

## Nano therapy Spotlight: Arestin™ Minocycline Microspheres

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Received: 29 Dec 2022; Accepted: 01 Feb 2023; Published: 05 Feb 2023

**Citation:** Drew Plemmons, KB Sneed, Yashwant Pathak. Nano therapy Spotlight: Arestin™ Minocycline Microspheres. Chem Pharm Res. 2023; 5(1): 1-8.

**ABSTRACT**

Within the last ten years, recent advancements in nanotechnology and repurposed pharmaceutical development has led several successful therapeutics through clinical trials and subsequently onto the market. On the nanotechnology side, size, shape, charge, and formulation are all considered in improving the overall efficacy or delivery of the therapeutic. Nanoparticle therapies hit the market in the late 90's when the FDA approved CosmoFer®, an iron sugar colloid that also saw use in the European market. While these early nano pharmaceuticals were primitive compared to today's standards, these medications proved that a nanoparticulate therapeutic can and would be accepted by the FDA, albeit under much scrutiny. On the pharmaceutical side, older legend drugs that have been proved efficacious for many years are beginning to be repurposed for other uses. For example, Pfizer's 2015 approval of Rapamune® (Rapamycin) is indicated for the treatment of Lymphangioleiomyomatosis (LAM) a rare lung disease infecting mostly women in early adulthood. The drug, however, was first approved in 1999 and was used in the prophylaxis of organ rejection as an immunosuppressant. Another indication for Rapamycin is in age related diseases; a 2006 paper published by Dr. Blagosklonny at the Roswell Park Comprehensive Cancer center showed that Rapamycin could inhibit certain pathways that are related to aging. Many other medications on the market such as monoclonal antibody therapies have also seen a rise in new implication discovery and there is much evidence to suggest other drugs will be researched in the future for other alternative treatments.

Because of such developments, pharmaceutical companies have tapped into the nanoparticle development world to find novel therapies for diseases we once thought were unavoidable. This is shown by the sheer expected market growth of about two billion dollars from 2021-2026, and the fifteen different nanoparticle-based therapeutics that have already been FDA approved since in just the last three years. Although the nanoparticle technology scope may seem to hover over novel cancer therapies, autoimmune disorders, blood borne diseases and neurological disorders, many therapies have come about in some interesting fields of study. One such therapeutic is called Arestin®, a new dentistry medication for the treatment of severe periodontitis, better known as gum disease. Gum disease is caused by poor oral hygiene and is attributed to various bacterial infections within the gum-line and if left untreated it can cause soft tissue damage or jawbone degradation. Typically, an antibiotic mouthwash or ultrasonic dental cleaner can be used to treat minor periodontitis but, in severe cases where there is significant gum-line recession, a more direct therapeutic is needed to treat the infection directly at the source. Arestin® is a nanoparticle formulation containing minocycline HCl impregnated within a bio-reabsorbable polymer that is delivered directly into the gum-line via a blunt tip syringe. Minocycline is a tried-and-true antibiotic with a rich history of over thirty years on the market as a second-generation tetracycline derivative. It is both a gram positive and gram negative [broad spectrum] antibiotic and is very well tolerated in patients making it an excellent candidate in late-stage gum disease intervention. Here, this review, discuss Arestin® and subsequently Minocycline Hydrochloride's: history, mechanism of action, formulation/production, side effects and the future of reformulated nano pharmaceuticals that are continuing to move the market share up.

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## Keywords

Arestin, Nanotechnology, Minocycline hydrochloride, Nano-particle based therapeutics, Dentistry medicines, Gum diseases.

