

**Management of Drop Attacks in Meniere's disease: A Systematic Literature Review**

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## **Abstract**

**Introduction:** Drop attacks (DA's) are described as an instantaneous fall to the ground, occurring without warning/ loss of consciousness, a consequence of abrupt deformation of the otolithic membrane due to high endolymphatic pressure. DA's present significant injury risk, therefore effective treatment is imperative. This review is the first to examine all evidence for the management of DA's in Meniere's disease (MD), and make recommendations.

**Methods:** We conducted a systematic literature review. Inclusion criteria consisted of all published English language examining treatments of DA's in MD.

**Results:** 105 articles were identified, 19 met criteria (case series/ cohort studies). 2 articles identified conservative treatments, 8 examined intratympanic Gentamicin, 7 examined surgery, 1 examined all three and 1 examined intratympanic dexamethasone (ITD).

**Conclusion:** Evidence for the management of DA's in MD is limited due to small studies. Some surgical approaches have limited effect. ITD remains a promising treatment, further research is recommended.

## **Keywords**

Meniere Disease

Endolymphatic Hydrops

Drop Attack

Syncopal Vertigo

## 1. Introduction

Alex Tumarkin was the first to describe a drop attack (DA) of peripheral vestibular origin in 1936, eponymously named Tumarkin's otolithic crisis <sup>1</sup>. It was defined as an instantaneous fall to the ground that occurs without warning and without loss of consciousness. The etiology of DA's is presumed to be an abrupt mechanical deformation of the otolithic membrane due to high endolymphatic pressure and subsequent stimulation of the vestibulospinal reflex pathways through the saccule and/or utricle <sup>2</sup>. DA's can be a feature of Meniere's disease (MD) or secondary endolymphatic hydrops (SEH) with an incidence of 7% <sup>3</sup> and often present at the end stage of disease <sup>1, 2, 4</sup>. There is heterogeneity in reports of onset, frequency and duration of DA's in patients suffering with MD/SEH; some can have an isolated episode, others can have weekly attacks lasting years. Wu et al. <sup>5</sup> observed disease duration of MD in patients suffering from DA's is longer than those without, additionally, MRI studies found significantly greater degrees of endolymphatic hydrops (EH) in this group. DA's present significant risk of injuries as a result of their unpredictable nature, as such, effective treatment of these events is imperative. Papers have reported various treatment strategies from conservative measures to ablative surgical procedures. To date there has not been a summary of evidence for treatment strategies of DA's. We propose to conduct a systematic review of the evidence and make recommendations to aid clinicians' management of this rare but disabling sequelae of endolymphatic hydrops.

## **2. Materials and methods**

### **2.1 Literature search strategy**

The review was conducted using the principles as recommended by Tawfik et al. <sup>6</sup>. The PICO (Population, Intervention, Comparison, Outcome) tool was utilized to develop our literature search strategy <sup>7</sup>. A structured literature search was conducted across 6 individual bibliographic databases: Cochrane Library, PubMed, Medline, Embase, Emcare, and CINAHL using a combination of natural (textword) and controlled (subject headings) vocabulary for terms related to Meniere's Disease AND Drop Attacks.

### **2.2 Inclusion criteria**

Inclusion criteria consisted of all published literature available in English examining treatment strategies for the management of DA's (including subgroup analysis). All study types were eligible, including conference publications.

### **2.3 Data extraction**

The data extraction process of the included articles was carried out by the author. Extracted data included year, country, study design, sample size, DA definition inclusion, treatment regime, follow up period, and findings (including subgroup analysis findings). The extracted data were then compared and summarized in tables.

## **2.4 Drop attack definition criteria**

Our definition of a DA includes the following criteria;

1. Occurs in patients with definite Meniere's disease or endolymphatic hydrops
2. A sudden fall that occurs without warning
3. No associated loss of consciousness
4. Other causes for falls eliminated; cardiac/ neurological/ musculoskeletal
5. OR drop attacks labelled as Tumarkin's otolithic crises

### **3. Results**

#### **3.1 Literature search results:**

The results of the literature search are shown in figure 1.

