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The ultimate hope for most tinnitus sufferers and clinicians is that a ‘pill for tinnitus’ will be developed and, indeed, there is considerable pharmacological research being conducted. Other therapeutic options being explored include talking therapies and treatments that incorporate physical modalities such as electrical, magnetic, sound, vibration or laser light stimulation. A literature search for treatments using physical modalities was undertaken, running from the end of 2015 to the current time. The findings are presented in this brief review.

**Novel sound therapies**

Sound therapy in multiple guises has been one of the main staples of tinnitus management over the years. Sounds that have been used vary from simple broadband sound to complex spectrally manipulated sounds. Despite its widespread usage, a robust evidence base for the use of sound therapy is still lacking.

**Spectrally altered music**

Several studies have been undertaken on the use of notched sound: patients listen to sound – usually music – that has been modified such that the sound is reduced or completely removed in the frequency range surrounding the pitch of the patients’ tinnitus. The rationale of this is that by stimulating the auditory system except in the frequency range around that of the tinnitus, maladaptive cortical reorganisation is reversed. Stein et al described a randomised controlled trial that recruited 100 participants [1]. 83 finished the treatment course. The chosen primary outcome measure was the Tinnitus Questionnaire (TQ) [2] and on this measure no benefit was seen in the treatment group compared to the placebo group. A small benefit was however demonstrated on a visual analogue scale of tinnitus loudness.

Kim et al developed a smart phone app to deliver notched music therapy and undertook a small pilot study (n=26) to assess its effect [3]. Patients were also given Ginkgo biloba. Some benefit was seen but as this was a small uncontrolled study, the results must be interpreted with caution.
Li et al. reported using spectrally altered music in a randomised controlled trial of 50 tinnitus subjects [4]. A computer model was used to generate customised classical music therapy based on patients’ individual tinnitus parameters and hearing levels. The placebo group listened to unaltered classical music. The treatment group demonstrated significantly less tinnitus distress as assessed using the Tinnitus Handicap Inventory (THI) questionnaire [5]. There was however a high level of attrition, with the results of only 34 of the 50 participants being analysed.

### Acoustic neuromodulation
Abnormal neuronal synchrony within the central auditory system has been proposed as one of the pathophysiological mechanisms of tinnitus and a commercial device is available that delivers a customised auditory stimulation with the aim of disrupting this increased synchrony. This technique has become known as acoustic co-ordinated reset neuromodulation. Several studies investigated this technique. Hauptmann et al. studied the feasibility of using existing consumer mobile devices to deliver the therapy and concluded that this is a viable option [6]. Zeitler and Tass presented the mathematical arguments underpinning a two-stage co-ordinated reset protocol [7]. Hauptmann et al. described a study using acoustic co-ordinated reset neuromodulation on 200 patients with chronic tonal tinnitus [8]. The trial was an open-label, non-randomised, non-controlled study. 189 participants completed the trial and results showed statistical improvement over a 12-month period.

### Nocturnal sound stimulation
In 2014, Pedemonte et al. made the observation that sensory processing continues during sleep and that there is a relationship between sleep and learning [9]. They performed a small (n=10) proof of concept study measuring patients’ electroencephalogram waves during sleep whilst a sound stimulus mimicking their tinnitus was applied. In a follow-up study by Drexler et al., the same team assessed tinnitus in 12 patients who received highly customised nocturnal sound therapy that reproduced their tinnitus, delivered via a small portable audio player and earbuds [10]. Significant improvement was seen in all outcome measures over a three-month period. The device is now commercially available. Its use is only recommended for specific tinnitus pitches. It will be interesting to see if larger independent trials can replicate the developers’ findings.

### Sound therapies with neural stimulation
As our understanding of tinnitus improved, it was recognised that other pathways outside the classical auditory system play a role in the generation of the symptom. Simultaneous stimulation of these neural and auditory pathways is being explored as a mode of managing tinnitus.

#### Sound and trigeminal nerve stimulation
One study recently published investigated the simultaneous stimulation of auditory and trigeminal nerve pathways [11]. A complex auditory stimulus was delivered via headphones at the same time as low-level electrical stimulation of the front of the tongue. The treatment was well tolerated and, in compliant patients, all outcome measures showed significant improvement. This was however an open-label pilot study undertaken by the developers of the treatment and further more rigorous independent research is required.