## Introduction

Nanotechnology advancements over the last twenty years have proved that our need to go smaller will be ever increasing. Technologies such as transistor development have begun to reach the physical limitations of our world, however, there seems to be no end in sight. The same can be said for its sister field; nano drug delivery development, as it is a quite recent technological advancement. Nanotechnology is the study of small particles usually within the diameter of about one hundred nanometers and involves many processes to achieve small evenly distributed particles [1]. Though nanotechnology was first coined in the late 1800s, recent advancements in nanoparticle fabrication has led to a boom in the nanotechnology space and has also gained interest in the pharmaceutical development world as it is becoming less expensive to manufacture said nanoparticulate [1]. The gained interest from the pharmaceutical world can be attributed from the fact that these small particles can be modified in such a way to reach specific areas of the body and deliver a therapeutic over a long period [1,2]. For example, one of the first FDA approved nano drug delivery therapeutics, CosmoFer®; an Iron III hydroxide sugar colloid solution, was first approved in 2005 for the treatment of iron deficiency or anemia and is still used widely today as shown in some of the European market [3,4]. It works by exploiting the bodies' ability to break down foreign substances into their primary constituents; the iron complex and the sugar moiety, allowing the free iron to replenish iron stores and major hemi complexes found in hemoglobin [3,4]. CosmoFer® was shown in its clinical trials to have an increased blood iron level over a period of six weeks compared to the more common Ferrous Sulfate [3,4]. Another nano-therapeutic recently on the market and in the news was Pfizer/BioNTech's SARS-COV-2 lipid nanoparticle mRNA vaccine. This vaccine was the culmination of many companies' efforts to get a working, safe and efficacious inoculation to combat the intense Covid-19 infections. The lipid nanoparticle houses a messenger RNA sequence for the SARS-COV-2 spike protein; when the nanoparticle comes in contact with a cell, it morphs with the lipid bilayer of the eukaryotic cell. It then delivers the mRNA sequence directly into the cytoplasm where the ribosomes can start producing the translated spike protein [11]. After enough spike protein has been manufactured by the ribosomes the cell initializes an immune response towards the foreign spike protein and is memorized by B cells for future SARS-COV-2 infections. While these two therapies (CosmoFer® and Pfizer's mRNA vaccine) differ drastically from one another, they both deliver a therapeutic to a specific area, and are dosed for a longer period than other therapeutics on the market at the time.

Another area of technology that has seen much advancement over the last twenty years is the repurposed pharmaceutical industry. Drug repurposing is the process of finding new uses for existing therapeutic compounds before or after market publication [18,19]. Popularity of drug reprofiling started rising in the early 2000s

as researchers began alluding to the fact that certain diseases sometimes share biological targets or pathways, and that certain drugs may hold efficacious to other diseases that were not originally thought to be indicated for use during FDA approval. Technologies such as high throughput screening; computer aided robotics systems capable of screening thousands of molecules in just a couple of days, can be attributed to the rising popularity of drug repurposing due to the ability to screen and mature drug candidates against any target, and can even preform toxicological assays after a few candidates have been selected from a round of screening [20,21]. This has ultimately led to a handful of reprofiled drugs to have multiple indications approved by the FDA and or entirely new therapeutic formulations based on generic legend drugs. For instance, take Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc., FDA approved drug Rapamune® (Sirolimus). It was initially approved in 1999 within the U.S market to proactively protect patients against organ rejection after receiving kidney transplantation [8,9,22]. Shortly after its approval, more news about Rapamune® came about when a paper published by Dr. Blagosklonny showed it could inhibit certain pathways related to aging in 2006. Blagosklonny's hypothesis was proven right eight years later in another paper published by Novartis, which showed sirolimus exposed fruit flies having a preventative effect on age related genetic pathways and certain biomarkers related to longer life span [7,8,9,22]. And in 2015, Pfizer announced the new FDA approval for Rapamune® for the treatment for Lymphangioliomyomatosis (LAM), a rare progressive lung disease affecting women in their middle-aged years [8,9]. Although Rapamune® is just one example of drug repurposing, it shows that therapeutics may have multiple indications and are able to be FDA approved for as such. Another therapeutic that has seen other uses is a drug called Minocycline; a broad-spectrum second-generation tetracycline derivative indicated for the use in the treatment of anaerobic bacterial infections [23,24]. Minocycline was patented in 1961 by American Cyanamid alongside their other flagship molecule Doxycycline in 1957. Minocycline was first described in literature in 1966 in a paper that focused on the antibacterial activity of new derivative of tetracycline within mouse models and was shown to be extremely effective; it was to gain traction quite quickly as it was FDA approved shortly after in 1971 with the name Minoicin® [23,24]. It was found that minocycline is an amazing broad-spectrum antibiotic and was shown to target over 36 different species of anaerobic bacteria. Shortly after Minoicin® gained generic status, another indication of minocycline was found in the treatment of acne vulgaris; and oral and topical form were composed and sold under other names such as Amzeeq®, Dynacin®, Ximino®, and Zilxi® [25,26]. Although minocycline can cause antibiotic resistance, it is still one of the most prescribed antibiotics in the world and is now in almost every major continent. Repurposed drugs will be continually found as there are now specialized companies dedicated to screening legend drug libraries against theorized targets.