#### **3.2 Conservative treatment for the management of drop attacks**

A total of 3 studies were identified examining the use of more conservative treatment strategies or simply observation. Baloh et al. <sup>2</sup> examined the use of salt restriction and as required vestibular sedatives in 12 patients. The Number of DA's ranged from 2-18 occurring with an Interval of 62 days to 1 year. They described the majority of DA's spontaneously remitting after a one year period (83%) but with persistence of vertigo symptoms. It is noteworthy that the time since the last attack was less than one year for 5/12 patients. Lelonge et al. <sup>8</sup> examined the use of high dose Betahistine and Acetylcysteine (vestibular sedative) in 7 patients. All patients had favourable outcomes, remaining DA free with a follow up of 1-10 years. It is important to mention that more severe cases in this study were managed with destructive treatments (Intratympanic Gentamicin (ITG)/ Vestibular nerve section (VNS)). Janzen et al. <sup>9</sup> observed 6 cases of DA's and noted all experienced spontaneous resolution within 6 months, with no recurrence up to 4 years follow up. All the cases observed suffered with an initial cluster of attacks ranging from one to five, occurring over a time period of one week to six months.

Table I. Summary of papers examining conservative treatment strategies

### **3.3 Intratympanic steroids for the management of drop attacks**

One case series was identified examining the effect of Intratympanic dexamethasone (ITD) on DA's and met our DA definition criteria <sup>10</sup>. A total of 7 patients were managed with ITD administered once a week for a total of 4 weeks, reviewed at 6 months and repeated if not controlled. These patients had failed an initial minimum 6 month trial of lifestyle modifications, Betahistine, diuretics and vasodilators. 5 patients (71%) had complete resolution of DA's after one round of ITD, one patient (14%) was satisfied after two rounds and one patient required ITG after two rounds of ITD failed. Follow up periods ranged from 19-34 months. No significant side effects were recorded; none showed conspicuous hearing loss, otitis media or tympanic membrane perforations during the follow up period.

Table II. Summary of papers examining intratympanic steroids

### **3.4 Intratympanic Gentamicin for the management of drop attacks**

A total of 9 papers were identified examining the effect of intratympanic Gentamicin (ITG) on drop attacks. 6 were case series, two were prospective cohort studies and one was a retrospective cohort study. 8 papers met our DA definition criteria. Drop attack outcomes were part of subgroup analysis in 6 papers. Pre-treatment management of patients was discussed in 6 papers, all of which failed lifestyle modifications and medical therapy. A combined total of 181 patients received ITG for treatment of drop attacks.

ITG regimes varied, The most common dosing regime was 0.5-1 ml of 40 mg/ml Gentamicin delivered with trans tympanic injection in staggered doses until the desired effect



was achieved (5 papers with a combined total of 160 patients) <sup>7,11-14</sup>. 2 papers used a lower dose of 0.5-1.5 ml of 30 mg/ml Gentamicin with trans tympanic injection, one <sup>15</sup> gave a one-off dose (1.5 ml) (16 patients) the other [16] gave daily doses (0.5-1 ml) until the effect was achieved (6 patients). 2 papers trialled novel delivery approaches; one <sup>17</sup> used a tympanostomy tube for infiltration of 1 ml of 26.7 mg/ml Gentamicin three times a day every three days for a period of 35 days (1 patient), the other <sup>18</sup> inserted an intratympanic microcatheter situated next to the round window and delivered an infusion of Gentamicin, totalling either 5.6 mg or 41 mg over a period of 40 days (6 patients).

Post treatment drop attack outcomes for patients given staggered doses of 1ml 40mg Gentamicin ranged from 43-100% success rate (no further attacks). The study with the largest population <sup>11</sup> demonstrated the poorest outcomes; 43% of 81 patients no longer suffered with drop attacks at 6 month follow up. Odkvist et al. <sup>13</sup> and Lelonge et al. <sup>7</sup> found all their patients were cured from DA's (28 patients with 1-9 year follow up and 7 patients with 1-19 year follow up respectively). Viana et al. <sup>14</sup> found 83% (20/24) of patients were cured from DA's after one cycle and 96% (23/24) after two cycles of ITG injections. Liu et al. <sup>12</sup> found a greater rate of DA resolution when treating patients without migraine (100% vs 83%).

