

CURRENT AND EMERGING PHARMACOLOGICAL TREATMENT OPTIONS IN THE MANAGEMENT OF SUDDEN SENSORINEURAL HEARING LOSS

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ABSTRACT

A fast decrease in hearing of 30 dB or more within 72 hours is known as Sudden Sensorineural Hearing Loss (SSNHL), which usually affects one or both ears and frequently manifests with no apparent explanation. This medical emergency has the potential to seriously harm social interaction, communication, and mental health. Although Sudden Sensorineural Hearing Loss is common, little is known about its origin, and there are few available treatments. Corticosteroids, which can be given orally or intratympanically, are the mainstay of current pharmacological therapy for inflammation reduction. Vasodilators like pentoxifylline and antiviral drugs like acyclovir have been studied, but their effectiveness is still up for debate. Although preliminary studies suggest potential benefits, further large-scale clinical trials are needed to establish the safety and efficacy of these emerging treatments. Investigational therapies such as gene editing and growth factor-based approaches offer hope for restoring hearing in patients with Sudden Sensorineural Hearing Loss. Continued research and clinical advancements are essential to refine these therapies and optimize their effectiveness in preventing permanent hearing loss and improving patient outcomes.

KEYWORDS: Sudden Sensorineural Hearing Loss (SSNHL), Corticosteroids, Antiviral Agents, Vasodilators, GeneTherapy, Stem Cells, Hyperbaric Oxygen Therapy, N-Acetylcysteine (NAC), Ebselen, AM-111, SPI-1005, CGF166.

INTRODUCTION

A sudden, unexplained decrease in hearing of 30 dB or more that affects one or both ears within 72 hours and usually involves the sensorineural pathway is known as Sudden Sensorineural Hearing Loss (SSNHL). Deafness and Other Communication Disorders National Institute, 2020^[1]. A rapid, frequently unanticipated decline in hearing is the hallmark of Sudden Sensorineural Hearing Loss, a medical emergency that impacts thousands of people annually worldwide. It can significantly impair a person's quality of life by influencing social interactions, communication, and emotional health.

Despite its severity, there are few available treatments for Sudden Sensorineural Hearing Loss, and its causes are still mostly unknown. In order to prevent irreversible hearing loss and enhance results, Sudden Sensorineural Hearing Loss must be identified and treated as soon as possible.

Current pharmacological treatment options for Sudden Sensorineural Hearing Loss include corticosteroids, antiviral medications, and vasodilators, which aim to reduce inflammation, combat viral infections, and improve blood flow to the affected ear. Emerging treatment options show promise, including gene therapies, stem cell therapies, and small molecule therapies that target specific molecular pathways involved in Sudden Sensorineural Hearing Loss. These innovative approaches may offer new hope for patients with Sudden Sensorineural Hearing Loss, potentially leading to improved hearing outcomes and enhanced quality of life.^[2]

PHARMACOLOGICAL TREATMENT OPTIONS

Pharmacological treatment of sudden sensorineural hearing loss involves corticosteroids, with oral prednisone and intratympanic steroid injections because of their anti-inflammatory properties. Emerging treatments include hyperbaric oxygen therapy as an adjunct to steroids, while vasodilators, antioxidants, and antiviral agents have shown limited success. Investigational therapies such as neurotrophic agents, anti-apoptotic drugs, and gene therapy are being explored to protect and regenerate inner ear structures. Novel approaches targeting inflammation, oxidative stress, and vascular factors are under investigation to enhance recovery outcomes and further research is needed to establish their efficacy.

PRESENT PHARMACOLOGICAL TREATMENT OPTIONS

The pharmacological treatment options for sudden sensorineural hearing loss include corticosteroids, antiviral medications, and vasodilators. Corticosteroids, such as prednisolone or methylprednisolone, are commonly administered either orally or intratympanically to reduce inflammation and swelling in the inner ear. Valacyclovir or acyclovir may be prescribed to address potential viral infections that could be contributing to sudden sensorineural hearing loss. Vasodilators like pentoxifylline or naftidrofuryl are used to enhance blood flow to the affected ear, potentially improving outcomes. These treatment options aim to mitigate damage and promote recovery in individuals experiencing SSNHL.