Finally, as the drug repurposing and the nanodrug delivery markets grew together, it was just a matter of time before a groundbreaking therapeutic using both technologies was conceived. Here we find

Arestin®, a minocycline microsphere formulation indicated for the use in gum disease treatment within dentistry. It was first released in 2001 by OraPharma; a Bausch Health Company subsidiary. Arestin® is administered deep into the gum-lining pockets with a blunt tip syringe and a gel like substrate containing the minocycline microspheres is delivered directly to the site of infection [13-15]. Arestin® is able to stay within these pockets for quite a while and delivers minocycline over a period of three weeks to a month; this is advantageous because bacterial biofilms are constantly being inoculated with the therapeutic, which is like the use of oral minocycline tablets to treat respiratory infections over a period of fifteen days [13-15]. Arestin® has now become a part of the FDA's dental standards, which is a guideline treatment within dentistry and is seeing use even in smaller mom and pop dentist offices. We will discuss the history and mechanism of minocycline and Arestin® to further the idea that drug repurposing and nanodrug delivery are innovative technologies with the capabilities to change our lives forever. Just as transistor technology has become commonplace, nanotherapeutics will also gain the same traction as more researchers and pharmaceutical companies flock to make profitable therapeutics.

### History of Minocycline

Tetracyclines are a class of antibiotics that were first described in 1948 and gained popularity as it found use in treatment of broad-spectrum microbial infections. Researchers found this natural product within actinomycetes, which are bacteria found in soil. They learned that these bacteria would kill off other bacterial cultures when exposed together and figured out after purification that a molecule was responsible for the antimicrobial response [23]. Soon after, commercialization of tetracyclines began in the late 1940s, and created a field of study within the process: Semi-synthesis of antibiotics. This led to the generation of second and third generation semisynthetic tetracyclines, which has spawned over ten different new drugs beginning from just one therapeutic [23]. In 1961, American Cyanamid patented minocycline hydrochloride as a broad-spectrum antimicrobial, alongside another hallmark medication, Doxycycline in 1957. A publication authored by Dr. Redin showed these new tetracycline derivatives antimicrobial activity within a mouse model, which has led to its mainstream use just years later. In 1971, Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc., launched minocycline under the name Minocin® [23,24]. It gained FDA approval in 1971 and is classified under the legend drug category; a category in which patients can only use the medication with a doctor's prescription [23,24]. After some time on the patented market, many formulations of minocycline hydrochloride would be produced for various routes of administration; Oral tablets, topical creams/gels, oral suspensions for children, and intravenous formulations. It was shown that minocycline hydrochloride can treat many bacterial infections including Ricketts, Cholerae, Chlamydia, Mycoplasma, Escherichia coli, and Shigella species [23,24]. While minocycline and its other derivatives are excellent antibiotics, the increasing use of such therapies has led to the creation of bacteria resistant to these compounds. There is now much focus on the limiting of antibiotics for simple bacterial infections as bacteria continue to

adapt to our technologies; instead of antibiotics, a doctor may ask the patient to fight off the infection themselves so that bacterium will not gain a mutation for minocycline resistance and so that the body may fight off the infection with its adaptive/innate immune system [23,24].

