ADVERSE EFFECTS OF PROCHLORPERAZINE

- Extrapyramidal effects like acute dystonic reactions, oculogyric crises, pseudo parkinsonism and akathisia are the major drawbacks - more common in children and adolescents.
- can also cause a life threatening condition called neuroleptic malignant syndrome
- sublingual preparation sometimes causes local erosive cheilitis of lips and tongue (patient can swallow the tablet in such situation)
- Hypotension, esp orthostatic hypotension not uncommon
- anticholinergic effects are often very distressing for the patient

CINNARIZINE

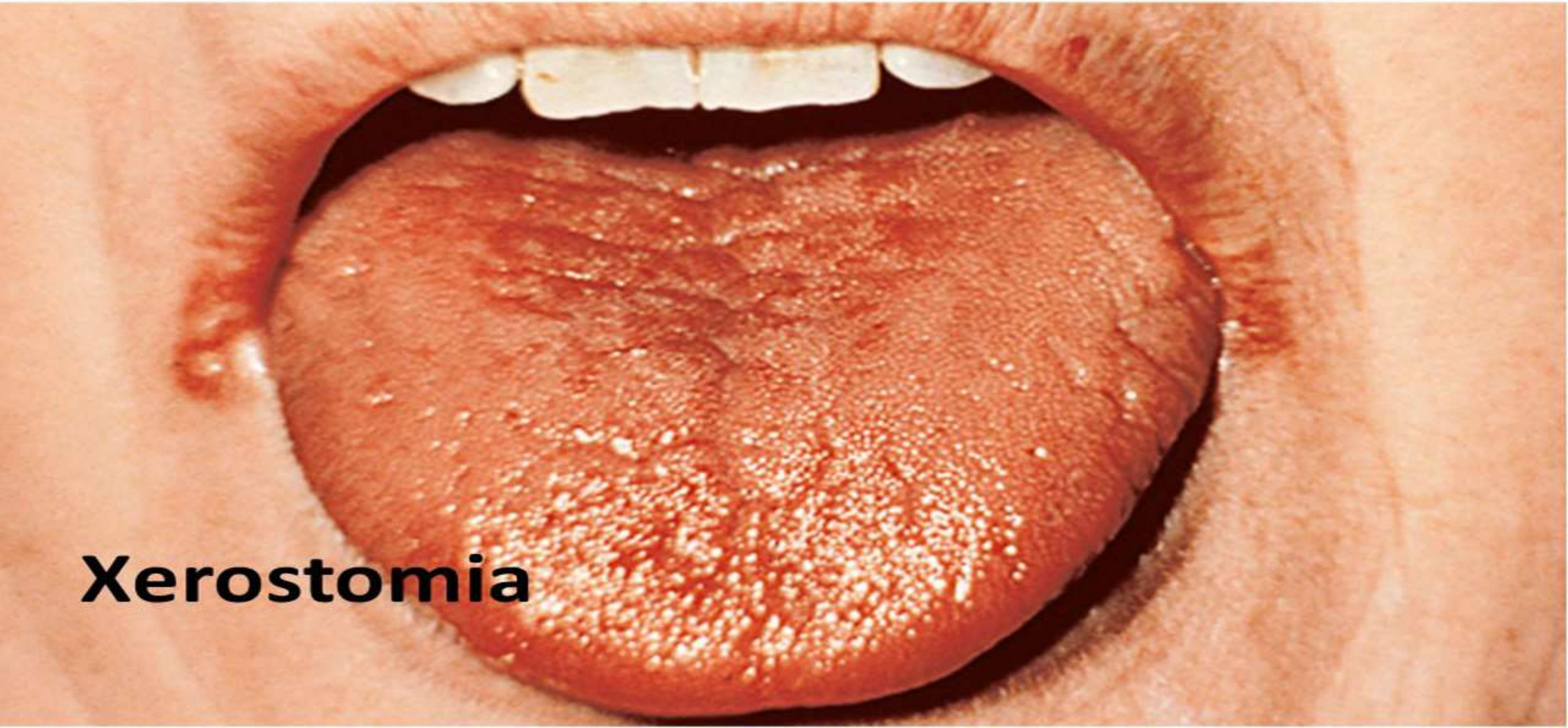
- **Provides good symptomatic relief**

- **Increases blood supply to the brain and inner ear**

- **Not known to have any teratogenic effect**

- **But has too many side-effects** *–hence best abhorred*

Adverse effects of Cinnarizine in long term use in high dosage



CINNARIZINE 25 to 75mg thrice daily

- labyrinthine sedative effect ; hence provides reasonably good symptomatic relief.
- anti-vasoconstrictive effect
- reduces slugging phenomenon of blood in narrow blood vessels
- stabilises vascular endothelium
- Anticholinergic drug hence induces CNS depression
- Side effects like pedal oedema, drowsiness, extrapyramidal symptoms like Parkinsonism/ tremor anticholinergic effects

