigo/dizziness

**Conclusion :** There is no solid evidence of the efficacy of acetylleucine in vertigo/dizziness. Given its frequent prescription and the cost generated for the French social security system, high-quality randomised trials should be carried out to assess its efficacy.

### Keywords

Acetylleucine – Dizziness - Randomised controlled trial - Treatment outcome—Vertigo

## Introduction

Dizziness is a general term for a sense of disequilibrium. Vertigo is a subtype of dizziness, defined as an illusion of movement which results in an impression of rotation or false movement [1]. It often occurs along with neurovegetative signs (nausea or vomiting), nystagmus and a tendency to fall without loss of consciousness during the attack [2,3].

In general medicine and emergency medicine, vertigo and dizziness have a lifetime prevalence of between 20 and 30% [4-7] with an annual incidence of about 11% [8]. These symptoms are also the single most frequent complaint among patient older than 75 years [9-11]. In primary care, up to 10% of all adults consult a physician because of vertigo [8,12].

Vertigo and dizziness have various aetiologies caused by physiological irritation (rotatory vertigo, motion sickness, visual height intolerance) or a pathological lesion (unilateral labyrinthine failure or vestibular nuclei lesion). Vertigo is either vestibular or neurological (transient ischaemic attack (TIA) or cerebellar stroke) and dizziness covers broader symptoms: vertiginous sensations, drunkenness or faintness attacks which are the result of cardiovascular (vasovagal, orthostatic hypotension), metabolic or psychological disorders [1].

In out-patient, cases seen by general practitioners, the most frequent four causes, accounting for about 90 % of cases, are benign paroxysmal positional vertigo (BPPV), vestibular neuritis (sudden idiopathic or viral unilateral vestibular deficit), vestibular migraine and Menière's disease [11-13]. Indeed, half of the cases of dizziness is associated to anxiety disorders [13].

In France, Acetylleucine (Tanganil<sup>®</sup>) is often prescribed to treat attacks of vertigo, whether in general practice clinics or in emergency wards. Its pharmacodynamics are not fully understood. The hypothesis is that it restores the membrane potential [14-16], via an interaction with membrane phospholipids on the injured side of vestibular neurons mainly in the thalamus or parietal region of the cortex [17]. The reimbursement rate of this drug is decided by a committee of experts who in 2016 concluded that it had a moderate medical effect and decided on a 30% reimbursement rate [18,19]. Consequently, according to data from the social security's financial branch (Caisse nationale de l'assurance maladie des travailleurs salariés; CNAMTS), acetylleucine cost about 6 million euros in 2016 (Table 1) [20].

Considering this cost, and to evaluate the efficacy of the acetylleucine to treat vertigo and dizziness (vertigo/dizziness), a systematic review was carried out in the hope that data could be meta-analysed to answer the question of its efficacy.

## **Materials and method**

### **Main objective**

The main objective was to evaluate the clinical efficacy of acetylleucine to reduce or stop attacks of vertigo/dizziness.

### **Research methodology**

A systematic review, following the PRISMA statement [21], was carried out by searching the main free-access databases up to the 15th of September 2018: Medline, Cochrane Central and the American database for recording clinical trials (ClinicalTrials.gov). Keywords used to find each of three drugs available were: "Acetylleucine" or "Tanganil<sup>®</sup>" or "Acetyl-DL-Leucine" or "Acetyl-leucine".

### **Eligibility criteria**

Randomized controlled clinical trials versus placebo with double blinding were included. Trials were included if the full-text was available in English or in French. The trials had to evaluate the clinical efficacy of the drug acetylleucine.

All causes or types of vertigo and dizziness were included and trials were included regardless of their duration.

### **Assessment criteria**

The primary endpoint was the significant improvement (or the disappearance) of vertigo/dizziness between baseline and the end of the trial.

### **Trial selection**

Two reviewers collected data for primary endpoint and data to assess trial quality and recorded it on separate spreadsheets.

