FIVE YEARS LATER:
What happened after the James Lind Alliance Tinnitus Priority Setting Partnership

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Introduction

The James Lind Alliance (JLA) was established in 2004 to bring patients, carers and clinicians together to identify and prioritise the unanswered questions about treatments that they agree are most important. These priorities may not necessarily be the same as those considered important by researchers and commercial interests, and so the purpose is to bring the ‘minority’ voice to drive the research agenda.

Priority Setting Partnerships (PSP) work together to gather uncertainties about the effects of treatments. The uncertainties are all checked to ensure they cannot be answered by existing knowledge, research or sources of information.

The JLA Tinnitus PSP began in October 2011. The initial founders were the British Tinnitus Association, the NIHR Nottingham Hearing Biomedical Research Unit (now the NIHR Nottingham Biomedical Research Centre) and the Judi Meadows Memorial Fund, with a wider working partnership of 56 UK stakeholders representing professional organisations, charities and patient support groups.

The priority setting process produced a final top ten clinical research questions (Table 1, column 1) [1], which demonstrates the breadth of research required to develop a better understanding of tinnitus, the need for a cure as well as the requirement to better understand and determine the effectiveness of existing treatments. Working in consultation with the Professional Advisers’ Committee of the BTA, the partnership also published ideas for future research.

ACKNOWLEDGMENTS

During 2016 and 2017, a series of articles rounding up developments in research appeared in Quiet, the journal of the British Tinnitus Association. These were written by Paul Chinnock and were invaluable in the writing of this review.
<table>
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<tr>
<th>Uncertainty in the diagnosis, assessment and treatment of tinnitus</th>
<th>Suggested research strategy</th>
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<tr>
<td>Is Cognitive Behaviour Therapy (CBT), delivered by audiology professionals, effective for people with tinnitus? Here comparisons might be with usual audiological care or CBT delivered by a psychologist.</td>
<td>1. Studies evaluating CBT and/or other psychological counselling approaches delivered by appropriately trained audiology professionals.</td>
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<td>What management strategies are more effective for improving tinnitus-related insomnia than a usual model of care?</td>
<td>1. A study comparing the effects of different management strategies specifically aimed at improving sleep for patients with tinnitus and insomnia, including CBT as one arm of the research design.</td>
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<td>Do any of the various available complementary therapies provide improved outcome for people with tinnitus compared with a usual model of care?</td>
<td>1. Studies comparing different complementary therapies for improving functional outcomes for people with subjective idiopathic tinnitus and compared with the usual model of care. Studies should consider those complementary therapies that have been shown to be beneficial in treating other chronic health conditions. Proceeding to: 2. Timely systematic review of the evidence from clinical trials.</td>
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<td>What type of digital hearing aid or amplification strategy provides the most effective tinnitus relief?</td>
<td>1. Studies to determine whether digital hearing aids are effective in reducing the functional impact of subjective idiopathic tinnitus. Proceeding if necessary to: 2. Parallel activities comprising: i. Studies evaluating the effects of different amplification strategies for people with subjective idiopathic tinnitus ii. Studies evaluating the effects of different hearing aid devices, including digital combination devices (hearing aid and sound masker) as one arm of the trial iii. Timely systematic review of the evidence from clinical trials.</td>
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<td>What is the optimal set of guidelines for assessing children with tinnitus?</td>
<td>1. Parallel activities comprising: i. A systematic approach to gain consensus among a multidisciplinary panel of experts about the most appropriate assessment methods and diagnostic criteria for children with tinnitus ii. Development of an evidence-based algorithm/pathway to aid clinical diagnosis based on existing research iii. Development of a systematic form of national data collection from existing services to provide an evidence base that would inform development of guidelines.</td>
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<td>How can tinnitus be effectively managed in people who are Deaf or who have a profound hearing loss?</td>
<td>1. Parallel activities comprising: i. Studies to evaluate the effects of non-audiological tinnitus interventions in reducing tinnitus symptoms for people with profound hearing loss and tinnitus ii. A systematic review of the effects of multichannel intra-cochlear implants to suppress tinnitus. Proceeding if necessary to: 2. Development of new treatment approaches for people with profound hearing loss or deafness and tinnitus.</td>
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<td>Are there different types of tinnitus and can they be explained by different mechanisms in the ear or brain?</td>
<td>1. Identification of: i. Meaningful criteria for tinnitus subtyping ii. The underpinnings of the different tinnitus subtypes in humans in terms of inner ear pathology and neurobiology and; iii. Their relevance for response to various treatments. Proceeding if necessary to: 2. Development of an evidence-based algorithm/pathway to guide patient assessment, diagnosis and management.</td>
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Uncertainty in the diagnosis, assessment and treatment of tinnitus