Now, minocycline is indicated for multiple uses: as a broad-spectrum antibiotic with other interesting antimicrobial activities, as an acne medication, and more recently have shown effectiveness as a mild immune suppressor in the treatment of asthma [27-29]. In the treatment of acne, a bacterial infection causing inflamed red to white pustules to form in most teenagers and adults, minocycline has been very effective in mitigating bacterial growth. However, bacterial infections that have shown resistance to these medications must be combined with other therapeutics such as benzoyl peroxide in a cream. This has led to the creation and FDA approval of multiple dual action acne medication containing minocycline and other acne therapies like benzoyl peroxide and isotretinoin [25,28]. Minocycline has also been used in specific bacterial infections where minocycline seems to be a better choice than other antibiotics on the market. For example, minocycline is currently used to treat methicillin resistant Staphylococcus Aureus; methicillin is an extremely powerful antibiotic that is only used within a hospital setting for major bacterial infections and because of its continued use, has created super bacteria that need other antibiotics to treat [28,30,31]. Another use for minocycline is in the treatment of certain bacterial infections that either don't respond to typical antibiotics like Anthrax, Bubonic plague, and Cholera [28,30,31]. The use of minocycline is also used when patients are allergic or do not respond well to certain antibiotics like penicillin and have been used widely in these types of patients. While the use of minocycline in antibiotic therapies has been essential, issues with antibiotic resistance have begun to limit certain situations where minocycline would respond well [28,30,31]. As we find better antimicrobial therapeutics, minocycline and other second-generation tetracycline derivatives will see a comeback and may find other therapeutic uses in the meantime. Such instances have already been seen within the last ten years and now minocycline is a staple in the treatment of sexually transmitted diseases.

### Minocycline Mechanism of Action and Side Effects

Minocycline inhibits bacterial protein synthesis by targeting the 30S ribosome subunit, a major subunit making up the total ribosomal unit [23,24]. It does this by binding to the 30S subunit on the ribosome and prevents the binding of tRNA, a key role in protein production in the ribosome. Bacterial protein production starts with the transcription of genomic DNA to messenger RNA; messenger RNA is a small single stranded molecule that holds specific genetic information like small molecule or protein sequences [23,24]. This mRNA is shot out into the bacterial cytoplasm from the nucleus and finds a ribosomal subunit to bind to. After binding, the mRNA is translated into a protein; three mRNA codons at a time alongside a cofactor called tRNA (transferRNA), holds the anti-mRNA codon as well as the amino acid related to the three-codon code [23,24]. tRNA holds one amino acid per three mRNA codons and a full protein is synthesized from these amino acids one at a time from the

mRNA strand by the ribosome. When minocycline hydrochloride is introduced as an oral tablet or intravenous injection, it is only able to enter bacterial cells through its linking with magnesium and subsequent entry of bacterial pores [23,24]. Because of the lipophilic properties of tetracyclines in general, it is practically guided into the periplasmic space within the bacteria, where it dissociates into the cytoplasm. While in the cytoplasm, the minocycline can bind to the 30S subunit of the bacterial ribosome where it blocks the ability for tRNA to bind to the 30S subunit, ultimately shutting down protein synthesis. Typically, a dose would need to be delivered over a period to allow for the drug to become fully incorporated in blood serum [23,24]. Minocycline is metabolized into three different metabolites: 9-hydroxyminocycline, Minocycline M3, Minocycline M7 metabolites and is discarded by biliary route ending up in the urine or feces [23,24]. The half-life of minocycline in the body is eleven hours and is typically given as a series of 100-200mg doses every 12 hours until fever subsides or in the case of Syphilis, an administration regiment of 10-15 days [23,24]. Minocycline hydrochloride is also formulated multiple different ways as of now: Instant release, Extended Release, Intravenous, Intramuscular, Capsules or Tablets.