The qualitative analysis was based on the data collected. A quantitative analysis using Revman 5.3<sup>®</sup> was planned with calculation of the relative risk expressed with a confidence interval of 95 % (significance  $p < 0.05\%$ ) according to the model of Mantel-Haenszel (because the hypothesis was that the trials would be very heterogeneous).

## Results

The flow chart is presented in fig. 1.

The systematic review did not find any articles that met the inclusion criteria chosen for this review.

No randomised clinical trial, comparative, even with active comparator was found. Other trials were preclinical or observational in patients with cerebellar ataxia (Fig. 1).

## Discussion

The main finding of this systematic review of the literature is the total lack of evaluation of the efficacy of acetylcholine. The search equation used did not find any randomised controlled clinical trial evaluating the efficacy of acetylcholine for vertigo although intermediate outcomes were considered, all trial durations and all types of vertigo/dizziness. It is possible that this review missed trials from unpublished or unreferenced databases. No trial was excluded because it was not available in English or French. However, the search did find an observational study available only in Italian. It was published in 1960 and apparently found promising results in favour of acetylcholine in patients with vertigo/dizziness, but the methodology was not available for critical review. [22] (*Fig. 1*).

Even though, clinical trials on animals showed an improvement in locomotor balance after forced rotation or unilateral vestibular neurectomy [15,16,22-24]. This review confirms the findings, 16 years after its publication, of a review by Neuzil [14] which also did not find any randomised clinical trial evaluating acetylcholine since its first launch on the market in the 1950s.

One clinical trial identified in the database search was a randomised controlled trial but was not included because of a particular study-design. It included 52 patients who underwent vestibular neurectomy to treat either an evolved form of Meniere disease or a neurinoma of the acoustic nerve. This study found that there was no significant improvement of dizziness in the group who received acetylcholine in comparison with the control group who underwent the surgery without any other treatment [9]. Another clinical trial which was carried out without randomisation but with blinding of participants found no improvement of vertiginous symptoms. In another clinical trial with double

blinding but without randomisation, no improvement of symptoms was found after vestibular training of 20 healthy patients in comparison to the control group who only had vestibular training and placebo treatment [25]. In two series of case-studies, significant improvement in Scale for the assessment and rating of ataxia (SARA) from baseline was observed in patients with cerebellar ataxia after 1 week [26] and 5 weeks [27] of acetyllecine treatment. A significant improvement of SARA score and quality of life was also noted on 12 patients with Niemann-Pick disease class C after 1 month of acetyllecine administration [28]. A randomised and placebo-controlled clinical trial testing acetyllecine in cerebellar syndrome (ALCAT) is currently underway and could provide more evidence [29,30].

In parallel, a recent *Cochrane* meta-analysis [31] on betahistine, another frequently prescribed anti-vertigo treatment, also concluded to insufficient clinical evidence. The included trials were heterogeneous and the level of evidence was poor (low number of participants, old trials) [31]. Moreover, this review did not include a recent randomized trial evaluating betahistine in Meniere disease [32]. In this trial, the primary endpoint (number of vertigo attacks) did not significantly decrease, whether with low or with high dosages ( $p = 0.76$ ). For vestibular neuritis, a 2011 meta analysis showed a significant effect of cortico steroid at 1 month but not at the end of 12 month follow up [33].

At present, vestibular rehabilitation has clinically proven efficacy with a good level of evidence and is therefore the treatment of choice for patients with vestibular dysfunction. [34]. For BPPV, Espley manoeuvre allows significant improvement of vertigo symptoms [35].

Despite the lack of clinical evaluation and the diverging results of available trials, the Transparency Committee in France continues to recommend the reimbursement of acetyllecine for the treatment of vertigo at a dose of 500 mg to 2000 mg per day in both its 2011 and 2016 re-evaluations of this drug [19]. Consequently, it is a frequently prescribed treatment as shown in a survey of 171 teaching supervisors and 305 interns in general medicine from 4 universities. 93% of respondents had already prescribed acetyllecine for vertigo, but only half of them knew that there was insufficient evidence of its efficacy [36].