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<td><strong>What is the link between tinnitus and hyperacusis (over-sensitivity to sounds)?</strong></td>
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<tr>
<td>1. A systematic review of the association between tinnitus and hyperacusis, including epidemiological data. Proceeding if necessary to:</td>
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<tr>
<td>2. Understanding the underpinnings of tinnitus and hyperacusis in terms of inner ear pathology and neurobiology.</td>
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<td><strong>Which medications have proven to be effective in tinnitus management compared with placebo?</strong></td>
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<td>1. Systematic reviews of the other classes of drugs that are prescribed to alleviate tinnitus and/or associated symptoms. Proceeding if necessary to:</td>
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<tr>
<td>2. Studies of drug treatments for reducing tinnitus symptoms, including reduced perception of the tinnitus sound.</td>
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Table 1: Top ten research uncertainties and suggestions for research strategies

strategies to address each uncertainty (Table 1, column 2) [2].

The research community was challenged to take on these uncertainties and to use the questions to devise high-quality research projects [1,2]. This article attempts to provide a summary of the research carried out since the publication of the top ten uncertainties which addresses each of the priorities.

**What management strategies are more effective than a usual model of audiological care in improving outcomes for people with tinnitus?**

The usual model of audiological care is to provide education and support for tinnitus, with the provision of digital hearing aids for managing tinnitus with a hearing loss, and other forms of sound therapy, as required [3].

Research is continuing into modifications of existing management strategies such as sound therapies and relaxation techniques. Whilst some of these studies show that such interventions are effective [4][5], there has been no strategy demonstrating a leap forward in effectiveness. Indeed, some studies have concluded that no significant improvements occur [6] or that it is not better than standard care [7].

The possible exception to this mindfulness. A Mindfulness Based Cognitive Therapy study led by Dr Laurence McKenna and Dr Liz Marks has demonstrated that the technique is more effective – and the results longer lasting – than relaxation techniques [8]. More details of this study can be found elsewhere in this review series.

Studies into transcranial direct current stimulation (tDCS) have had variable results and systematic reviews have been contradictory [9] [10].

People who receive a cochlear implant for hearing problems often report that their implant has reduced their tinnitus [11]. Using implants which provide environment sounds give a similar benefit to standard implants [12].

Currently in press is a review into tinnitus apps with the aim of giving users and clinicians a more informed choice about the best app for tinnitus management [13].

In addition to clinician-led management, self-help programmes are used by people with tinnitus to reduce the impact of the condition. A systematic review [14] identified the self-help techniques used by adults with chronic tinnitus and assessed their effectiveness. Five previous studies reported eight self-management components and behaviour change techniques, but the effectiveness of these could not be stated with any certainty.
Is Cognitive Behaviour Therapy (CBT), delivered by audiology professionals, effective for people with tinnitus? Here comparisons might be with usual audiological care or CBT delivered by a psychologist.

Psychological approaches to tinnitus treatment are a popular management strategy and subject for research. A recent review [15] found there have been over 5,000 studies. Very little of this research has involved RCTs so the quality of the evidence available is not high.

A pilot RCT aimed to evaluate the feasibility of comparing a psychologically informed guidance manual developed to support audiologist management of tinnitus with usual treatment is currently underway. The study will assess the acceptability of the counselling intervention, compliance and whether there is sufficient interest and need for a full RCT [16].

What management strategies are more effective for improving tinnitus-related insomnia than a usual model of care?

Sleep disturbance affects over one half of people attending tinnitus clinics [17]. Cognitive Behavioural Therapy (CBT) has been shown to help manage insomnia and CBT for insomnia (CBTi) is now part of the NICE guidelines for the management of long-term insomnia [18]. In a BTA-commissioned study, Dr Laurence McKenna and Dr Liz Marks are investigating the effectiveness of CBTi as a treatment for tinnitus-related insomnia [19].

Do any of the various available complementary therapies provide improved outcome for people with tinnitus compared with a usual model of care?

Whilst there have been a number of systematic reviews into complementary therapies and dietary supplementation, the number of studies eligible for consideration is generally small, and often considered to be of low quality and at risk of bias [20].

A systematic review into acupuncture for tinnitus found a total of 18 RCTs, half of them performed...
in China and half elsewhere [21]. Nearly all the Chinese studies reported positive results, whilst most studies from other countries had negative findings. The reviewers were unable to conclude whether acupuncture is or is not an effective treatment for tinnitus.

There is no evidence that electroacupuncture, in which electrical stimulation is applied via acupuncture needles, works [22].

Ginkgo biloba has been investigated over many years for potential benefit in tinnitus. An updated Cochrane Review in 2013 concluded that the limited evidence offered did not demonstrate that Ginkgo biloba is effective for tinnitus where this is the primary complaint [23].

