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Clinical trials in otology: Examining trends and framework for prioritization

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ABSTRACT

Objective: To characterize otologic clinical trials and examine otologic clinical trial trends from 2008 to 2018 using the clinicaltrials.gov database.

Methods: Data was collected from clinicaltrials.gov and included all clinical trials that focused on otology from 2008 to 2018. Outcome measures include status of trials, funding sources, details regarding otologic conditions studied, and trends in clinical trials.

Results: There were 992 otology clinical trials from 2008 to 2018.457 (46.1%) were completed and 94 (9.5%) were discontinued. Industry remained the highest (76.5%) contributor to otology clinical trials. The otologic conditions studied, from most common to least common, include hearing loss (40.6%), vestibulopathy (18.8%), tinnitus (18.8%), and otitis media (15.1%). The number of otology clinical trials increased by an average of 12.0 trials per year from 2008 to 2018 ($p < 0.001$). The number of otology clinical trials focusing on hearing loss and vestibulopathy significantly increased over the studied period ($p < 0.001$), while those focusing on tinnitus and otitis media did not ($p = 0.09$ and $p = 0.20$, respectively). The majority of clinical trials on each of these four conditions focused on treatment options.

Conclusion: Our study describes trends in otology clinical trials registered on clinicaltrials.gov from 2008 through 2018. The total number of clinical trials over this time period increased significantly, driven by trials investigating hearing loss and vestibulopathy. Furthermore, most clinical trials were industry-sponsored and focused on treatment modalities. Our study provides an outline of otology clinical trials registered in a US web-based database, which may be of use for the development of future clinical trials.

1. Introduction

Otologic complaints, such as hearing loss, tinnitus and otitis media, are very commonplace in our society and can place a significant burden on emergency departments (ED) in the United States. According to the National Hospital Ambulatory Medical Care Survey, over 2 million patients were seen in an ED for otitis media and eustachian tube disorders in 2010 alone which accounts for 1.0% of all adult and 6.8% of all pediatric ED visits (Kozin et al., 2015). Hearing loss alone is the most common sensory impairment worldwide affecting greater than one-half of a billion individuals (Brown et al., 2018). The economic burden of this is significant in the United States, with costs associated with hearing loss approach 175 billion US dollars each year (Brown et al., 2018). Hearing loss has also been shown to be a modifiable risk factor for dementia, falls, depression, social isolation, unemployment, and functional dependence in the older population (Ramsey et al., 2018). Furthermore, Agrawal et al. demonstrated that the lifetime cost of vestibular diseases in patients older than 60 in the US is 227 billion dollars (Agrawal et al., 2018).

In an effort to reduce this economic burden and improve hearing health, further inquiry is needed to guide the scientific community on the gaps in otologic research. Our objective for this study was to characterize otologic clinical trials and examine otologic clinical trial trends from 2008 to 2018 using the clinicaltrials.gov database.

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2. Methods

The data for this study was collected from clinicaltrials.gov, a United States (US) web-based resource funded by the US National Institutes of Health (NIH) that provides information on past and current clinical trials on human volunteers. Our comprehensive database was compiled to include all otologic clinical trials on clinicaltrials.gov from 2008 to 2018. Our search terms included "otology" and "neurotology". The requirement to register clinical trials conducted in the US on clinicaltrials.gov occurred in 2007, so we used 2008 as the starting time point when compiling our database. Clinical trials conducted outside the US are not required to register on clinicaltrials.gov, however, this does not prevent them from doing so. Studies based outside the US that were registered on clinicaltrials.gov were included in our study in addition to the US-based studies. Trials posted prior to January 1, 2008 or after December 31, 2018, or those that did not focus on otologic conditions were excluded. We recorded the following variables as they pertained to each clinical trial: trial status, results status, funding source(s), study design, otologic condition studied, number of participants, and study focus. We manually reviewed and recorded study parameters that were not automatically populated into our database by clinicaltrials.gov to ensure accuracy and consistency.

Descriptive statistics were used to analyze categorical variables. Study variables that did not fit into any of the most common subcategories were subcategorized as "other" on each table. Simple linear regression was used to analyze trends of otologic clinical studies from 2008 to 2018. Such trends were represented graphically and were determined to be statistically significant at the $p < 0.05$ level.

