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Treatment of Patients with Addiction Problems by Means of Electrical Stimulation: A Review of the Rationale and Studies, for AWP Clinical & Practice Governance Effectiveness and Therapeutics Committee

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(Written for the AWP Trust Effectiveness & Therapeutics Committee 14/11/05)

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ABSTRACT

Electrostimulation is now a relatively sophisticated technique with broad applications in medicine and psychiatry. It has been used for over 30 years in the addiction field, and is widely used internationally for this indication especially in America. It is also used for sleep problems, anxiety, depression, and cognitive dysfunction as well as for pain and other physical conditions, many of which are common problems in addicts and are often given by them as the explanation for the maintenance of their addiction. The authors review the neurophysiological basis for electrostimulation, and the evidence from controlled clinical trials in addiction, and also summaries provided by other authors of the evidence for the treatment of anxiety, sleep, depression and cognitive dysfunction. The animal and pre-clinical literature strongly suggests that electrostimulation has definite neurobiological effects. Most of the clinical studies reviewed find superiority for electrostimulation over the control treatment for all these conditions. In addiction 25 out of 32 (78%) controlled studies were in favour of electrostimulation. Although some of these studies suffer significant methodological problems, the authors' opinion based on this evidence to date is that this is a promising treatment, worthy of further investigation, and that it is justified to continue its clinical use as a treatment with addiction patients within AWP.

INTRODUCTION

The use of electric currents in medical practice dates back more than 2000 years, and was initially performed using animal electricity, then electrostatic electricity, then direct current, then interrupted direct currents, and now the safer alternating currents (Macdonald 1993). Modern electrostimulation really had its research beginnings in France in 1903 by Leduc and Rouxeau, and subsequently by Anan'ev and colleagues in 1957. Many authors designed their own electrostimulation devices with specific types of stimulation parameters, and often invented their own terms to describe their own particular type of therapy (see table 2 below). By electrostimulation we mean both electroacupuncture and other electrical stimulation techniques with or without needles, although the review of studies focuses only on techniques using surface electrodes. Its best known application is its use as Transcutaneous Electrical Nerve

Stimulation (TENS) used for pain relief including during pregnancy, from which some types of electrostimulation derive. Although electrostimulation is sometimes confused conceptually with electroconvulsive therapy (ECT), these are very different techniques. Although both are used to treat a range of psychiatric conditions, modern electrostimulation devices provide very small amounts of power in conscious individuals and are typically powered by a 9 volt PP3 battery, whereas ECT involves the use of mains power to induce epileptic seizures and temporary unconsciousness.

The scientific community have largely rejected the traditional explanations for the actions of acupuncture, and replaced these by mechanisms based on scientific research. What is clear however is that the simple ideas initially proposed to explain acupuncture effects (e.g. endogenous opioids) are only a part of the story, and the evidence suggests a whole range of mechanisms are typically in operation. Brain scanning studies have now identified both specific and non-specific effects of acupuncture (Hui et al 2000, Pariente et al 2005). A simple classification of the main categories of mechanism are described in table 4 below.

The main attractions of acupuncture and electrostimulation are that it is not a medication, appears not to be addictive even after 12-18 month follow up (Schmitt et al 1984, Jarzembski 1985, Smith 1999), is very safe and has relatively few side-effects. It also has potential as a substitute for drug therapy for a number of conditions such as pain, anxiety, depression, insomnia and addiction, where the drugs normally used have undesirable side effects or addictive potential or are needed chronically. The primary advantages of electrostimulation over acupuncture is that the electrical treatment parameters may be optimised to give specific focused types of neuro-physiological effects, and to give a higher more consistent treatment dose, which penetrates and stimulates the tissues more effectively. Electrostimulation while still a relatively poorly researched field is now a sophisticated technique with wide applications in medicine, physiotherapy, psychiatry and addiction (see table 1 below), and which may be effective in conditions resistant to conventional treatments. In the United States of America, as early as 1978 the FDA approved the use of Cranial Electrostimulation Therapy for the treatment of anxiety in addiction patients. In 1993 the FDA requested cranial electrostimulation (CES) manufacturers to go through a formal premarketing approval process, rather than just claiming substantial equivalence to previously marketed devices (FDA 1993). The FDA currently approves CES devices for the treatment of anxiety, depression and insomnia.