88% of 16 patients receiving 1.5 ml of 30 mg/ml Gentamicin had no further DA's (6 months to 2 years post treatment) <sup>15</sup>. Murofushi et al. <sup>16</sup> found 50% of 6 patients receiving staggered doses of 0.5-1.5 ml of 30 mg/ml Gentamicin were cured at 1 year follow-up.

The microcatheter delivery system <sup>17</sup> showed a 67% resolution (4/6) of DA's at 9-12 months and the tympanostomy tube technique completely resolved DA's for the individual case it was used in <sup>18</sup>.

Side effects experienced by patients receiving staggered doses of 1ml 40 mg Gentamicin include vestibular and audiological. Guan et al. <sup>11</sup> reported 10.2% suffered with persistent disequilibrium along with 54% of Liu et al.'s patients <sup>12</sup>. In terms of audiological side effects: Guan et al. <sup>11</sup> report an average increase in pure tone audiometry thresholds by 18.6 dB and a decrease in word discrimination by 33%, Viana et al. <sup>14</sup> report 47% of patients PTA thresholds increased by >10 dB and Odkvist et al. <sup>13</sup> report 14.3% of patients develop post treatment dead ear, an overall average of 6 dB threshold increase on PTA, and a mean speech discrimination drop by 5%.

Wu et al. <sup>15</sup> reported no significant hearing loss post treatment with an individual dose of 1.5ml 30 mg/ml ITG, Murofushi et al. <sup>16</sup> (staggered doses of 0.5 -1 ml of 30 mg/ml ITG) reported 94% of patients developed acute vestibular symptoms and 28% continued to have chronic symptoms.

Thomsen et al. <sup>18</sup> (microcatheter delivery system to the round window) noted 22.2% of patients developed anacusis of the treated ear, whilst the tympanostomy tube delivery system<sup>17</sup> noted their patient developed a transient disequilibrium that resolved with vestibular rehabilitation.

Table III. Summary of papers examining intratympanic Gentamicin

### **3.5 Surgical treatment for the management of drop attacks**

A total of 8 papers examined surgical interventions for the management of DA's. All studies were retrospective case series or case reports. Drop attack outcomes were part of subgroup analysis in 4 papers. 5 papers met our DA definition criteria.

Pre-treatment management of patients was not discussed in 4 papers. Black et al.<sup>19</sup> had trialled patients on oral or intravenous vestibular suppressants prior to surgical management. 86% of all patients in the Bergmark et al. study<sup>20</sup> had prior treatment with ITG and Montandon et al.<sup>21</sup> had trialled all patients on anti-vertiginous medication. Veleine et al.'s patients<sup>22</sup> had all received prior medical treatment, 21% had non-specified surgical treatment and 13% had chemical labyrinthectomy (ITG).

Surgical approaches for the treatment of drop attacks can be subdivided into shunt or ablative procedures.

A total of 6 patients across 2 studies received shunt procedures (3 had endolymphatic sac decompression (ELSD)<sup>19</sup>, 3 had cochleosacculotomy (CS)<sup>23</sup>. Of the 3 patients who had ELSD; one had no further DA's but persistent vertigo and 2 had persisting DA's (overall 33% success rate). No specific complications were discussed for these patients undergoing shunt procedures, however 2 patients proceeded with vestibular nerve sections and one had a revision cochleosacculotomy.

A total of 83 patients across 6 studies underwent ablative procedures; 59 patients had transmastoid labyrinthectomies (TML), 24 patients underwent vestibular nerve sections (VNS). All patients post TML or VNS procedures were free from DA's. Two studies examining ablative procedure outcomes did not comment on complications<sup>7, 24</sup>. In regards to VNS's; complications included transient facial nerve palsy (2.7% and 40% for Veleine et al.<sup>22</sup> and Black et al.<sup>19</sup> respectively). Complete hearing loss (20% for Black et al. [19]) and increased PTA thresholds of 15.6% for Veleine et al.<sup>22</sup>. Other complications included: diplopia (9.5%), CSF leak (6.8%), cicatricial (9.5%), bilateral pulmonary emboli (2.7%) and 2.7% incomplete section<sup>22</sup>.