3. Results

There were 992 otology clinical trials, dating from 2008 to 2018, that met the criteria for analysis. Table 1 highlights the general characteristics of the trials included in this study. Of these trials, 457 (46.1%) were completed, 94 (9.5%) were discontinued and 286 (28.8%) were ongoing. The otologic conditions studied, from most common to least common, include hearing loss (40.6%), vestibulopathy (18.8%), tinnitus (18.8%), and otitis media (15.1%). Industry represented the funding source for the majority of trials (76.5%). Of the 992 clinical trials, 50.1% were randomized and 35.0% were blinded.

Table 1
General characteristics of otologic clinical trials listed on clinicaltrials.gov from 2008 to 2018.

Status of trial	Complete	46.1%
	Discontinued	9.5%
	Ongoing	28.8%
	Unknown	10.7%
Otologic condition studied	Hearing loss	40.6%
	Vestibulopathy	18.8%
	Tinnitus	18.8%
	Otitis media	15.1%
	Other	6.6%
Results posted	Yes	11.8%
	No	88.2%
Number of participants in trial	<50	46.8%
	51–100	21.1%
	101–150	6.4%
	151–200	6.9%
	>200	14.7%
Funding source	Industry	76.5%
	NIH	12.6%
	Federal	10.9%
Randomized	Yes	50.1%
	No	49.9%
Study Design	Single-blinded	11.3%
	Double-blinded	9.2%
	Triple-blinded	6.6%
	Quadruple-blinded	8.0%
	Other	65.0%

Table 2 highlights the study focus and treatment categories examined in these trials. In all four of the common otologic conditions studied, the study focus was on mainly on treatment (rather than prevention, risk factors, diagnosis, epidemiology, and etiology). Device treatments were most commonly investigated in hearing loss trials (63.6%) and tinnitus trials (50.7%). However, medication treatments were most commonly investigated in vestibulopathy trials (44.0%) and otitis media trials (54.8%).

Our data illustrates a steady increase in the number of clinical trials in otology reported on clinicaltrials.gov, with Fig. 1 demonstrating an average increase of 12.0 trials per year from 2008 to 2018 ($p < 0.001$). The trends in disease focus of otology clinical trials from the years 2008–2018 are summarized in Fig. 2. The number of clinical trials focusing on hearing loss increased by an average of 6.6 trials per year from 2008 to 2018 ($p < 0.001$). The number of clinical trials focusing on vestibulopathy has increased by an average of 2.6 trials per year from 2008 to 2018 ($p < 0.001$). The number of clinical trials focusing on tinnitus or otitis media did not significantly change from 2008 to 2018 (increased by an average of 0.7 trials per year, $p = 0.09$ and increased by an average of 0.6 trials per year, $p = 0.20$, respectively).

4. Discussion

In order to improve clinical care for patients with otologic conditions, it is imperative that clinical trials are developed, completed, and disseminated to the public and healthcare professionals in a timely fashion. In this review, we highlighted significant trends in the focuses of clinical trials in otology registered on clinicaltrials.gov, a US web-based database funded by the US NIH. This is the first analysis, to our knowledge, to comprehensively characterize the scope of all otology clinical trials registered on clinicaltrials.gov. It also exposes gaps and redundancies in otologic research in order to offer a framework for future clinical trials. As funding and resources for otologic research are finite, physicians should carefully select topics for clinical trials with the aim of maximizing potential patient benefit.

A notable portion of the studies (9.5%) were discontinued. This is problematic because reporting causes for trial discontinuation is important for informing the design of and resource allocation for future trials. In our study, the reasons for study discontinuation were unclear. Some potential causes include recruitment failure, trial adverse events and institutional staff changes. In a study by Briel M et al., there were 28 reasons for recruitment failure with the most common being overestimation of prevalence of eligible participants and prejudiced views of recruiters and participants (Briel et al., 2016; Johnson et al., 2019). Therefore, clinical trials should plan protocols carefully to avoid waste of medical resources. Ideally, this planning should focus on estimating the number of eligible participants in a given population so as to ensure an adequately powered study.