Anirban Biswas,
Neurotologist

BETAHISTINE 24-1440mg/day

- Provides symptomatic relief by *? sedating ? stimulating* the vest labyrinth
- Increases blood flow to brain and inner ear
- Does not depress the CNS
- **Only non-sedative anti-vertigo drug without any anti-cholinergic and anti-dopaminergic effects**

but

- Mechanism of action very confusing and unclear
- Controversies in dosage (24 - 900mg/day)
- Proved to be a *placebo* only without any medicinal effect

What is it actually?

- H1 and H2 receptors have postsynaptic excitatory action on the vestibular system.
- H3 receptor presynaptic autoreceptor (reduces histamine)
- H4 receptors outside CNS have inhibitory vestibular action.

This drug has both excitatory and inhibitory actions, hence, delusion lies in its very existence.

It used to be advocated as a vestibular suppressant but now clamed to be a stimulant of the vestibular system

What the manufacturers /promoters have understood about mechanism of action of BETAHISTINE

Source

PRODUCT MONOGRAPH

Pr SERC®
betahistine dihydrochloride
tablets (16 mg and 24 mg)

Anti-vertigo Agent

® Registered Trade-mark Abbott Products Operations AG, Licensed use by BGP Pharma ULC, Etobicoke, Ontario, M8Z 2S6

BGP Pharma ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

Date of Preparation:
December 18, 2014

Date of Previous Revision:
August 19, 2015

Date of Revision:
January 8, 2016

Submission Control No: 180426

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of betahistine dihydrochloride is only partly understood. There are several plausible hypotheses that are supported by animal studies and human data:

Betahistine dihydrochloride affects the histaminergic system: Betahistine dihydrochloride acts both as a partial histamine H_1-receptor agonist and histamine H_3-receptor antagonist in neuronal tissue, and has negligible H_2-receptor activity. Betahistine dihydrochloride increases histamine turnover and release by blocking presynaptic H_3-receptors and inducing H_3-receptor downregulation.

Betahistine dihydrochloride may increase blood flow to the cochlear region: Pharmacological testing in animals has shown that the blood circulation in the striae vascularis of the inner ear improves, probably by means of a relaxation of the precapillary sphincters of the microcirculation of the inner ear.

Betahistine dihydrochloride alters neuronal firing in the vestibular nuclei: Betahistine dihydrochloride was also found to have a dose dependent inhibiting effect on spike generation of neurons in lateral and medial vestibular nuclei.