Glucocorticoids

Systemic glucocorticoids are commonly prescribed as the primary treatment for idiopathic sudden sensorineural hearing loss, but the effectiveness and risk differences between high-dose and lower-dose regimens remain unclear. The patients with hearing loss of at least 50 dB within seven days were randomly assigned to receive either high-dose intravenous prednisolone (250 mg/day), high-dose oral dexamethasone (40 mg/day), or a control regimen of oral

prednisolone (60 mg/day) with tapering doses over ten days. The primary measure was the change in hearing threshold at three key frequencies after 30 days. The study involved 325 participants and found no significant difference in hearing improvement between groups, with the high-dose treatments not proving superior to the lower-dose regimen. However, adverse effects were more common in the high-dose groups. These findings suggest that high-dose glucocorticoid therapy does not offer better outcomes than standard doses and may pose a higher risk of side effects.^[4]

Prednisolone is administered orally at 1 mg/kg/day for 7-14 days, followed by a tapering dose over the next 7-14 days, while intratympanic administration involves 20-40 mg/mL injected into the middle ear space, typically with 1-2 injections per week for 2-4 weeks. Methylprednisolone can be given orally at 48-64 mg/day for 7-14 days, followed by tapering, or intravenously at 250-500 mg/day for 3-5 days, often followed by oral prednisolone. Intratympanic methylprednisolone is administered at 40-80 mg/mL with 1-2 injections per week for 2-4 weeks. Dexamethasone is used orally at 4-8 mg/day for 7-14 days with subsequent tapering, while its intratympanic form is delivered at 4-10 mg/mL, also with 1-2 injections per week for 2-4 weeks. These regimens aim to reduce inflammation and improve hearing outcomes, with intratympanic injections often used in cases where oral steroids are ineffective or contraindicated.

Antiviral agents

Sudden sensorineural hearing loss has been linked to viral infections, particularly those caused by the herpes virus family. So antiviral agents like acyclovir and valacyclovir have been explored as potential treatments. These medications work by inhibiting viral replication, which may help reduce inflammation and damage in the cochlea. Some studies have suggested that when used in combination with corticosteroids, antiviral therapy might offer a slight benefit in certain cases, particularly if treatment is initiated early. However, large-scale clinical trials have not consistently demonstrated a significant improvement in hearing recovery with antiviral use alone. While the role of antiviral drugs in SSNHL treatment remains debated, they may still be considered in cases where a viral etiology is strongly suspected.^[5]

Acyclovir is administered orally at a dose of 800-1000 mg, 3-5 times a day for 7-14 days, or intravenously at 500-1000 mg, 3 times a day for 7-14 days in more severe cases. Valacyclovir, a prodrug of acyclovir with better bioavailability, is given orally at 1000-2000 mg, 2-3 times a day for 7-14 days. Although the efficacy of antiviral therapy in SSNHL remains uncertain, these agents are considered in cases where viral infections, such as herpes simplex virus, are suspected to be contributing factors.

Vasodilators

Pentoxifylline has been explored as a treatment option for sudden sensorineural hearing loss (SSNHL) due to its ability to improve blood circulation by increasing red blood cell flexibility and reducing blood viscosity. Since cochlear ischemia is considered a possible cause of SSNHL, pentoxifylline has been investigated for its potential to enhance microcirculatory flow in the inner ear. Studies comparing pentoxifylline to corticosteroids in SSNHL treatment, particularly in diabetic patients, have found similar hearing recovery rates between the two therapies. However, pentoxifylline appears to have an advantage in maintaining better blood sugar control, making it a potentially safer alternative for patients with diabetes who are at risk of hyperglycemia-related complications.^[6]

Pentoxifylline is administered orally at 400-800 mg, 2-3 times a day for 7-28 days, or intravenously at 200-400 mg, 2-3 times a day for 7-14 days. Naftidrofuryl, another vasodilator, is given orally at 200-600 mg, 2-3 times a day for 7-28 days, or intravenously at 100-200 mg, 2-3 times a day for 7-14 days. While the effectiveness of these agents in SSNHL remains inconclusive, they may be considered in cases where vascular insufficiency is suspected as a contributing factor.