In our study, we found that industry (76.5%) was the highest contributor to otology clinical trials, and this remained constant during the studied time interval. Multiple studies have shown that industry funded trials are more likely to produce positive results and more frequently compare their products to placebo instead of pre-existing drugs or devices available on the market. Among the various subspecialties within otolaryngology, otology ranks second highest in payments from industry based on the Centers for Medicare & Medicaid Services Open Payments. Therefore,

Table 2
Study focus and treatment options examined in otologic clinical trials listed on clinicaltrials.gov from 2008 to 2018.

	Type of Study						Type of Treatment			
	Diagnosis (%)	Etiology (%)	Prevention (%)	Risk Factors (%)	Epidemiology (%)	Treatment (%)	Behavioral (%)	Medication (%)	Device (%)	Procedure (%)
Hearing Loss (n = 264)	8.5	4.2	4.2	2.7	0.5	78.3	19.7	12.1	63.6	4.6
Vestibulopathy (n = 116)	11.5	4.2	0.0	2.4	0.0	77.7	23.3	44.0	15.5	17.2
Tinnitus (n = 136)	4.6	3.5	0.6	0.6	0.6	82.7	17.7	22.1	50.7	9.6
Otitis Media (n = 93)	8.9	8.2	11.9	3.7	1.5	63.0	0.0	54.8	31.2	14.0
Total (n = 992)	8.4	5.0	4.2	2.4	0.7	75.4	13.7	33.3	40.3	11.4

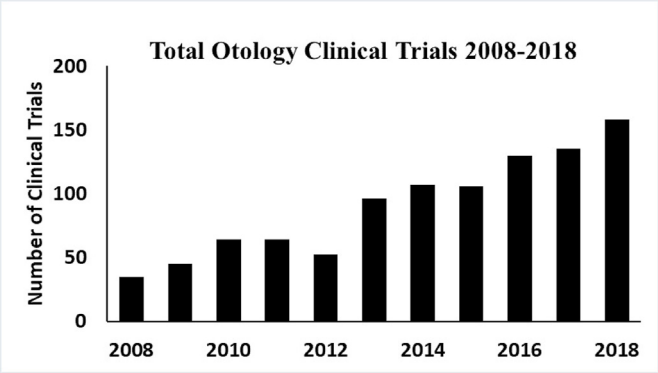

Fig. 1. Trends of Otology Clinical Trials from 2008 to 2018. The number of clinical trials conducted from 2008 to 2018 increased by an average of 12.0 trials per year ($p < 0.001$).

otologists should be aware that industry involvement may affect their practice patterns and publication bias (Cho and Bero, 1996; Davidson, 1986; Morse et al., 2018; Rochon et al., 1994). In the United States, the industry contributes enormously to developing new drugs and devices, with an average of 75% of all clinical trial funding coming from industry (Bodenheimer, 2000). Drugs developed by the industry play a significant role to the growth and advancement of medicine. Physicians employed by the industry have an important task of evaluating drug safety and efficacy prior to their introduction to the market.

It is important to determine whether the focus of clinical trials reflects the prevalence of disorders most commonly seen. The greatest portion of otology clinical trials we found focused on hearing loss, followed by vestibulopathy, tinnitus, and otitis media. These diseases continue to impact patient quality of life and carry a significant financial burden (Roche et al., 2013; Shekelle et al., 2002). The shift in focus of clinical trials towards hearing loss could potentially be explained by newer technologies geared toward hearing rehabilitation (i.e. cochlear implants). The continued demands for improvements in design and expansion in candidacy in cochlear implant likely contribute to this rising trend (Boerner et al., 2018; Ear Foundation, 2020; Leigh et al., 2013, 2016).