	Table 1: Potential Uses of Electrostimulation in Addiction Patients
1	Acute withdrawal syndromes from a wide range of drugs
2	Protracted withdrawal syndrome
3	Craving
4	Stress related symptoms
5	Sleep
6	Anxiety
7	Depression
8	Pain including fibromyalgia
9	Cognitive dysfunction
10	Reduction in medication use and enhanced tissue healing for physical conditions

The effectiveness of manual acupuncture (with needles) has been compared to TENS and electroacupuncture in animals. The electrical techniques were clearly superior to manual acupuncture in analgesic effect and when electrodes consisting of conducting polymer pads were used instead of needles they were found to be as effective as needles (Wang et al 1992a,b). In humans it was shown that acupuncture alone gave some pain relief, but when electricity was added the modulation was 100% more effective (Saletu et al 1975). In China, electricity was originally added to the acupuncture needles used for surgical pain control in order to avoid the need of having to "twirl" the needles in order to provide a more effective level of stimulation, and also required much less effort on the part of the acupuncturist. In addition a number of authors have found clinically that stimulation of human tissues non-invasively using skin electrodes (electrostimulation without needles) is as effective as electrical stimulation of needles inserted or implanted into tissues (electroacupuncture performed with needles) (Wen et al 1972, Patterson 1975, Fox et al 1976, Wall 1986). The use of needles was therefore seen as unnecessary.

ELECTROSTIMULATION TREATMENT OF CONDITIONS COMMON TO ADDICTION PATIENTS

PAIN AND REDUCED NEED FOR ANALGESIC MEDICATION

"The ability of a clinician to reduce pain in a patient by exploiting the patient's own in-built neurobiological control mechanisms must surely rank as one of the great achievements of contemporary medical science" (Woolf 1989). Although Woolf was referring to pain, the same argument would apply to electrostimulation in general. Early meta-analysis of TENS treatment for pain in fact showed little evidence for its effectiveness, but more recent meta-analyses have demonstrated its effectiveness (Bjordal et al 2003, Manheimer et al 2005). Pain is one of the better researched areas: "Acute pain can be diminished in over 60% of all patients, and chronic intractable pain, refractory to all conventional treatments, can be controlled for prolonged periods in up to 30% of patients, by the selective stimulation of particular subtypes of primary afferent nerve fibres . . ." (Woolf 1989). Indeed there is evidence that even the generalised pain of fibromyalgia which is very difficult to treat conventionally may respond to electrostimulation (Lichtbroun et al 1999, 2001; Smith 2001; Tyres & Smith 2001a,b). The use of electrostimulation can also lead to a reduction in medication use by one-third or more, and particularly in terms of narcotic requirements for painful conditions (Winick 1999, Alpher & Kirsch 1998, Champagne et al 1984, Childs 1995, Naveau et al 1992, Stanley et al 1982, Mantz et al 1992, Stinus et al 1990, Warner et al 1990).

SLEEP

The treatment of sleep with electrostimulation goes back 250 years, for as early as 1745 Christian Kratzenstein wrote a report on electrostimulation following his discovery that it helped him sleep better (Kratzenstein 1745). The sleep inducing effects of electrostimulation were then explored by Leduc (1902) although his technique was painful. In 1914, Robinovitch (one of Leduc's students) claimed that electrostimulation could be used to induce sleep. In 1954, the Russians and then other Europeans began to explore electrostimulation induced sleep scientifically (Gilyarovski 1958, Anan'ev et al 1960). A number of controlled studies were performed around this time (see table 14 below which includes 4 studies of sleep in

addiction patients). For example a sleep EEG study of CES vs sham treatment resulted in patients on the active treatment having faster sleep onset, more stage IV (deeper) sleep, fewer awakenings, and returning to sleep faster when awaking in the night (Weiss 1973), and these results were sustained over a two year follow up (Cartwright and Weiss 1975). It is thought that if patients have been kept awake by stress or pain, then when this is relieved they may sleep because of tiredness. However in individuals who are not sleep deprived, the electrical signal produces only an alert waking state. It was also found that measures of stress, not just the sleep, improved whether or not the patient slept during treatment (Ryan & Souheaver 1977).