Side effects from minocycline are like many other antibiotics on the market but have some major effects that are only found in tetracycline derivatives that can be dangerous if not treated [30,31]. Like most antibiotics, minocycline can cause gastrointestinal issues like nausea, vomiting, diarrhea, drowsiness, and or headache. Major issues amongst most antibiotics are a sensitivity to sunlight and a possibility of autoimmune disorders that can be permanent [30,31]. Vertigo and other vestibular disturbances can be enhanced by minocycline addition, and it is thought that it is related to the penetration of central nervous system tissue. Another side effect of minocycline and tetracycline derivatives as a whole, is the increased toxicity of the drug after its expiry date. It is thought that the degradation of minocycline forms anhydro-4-epitetracycline and is shown to cause serious damage to the kidneys [30,31]. Although minocycline is a better alternative than first generation tetracyclines in patients with kidney disease, it aggravates lupus symptoms and may trigger autoimmune induced hepatitis making the drug less desirable to those with autoimmune disorders in general [29]. Minocycline has many drug or natural product interactions as well and must be considered when prescribing such a therapeutic. Combinations with food containing calcium, magnesium, or iron products will decrease the effectiveness of minocycline due to the interactions with minocycline and metals like those described above [23,24]. Combinations with other acne medications: isotretinoin, retinoids or acitretin increase the risk of brain hypertension in patients suffering from advanced forms of acne [23,24]. Minocycline also reduces concentrations of an HIV drug, Atazanavir, which would be deadly to those suffering from HIV if that is their last line of defense. Although minocycline has some major side effects it has a rich history and has been around on multiple global markets because it is a highly efficacious drug with reasonably manageable side effects in the majority of the population.

## History of Arestin®

In 1999 OraPharma, a subsidiary of the Bausch Health Company, patented a new oral antibiotic that was indicated to treat severe periodontitis. Arestin® (minocycline hydrochloride) microspheres, is a new form of an old antibiotic that was proven safe by the FDA many years before Arestin's inception. After subjection to clinical trials, it was approved shortly after in 2001 by the FDA and would be used all over the world as the therapeutic gained popularity [13-16]. Arestin® is used to treat severe gum infections (periodontists); which is a bacterial infection between the gum-lining and tooth that is left untreated. If untreated, the gum or jawbone could degrade as the bacterial infection spreads [13-16]. Bacteria within the gum-lining are perfectly normal, but the buildup of plaque and other bacteria, coupled with poor oral hygiene, lead to the need for an antimicrobial wash or treatment in late-stage gum disease. There are many ways to determine the level of gum disease in an individual: x-ray, gum-line pocket depth ruler, and visually. The depth ruler is the most common and is placed in between the gumline and tooth; if the measurement is around 4mm, the individual has early-stage gingivitis, if it is larger than 6mm, dental standards call for immediate action in the form of treatment. Common mechanical treatments for gum disease involve scaling and root planing (SRP), a process where a small metal scraper is used to remove patches of bacterial growth or biofilms that are hard to reach with dental floss or brushing due to the extreme depth of gum pockets [16]. Although this technique is very effective in removing biofilms and bacterial patches, small micro abrasions on the tooth's surface can hold bacterium or bacteria deep within the gum pocket can be left behind ultimately not clearing the infection. Before Arestin®, mild antimicrobial mouthwashes like Peridex (Chlorhexidine), were the only option for direct targeting of the bacteria buildup left over from such treatments; though, it is still used to treat early-stage gingivitis treatment in teenagers and adults and is now sold as a generic drug all around the world [32,33]. Because Arestin® is used for severe cases of gum disease, its use is limited to those who are major sufferers of periodontitis and is also limited due to the fact that it is an antibiotic which if used constantly, can create antibiotic resistance in such bacteria's. Therefore, a certain depth of gum pocket must be reached before treatment with Arestin® and hints at the need for the gum-line pocket depth ruler [16]. When antimicrobial mouthwashes and SRP are unable to treat the infection, dentists move onto Arestin® as it has become a gold standard in the dentistry standards in America [13-16]. The goal of Arestin® treatment is to deliver an antibiotic directly to the site of infection (between the tooth and gum lining) after SRP, as well as to deliver the antibiotic for a longer period of time than other currently available antibiotic therapeutics. It was shown in the Arestin® clinical trials that a dose of microspheres introduced into the pockets of an infected gum would be delivered for a period of over three weeks, compared to a common antibiotic regiment with minocycline oral capsules over the period of fifteen days [16]. Arestin® is delivered in 1mg doses containing minocycline hydrochloride impregnated within a polymer, each dose (1mg) is delivered into the gum pocket so that the minocycline can slowly release over a period of three weeks to a month [16]. Because of the relatively new nature of Arestin®, it tends to be quite