Bergmark et al. <sup>20</sup> reported the following TML complications; wound infection (2.5%), transient facial nerve palsy (2.5%), return to the emergency department (for side effects related to postoperative medication) (4.2%), CSF leak (1.4%) and the need for mastoid obliteration (1.4%). There was a report of a stroke by McCall et al. <sup>25</sup> (12.5%).

Montadon et al. <sup>21</sup> examined the use of transtympanic ventilation tubes but no effect was observed.

Table IV. Summary of papers examining surgical strategies

## 4.0 Analysis

Drop attacks are an infrequently encountered symptom of a rare pathological process. NICE quotes the incidence rate for Meniere's disease in the UK to be 13.1 per 100,000 <sup>26</sup> and the pooled incidence of criteria-meeting-DA in MD is 7% <sup>3</sup>. The rarity of this phenomenon results in small population study groups, making opportunities to conduct high quality research difficult. Our systematic literature review identified that current evidence consists mainly of case studies/ reports with only a few prospective/retrospective cohorts. Therefore this body of evidence currently lacks statistical significance. Furthermore some studies included in this review examine DA treatment outcomes as subgroup analysis <sup>11-13,15,16,20-23</sup> this reduces the power of the results as the risk of false positives and negatives increases <sup>27</sup>.

Our literature review highlights four main treatment approaches to the management of DA: conservative approaches with use of lifestyle and medication (such as vestibular sedatives and Betahistine), intratympanic steroids, intratympanic Gentamicin, and surgery (shunt or ablative procedures).

### 4.1 Conservative treatment for the management of drop attacks

The papers examining conservative approaches have significant heterogeneity and examine DA patients at varying stages and severities of disease. Broadly the patients managed with diet/ lifestyle and medication alone had lower symptom severity or had acquiescent periods after an initial cluster of attacks. The follow up period for a proportion of these patients was also relatively short therefore limits reliability. The field of novel conservative treatment options

remains promising, an in-vitro mouse model investigating the effect of spironolactone (aldosterone antagonist) on endolymphatic hydrops has identified several molecular pathways in which spironolactone inhibits EH progression, and some which do not. Furthermore immunostaining has identified aldosterone target receptors in the apical part of the human saccule, indicating its translational potential for human use. The results indicate a personalized medical approach may need to be taken in the future, depending on which molecular mechanism induces EH in the individual <sup>28</sup>.

#### **4.2 Intratympanic steroids for the management of drop attacks**

One paper <sup>10</sup> examined the use of intratympanic dexamethasone where previous maximal medical therapy had failed. The sample size was small (7) but the results seem promising with 6/7 not requiring further destructive techniques, furthermore this technique had very low associated morbidity which gives it significant advantage over ITG methods. Evidence for the effectiveness of ITD can be sought from a double-blinded randomized controlled trial investigating the use of intratympanic steroids for the management of Meniere's disease where 82% of patients achieved complete vertigo control with Dexamethasone compared to 57% with placebo <sup>29</sup>.

#### **4.3 Intratympanic Gentamicin for the management of drop attacks**

Intratympanic Gentamicin has the largest body of evidence with the predominant indication being prior failure to manage symptoms with diet/ lifestyle and maximal medical therapy. There was significant variation of dosing and frequency of treatment regimes. Due to heterogeneity it

is not possible to collate results, however broadly speaking this method appears to be effective for the management of DA with a success range of 43- 100%.

Limitations of this method include requirement for multiple courses and therefore hospital visits and side effects such as persistent disequilibrium and increased PTA thresholds.

Examining two double-blinded randomized controlled trials <sup>30-31</sup> investigating the use of ITG for management of MD found an average increase of 18.1dB HL, which is comparable to our literature search findings. An additional limitation to consider is the possibility of salvage labyrinthectomy where there is treatment failure with ITG; two such patients underwent this in Murofushi's study <sup>16</sup>.

#### **4.4 Surgical treatment for the management of drop attacks**

Surgical management of DA has the second largest body of evidence with 8 papers identified.