ANXIETY, STRESS AND DEPRESSION

Electrostimulation has been shown in meta-analyses to be effective in the treatment of anxiety (O'Connor et al 1991, Klawansky et al 1995, Kirsch & Smith 2004) and depression (Kirsch & Smith 2004). The pooled results of the 8 studies in anxiety (or the five with the better sham control) showed CES to be better than sham treatment ($p<0.05$), although only two of the studies (Ryan & Souheaver 1976, Schmitt et al 1986) independently showed CES to be better than sham treatment ($p<0.05$) in terms of the independently calculated confidence intervals (Klawansky et al 1995). Electrostimulation results in reduced stress levels, and indeed this is thought to be the mechanism by which sleep is improved (Ryan & Souheaver 1977). Reduced stress has been demonstrated by physiological measures during withdrawal from alcohol and opiate drugs (Patterson et al 1994). See tables 12 and 13 below which include 6 studies of anxiety and 5 studies of depression in addiction patients. Treatment is typically given for one hour each day for 2 to 3 weeks, with the patient determining the comfortable level of stimulation (Kirsch & Smith 2004).

ENHANCED TISSUE HEALING

Electrostimulation has been used to treat soft tissue for 300 years, and to heal non-union of bone fractures for 150 years (reviewed in Mercola & Kirsch 1995). Chronic leg ulcers due to venous stasis are not uncommon in injecting drug users, and a randomized controlled trial has confirmed the results of open studies in non-drug users demonstrating accelerated healing with electrical stimulation (Carley and Wainapel 1985). Living tissues have multiple direct current surface potentials which are combined to form a steady state electric field. Injuries cause a localised shift in current flow known as the current of injury which triggers repair, as has been demonstrated in humans. As repair occurs the signal decreases, and ceases when the repair is complete. (Becker 1961, Illingsworth & Barker 1980, Becker 1990). The current used is typically typically 1000 times less than that of TENS (microamperes rather than milliamperes), and involves a pulse 2500 times longer than that of a typical TENS device, and is below the sensation threshold. These types of electrical parameters are used not only in pain treatment and tissue healing, but also in the conditions specified above.

ADDICTION AND CRAVING

Electrostimulation and auricular acupuncture for addiction treatment did not derive historically from acupuncture, nor as is often claimed from traditional Chinese medicine, but was first used in France in the early nineteenth century (Sarlandière 1825). Indeed it was not until 1972 that a Hong Kong neurosurgeon studied the Chinese practice of applying an electric current to acupuncture needles inserted into the pinna of the ear, and found improved pain relief and also coincidentally found a reduced severity of heroin and opium withdrawal symptoms (Wen & Cheung 1973).

Patterson who worked with Wen found clinically that the use of electrodes applied to the mastoids was as effective and that the needles were not required (Patterson 1975), that the use of electrodes permitted stimulation at night in order to assist sleep, and strongly promoted this new drug free treatment for withdrawal from all types of drugs (NeuroElectric Therapy or NET) around the world with her published articles and books (Patterson et al 1975, 1983, 1988). Since then, electrostimulation has been used in animal experiments and clinically to relieve the distress of withdrawal from drugs of abuse and other conditions in addicted patients.

Thus in rats auricular electrostimulation has been shown to produce analgesic effects (Skolnick et al 1987, Auriacombe et al 1990) and to reduce physical signs of opiate abstinence in rats (Ng et al 1975, Malin et al 1988, Auriacombe et al 1990). Different stimulation frequencies in rats were also shown to be important in determining the rapidity of detoxification from barbiturates (Capel et al 1982a) and in determining the types of endogenous opiates released (Han et al 1991).