expensive due to the need for each 1mg dose to be delivered to a gum pocket. If multiple teeth are affected, multiple 1mg doses are needed for each pocket infected. According to SingleCare Pricing of pharmaceuticals, a thirty count of 1mg Arestin® (minocycline hydrochloride) microspheres costs over three thousand dollars without patient insurance [34-37]. Because not all thirty cartridges will be used, and hopefully only a couple of teeth are infected, the patient should only pay about sixty to ninety dollars per infected site without any insurance according to howmuchisit.org [34-37]. Of course, as the production of nano therapeutics becomes cheaper, Arestin® will find itself costing much less and may even reach the price of some legend antibiotic treatments on the market. Next, we will discuss the mechanism of action of Arestin®, and how it is produced on a massive scale for global use.

### **Arestin® Mechanism of Action and Production**

Arestin® (minocycline hydrochloride) 1mg microspheres' mechanism of action is extremely similar to minocycline hydrochloride and other first, second and third generation tetracycline derivatives as the active pharmaceutical ingredient is based off of the original minocycline hydrochloride mechanism described above [16,38]. Arestin® is formulated within a poly glycolide-co-dl-lactide (PGLA), which is a bioresorbable material that can hold minocycline hydrochloride and is slowly dissolved by the enzymes and water in our saliva. During manufacturing a micronized or "finely milled" minocycline hydrochloride powder is dispensed within a solution of PLGA in dichloromethane [38,39]. The suspension is added to a glass vial and mixed with a silicone polymer called polydimethylsiloxane to create the microspheres. It is then discharged and allowed to dry so that the particles will solidify; subsequent filtration and drying lead to a powdery compound with an off-white color [38-40]. Much precaution must be taken at every step of the manufacturing process as these micronized and microparticulate have been shown to increase respiratory inflammation as well as cardiovascular issues in those who have been exposed for a prolonged period of time [39]. Arestin® is known to kill common mouth bacteria such as: Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Eikenella corrodens, and Actinobacillus actinomycetemcomitans, which are all associated with periodontitis disease [16]. Arestin® works by targeting the same pathway minocycline hydrochloride does, which is inhibition of bacterial protein synthesis via ribosomal binding. As bacterial synthesis is inhibited, bacteria colonies start to die off leading to decreased bacteria within the gum pocket for a prolonged time. The goal after Arestin® administration is to keep the gum pockets healthy by having increased oral hygiene due to the drug being delivered for over a month; correct oral hygiene would mitigate the amount of bacterial build up so that SRP and Arestin® are not needed and a normal dental cleaning can suffice [16]. Another target of Arestin® administration is for the ability to decrease biofilm aggregation within deep gum pockets, biofilms are notoriously hard to fight off as the bacteria start to make a sort of 'pseudo shield', decreasing the effectiveness of antibiotics and antimicrobials due the therapeutics inability to reach major colonies of bacteria [41]. Much research has gone into bacterial biofilms as they are found naturally in nature and would further