**What type of digital hearing aid or amplification strategy provides the most effective tinnitus relief?**

Published in 2014, a Cochrane Review [24] to examine the evidence that already exists about hearing aid interventions for tinnitus with hearing loss found only one previous trial. This highlights the need for further research in this area. Dr Magdalena Sereda – in a post funded by the BTA – is researching the clinical efficacy of NHS contracted sound therapy options for tinnitus including hearing aids and combination hearing aids [25]. A Delphi review was conducted as a pre-cursor to this work, and this suggests a lack of consensus among clinicians with regard to fitting hearing aids for patients presenting with tinnitus and a mild hearing loss [26].

Researchers in Germany fitted patients with hearing aids which delivered sounds from which a ‘notch’ of frequency had been removed [27]. This technique was called notched environmental sound technology [NEST]. A control group received hearing aids only. Whilst the NEST group showed more improvement, the difference between the two groups was not statistically significant. Similarly, a trial [6] conducted using notched music without amplification showed no significant improvement levels in tinnitus measured by questionnaire.

**What is the optimal set of guidelines for assessing children with tinnitus?**

The Paediatric Audiology Interest Group (PAIG) of the British Society of Audiology (BSA) formed a working party of national specialists in paediatric tinnitus in response to the challenge posed by the JLA tinnitus PSP. They published the Tinnitus in Children: Practice Guidance document in March 2015 [29].
Five years later

The practice guidance was written using the available evidence base, and from the clinical experience and practice of the working party members.

A number of other resources for professionals working with children with tinnitus have subsequently been developed. These include a training course [30] and award-winning information [31] and activity booklets for children [32].

Ms Harriet Smith – in a PhD Studentship funded by the BTA – is now developing a questionnaire measure of tinnitus in children.

How can tinnitus be effectively managed in people who are Deaf or who have a profound hearing loss?

The BTA commissioned The Ear Foundation to investigate people’s experiences with tinnitus and severe/profound hearing loss. Their report [33] presented the views of over 1,400 people with varying degrees of hearing loss on the treatment they received, what was effective, and their hopes for the future. Forty-four per cent of those with severe/profound hearing loss classed tinnitus as a severe problem. This impacted on stress, relationships, concentration and attention, and sleep. Those with severe/profound hearing loss had the greatest impact from tinnitus, but were less likely to receive help and more likely to be discharged. For those receiving professional care, it was reported that professional advice may be insensitive – for example, suggestions to use maskers or sound therapy – with the concentration being on the hearing loss and not the tinnitus.

Twenty-three people who had received a cochlear implant for hearing loss in one ear in the previous three to ten years were interviewed and completed standard Tinnitus Questionnaires [11]. All patients switched on their implants on waking and used them throughout the day. Seventy per cent said that their tinnitus level decreased within one minute of switching them on. Scores from the questionnaires showed improvement in tinnitus typically began three months after implantation and then remained stable. This is not a rigorous experimental study, but the results are encouraging.

Several studies have explored the benefit of cochlear implantation in people with severely impaired hearing in one ear and moderate to normal hearing in the other (single-sided deafness). Arts et al 2016 [12] investigated whether an implant that was programmed to deliver tinnitus suppressing sounds would have greater benefit than a standard algorithm optimised for speech perception. Tinnitus reduced in both cases, with no difference between.

Another type of implant called a percutaneous osseointegrated auditory implant has also been investigated [34]. These implants are inserted through the skin and integrated into bone tissue. Ten patients with single-sided hearing loss were given implants in the deaf ear. Most showed an improvement in their tinnitus, particularly those with the most profound hearing loss.

Are there different types of tinnitus and can they be explained by different mechanisms in the ear or brain?

The heterogeneity of tinnitus – explored by other articles in this review – is often cited as a stumbling block for developing effective treatment approaches. There is no agreed classification and so perhaps a new approach is required. Eleni Genitsaridi and Theo Kypraios present progress on this topic, in this review series.

What is the link between tinnitus and hyperacusis (over-sensitivity to sounds)?

Between 40 and 60% of patients with tinnitus report hyperacusis, a decreased tolerance to sound [17][39][40] although it has been estimated to be as high as 80% [41]. The frequent appearance of both these conditions in the same individual is suggestive of a common mechanism [42].
Researchers used the Tinnitus Research Initiative (TRI) database to compare clinical and demographic data of tinnitus patients with and without tinnitus [40]. Hyperacusis with tinnitus was associated with younger patients, higher levels of tinnitus-related, mental and general distress; higher tinnitus pitch in relation to measured tinnitus pitch; worse subjective hearing; greater influence on tinnitus from external factors; and higher rates of pain disorders and vertigo, leading the authors to conclude that there is an over-activation of some unspecified network in these patients. Based on animal research; Knipper et al proposed a putative universal model for the mechanisms of tinnitus and hyperacusis [43] whilst acknowledging that there may be a range of such mechanisms. They suggested that tinnitus and hyperacusis may be associated with various degrees of deafferentation (the interruption or destruction of inward connections of nerve cells); differences in central gain; or abnormal stress effects that may act in the cochlear periphery.