EMERGING PHARMACOLOGICAL TREATMENT OPTIONS

Emerging pharmacological treatment options for sudden sensorineural hearing loss (SSNHL) include several promising approaches. N-Acetylcysteine (NAC), an antioxidant, may protect the inner ear from damage by reducing oxidative stress. Similarly, ebselen, a synthetic antioxidant, has shown potential in minimizing oxidative damage in the inner ear. Hyperbaric oxygen therapy, when combined with pharmacological adjuncts such as edaravone, a free radical scavenger, may enhance the therapeutic effects by improving oxygen delivery and reducing oxidative injury. Stem cell-based therapies, particularly those using mesenchymal stem cells, offer the possibility of regenerating damaged hair cells in the cochlea. Additionally, gene therapies, such as AAV-mediated gene therapy, aim to restore hearing by repairing or replacing defective genes associated with hearing loss. These emerging therapies hold promise for improving outcomes in patients with SSNHL.

N-Acetylcysteine (NAC)

N-acetyl-cysteine (NAC) has shown potential as a treatment for sensorineural hearing loss, particularly in animal models of noise-induced hearing damage. However, human studies have produced conflicting results. A meta-analysis of seven studies involving 1,197 participants examined NAC's effectiveness for different types of hearing loss, including sudden idiopathic and drug-induced cases. The overall findings indicated that NAC did not significantly improve hearing recovery, except in cases of sudden hearing loss, where some positive effects were noted. Further research with larger sample sizes is necessary to clarify NAC's role in hearing loss treatment.^[7]

Oral administration typically involves a dose of 600-1200 mg, 2-3 times a day for 7-14 days, while intravenous administration is given at 300-600 mg, 2-3 times a day for 3-7 days.

Ebselen

Ebselen is a synthetic organoselenium compound with strong antioxidant and anti-inflammatory properties, has been investigated as a potential treatment for sudden sensorineural hearing loss (SSNHL). Its mechanism of action involves mimicking glutathione peroxidase, which helps reduce oxidative stress and inflammation in the cochlea—two factors believed to contribute to SSNHL. Research suggests that ebselen may protect inner ear cells from damage caused by excessive free radicals and improve hearing outcomes. While preliminary studies indicate its potential effectiveness, further clinical trials are needed to establish its role as a standard treatment for SSNHL, either alone or in combination with existing therapies like corticosteroids.^[9]

Intravenous administration typically involves a dose of 30-60 mg given twice a day for a duration of 14-28 days

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) has been proposed as a beneficial option, its widespread use remains limited. A systematic review and meta-analysis examined the impact of HBOT on SSNHL treatment, analyzing randomized

controlled trials that adhered to standard diagnostic criteria. The study found that when used alongside medical therapy, HBOT was significantly associated with better hearing recovery compared to control treatments. These findings suggest that HBOT could be a valuable addition to existing treatment protocols for SSNHL.^[10]

Hyperbaric oxygen therapy (HBOT) aimed at improving oxygen delivery to the inner ear. The standard treatment protocol involves administering oxygen at a pressure of 2.0-2.5 ATA (atmospheres absolute) for 60-90 minutes per session. Sessions are typically conducted 1-2 times per day, with a total of 10-20 sessions recommended depending on the severity of hearing loss and patient response. Although HBOT has shown potential benefits, particularly when initiated early, its effectiveness in improving hearing outcomes remains variable, warranting further investigation.

