

**NANOTECHNOLOGY IN MEDICINE:  
METHODS OF DRUG DELIVERY USING NANOTECHNOLOGY  
AND THE NEXT STEP IN THE MANAGEMENT OF  
NON-MALIGNANT LONG TERM CHRONIC PAIN.**

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Nanotechnology research paper based on pathology lectures at Medlink 2010.

## **ABSTRACT**

This project will look at the current uses of nanotechnology in diagnostic and therapeutic medicine and explore the next possible step in development, specifically with regards to using nano particles in new forms of drug delivery systems. Using current controlled release methods could allow pain drugs to be realised in a specific location in optimum conditions allowing the best form of pain management – one which decreases the possibility of tolerance and therefore dependence.

## **INTRODUCTION**

The original concepts of 'nano technology' stem from the ideas put forward in 1959 by American physicist Richard Feynman; he suggested that a technique to manipulate atoms at a molecular level might be developed. Nanotechnology concerns substances at a molecular level; a nanometre is  $1 \times 10^{-9}$  meters and the size range considered in this field of science is 1 to 100nm ( $1 \times 10^{-9}$  –  $1 \times 10^{-7}$ m).

The medical uses of nanotechnology are ever increasing and the nanomedicine industry was worth over \$6.8billion in 2004 and up to 130 nanotechnology based drugs and delivery systems are being developed at any one time.

Important developments in uses of nanotech include the use of 'nanobots' to perform functions in the body and even build other nanobots. A 'machine' made from seventeen molecules of duroquinone (a derivative of 1,4-benzoquinone), one molecule surrounded by a ring of sixteen others allows the centre duroquinone to be controlled with chemical.

A specific use currently being considered is the repairing of damaged tissue without invasive and dangerous surgery by using nanobots as internal and self controlling tools and workers controlled by chemical impulses.

The capacity to create over four billion outcomes, each essential for a number of jobs allows for great variation in the possible applications

The use of nanochips implanted in deep brain tissue can be used to monitor brain signals, specifically profiled for an individual patient. When abnormal signals are detected the nano chips can stimulate the left vagus nerve, which maintains heart rate, gastrointestinal peristalsis, sweating and the opening of the larynx for breathing. This method of stimulating the vagus nerve has been FDA approved for over 10 years but the internal, and somewhat automatic, prevention of abnormal signals is a relatively new technology - yet to demonstrate long term widespread positive results.

In an ongoing search for innovative cancer treatments many feel that nanotechnology may hold the key. The 'leaky' vessels around tumours can be harnessed in cancer treatment, a nanoparticle bound cytotoxic drug will lodge in the tumour and the higher acidity associated with cancer cells will cause the drug to be released, leading to minimal toxicity to other tissues.

The 'Trojan horse' method, by which dendromere arms can hold folic acid (a cancer cell nutrient) and a cytotoxic drug, such as methotrexate, can access cells and kill them with very little defensive response from the cell as it focuses on the nutrients present. Still in its experimental stage this kind of drug delivery system is just one of the many types of cancer treatment aiming to increase effectiveness and reducing side effects by reducing 'flooding' the body with drugs and instead specifically targeting cells.

The size nanoparticles allow them to enter the body with little or no immune response and to interact with cells and nerves on a molecular level.

## **DISCUSSION**

Severity of pain is subjective, often influenced by one's environment and personal experience and many think certain physiological factors. It cannot be measured by a test or neurological measurements and therefore medical practitioners must rely on a patients report. There is no standard way of measuring the severity of such pain as often there is no obvious cause.

While the definition of chronic pain is widely disputed a commonly used definition is, "pain that lasts beyond the term of an injury or painful stimulus, for more than twelve weeks. It can also refer to cancer pain, pain from a chronic or degenerative disease, and pain from an unidentified cause."

A serious public health problem often with a serious effect on the patient's quality of life, it also places a huge burden on the state. Chronic back pain alone costs the tax payer £5 billion a year in incapacity benefits paid to patients who are unable to work because of unmanageable pain.

Management varies widely from person to person and is largely trial and error, often developed over a period of years changing the strength and type of pain relief used until a suitable combination is found. Pharmacological, physical and psychological treatments are all commonly used with mixed results.

Focusing on the currently used drugs used to treat chronic pain, I will look into the current drug treatments and their application with nanoparticle drug delivery systems.

### Paracetamol

The most commonly used analgesic (pain reliever) and antipyretic (fever reducer) with a general sales licence; it has been used all over the world since 1893. Acetaminophen is used for the treatment of all types of condition from mild headaches to post operative pain. It works by inhibiting the enzyme cyclooxygenase (COX) and reducing the formation of the oxidised preparation to prevent inflammatory chemicals.

Acetaminophen generally has an onset time of 11 minutes and a half life of 1-4 hours. The occurrence of side effects is very rare, the dependency rate is markedly low when used as an individual preparation and the interactions are likewise few, it is suitable from aged 3 months.