our understanding of bacterial pathways, we don't fully understand yet. Before administration of Arestin®, a certified dentist or dental technician will perform a scaling and root planning procedure. Here they will employ a mechanical method where the plaque, tartar and bacterial biofilm buildup are scrapped off using a metal scraper (SRP) [41]. Patients are usually given a local anesthetic like Lidocaine or Novocain to mitigate any sensitivity and pain that may be felt during the procedure; it is quite well tolerated in patients with mild gum disease but can be quite painful in late-stage illnesses (personal experience) thus the need for a patient pain relief plan if the individual asks or on request of the dentist. During administration, an Arestin® cartridge containing 1mg of active ingredient is loaded into a syringe that is capped with a blunt tipped needle to ease the patients mind and to avoid puncturing the gum [16]. The pocket depths are measured once again after the SRP procedure and affected gum pockets are marked to ensure the patient is receiving the correct treatment at the site of infection. Within the cartage, the minocycline hydrochloride microspheres are as a powder; dispensing with the syringe plunger pours the microspheres into the gum pocket and with the help of a blunt tipped needle, can be delivered accurately so that no medication is wasted [16]. As the microspheres are dispensed, they are mixed with the individual's saliva and the particulate becomes a semi-solid gel that can incorporate itself within the small crevasses of the gum pocket and tooth. Each 1mg dose is dispensed into one infected area until all areas have been treated; as the patient's mouth moves around after inoculation, the microsphere gel compound can move around to better coat the area of infection. During the period of three weeks to a month, the microspheres will slowly dissolve releasing minocycline for the period; this allows the drug to get incorporated around the area and can coat biofilms for direct targeting of these species. It is this prolonged dissolution of minocycline that was sought after when creating Arestin® and it is shown to do this quite well as it was FDA approved just three years after its conception. According to iHealthcareAnalyst, the global market for periodontal disease therapeutics is expected to rise by \$1.3 billion from 2022 – 2029 due to the correlation between gum disease and age [42].

### **Side Effects from Arestin®**

Like minocycline hydrochloride's side effects, Arestin® side effects can cause autoimmune disorders, nausea, vomiting, diarrhea and or headache. Other ailments like vertigo can be enhanced by minocycline administration but would be lower due to the shear difference of the amount of drug exposed to during treatment. It is not fully understood if Arestin® would increase Lupus or auto autoimmune disorders but at the dose prescribed it can only be thought that the interactions would be limited, especially if just a couple of areas are infected within the individual. During a typical antibiotic regiment to treat an E.Coli infection, physicians are supposed to prescribe 100-200mg doses every 12 hours for a period of 15 days; whereas and Arestin® therapy may only expose a patient to a minimum of 1mg over a period of a month [41]. However, due to our knowledge of the drug minocycline, Arestin® wouldn't be treated any differently and is treated with more respect as our understanding of nanoparticles is limited. Precautions could be in place if a patient were to have ailments

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that would be triggered by Arestrin® and a registered pharmacist is typically aware if you have any drug – drug interaction with a drug interaction database [43]. Common issues with tetracycline derivatives are associated with increased toxicity of the therapeutic past its expected expiry date. This can be mitigated by extensive short term/long term stability testing and ensuring the expiry date is clearly labeled not only on the package but on every cartage that is used by the dental professional. Minocycline and Arestrin® have many drug/natural product interactions and is considered by a pharmacist when a doctor prescribes these therapeutics. Food combinations with high calcium, magnesium, or iron content will decrease the effectiveness of minocycline and especially Arestrin®, due to the interactions with minocycline and metals like those described above [41]. Other interactions like in those who take antivirals must be aware that minocycline, and subsequently Arestrin®, can decrease the effectiveness of such medications and is backed up by a known negative interaction with an HIV drug called Atazanavir; this could be deadly to those who suffer from such disease because there are only a handful of long term use antivirals on the market and cannot be switched to rapidly without major consequences [16]. Tetracyclines have also been known to permanently discolor teeth into a yellowish grey color with is obviously undesirable for a dental medication, although the medication is delivered into the gumline, or root area of the tooth, luckily those areas cannot be seen by other individuals. [16]. After administration of Arestrin®, patients must avoid chewing hard or crunchy foods with treated teeth for about a week and must prevent themselves from also touching the treated areas with their hands.