Stem cell-based therapies

Stem cell-based therapy is being explored as a potential treatment for sudden sensorineural hearing loss (SSNHL) due to its regenerative properties. The inner ear's sensory hair cells and neurons, which are often damaged in SSNHL, have limited capacity for self-repair. Stem cells, including mesenchymal stem cells and induced pluripotent stem cells, have shown promise in regenerating these damaged structures by differentiating into functional auditory cells and promoting tissue repair. Experimental studies in animal models suggest that stem cell therapy may help restore hearing by replacing lost cells and reducing inflammation. While early research is promising, clinical applications are still in the investigational stage, and more studies are needed to confirm its safety, efficacy, and long-term effects in humans.^[11]

Gene therapies

Gene therapy is emerging as a promising approach for treating sensorineural hearing loss by targeting damaged inner ear cells that are unable to regenerate naturally. Recent research has focused on the use of gene editing technologies such as CRISPR/Cas9 and viral vector delivery systems to stimulate hair cell regeneration and restore auditory function. Several transcription factors and signaling pathways have been identified as key regulators of hair cell development and repair. Although gene therapy has shown encouraging results in preclinical studies, challenges remain in optimizing its efficiency and ensuring safety for clinical application. Continued research is necessary to refine these techniques and translate them into effective treatments for hearing loss.^[12]

INVESTIGATIONAL AGENTS

Investigational agents for the treatment of sudden sensorineural hearing loss (SSNHL) include promising therapies that target different mechanisms of inner ear protection and regeneration. AM-111, a JNK inhibitor, may help prevent apoptosis in the inner ear, thereby protecting auditory cells from damage. SPI-1005, a synthetic antioxidant, is being investigated for its potential to reduce oxidative stress in the inner ear and prevent further damage. Additionally, CGF166, a growth factor-based therapy, aims to promote hair cell regeneration, offering the potential to restore hearing. These investigational agents represent innovative approaches that may improve outcomes for patients with SSNHL in the future.

AM-111

AM-111, a cell-permeable peptide that inhibits the c-Jun N-terminal kinase (JNK) stress pathway, has been studied for its potential to treat acute idiopathic sudden sensorineural hearing loss (ISSNHL). In a phase 3 clinical trial, patients received a single intratympanic injection of AM-111 at either 0.4 mg/ml or 0.8 mg/ml, while a control group received a placebo. The primary goal was to assess hearing improvement after 28 days. Although the overall study population did

not show significant improvement with AM-111 compared to placebo, post-hoc analysis suggested that the 0.4 mg/ml dose had a beneficial effect in patients with profound ISSNHL. The drug was well tolerated, and no major safety concerns were reported. These findings indicate that AM-111 could provide protective benefits in cases of severe cochlear injury.^[13]

SPI-1005

SPI-1005, a drug containing ebselen, has been investigated as a potential treatment for sudden sensorineural hearing loss (SSNHL) due to its antioxidant and anti-inflammatory properties. Ebselen mimics glutathione peroxidase, an enzyme that helps protect cochlear cells from oxidative stress and inflammation, which are believed to contribute to SSNHL. Clinical trials have suggested that SPI-1005 may improve hearing recovery, particularly in patients with severe hearing loss, by reducing cellular damage in the inner ear. While early results are promising, further large-scale studies are needed to confirm its effectiveness and establish its role as a standard treatment for SSNHL.^[14]

CGF166

CGF166, an investigational gene therapy, has been explored as a potential treatment for sudden sensorineural hearing loss (SSNHL) by promoting the regeneration of inner ear hair cells. This therapy utilizes an adenovirus vector to deliver the Atoh1 gene, which plays a crucial role in hair cell development and repair. Early clinical trials have suggested that CGF166 may help restore hearing in some patients by stimulating hair cell regrowth in the cochlea. However, challenges such as safety concerns, immune responses, and variability in treatment outcomes remain. Further research is necessary to optimize its delivery and confirm its long-term efficacy in SSNHL patients.^[15]

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