As the benefit is questionable at best, the risks must be considered. Acetyllecine is known to cause only very rare adverse effects such as skin rash (with or without pruritus) and urticaria [37]. The risk is low in case of over-prescription. Acetyllecine is an unassessed drug and until proven otherwise can be considered as an impure placebo [38]. Indeed, it has established pharmacological effects but clinical efficacy is not sufficiently assessed.



The question of drug efficacy is an important one. In 2010, an American study [39] including 412 general practitioners showed that 56% of them reported using placebo treatments in their practice, impure in 89% of cases. Using such treatments may seem harmless, but this attitude encourages over-treatment, as a patient comes to expect a drug for each ailment. Moreover, the use of impure placebos raises an ethical dilemma because, unlike pure placebos, these pharmacologically active substances can cause adverse effects. How can the practitioner decide between the unknown benefits and the possible risks associated with this kind of prescription?

## **Conclusion**

Acetylleucine has a marketing authorisation and is reimbursed in France in the symptomatic treatment of vertigo/dizziness although there is no evidence of its efficacy. Due to its frequent prescription and considering the cost supported by the national healthcare system, randomised trials of high quality specifically carried out to measure the efficacy of this drug seem indispensable. Until sufficient data is gathered, evidence-based minded clinicians should remember that it is at best an impure and a costly placebo.

## **CONTRIBUTIONS OF AUTHORS**

Paul Vanderkam: performed the research, analysed the data and wrote the paper.

Clara Blanchard: contributed to the writing of the paper and the data analysis.

Florian Naudet: contributed to the writing of the paper.

Denis Pouchain: contributed to the writing of the paper.

Marie-Christine Perrault-Pochat: contributed to the writing of the paper.

Hélène Vaillant-Roussel: contributed to the writing of the paper.

Nematollah Jaafari: contributed to the writing of the paper.

Remy Boussageon: conceived the study and analysed the data.

## REFERENCES

1. Sloane PD (2001) Dizziness: State of the Science. *Annals of Internal Medicine* 134:823. [https://doi.org/10.7326/0003-4819-134-9\\_Part\\_2-200105011-00005](https://doi.org/10.7326/0003-4819-134-9_Part_2-200105011-00005)
2. Adams RD, Victor M, Ropper AH (1997) *Principles of Neurology*, 6th edn. McGraw-Hill, Health Professions, pp300-1
3. Hanley K, O' Dowd T (2002) Symptoms of vertigo in general practice: a prospective study of diagnosis. *Br J Gen Pract* 52: 809-12
4. Brandt T, Dieterich M, Strupp M (2013) *Vertigo and Dizziness: Common Complaints*, 2nd ed. Springer-Verlag, London
5. Karatas M (2008) Central Vertigo and Dizziness: Epidemiology, Differential Diagnosis, and Common Causes. *The Neurologist* 14:355. <https://doi.org/10.1097/NRL.0b013e31817533a3>
6. Rojl G, Ploner CJ, Möckel M, Leithner C (2010) [Neurological chief complaints in an emergency room]. *Nervenarzt* 81:1226–1230. <https://doi.org/10.1007/s00115-010-3020-x>
7. Sloane PD (1989) Dizziness in primary care. Results from the National Ambulatory Medical Care Survey. *J Fam Pract* 29:33–38
8. Corrales CE, Bhattacharyya N (2016) Dizziness and death: An imbalance in mortality. *The Laryngoscope* 126:2134–2136. <https://doi.org/10.1002/lary.25902>
9. Chawla N, Olshaker JS (2006) Diagnosis and Management of Dizziness and Vertigo. *Med Clin North Am* 90:291–304. <https://doi.org/10.1016/j.mcna.2005.11.003>
10. Neuhauser HK, von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, et al. (2005) Epidemiology of vestibular vertigo: a neurotologic survey of the general population. *Neurology* 65(6):898-904. <https://doi.org/10.1212/01.wnl.0000175987.59991.3d>
11. Neuhauser HK (2016) Chapter 5 - The epidemiology of dizziness and vertigo. In: Furman JM, Lempert T (eds) *Handbook of Clinical Neurology*. Elsevier, pp 67–82
12. Rieger A, Mansmann U, Maier W, et al (2014) [Management of patients with the cardinal symptom dizziness or vertigo]. *Gesundheitswesen* 76:e32-38. <https://doi.org/10.1055/s-0033-1357145>