Broadly two surgical strategies are employed; shunt procedures such as endolymphatic sac decompression/ cochleosacculotomy and ablative procedures such as transmastoid labyrinthectomy and vestibular nerve sections. Overall only 6 patients identified in the literature were managed with shunt procedures and details of previous treatment strategies for these patients were not discussed. Additionally there is a high conversion or revision rate, with half requiring further procedures. DA outcomes for the ablative procedures are very good with 100% resolution across the board, however there is significant associated morbidity.

## 5.0 Discussion

This publication represents the first literature review examining all the current evidence for the management of drop attacks in Meniere's disease. The body of evidence is currently limited to case studies/series or cohort studies of small sample sizes. The conclusions that can be drawn from the limited data available support a treatment escalation strategy (figure 2), starting with interventions with lowest associated morbidity. The authors would recommend an initial trial of optimized maximal medical therapy (diet, Betahistine, infrequent use of vestibular sedatives and consider a trial of Spironolactone) with close clinical review. If drop attacks persist we recommend early intervention with intratympanic dexamethasone, to be repeated if symptom control is not achieved. Failing this, ablative interventions should be considered starting with a trial of intratympanic Gentamicin - noting a single injection may be sufficient, whilst limiting the chances of hearing loss. Repeated dosing and time intervals should be based upon local experience and services. Patient's should be counselled for hearing loss and disequilibrium risks. The authors would recommend salvage treatment with ablative surgery if ITG fails, DAs remain troublesome, and once patients have been fully counselled of the risks. The operative technique should depend on local expertise.

We recommend further large scale studies to be conducted to improve the reliability of the interventions discussed, particularly studies examining the effect of intratympanic dexamethasone on drop attacks.

### Summary:



- Drop attacks are a rare phenomenon of Meniere's Disease (occurring in 7%)
- There is no current consensus on the management of drop attacks
- We have Identified a step wise approach to managing drop attacks though conducting a systematic literature review
- Management of drop attacks mirrors the step wise management recommendations for traditional Meniere's disease
- Use of intratympanic dexamethasone is a particularly promising strategy however little research currently exists for its use in drop attacks

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### **Competing Interests**

The authors declare none

## Ethical Standards

Not relevant

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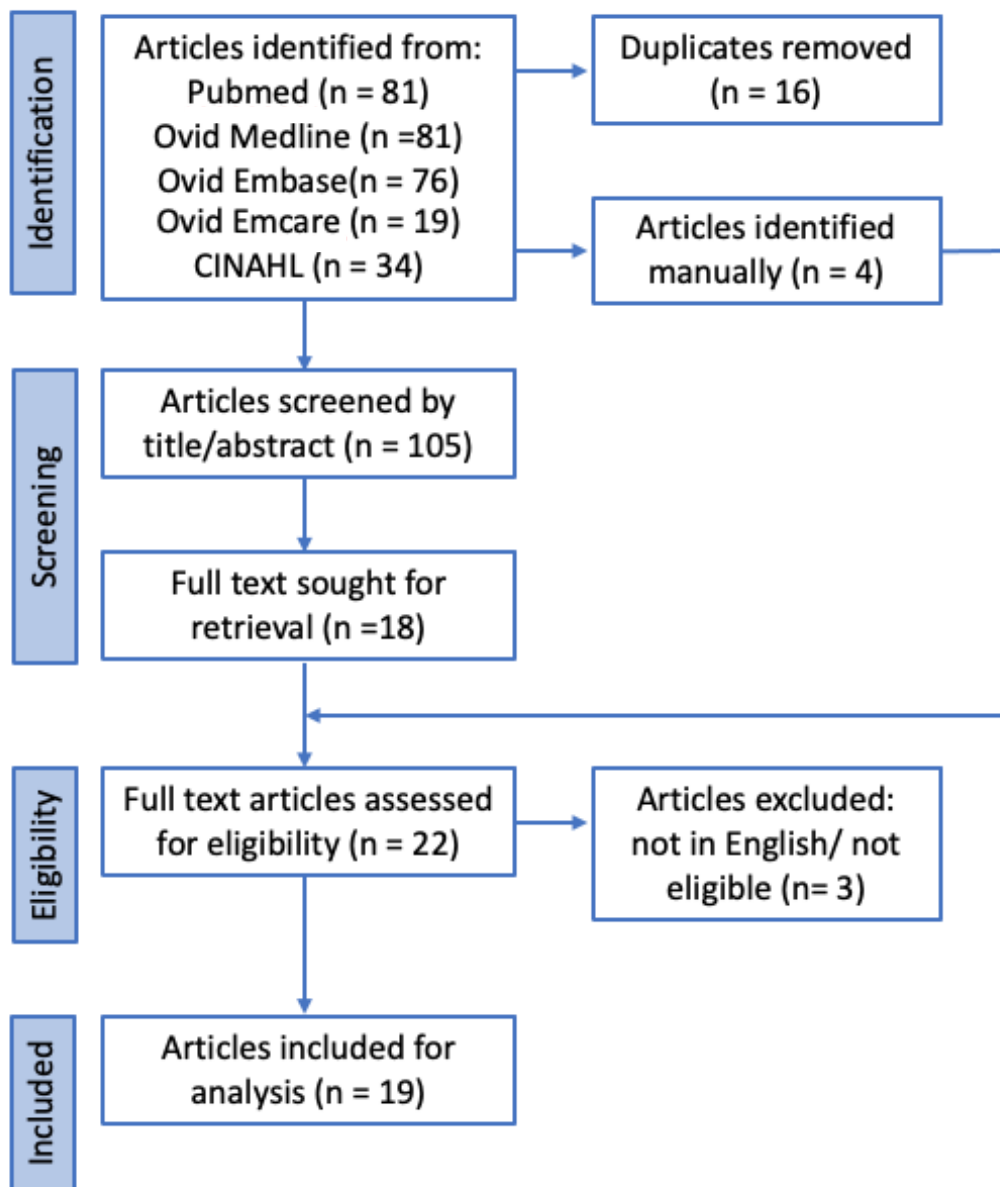