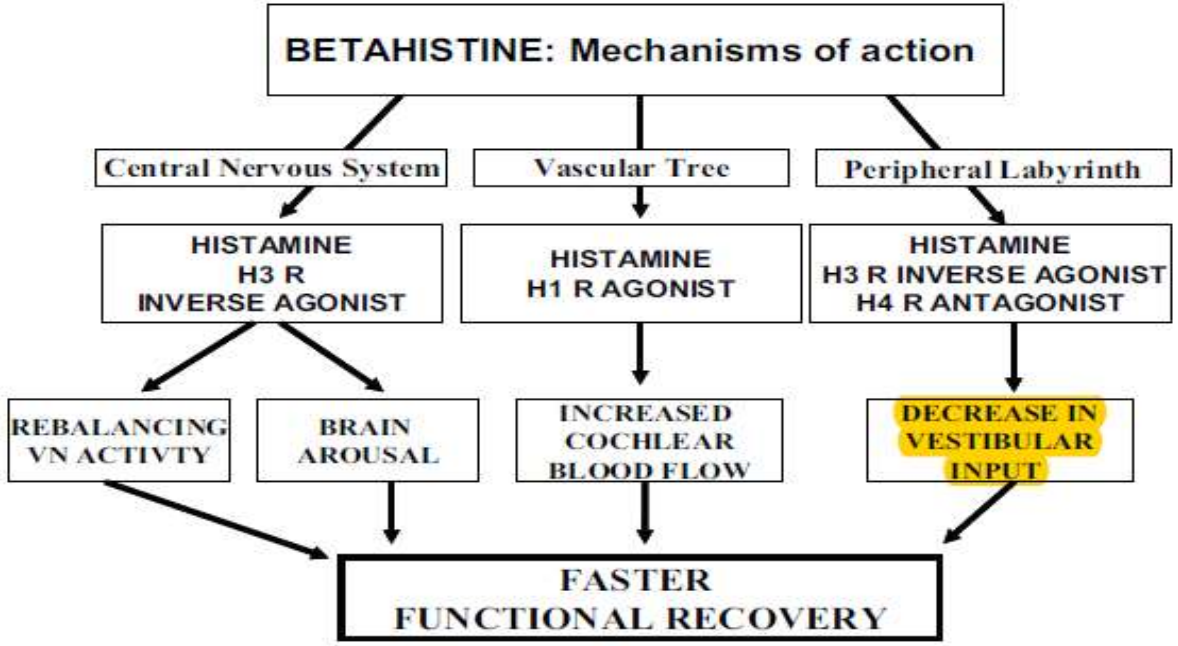
Betahistine is a vestibular SUPPRESANT

Journal of Vestibular Research 23 (2013) 139–151
DOI 10.3233/VES-130496
IOS Press

Betahistine treatment in managing vertigo and improving vestibular compensation: Clarification

Michel Lacour*
UMR 7420, CNRS/Université Aix-Marseille, Marseille, France

M. Lacour / Vertigo, vestibular compensation, and betahistine



DILEMMA

- It was suggested that betahistine causes inhibition of activity in the vestibular nuclei (Timmerman 1994).
- Betahistine reduces vestibular input (Lacour 2013)
- But, vestibular sedatives cannot be prescribed for more than 3-5 days as per current consensus, ***so now touted as vestibular stimulant!***
- Doesn't this leave us all the more deluded?

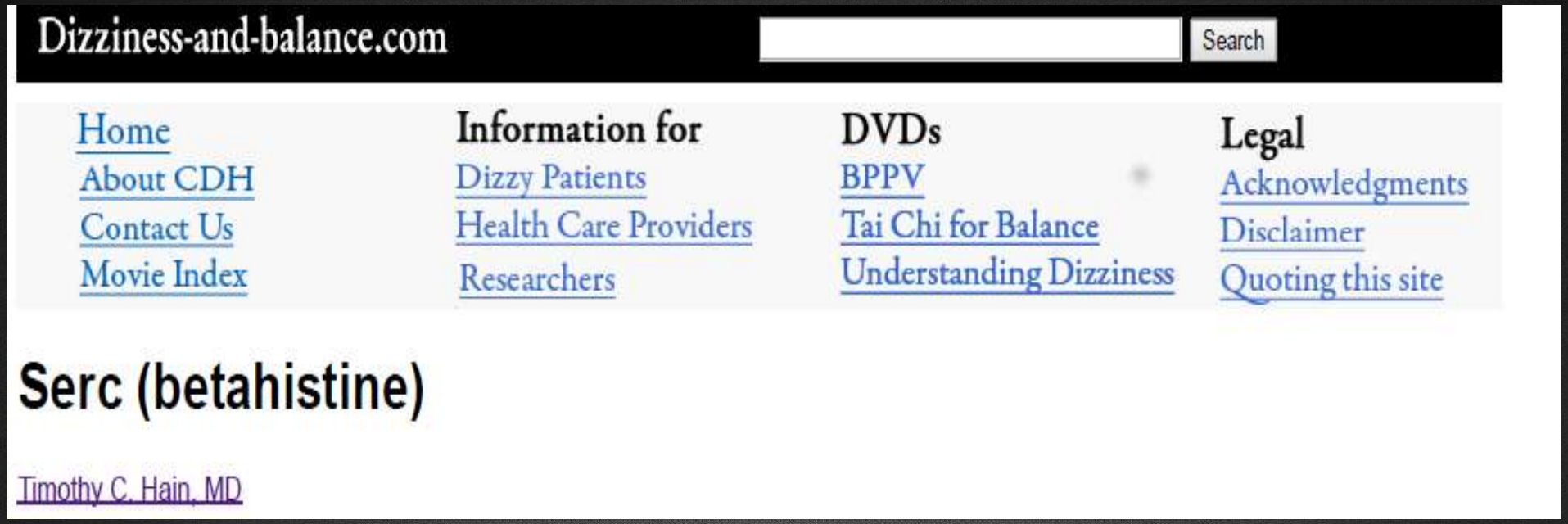
The chequered history of Betahistine

- Serc(brand name for betahistine)was approved by the US FDA about 50 years ago for roughly 5years, but later approval was withdrawn.