Additionally, our study found that the number of otitis media clinical trials has not increased, despite its contribution to a significant proportion of otologic ED visits each year. This may be due to a shift in focus to other ear diseases that deserve further research, such as vestibular migraines or temporal bone encephaloceles, or because the otologic community has reasoned that otitis media has been studied redundantly. Such redundancy could create waste and divert resources away from important groundbreaking studies. If researchers are interested in studying otitis media, they may consider examining prevention techniques and non-medication therapies as previous clinical trials have not focused on this. Similarly, tinnitus affects up to 30% of adults above 55 years old and was the most common service-related disability among veterans in 2013, but currently treatment approaches are unsatisfactory. The static trends of tinnitus clinical trials found in our study are concerning; therefore, studies on tinnitus treatment, perhaps

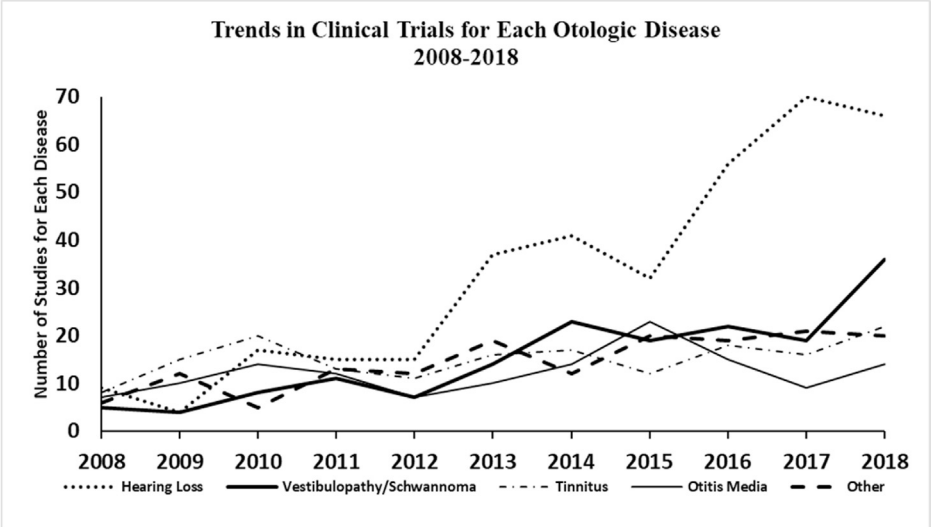

Fig. 2. Trends in otologic disease studies from 2008 to 2018. The number of studies focusing on hearing loss increased by an average of 6.6 trials per year ($p < 0.001$), and the number of clinical trials focusing on vestibulopathy increased by an average of 2.6 trials per year ($p < 0.001$). The number of clinical trials focusing on tinnitus or otitis media did not significantly change from 2008 to 2018 (increased by an average of 0.7 trials per year, $p = 0.09$ and increased by an average of 0.6 trials per year, $p = 0.20$, respectively).

those focused on procedure or behavioral options, should continue to be pursued to reduce its burden (Hesse, 2016; Sindhusake et al., 2003). Although hearing loss is a common cause of tinnitus and trials investigating hearing loss have increased significantly, there are many other causes (i.e. head trauma, loud noise exposure, eustachian tube dysfunction) of which clinical trials may investigate for potential treatments.

The limitations of this study are inherent in the database we used. First, clinicaltrials.gov is a US web-based database and may not house a complete listing of all otologic clinical trials. Clinical trials conducted outside of the US are not required to register on clinicaltrials.gov, so the scope of our study is limited to those which were registered voluntarily. However, the requirement for trials conducted inside the US to register occurred in 2007, so this law was in place throughout our study time period. Some investigators may also fail to update the progress of their studies, which could lead to underestimating the number of discontinued studies. Moreover, industry-driven clinical trials were required to be listed on clinicaltrials.gov earlier than institutional-driven trials, and thus our funding sources may be skewed toward industry sponsors. Furthermore, many studies may have overlapping objectives such as new hearing aid devices that may help reduce tinnitus and improve hearing loss. Therefore, the classification on study focuses is not always clear. However, we categorized the focus of each study based on its first objective. Also, although our study shows a shift in the focus of otologic conditions studied, it does not directly compare this shift with changes in the prevalence of these conditions over the same time period. Therefore, this study cannot definitively comment on whether this change in shift was appropriate or not. Additionally, many other countries have web-based clinical trial registries, several of which contribute their data to the World Health Organization International Clinical Trials Registry Platform (ICTRP). A future study of otologic clinical trials registered in the ICTRP may provide a broader analysis of research efforts on an international scale.