13. Kroenke K, Lucas CA, Rosenberg ML, Scherokman B, Herbers JE, Wehrle PA, et al. (1992) Causes of Persistent Dizziness: A Prospective Study of 100 Patients in Ambulatory Care. *Ann Intern Med* 117:898–904. <https://doi.org/10.7326/0003-4819-117-11-898>
14. Neuzil E, Ravaine S, Cousse H (2002) La N-acetyl-DL-leucine, médicament symptomatique des états vertigineux. *Bulletin de la société de pharmacie de Bordeaux* 141:15-38
15. Vibert N, Vidal PP (2001) In vitro effects of acetyl-DL-leucine (Tanganil) on central vestibular neurons and vestibulo-ocular networks of the guinea-pig. *Eur J Neurosci* 13:73548. <https://doi.org/10.1046/j.0953-816x.2000.01447.x>
16. Ferber-Viart C, Dubreuil C, Vidal PP (2009) Effects of acetyl-DL-leucine in vestibular patients: a clinical study following neurotomy and labyrinthectomy. *Audiol Neuro-otol* 14:1725. <https://doi.org/10.1159/000148206>
17. Becker-Bense S, Feuerecker R, Xiong G, et al (2015) P37. Effects of acetyl-dl-leucine on the cerebral activation pattern in cerebellar ataxia (FDG-PET study). *Clinical Neurophysiology* 126:e115. <https://doi.org/10.1016/j.clinph.2015.04.175>
18. Commission de la Transparence HAS – avis du 6 juillet 2011: Tanganil®. [http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-07/tanganil\\_-\\_ct-9859.pdf](http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-07/tanganil_-_ct-9859.pdf). Accessed 19 november 2016.
19. Commission de la Transparence HAS – avis du 9 novembre 2016: Tanganil®. [http://www.has-sante.fr/portail/upload/docs/evamed/CT-14961\\_TANGANIL-TANGANILPRO\\_PIS\\_RI\\_Avis1\\_CT14961.pdf](http://www.has-sante.fr/portail/upload/docs/evamed/CT-14961_TANGANIL-TANGANILPRO_PIS_RI_Avis1_CT14961.pdf). Accessed 1st december 2016
20. Medic'AM (2018) Données mensuelles et annuelles sur les médicaments remboursés par l'Assurance Maladie en 2017. Ameli. <https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/medicament/medic-am/medic-am-mensuel-2018.php>. Accessed 1st october 2018
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med* 6(7):e1000100. <https://doi.org/10.1371/journal.pmed.1000100>
22. Chinellato F (1960) Experimental research on the behavior of vestibular function after the administration of certain drugs. II. Acetyl-DL-leucine. *Boll Soc Ital Biol Sper* 36:112830