- Subsequently, four double blind studies have been done reporting reduction of vertigo attacks with betahistine (Frew and Menon, 1976: Wilmot and Menon; 1976; Meyer, 1985; Mira et al, 2003).

The chequered history of Betahistine

- A review suggested that it is presently still unclear if betahistine has any effect in Meniere's disease (James and Burton, 2001).
- Reviewed by the "Cochrane database“, in 2009 which concluded insufficient evidence to prove its action.
- A recent study of hydrops also found that betahistine had no effect (Gurlov et al, 2012).
- Currently not approved by FDA for use in USA



So to summarize, evidence is weak for betahistine being an effective treatment of Meniere's. Our guess is that it is mildly effective, and fortunately it has very few adverse effects (see following).

Betahistine increases cerebral and inner ear blood flow

- The increased blood flow is due to its action both on H1 and H3 receptors
- The much hyped H1 agonistic action is pretty weak-*this action was observed only at levels which were 100 fold higher than therapeutic.*
- Moreover this action is negated by the antihistaminic group of drugs
- However due to its H3 antagonistic effect ?some increase in vestibulo-cochlear blood flow may be possible

BETAHISTINE and vest. comp

Betahistine has been shown to enhance vestibular compensation and facilitate recovery of balance function in a 1995 study by Tighilit et al

But this study was on cats and not a human study and dose used was 100 times the recommended therapeutic dose for humans

Placebo and betahistine have same results .

RESEARCH

OPEN ACCESS

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)

Christine Adrion,[1,2] Carolin Simone Fischer,[1] Judith Wagner,[3] Robert Gürkov,[4] Ulrich Mansmann,[2] Michael Strupp[1,3] On behalf of the BEMED study group

WHAT THIS STUDY ADDS

- Long term prophylactic treatment with betahistine dihydrochloride (at daily doses 2×24 mg or 3×48 mg) does not change the time course of vertigo episodes related to Meniere's disease compared with placebo
- Placebo intervention as well as betahistine treatment showed the same reduction of attack rates over the study's nine month treatment period
- Reliable and valid instruments that measure subjective vertigo symptoms (in particular, vertigo attacks caused by Meniere's disease) are lacking; derivation of definite or probable attacks caused by Meniere's disease, on the basis of raw patient recordings in vertigo diaries, is methodologically challenging and requires prespecified rules

the bmj | *BMJ* 2016;352:h6816 | doi: 10.1136/bmj.h6816

RESEARCH

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 2016; 352 doi: https://doi.org/10.1136/bmj.h6816 (Published 21 January 2016)

Discussion

Principal findings

For patients with Meniere's disease, unpredictable vertigo attacks are the most unpleasant symptom, leading to not just physical but also psychological strain. Clinical experience and several studies have supported a potential beneficial effect of prophylactic drug treatment with betahistine on the attacks of vertigo as well as on vestibular and, to a lesser degree, audiological symptoms. However, **according to a Cochrane review of betahistine for Meniere's disease or Meniere's syndrome, there is insufficient evidence to say whether betahistine has any effect.**

RESEARCH

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)

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The key findings of the BEMED trial are as follows:

- A significant decline of attack rates in each treatment arm was observed over the nine month treatment period
- The effects of two different doses of betahistine could not be distinguished from a patient reported effect caused by placebo intervention in terms of the incidence of attacks as well as vestibular and audiological function and quality of life. **Therefore, the results do not give clear evidence that patients have a relevant clinical reduction in the number of attacks after nine months of treatment with betahistine at a daily dose of 48 mg or 144 mg, compared with a placebo (sham) intervention**
- There were no safety concerns, and betahistine was well tolerated even in the high dose group of 144 mg betahistine per day.