5. Conclusion

Our study demonstrates that the total number of otology clinical trials registered on clinicaltrials.gov has increased significantly from 2008 through 2018. The number of otology clinical trials focusing on hearing loss and vestibulopathy has significantly increased over this time period, while the number of studies focusing on tinnitus and otitis media has not significantly changed. Treatment was the most common study focus for all four of these disease conditions. Clinicians should consider that most otology clinical trials are industry sponsored when using their data to inform clinical decision making. Future studies combining our data from clinicaltrials.gov with other national and international clinical trial registries may help further characterize otology research efforts.

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Declarations of interest

None.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Agrawal, Y., Pineault, K.G., Semenov, Y.R., 2018. Health-related quality of life and economic burden of vestibular loss in older adults. Laryngoscope Investig Otolaryngol 3 (1), 8–15.
Bodenheimer, T., 2000. Uneasy alliance–clinical investigators and the pharmaceutical industry. N. Engl. J. Med. 342 (20), 1539–1544.
Boerner, R., Hatch, J.L., Harruff, E., et al., 2018. Publishing trends in otology and neurotology. Otol. Neurotol. 39 (1), 127–132.
Briel, M., Olu, K.K., Von elm, E., et al., 2016. A systematic review of discontinued trials suggested that most reasons for recruitment failure were preventable. J. Clin. Epidemiol. 80, 8–15.
Brown, C.S., Emmett, S.D., Robler, S.K., Tucci, D.L., 2018. Global hearing loss prevention. Otolaryngol. Clin. 51 (3), 575–592.
Cho, M.K., Bero, L.A., 1996. The quality of drug studies published in symposium proceedings. Ann. Intern. Med. 124 (5), 485–489.
Davidson, R.A., 1986. Source of funding and outcome of clinical trials. J. Gen. Intern. Med. 1 (3), 155–158.
Ear Foundation. Available at: http://www.earfoundation.org/files/download/1221. (Accessed 19 March 2020).
Hesse, G., 2016. Evidence and evidence gaps in tinnitus therapy. GMS Curr. Top. Otorhinolaryngol., Head Neck Surg. 15, Doc04.
Johnson, A.L., Fladie, I., Anderson, J.M., Lewis, D.M., Mons, B.R., Vassar, M., 2019. Rates of discontinuation and nonpublication of head and neck cancer randomized clinical trials. JAMA Otolaryngol Head Neck Surg 146 (2), 176–182.
Kozin, E.D., Sethi, R.K., Remenschneider, A.K., et al., 2015. Epidemiology of otologic diagnoses in United States emergency departments. Laryngoscope 125 (8), 1926–1933.
Leigh, J., Dettman, S., Dowell, R., Briggs, R., 2013. Communication development in children who receive a cochlear implant by 12 months of age. Otol. Neurotol. 34 (3), 443–450.
Leigh, J.R., Dettman, S.J., Dowell, R.C., 2016. Evidence-based guidelines for recommending cochlear implantation for young children: audiological criteria and optimizing age at implantation. Int. J. Audiol. 55 (Suppl. 2), S9–S18.
Morse, E., Fujiwara, R.J.T., Mehra, S., 2018. Increasing industry involvement in otolaryngology: insights from 3 Years of the open payments database. Otolaryngol. Head Neck Surg. 159 (3), 501–507.
Ramsey, T., Svider, P.F., Folbe, A.J., 2018. Health burden and socioeconomic disparities from hearing loss: a global perspective. Otol. Neurotol. 39 (1), 12–16.
Roche, J.P., Adunka, O.F., Pillsbury, H.C., Buchman, C.A., 2013. Cost of cholesteatoma care at a tertiary medical center. Otol. Neurotol. 34 (7), 1311–1315.
Rochon, P.A., Gurwitz, J.H., Simms, R.W., et al., 1994. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. Arch. Intern. Med. 154 (2), 157–163.
Shekelle, P., Takata, G., Chan, L.S., et al., 2002. Diagnosis, natural history, and late effects of otitis media with effusion. Evid. Rep. Technol. Assess. (55), 1–5 (Summ) 2002;1–5.
Sindhusake, D., Mitchell, P., Newall, P., Golding, M., Rochtchina, E., Rubin, G., 2003. Prevalence and characteristics of tinnitus in older adults: the blue mountains hearing study. Int. J. Audiol. 42 (5), 289–294.