#### Sound and vagal stimulation
Stimulation of the vagus nerve has long been recognised as one means of modulating central neural activity. Following a series of animal experiments [12], the possibility of treating tinnitus patients with sound therapy paired with stimulation of the vagus nerve using either a surgically implanted electrode or by transcutaneous stimulation has been explored.

A pilot study [13] used electrical stimulation of the vagus nerve by applying an electrode to the concha of the left external ear together with sound stimulation using notched music. This trial demonstrated that the transcutaneous route of stimulation is safe, well tolerated and can improve symptom scores, but as it was relatively small (n=30) and uncontrolled the findings need to be interpreted with care. De Ridder et al. published a case report of a patient with refractory tinnitus who showed improvement after implantation of a vagal nerve stimulator [14]. They paired vagal stimulation with sound stimulation and showed that bimodal stimulation improved the patient’s symptom but sound stimulation on its own did not. Neither of these studies provide enough evidence to recommend this treatment modality and further work is needed.
Somatosensory stimulation
There are putative links between auditory and somatosensory neurones in the brainstem and stimulation of somatic sensory pathways has been suggested as a way of modulating tinnitus. A small handheld vibrating device, resembling a rechargeable electric toothbrush but with a range of solid tips instead of a brush, is currently being marketed for use in a variety of medical conditions including tinnitus. A study by Jonsson et al concluded that it does result in temporary reduction of tinnitus but this is due to residual inhibition from the sound created by the device rather than due to somatic sensory stimulation [15].

Magnetic brain stimulation
Repetitive transcranial magnetic stimulation (rTMS)
It is 14 years since the first peer reviewed scientific paper was published on the subject of rTMS for the treatment of tinnitus. It is therefore perhaps a bit surprising that there are still no definitive answers regarding this modality. An optimistic note was sounded by Soleimani et al who performed a systematic review and meta-analysis of rTMS for tinnitus [16]. Results from 15 randomised controlled trials were analysed with the conclusion that rTMS is beneficial for tinnitus – albeit at a modest level. However, the studies that were subjected to meta-analysis showed considerable heterogeneity and it is doubtful whether performing meta-analysis was justified.

rTMS continues to be an attractive topic for research with a dozen papers published between the last quarter of 2015 and the present. These addressed a wide variety of research questions including the optimum site and duration of treatment, the best outcome measures to use, whether neuronavigation helps the outcome, whether repeated courses of treatment are effective, whether tinnitus specific biological treatment effects can be detected and whether there are any predictors of which people will benefit from rTMS. A brief synopsis of these studies is presented in Table 1.