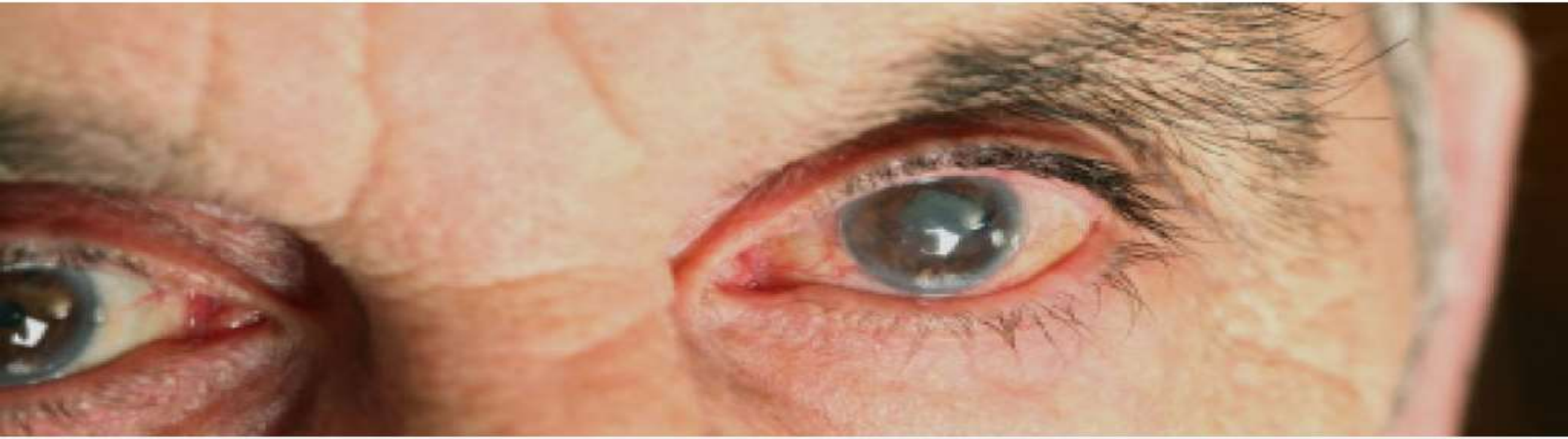
DIMENHYDRINATE

- Conventional antihistaminic with high anti-cholinergic activity.
- Mechanism of action: inhibits spread of hyperactive vestibular input via MLF to centers for vegetative regulation in medulla *-e.g-centers for heart rate, respiration, vomiting, sweating etc.*
- Thus very effective in acute vertigo with pronounced vegetative symptoms
- Absence of extrapyramidal features is the biggest advantage of this antiemetic.

Adverse effects of DIMENHYDRINATE in recommended therapeutic dosage

Highly sedative-impairs psychomotor skill. Concomitant use of alcohol or other CNS depressant should thus be discouraged.

Adverse effects of DIMENHYDRINATE in long term use



Better avoided in patients having enlarged prostate, glaucoma, emphysema, chronic bronchitis. – *applies to other anticholinergics too like cinnarizine meclizine*

Adverse effects of DIMENHYDRINATE in long term use

At very high doses it can affect color discrimination, night vision, visual reaction time, stereopsis

A new entrant in the anti-vertigo drug market

FIXED DRUG COMBINATION OF

CINNARIZINE AND DIMENHYDRINATE

Cinnarizine + Dimenhydrinate - Summary of Literature review

1) first line drug for symptom control in VERTGO in different disorders
2) high Anti-vertiginous efficacy for the fixed combination in various vestibular disorder
3) more efficient in reducing vertigo and associated vegetative symptoms than the routinely prescribed Betahistine
4) as effective as Betahistine in Meniere's disease
5) no signs of a possible detrimental influence of the 4-week treatment with the fixed combination compared with Betahistine in terms of recovery of caloric responsiveness and abatement of rotation-induced nystagmus.
6) Does not impair alertness

Anirban Biswas,
Neurotologist

The current consensus on management-

- **Diagnose the cause of the balance disorder and treat the cause of the vertigo rather than camouflage the symptom of vertigo by eternal continuation of anti-vertigo drugs/ vestibular sedatives**
- **Treat holistically taking care of the co-morbidities like psychological and cognitive problems induced by the balance disorder**
- **Ethical and rational treatment consists of:-**

  - diagnosing the cause and
  - treating the cause by

Take home message:-

-Today the UNDERLYING PATHOLOGY AND SITE OF LESION CAN BE DIAGNOSED very accurately in most if not all patients of vertigo

-RESTRICT use of symptom relieving anti-vertigo drugs to 3-5 days and only for acute vertigo; only use drugs that are efficacious and has a logical mech. of action

-TREAT the underlying disorder causing the vertigo, rather than camouflage the symptom of vertigo

-EXPEDITE vestibular compensation through organ targeted physical therapy as this is the only way to restore balance

-TREAT the concomitant PSYCHOLOGICAL and COGNITIVE impairment for a complete recovery


THANK YOU


ultra