Figure 1. PRISMA flowchart showing the article selection process for this review.



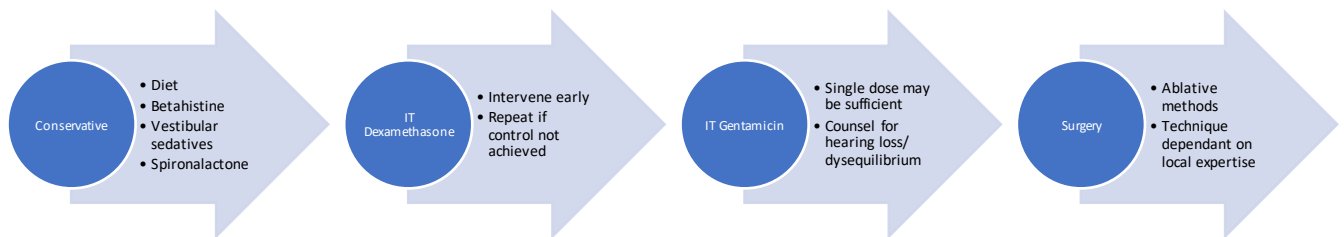


Figure 2. Treatment escalation strategy for management of drop attacks

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Baloh et al	1990	USA	Case series	12	Yes	No	Salt restriction and vestibular sedatives	Spontaneous remission of DA's with persistence of vertigo (short follow up period)
Janzen et al.	1988	Canada	Case series	6	Yes	No	Observation post intial treatment failure (vestibular sedatives, 2 had endolymphatic shunts)	Spontaneous resolution within 6 months of onset, with 4 year follow up.
Lelonge et al.	2021	France	Case series	7	Yes	No	Oral betahistine (48 mg/day) plus acetylcucine (2 g/day) with salt modificaitons	No further DA's (follow up 1-19 years). Destructive techniques (ITG/VNS) offered for severity of vertigo and high risk outocmes of DA's (7/15).

Table I. Summary of papers examining conservative treatment strategies

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Liu et al	2016	China	Case series	7	Yes	No	Stacked dosing ITD (once a week for 4 weeks, repeated at 6 months if required)	5/7 no further DA's after one ITD, 1 no further DA's after 2 ITD, 1 no further after 2 ITD and 2 ITG.