<table>
<thead>
<tr>
<th>Study (lead author, year and location)</th>
<th>Design including stimulation site(s)</th>
<th>n</th>
<th>Main outcome measure(s)</th>
<th>Results / conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noh 2017 Seoul, South Korea [17]</td>
<td>Single site (left DLPFC) vs dual site (left DLPFC and left AC) stimulation.</td>
<td>17</td>
<td>THI, VAS</td>
<td>Dual stimulation more effective than single site.</td>
</tr>
<tr>
<td>Wang 2016 Shanghai, China [18]</td>
<td>Factor analysis following left TP stimulation.</td>
<td>289</td>
<td>VAS</td>
<td>Tinnitus suppression better with shorter duration tinnitus, normal hearing, absence of sleep disturbance.</td>
</tr>
<tr>
<td>Study (lead author, year and location)</td>
<td>Design including stimulation site(s)</td>
<td>n</td>
<td>Main outcome measure(s)</td>
<td>Results / conclusions</td>
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<tr>
<td>Wang 2016 Shanghai, China [19]</td>
<td>Left TP. Study of outcome measures.</td>
<td>14</td>
<td>GIN [20], VAS</td>
<td>GIN potentially a useful research tool.</td>
</tr>
<tr>
<td>Lehner 2016 Regensburg, Germany [21]</td>
<td>Single site (left TP) vs triple site (left DLPFC and left and right TP) stimulation.</td>
<td>49</td>
<td>TQ</td>
<td>Both groups improved. Triple site stimulation better at 90 days. No long term statistical difference between groups.</td>
</tr>
<tr>
<td>Schecklmann 2016 Regensburg, Germany [22]</td>
<td>Pilot study. Neuronavigated theta burst to left AC vs sham control.</td>
<td>23</td>
<td>TQ, numerical rating</td>
<td>Both groups improved. No difference between groups.</td>
</tr>
<tr>
<td>Wang 2015 Shanghai, China [25]</td>
<td>Pilot study. Neuronavigated by EEG, Left TP or sham.</td>
<td>7</td>
<td>THI, VAS</td>
<td>EEG navigation improved outcome.</td>
</tr>
<tr>
<td>Study (lead author, year and location)</td>
<td>Design including stimulation site(s)</td>
<td>n</td>
<td>Main outcome measure(s)</td>
<td>Results / conclusions</td>
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<tr>
<td>Kreuzer 2015 Regensburg, Germany [26]</td>
<td>Pilot study. Left TP and ACC vs Left DLPFC and TP.</td>
<td>40</td>
<td>TQ</td>
<td>No difference between groups.</td>
</tr>
<tr>
<td>Folmer 2015 Portland, Oregon, USA [27]</td>
<td>Temporal stimulation with active coil or a placebo coil that had a metal plate blocking most of the magnetic field.</td>
<td>64</td>
<td>TFI [28]</td>
<td>Statistically more responders in active group: 56% vs 22%.</td>
</tr>
<tr>
<td>Lehner 2015 Regensburg, Germany [29]</td>
<td>Participants who had previous rTMS could self-refer for a second course. Gap between courses 20.55 weeks, +/- 18.56. Multiple stimulation protocols.</td>
<td>23</td>
<td>TQ</td>
<td>Improvement seen particularly among those whose reason for seeking second treatment was that their tinnitus had worsened.</td>
</tr>
<tr>
<td>Schecklmann 2015 Regensburg, Germany [30]</td>
<td>EEG changes following rTMS. Multiple stimulation protocols.</td>
<td>20 tinnitus controls</td>
<td>EEG</td>
<td>Left TP and right frontal stimulation altered the EEG in tinnitus patients only.</td>
</tr>
</tbody>
</table>

Table 1
Summary of recent experimental studies using rTMS to treat tinnitus.

Key to abbreviations:
- AC: Auditory Cortex
- ACC: Anterior Cingulate Cortex
- DLPFC: Dorsolateral Prefrontal Cortex
- EEG: Electroencephalogram
- GIN: Gap in Noise
- MRI: Magnetic Resonance Imaging
- THI: Tinnitus Handicap Inventory
- TP: Temporoparietal
- TQ: Tinnitus Questionnaire
- VAS: Visual Analogue Scale
Magnetic brain stimulation in conjunction with other treatment modalities

In addition to trials as a stand-alone therapy, rTMS has been investigated as a component of combination therapy.

**rTMS and relaxation**

In a small proof of concept trial 42 patients were treated with TMS while listening to relaxation audio recordings [35]. 38 subjects finished the treatment course and although trend towards improvement was seen this did not reach statistical significance.

**rTMS and laser**

In another small trial, 32 patients were randomly allocated to three groups, receiving TMS alone, low level laser therapy alone or a combination of the two treatment modalities [36]. All but two patients completed the study. Combined therapy demonstrated improvement whereas using single modality treatment did not. However, numbers in each arm of the trial were low and the maximum follow-up time at four weeks was short. This trial is best regarded as a pilot.

Although these studies offer some worthwhile new information regarding rTMS for tinnitus, the more interesting recent papers on the subject are not clinical studies but editorial explorations of how to improve our investigation of rTMS. Three publications [31][32][33] make similar points: evidence regarding rTMS for treatment resistant depression was unclear until large multicentre trials were devised. These proved that rTMS does have a role in depression, for specific patients and with specific treatment protocols. All these editorials recommend that a similar approach is taken for tinnitus.