23. Günther L, Beck R, Xiong G, Potschka H, Jahn K, Bartenstein P, et al. (2015) N-acetyl-L-leucine accelerates vestibular compensation after unilateral labyrinthectomy by action in the cerebellum and thalamus. *PLoS ONE* 10: e0120891. <https://doi.org/10.1371/journal.pone.0120891>
24. Platt F, Strupp M (2016) An anecdotal report by an Oxford basic neuroscientist: effects of acetyl-DL-leucine on cognitive function and mobility in the elderly. *J Neurol* 263:123940. <https://doi.org/10.1007/s00415-016-8048-9>
25. Clément G, Deguine O, Bourg M, Pavy-LeTraon A (2007) Effects of vestibular training on motion sickness, nystagmus, and subjective vertical. *J Vestib Res* 17: 22737.
26. Strupp M, Teufel J, Habs M, Feuerecker R, Muth C, van de Warrenburg BP, et al. (2013) Effects of acetyl-DL-leucine in patients with cerebellar ataxia: a case series. *J Neurol* 260:255661. <https://doi.org/10.1007/s00415-013-7016-x>
27. Schniepp R, Strupp M, Wuehr M, Jahn K, Dieterich M, Brandt T, et al. (2016) Acetyl-DL-leucine improves gait variability in patients with cerebellar ataxia-a case series. *Cerebellum Ataxias* 3:8. <https://doi.org/10.1186/s40673-016-0046-2>
28. Bremova T, Malinová V, Amraoui Y, et al (2015) Acetyl-dl-leucine in Niemann-Pick type C: A case series. *Neurology* 85:1368–1375. <https://doi.org/10.1212/WNL.0000000000002041>
29. Feil K, Adrion C, Teufel J, et al (2017) Effects of acetyl-DL-leucine on cerebellar ataxia (ALCAT trial): study protocol for a multicenter, multinational, randomized, double-blind, placebo-controlled, crossover phase III trial. *BMC Neurol* 17:7. <https://doi.org/10.1186/s12883-016-0786-x>
30. Feil K, Bremova T, Muth C, et al (2016) Update on the Pharmacotherapy of Cerebellar Ataxia and Nystagmus. *The Cerebellum* 15:38–42. <https://doi.org/10.1007/s12311-015-0733-1>
31. Hussain K, Schilder AG (2016) Betahistine for symptoms of vertigo. *Cochrane Database Syst Rev* 21;6:CD010696. <https://doi.org/0.1002/14651858.CD010696.pub2>
32. Adrion C, Fischer CS, Wagner J, Gürkov R, Mansmann U, Strupp M, BEMED Study Group (2016) Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial). *BMJ* 352:h6816. <https://doi.org/10.1136/bmj.h6816>

33. Fishman JM, Burgess C, Waddell A (2011) Corticosteroids for the treatment of idiopathic acute vestibular dysfunction (vestibular neuritis). *Cochrane Database Syst Rev* CD008607. <https://doi.org/10.1002/14651858.CD008607.pub2>
34. McDonnell MN, Hillier SL (2015) Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. *Cochrane Database Syst Rev* 1:CD005397. <https://doi.org/10.1002/14651858.CD005397.pub4>
35. Hilton MP, Pinder DK (2014) The Epley (canalith repositioning) manoeuvre for benign paroxysmal positional vertigo. *Cochrane Database Syst Rev* 12:CD003162. <https://doi.org/10.1002/14651858.CD003162.pub3>
36. Boussageon R., Foucher E., Huas C (2017) Connaissances des médecins généralistes sur l'efficacité de sept médicaments courants : Enquête par questionnaire. *Médecine* 13:205-210.
37. ANSM. Notice patient Tanganil. ANSM. 2018. <http://agence-prd.ansm.sante.fr/php/ecodex/notice/N0274438.htm>. Accessed 15 december 2018
38. Louhiala P, Hemilä H, Puustinen R (2015) Impure placebo is a useless concept. *Theor Med Bioeth.* 36(4):279- 89. <https://doi.org/10.1007/s11017-015-9336-6>
39. Hasham I (2010) Family Physicians Believe the Placebo Effect Is Therapeutic But Often Use Real Drugs as Placebos. *Family Medicine* 42:636-42

**Table**

*Table 1* Prescriptions and reimbursement of acetylleucine in France in 2017

	<b>Number of boxes reimbursed (30 pills)</b>	<b>Reimbursed amount (€)</b>
<b>Acetylleucine</b>	4 926 023	5 713 701

**Figure Caption**

**Fig. 1 Flow Chart**