### Ibuprofen

Part of the NSAID drug family which, like paracetamol, work by inhibiting the COX-1 and COX-2 enzymes responsible for the synthesis of prostaglandins and therefore reducing pain and swelling in an affected area. It is available in both oral and topical preparations.

### Diclofenac

A broad basis NSAID it is commonly used a wide range of pain types, including post operative and muscular pain; it is available in both oral and topical preparations. It is thought to inhibit the lipoxygenase pathways, important in the mammalian physiological response to wounding and injury. As with most NSAIDs there are several contraindications in asthmatic and diabetic patients as well as anyone with stomach complaints and a history of peptic ulcers.

### Codeine

Codeine is an opioid derivative available over the counter, most commonly in combination with paracetamol or ibuprofen for short term use – due to its addictive qualities. It is the most commonly prescribed treatment in Britain and America for chronic pain. Codeine and dihydrocodeine are thought to be absorbed by the metabolic uptake of pro-Morphine drugs - resulting in a high failure rate of analgesia as an individual preparation.

### Tramadol

An orally active drug, it is clinically very effective and is commonly used in several types of pain complaints – including post-operative pain and arthritis. A neural uptake inhibitor, it works by preventing the neurotransmitters responsible for the response to painful stimuli. The side effects, of nausea, vomiting and dizziness, are more common and severe than those felt from codeine; however any constipation is much

less pronounced. The side effects can be minimised by a gradual introduction to increasing strengths before commencing long term usage.

### Holistic Approaches (TENS therapy and acupuncture)

A TENS machine (transcutaneous electrical nerve stimulation machine) works through stimulation of nerves, but are specifically thought to stimulate various types of opioid receptors in the central nervous system, depending on the frequency, and effectively blocking the “pain gate”. Such machines are commonly used in labour, due to the complete lack of toxicity risk to a baby, and by many long term pain sufferers with no chance of addiction forming - and in the majority of cases – no side effects. Due to a lack of hard evidence it is difficult to determine the success rate in the general population – it seems to exhibit the effectiveness of the placebo effect to the point that a 1997 study by Oxford University concluded it "has been shown not to be effective in postoperative and labour pain."

When pharmaceutical approaches seem to have little effect, patients can be referred to acupuncturists. Acupuncture works on the principle that blockages disrupt the flow of “chi” and stimulating these points can clear blockages restoring health and vitality. According to the 2007 National Health Interview Survey, pain and musculoskeletal complaints account for 70% of the conditions for which acupuncture is used.

While there are many methods of pain management, often even a combination cannot provide full relief from pain symptoms. A reason for the difficulty of managing pain based conditions, being the “flooding” method of drug delivery used by the majority of drug preparations. Medications are absorbed into the blood stream and distributed to all bodily cells. Lack of a method of directing drugs properly can be the reason that pain is not lessened, not relieved.

This problem has been approached with the use of medicated topical ointments but the absorption time and still relatively large spread of treatment to the pain at the cellular level concerning nerve endings and damaged cells.

An issue in pain management lies in the preciseness of dosage required for optimum relief with minimum side effects and the lack of ability target areas when consuming or topically applying drugs.

In order to avoid the first pass effect, where a large quantity of the drug are lost during digestion before it can be metabolised and then passed into the circulatory system, drugs can be implanted as a slow release preparation which can last for up to six months.

With this constant release of medication there are many benefits there is no ‘unmedicated’ time between doses, onset time, less risk of overdose and - in the case of aspirin and ibuprofen – no peptic upset. Existing uses of this constant medication uses include implantable contraceptives and certain drug replacement therapies.

This medication release method would be particularly beneficial as there is no unmedicated time due to the uninterrupted pain relief provided.

On a nanoscale the implants can be specifically placed at nerve endings to inhibit COX-1 and COX-2 enzymes (paracetamol and ibuprofen) or to prevent the uptake of neurotransmitters (tramadol).

To increase the speed and efficiency with which drugs are metabolised, a very specific temperature and pH are required. A problem easily overcome by the use of buffer solutions – which can again be contained in a nanoparticle - and internal body heat being appropriate for the most efficient uptake of the chosen analgesic drug.

## **CONCLUSION**

With specific targeting of pain medications to affected areas it may be possible to manage chronic pain. It could improve the quality of life of millions of patients who suffer with debilitating pain that prevents them from taking part in day to day activities.

Due to the infancy of nanotechnology in medicine it is not yet determined what the long term effects are. It is yet unknown if nanoparticles have any toxic effects on the body. The use of nanobots which can 'control' themselves raises an ethical issue of creating a form of artificial intelligence – able to perform millions of tasks and to build other nanobots.

It is easy to say that further research must be carried out on such a technology before considering the possibility of applying it to the treatment of any condition, including the one I have looked at of non-malignant long term chronic pain.

As with many technological developments it may come down to the financial constraints. The cost of lifetime care for chronic pain sufferers with traditional prescribed medications and any government benefits claimed must be considered against the cost of an undeniably expensive treatment - along with the potential method of reasonable management of a life limiting condition.

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