### Future Trends

As stated above, the global market for periodontal disease therapeutics is expected to grow by over \$1.3 billion from 2022 – 2029; this is backed up by the correlation between age and gum disease, but has other contributing factors such as location, age, and wealth [42,44]. As researchers continue to refine nanotherapeutics, Arestrin® will start to become a layman’s technology as there are nanotherapeutics currently in clinical trials that are extremely complex, treating rare or difficult diseases with extremely thin lines for error. In general, as medicine advances, better technologies and formulations will come about that may ultimately beat out a tried and true therapeutic. For instance, a paper published within an Indian dentistry journal compared the effectiveness of Arestrin® and a new formulation of Chlorhexidine. They proved that both therapeutics reduced average plaque, gum pocket depth and gum health the same amount, leading to a thought process as to why we use Arestrin® in the first place. It was then shown that long term treatment time was reduced by Arestrin® to six weeks compared to the chlorhexidine mouthwash at three months, subsequently backing up microsphere technology.

Nanoparticle technology is beginning to become a hot topic in almost every field. Within dentistry, scientists are beginning to realize the advancement nanotechnology could bring to their field. For example, a paper published in the Journal of Oral Biology and Craniofacial Research titled "Nanoparticles used in dentistry: A Review", explains some of the recent advancements and thought

processes using nanoparticle technology. One application that has already seen market value is the use of silica; silica is a naturally occurring element usually in the form of silicon dioxide. Silica has been used as a polishing agent for years and has become standard practice in tooth polishing [44,45]. Some toothpastes today contain small nanoparticles of silica to help take food particulate from the tooth and to make them pearly white. Another use of silica is in the treatment of dental hypersensitivity via the use of desensitizing agents [44,45]. If you have ever eaten ice cream and it has touched a sensitive tooth, you know about hypersensitivity; now imagine this feeling without ice cream when you eat your favorite foods. Because of the constant drive to have better oral hygiene due to our increase consumption of sugary foods, better materials will be needed to combat tooth hypersensitivity and there are already some compounds that aid in protecting the tooth by coating it in a nano silica hydrocarbon [44,45]. Another trend in dental nanomedicine is focused on better cavity fillers. Hydroxyl apatite nano particles have been widely used in dentistry because of their bio similarity to tooth and bone structure. When applied, the calcium-based compound adds to the tooth enamel, ultimately making them stronger in the process; it forms crystals, like the structure of the tooth making it a perfect candidate for dental implantation or fillings [44,45]. It is clear that the use of nanotechnology will be continually refined to produce amazing products not only in the world of dentistry, but also in many fields who have yet to see the advancements of such technologies.

### Conclusions

To close, here we discussed the use of repurposed drugs and nanotechnology advancements to describe a recent therapeutic on the market for the treatment of periodontitis: Arestrin®. It has become an American dental standard of care and has singlehandedly created a market for the treatment of periodontist nanotherapeutics. Nanodrug delivery technologies and the nanotechnology industry as a whole are continuing to create groundbreaking products that are constantly coming out of research and development. While there is much to learn when it comes to the long-term effects of nanoparticle exposure both in the workplace and in the general population, the technologies described above showed that it is possible to get a nanoparticle technology through FDA approval by proving products and workplaces that are safe and efficacious [46-48]. Although the surface of nanotechnology has been just scraped by our knowledge, the therapeutics that will come out will be steppingstones for other therapeutics to come. As the FDA and other regulatory bodies continue to learn about the advancements in nanotechnology, regulations will be in place so that a smoother development of such drugs can be accomplished with data driven processes [49,50]. Just as the manufacturing world has accepted the use of cGMP (current good manufacturing processes), they must also accept concurrent updates to this ever-increasing knowledge base to keep compliant through technological advancements. As more nanotherapeutics come on the market and research & development continue to drive forward, the understanding of nanotherapeutics production will be better understood so that a safe and effective drug can be made and administered to patients.

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