Patterson in a large open study in humans described that 95% of patients claimed they were free of cravings, and 75% that they were free of anxiety at the end of 3-10 days NET treatment in a group that had an unusually high detoxification success rate and a relatively low recidivism even after long term followup (Patterson et al 1984). Patterson describes that in contrast to patients undergoing drug assisted withdrawal, NET treated patients had a high level of mental and emotional clarity and were more positive and hopeful (Patterson et al 1994). She attributed this to the extent of the relief of the withdrawal symptoms, with the majority getting 50-75% relief and some getting 75-95% relief, and felt that relief at the 50% level meant that patients no longer required medication for the treatment of withdrawal (Patterson et al 1993). A RCT of alcohol dependent and abusers found significantly reduced craving with the active treatment but not in controls (Rampes et al 1997). Other authors have found that the most significant improvement in opioid withdrawal symptoms in heroin addicts was found when alternating low (2Hz) and high frequency (100Hz) stimulation was given (Han et al 1994), which releases endogenous opioids such as met-enkephalin and dynorphin (Han et al 1991). A large open clinical study of over 500 withdrawing heroin addicts showed that electrostimulation reduced the objective signs of withdrawal and improved sleep and well being (Wu et al 1995). The controlled studies of electrostimulation in addiction are reviewed in table 11 below.

COGNITIVE DYSFUNCTION & PROTRACTED DRUG WITHDRAWAL

A protracted withdrawal syndrome is known to follow acute withdrawal from many drugs of abuse, and this syndrome is associated with a degree of cognitive dysfunction, which correlates with the confusion/bewilderment factor on the POMS questionnaire (Smith and O'Neill 1975). Such abnormalities may take two years to resolve (Smith 1982), but it has been suggested that this period may be shortened to three weeks with a one hour electrostimulation treatment daily (Smith and Day 1977, Smith 1982, Schmitt et al 1984) or up to 10 days NET treatment (Patterson et al 1992). Other types of cognitive dysfunction may also respond to electrostimulation. See table 15 below which includes 7 studies of cognitive functioning in addiction patients.

A number of types of acupuncture and electrostimulation exist, and their relationship is quite complicated. This is expressed in Figure 1 below:

Figure 1: Relationship between manual acupuncture and electrostimulation:

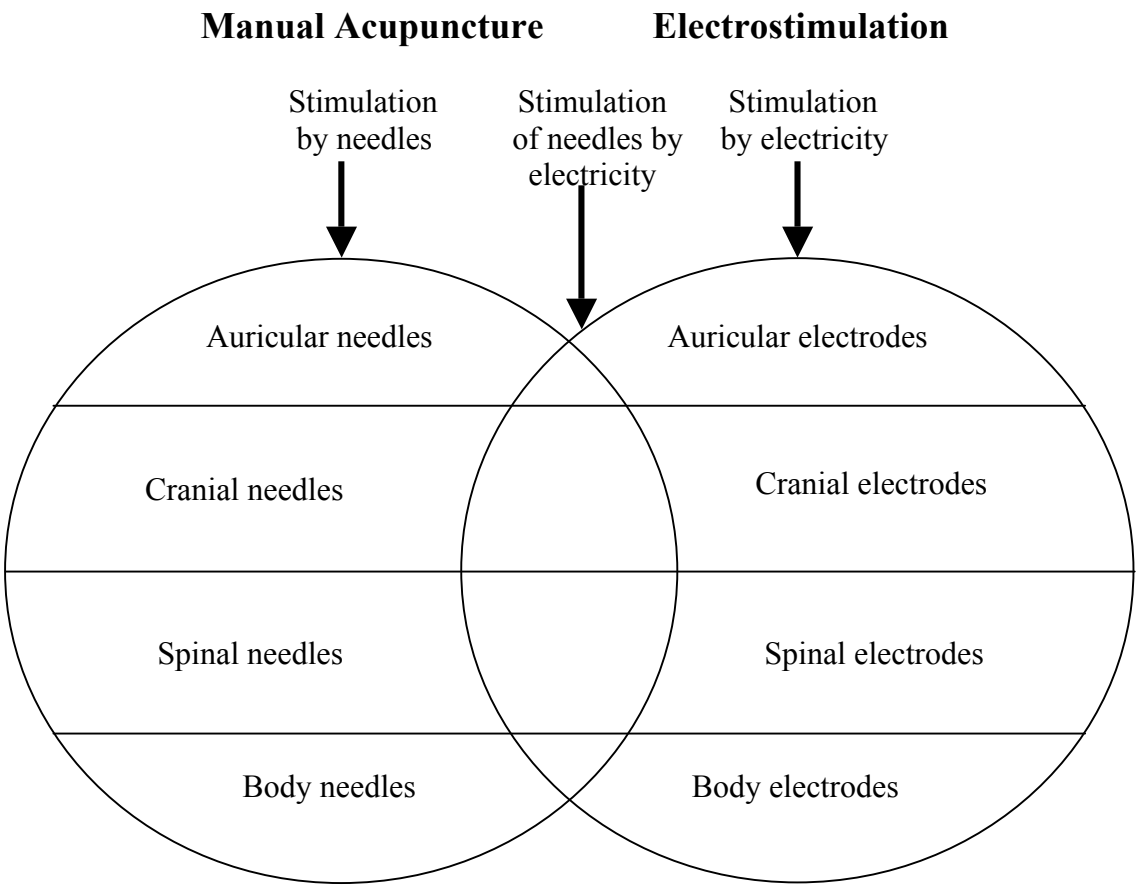

Table 2: The Names for the Various Techniques Based on The Classification in Fig 1

	Stimulation by needles	**Stimulation of needles by electricity**	**Stimulation by electrodes**
Auricular	Auricular acupuncture: Acudetox	Wen et al (1972), Patterson (1974)	Auricular electrostimulation, Cranial Electrostimulation (CES), Sub-Perception Electrical Stimulation (SPES)
Cranial			Cranial Electrostimulation (CES), Electrosleep, NeuroElectric Therapy (NET), Transcranial Electrotherapy (TCET), Transcutaneous Cranial Stimulation (TCES), Limoge techniqiue, Cerebral Electrotherapy (CET), Transcranial Electric Treatment (TET), neuromodulation, alpha induction therapy
Spinal		Dorsal Column Stimulation Shealy et al 1967, Krainick & Thoden 1989	Transcutaneous Spinal Electroanalgesia (TSE)
Body	Acupuncture	Melzack *et al* 1965, Fox et al 1976, Wall 1986	Transcutaneous electrical nerve stimulation (TENS or TNS), Acupuncture-like TENS (AL-TENS, Ericksson et al 1989), Microcurrent Electrical Therapy (MET)
Auricular & Body	Acupuncture		Transcutaneous Electrical Acupoint Stimulation (TEAS), NeuroElectric Acupuncture (NEAP), Electro-Stimulation Therapy (EST or NEAP applied to addiction)

Two types of technique have been particularly widely used in addiction – auricular acupuncture and electrostimulation - and are compared below:

Table 3: Comparison of Manual Acupuncture and Electrostimulation		
	Manual Acupuncture and especially Auricular Acupuncture (with needles only)	**Electrostimulation (with electrodes only)**
Training	Relatively complex requiring several days training and precise needle location	Relatively simple as very precise location of the electrodes is not required (as current spreads and electrodes are much larger than needles anyway). Can be learnt in half a day (Ulett 1992)
Stimulation Characteristics	Relatively inflexible. Main stimulation provided by point of needle, but improved by twirling or heating the needles	Stimulation optimised by consistent flow of current and manipulation of electrical parameters to improve tissue penetration and cause specific types of effects (depending on frequency, pulse duration, amplitude, pulse shape, length of treatment etc)
Equipment	Relatively cheap – main equipment cost is the sterile needles	Relatively expensive because of the cost of each device and the disposable electrodes. TENS devices cost £20 -£80. Other electrostimulation devices cost £100 - £1000
Patient Situation	Lends itself to treatment in group settings, with consequent efficient use of staff resources. Patients must be non-ambulatory	One stimulator required per patient, so use in a group setting is less usual. However most types of electrostimulation can be given to ambulatory patients
Mechanism	Useful acupuncture points are mostly motor points or areas near major nerve pathways (Liu et al 1975, Gunn 1978, Ulett 1982), although the ear is an exception. The pinna is innervated in part by the Vagus which runs to most organs of the body, and its stimulation is thought to reduce stress via the autonomic nervous system	TENS produces not only a localised segmental analgesic effect which tends not to blocked by naloxone, but also at high intensity it becomes Acupuncture-like TENS (AL-TENS) which produces a generalised analgesic effect (due to humoral factors) that is blocked by naloxone. TENS works best at the maximum comfortable tolerance which maximises the gating effect on pain. There are also a wide number of other mechanisms in operation. See Table 4 below
Side-effects	Pain or bleeding and (as it is an invasive treatment), there is a risk of infection from needle insertion (which is difficult to treat in the cartilage of the ear)	Non-invasive treatment. Erythema at site of stimulation may occur. Allergic dermatitis, pain, burning or prickling sensation possible. Avoid placing over carotid sinus (may cause hypotension) and in patients with demand type cardiac pacemakers
Speed of Onset & Length of Effect of Treatment	Acupuncture analgesia takes 20-40 minutes to develop and wears off after 90 minutes (consistent with humoral factors). Effect may accumulate over time as cause of problem reversed	TENS analgesia wears off rapidly when stopped. Other electrostimulation type treatments may have central effects lasting 6 hours or longer and the effects may accumulate as cause of problem reversed
Evidence	Limited evidence base in addiction despite some major trials with good methodology. Evidence suggests the treatment works best in combination with psychosocial therapy, and that it may enhance engagement in treatment	Good evidence base in addiction, although no major studies with good methodology. Not clearly effective in smoking cessation, but may reduce withdrawal symptoms, anxiety, depression and improve cognitive dysfunction

CAN SUCH METHODS BE SUBJECTED TO CONTROLLED TRIALS?

Sjölund 2005 described the difficulties in performing double-blind, placebo controlled trials of a therapy that a patient can feel. Although he was referring to acupuncture, his comments also apply to electrical stimulation that produces a tingling sensation. He writes "I think that even if Ernst and others strictly adhere to the Oxford criteria (Jadad *et al* 1996) for distinguishing successful RCT designs, they overlook one important factor when performing their reviews of acupuncture . . . Acupuncture is a physical technique for sensory stimulation. The evaluation of acupuncture is therefore far more difficult than that of pharmacological agents, where compliance and uniformity is largely limited to the swallowing process …". So this means that a form of therapy that can be felt by the patient cannot easily be subject to a double-blind placebo controlled trial, and that the randomised controlled trials that have been performed are typically single-blind.

Only studies when no sensation is felt (electrosleep studies, e.g. Ellison et al 1987), or the sensation is kept below the sensory threshold (e.g. Schmitt et al 1984, 1986) such as when microamperes of current are used (Brovar 1984, Overcash & Siebenthall 1989) or where sensation is matched in the control group are truly double blind. A number of authors have tried using so called "non-active" acupuncture points or low electrical currents in their control groups (e.g. Gariti et al 1992). The results of these studies suggest that these interventions are probably active treatments because of the surprisingly good outcomes obtained, and non-specific "placebo" effects are also likely to be very large in this field. In addition one of the common problems is that when studies in the literature are described as "double-blind", this typically means that the patient and assessor were unaware of whether the treatment was real or sham. However in most of these studies, the therapist providing the active or sham treatment was not blinded, which potentially leads to bias (Klawansky et al 1995). In electrostimulation studies, however, the therapist can be blinded to the treatment intervention by the use of preset circuits/devices (e.g. Hearst et al 1974, Schmitt et al 1984).

In studies of manual acupuncture the need has been to develop a placebo needle that gives the impression of skin penetration without actually piercing the skin. This has been achieved by the Streitberger needle which acts like a stage dagger, as when the blunt tip is pushed against the skin the shaft moves into the needle handle. This is made to look like real acupuncture as both the Streitberger needle and the acupuncture needle are inserted through a plastic O-ring which holds them in place, and allows them to be manipulated in an identical way. The patients believe that they are receiving real acupuncture, although the needle sensation is less than with real acupuncture (Streitberger and Kleinhenz 1998, Kleinhenz et al 1999, Pariente et al 2005). However the practitioner can tell when the false needle is employed, so such trials are not double-blind.