**Which medications have proven to be effective in tinnitus management compared with placebo?**

Jufa and Wood carried out a systematic review to assess the effectiveness of benzodiazepines against tinnitus [44]. Although the number of studies was small and some were of poor quality, the researchers concluded that there is no evidence to support the use of diazepam, and only weak evidence for the use of clonazepam. Ciodaro et al combined gabapentin with lidocaine injections given just under the skin of the ear canal [42]. Seventy-two patients were randomly allocated to receive gabapentin only, gabapentin plus lidocaine, or placebo treatment. The improvement in THI scores was significantly higher in the gabapentin group than in the control group, and those in the gabapentin plus lidocaine group did significantly better than those receiving gabapentin alone. An Iranian study [43] also showed improvement in tinnitus for patients given gabapentin compared to a control group but commented on the ‘remarkable’ placebo effect.

Kumral et al performed a double-blinded RCT into trimetazidine dihydrochloride [44]. There were no significant differences between the treatment and control groups after treatment, leading to the conclusion that trimetazidine dihydrochloride offers no benefits for people with tinnitus.

Zinc is known to play a role in the functioning of the ear. A Cochrane systematic review of studies using zinc supplementation [45] found only three RCTs, only one of which had used a validated scale for tinnitus. This study found that 5% of the patients given zinc showed benefit, compared to 2% of the control group who also improved. The remaining studies also found no significant differences between treatment and control groups.

Intratympanic membrane injections have been attracting some interest. The steroid dexamethasone was used on 27 patients, with 27 others in the control group receiving a
saline injection. There was some improvement in both groups, but there was no significant difference between them [46]. An initial safety study of intratympanic injections of esketamine hydrochloride (AM-101) showed some limited promise [57]. A larger multi-centre double-blind placebo controlled trial however only showed improvements in patients following noise-induced hearing loss or after middle ear infection [48] and Phase III studies were ended after initial results showed no significant improvements between treatment groups and control groups [49].

**Mapping a cure**

Whilst the research above is undoubtedly of value, the overwhelming cry from people living with tinnitus is that they want a cure. The BTA’s vision is for ‘a world where no one suffers from tinnitus’. Pivotal to that aim is working towards an ultimate cure for tinnitus. As part of that aspiration, the BTA has instituted a series of strategic work streams, one of which is specifically aimed at achieving a cure.

The first step in this process has been to take stock of what has been achieved to date and what current research is being conducted. To try and identify areas where gaps in our knowledge are hampering progress, the BTA has developed a mind map which synthesises the position of current tinnitus research [Figure 4] [50].

It is hoped that by being able to see where our knowledge is deficient, we can more effectively apportion research resources. This should also help to ensure that research funding is not directed towards areas that have already been fully explored. This project is an update and follow-up to the JLA Tinnitus PSP which focused purely on treatments and outcomes.

The mind map is a complex diagram, reflecting the complex and heterogeneous nature of...
tinnitus, and the uncertainties that still exist about causes, mechanisms and management. The map is split into five different groups, representing the big themes that will need to be addressed before a cure can be declared. These over-arching themes are then broken down into general areas of research which are then further divided into specific research topics, individual projects and further subdivisions.

Work is still ongoing to further refine the mind map, with contributions having been sought from the wider tinnitus community, including clinicians, patients and researchers.

Conclusion

It is important that more research into tinnitus is carried out, but it needs to be of good quality. A systematic review by US researchers [51] examined aspects of study quality in tinnitus RCTs and found that in over half of the trials, researchers had failed to define specifically how they defined ‘tinnitus’, and only 20% of trials had a low risk of bias. It is a common theme of the recent systematic reviews undertaken in the tinnitus field that there have been insufficient studies of good enough quality for inclusion.

However, whilst many studies have been inconclusive, the trend over the last five years has been for increasing numbers of positive results from studies. This review has shown that there is much to be celebrated and much progress has been made since the publication of the Top Ten Priorities. From scattered nuggets of clinical experience have come a whole suite of resources for those clinicians, parents and young people dealing with tinnitus in childhood, and an increased acceptance and interest in paediatric tinnitus.

There is a real drive to explore and evaluate existing tinnitus management techniques and introduce novel technologies and interventions. It will be interesting to see where the next five years takes us in addressing the challenges the JLA Tinnitus PSP threw out to the tinnitus research community.

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Annual Tinnitus Research Review 2018
Five years later


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Five years later