One problem with rTMS is that the stimulating device is very noisy, creating loud clicks with intensities estimated to exceed 140dB. This means that it is possible some of the effect of this modality is through sound stimulation rather than electromagnetic stimulation. Furthermore, there is a risk that the loud sounds could damage the auditory system and potentially could exacerbate tinnitus. The noise also means that some studies that have been described as double blinded may have had ineffective blinding. An interesting paper discusses potential ways of producing quieter rTMS equipment [34].
Transcranial electrical brain stimulation

Transcranial direct current stimulation (tDCS)
Shortly after humans learnt how to harness electrical energy we have been studying it as a means of modifying a wide range of ailments. Tinnitus is no exception. Hoare et al produced a detailed review of this treatment modality with regard to tinnitus [37]. Previous studies have suggested that low-level transcranial direct current stimulation (tDCS) of certain areas of the brain can transiently reduce several tinnitus parameters. In a small (n=22) but randomised, placebo-controlled, double-blind trial [38] Forogh et al investigated direct current stimulation of the left temporoparietal area in tinnitus patients, finding no statistical difference between active stimulation and sham stimulation. The results of this study concur with a similar trial [39] that investigated application of tDCS to the auditory and prefrontal cortices of 42 patients with tinnitus, finding no tinnitus effect. The results of these two trials are at variance with some of the previous work and clearly further investigation is needed.

Highly Defined transcranial direct current stimulation (HD-tDCS)
Standard tDCS uses large sponge electrodes which deliver the electrical stimulus to a large area of scalp with the electrical current spreading to deep brain structures. A variation of this technique uses smaller gel electrodes which allows more precise delivery, limiting the stimulating effect to superficial areas of the brain. This method is called Highly Defined Transcranial Direct Current Stimulation (HD-tDCS) and its effects on tinnitus have been recently studied [40]. This was a small preliminary study to try and determine optimum stimulation parameters and concluded that stimulation at 2mA for 20 minutes was the most effective. Stimulation was applied to the left temporoparietal or dorsolateral prefrontal cortex with equal efficacy. Further work on this modality is awaited.

Transcranial random noise stimulation (tRNS)
A modified form of transcranial electrical brain stimulation has recently started clinical trials. In this form of stimulation, the electrical current is varied randomly within a predetermined bandwidth. Known as transcranial random noise stimulation (tRNS) it has been investigated for use in tinnitus.

Kreuzer et al issued a case report of a patient who described tinnitus in association with erythema and pain of the ipsilateral external ear [41]. This ‘Red Ear Syndrome’ had proved treatment resistant and tRNS was suggested as a possible way of reducing the tinnitus component. To the clinicians’ surprise the pain improved but not the tinnitus.

To et al studied 40 tinnitus patients who received either bifrontal tDCS on its own or bifrontal tDCS followed by bilateral auditory cortex tRNS and concluded that multisite treatment was more effective [42].

Direct electrical brain stimulation
Few patients with tinnitus would consider subjecting themselves to invasive brain surgery but for a small minority this remains a therapeutic option. De Ridder et al reported two patients who had electrodes surgically implanted on the dorsal anterior cingulate cortex [43]. One patient responded to this treatment: the other did not.

Electrical ear stimulation
Although much of the interest in electrical and magnetic stimulation for tinnitus is directed at stimulation of brain pathways, some researchers continue to study direct stimulation of the ear. Mielczarek et al report a small (n=12) uncontrolled pilot study, stimulating the ears of six patients with unilateral tinnitus and six with bilateral tinnitus [44]. Some improvement of visual analogue scale measures of tinnitus was observed and electroencephalographic changes were detected in a subgroup of the participants.

Laser to the ear
There were no new publications regarding laser treatment of tinnitus as a stand-alone therapy during the time period of this review.

Conclusion
The majority of studies in this review are small with many being described as pilot studies or feasibility studies. Methodology is often poor with inadequate controls. In most cases the treatment modality being tested has been available for decades – in some cases centuries. It is therefore disappointing to see the overall quality of the research. If this field of tinnitus is to advance, better methodology and large multisite trials are urgently required. This is particularly so for rTMS where there is a suggestion that this may be clinically helpful for a subgroup of tinnitus patients.
References


Technological management of tinnitus: an update

( T ) British Tinnitus Association


Conflicts of interest: I have undertaken work for (and been paid by) the following drug companies who were/are trialing drugs for tinnitus or conditions that incorporate tinnitus as one of the constituent symptoms: GSK, Audiology, Otonomy. I have received fees for lecturing about the treatment - including drug treatment of tinnitus.

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