Table II. Summary of papers examining intratympanic steroids

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Guan et al.	2021	China	Retrospective Cohort	81	No	Yes	ITG (1 ml of 40mg/ml), repeat after 1/12 if failed, then stacked treatment (2/7days)	Non subgroup analysis; DA's persisting after ITG 46/81 (56.7%), 41.2% success (62.4% 1 injection, 27.9% 2 inj, 9.7% 3-7 inj), 11.4% failure, 47.4% relapse (31.4% in 1 yr, 31.4% 1-2 yrs, 37.2 >2yrs)
Dallan et al.	2005	Italy	Case report	1	Yes	No	TTG (tympanostomy tube) 1ml of 26.7mg/ml Gent TDS every 3 days for 35day period. Continued until no further vertigo/ DA's occurred.	No further DA/ vertigo (10m post treatment)
Thomsen et al.	2000	Denmark	Case series	6	Yes	Yes	IT microcatheter to RW, delivery of Gent at either 1 µl/hr or 10µl/hr (mean of 5.6 or 41mg Gent /mean 40days.	4/6 no longer had DA
Viana et al.	2014	USA	Case series	23	Yes	No	1m of 40mg/ml ITG injection, repeat at 1/12 if no resolution, if >3/12 post first then consider a new cycle	20/24 DA controlled after 1 ITG cycle, 23/24 after 2-4 ITG cycles
Wu et al.	2019	China	Prospective Cohort	16	Yes	Yes	1 x ITG (1.5ml of 30mg/ml) no. of DA measured/month for 6m prior 14/16 no further DA. 11/13 complete control vertigo, 1/13 and after ITG	14/16 no further DA. 11/13 complete control vertigo, 1/13 class B, 1/13 class c.
Lelonge et al.	2021	France	Prospective Cohort	7	Yes	No	ITG 0.5ml of 40mg/ml (2-10 injections, one month interval)	No further DA's at 3yrs+ post ITG
liu et al.	2017	USA	Case series	13	Yes	Yes	ITG 1ml 40mg/ml titrated (2, 1month apart then 2, 3-4days apart until sx improved ) if failed offered Labarynthectomy.	83% complete control DA in MD+ Migrane and 100% in MD without Migraine. (P>0.999)
Murofushi et al.	1997	Australia	Case series	6	Yes	Yes	ITG 0.5-1ml 30mg/ml given 2-5 injections on consecutive days (if signs /sx of inner ear destruction then stopped). Second set given of 2-5 injections. Total activity in the caloric tests measured at 1-2 months post injections.	3 no further DA/ Vertigo, 3 persistent vertigo, 2 salvage Labarynthectomy
Odkvist et al.	1988	Sweden	Case series	28	Yes	Yes	ITG 0.5-1ml of 40mg/ml buffered with 25% Sodumbicarb given daily until destruction type nystagmus seen. 3-11 doses given.	No further DA's, 18/29 vertigo abolished, 9 occasional attacks, 2 recurrent attacks

Table III. Summary of papers examining intratympanic Gentamicin

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Black et al.	1982	USA	Case series	9	Yes	No	6 ablative (3 Labarynthectomy, 3 vestibular nerve section), 3 shunt procedures (endolymphatic sac decompression) (2 converted to VNS)	No further DA's after definitive intervention.
Kinney et al.	1995	USA	Case series	3	No	Yes	3 shunt procedures (cochleosacculotomy)	No further DA's, one patient's vertigo returned after one year.
McCall et al.	2007	USA	Case series	8	Yes	No	8 transmastoid labarynthectomy	No further DA's
Bergmark et al.	2020	USA	Case series	43	No	Yes	43 transmastoid labarynthectomy	No further DA's, 3 had persistant vertigo
Ishiyama et al.	2001	USA	Case series	7	Yes	No	2 vestibular nerve sections, 5 transmastoid labarynthectomies	No further DA's, 5 had persistant vertigo
Montandon et al.	1988	Swizerland	Case series	2	No	Yes	2 ventilation tubes	DA's persisted
Veline et al.	2022	France	Case series	18	Yes	Yes	18 retrosigmoid vestibular nerve sections	No further DA's, 10% had persistant vertigo
Lelonge et al.	2021	France	Case report	1	Yes	No	1 vestibular nerve section	No further DA's

Table IV. Summary of papers examining surgical strategies