MECHANISMS

There are a large number of mechanisms involved in the effectiveness of acupuncture and electrostimulation. Each type of technique appears to utilise several of these mechanisms simultaneously. It may be that the more effective techniques involve using all or almost all these mechanisms simultaneously. Stimulation of the peripheral nervous system produces central effects via a variety of mechanisms. The types of mechanisms involved are summarised in table 4 below:

Table 4: Mechanisms of Manual Acupuncture and Electrostimulation

	Type of Mechanism	Evidence
1	Non-specific (placebo)	The non-specific effects of manual acupuncture and electrostimulation are difficult to determine as double blind studies are difficult to perform where sensation occurs. However, high placebo response rates are found in double-blind trials in the pharmacological treatment of depression (Kirsch et al 2002). This is probably related to the natural history of the illness and both physiological and psychological factors including the therapeutic relationship, the process and rituals of the treatment, expectation & belief, suggestion, conditioning, attention, distraction, and mental calming of the mind. (Blitz & Dinnerstein 1975, Sheppeard & Wigley 1984, Peck & Coleman 1991, Araujo 1998, Pariente et al 2005). Addicts are attracted particularly to physical rather than cognitive interventions. Stress induced analgesia may also explain some of the effects (Sjolund 2005).
2	Relaxation & stress reduction	Electrostimulation results in reduced stress levels, and indeed this is thought to be the mechanism by which sleep is improved (Ryan & Souheaver 1977). See table 12 for a review of studies on anxiety reduction
3	Humoral factors	Reviewed by Ulett et al (1998). Excitation of Aβ and Aδ fibre afferents release β-endorphin from the pituitary, and met- and leu-encephalin and dynorphin from the spinal cord (Salar *et al* 1981), which increase pain threshold throughout the body. Analgesic effects of AL-TENS can be blocked by naloxone (Sjolund & Eriksson 1979). 2 Hz stimulated met-enkephalin release, while 100Hz increased dynorphin modestly but reduced met-enkephalin (Han *et al* 1991)
4	Autonomic nervous system	Afferent nerve stimulation has a significant effect on autonomic functions (Andersson & Lindeberg 1995). This could include stimulation of the Vagal nerve by auricular techniques. Acupuncture produces localised and generalised effects on the circulation (Kadda 1982, Rayman et al 1985)
5	Peripheral nervous system interacting with central nervous system	Segmental effects: Excitation of Aβ afferent fibres only produces a segmental release of GABA (Gobel *et al* 1980). The localised segmental effect of TENS is not blocked by naloxone indicating that it is not opioid in origin. The Gate control theory of pain suggests that C-fibre stimulation opens the pain gate in the spinal cord, while activity in the Aβ fibres shuts it. However a segmental increase in cerebrospinal opioids occurred when TENS was employed at high intensity to produce bursts of 100Hz pulses repeated at a rate 0.5-3Hz to mimic the firing of peripheral nerves supplying muscle (Sjölund *et al* 1977). Electrostimulation activates central inhibitory mechanisms (Sytinski & Galebskaya 1997). Acupuncture modulates the limbic system and subcortical structures (Hui et al 2000), and the insula (Pariente et al 2005). Ascending and descending central activity is accompanied by changes in the dopaminergic pathway (Gear *et al* 1999). Serotonin and noradrenalin are probably also involved (Terenius 1981, Han 1986), as well as endogenous opioids
6	Electromagnetic fields	Physiological effects occur even in the absence of sensation (meaning peripheral nerves may not be firing) and with stimulation parameters that mean it is impossible for the nerves to fire (e.g. ultra short pulse durations). The collective behaviour of cellular networks may recruit and aggregate the very low electrical voltages characteristic of individual cells (Grundler et al 1992).

	The collective electrical properties of groups of cells may yield voltage levels comparable to and thus potentially responsive to the voltages used in typical electrostimulation devices, which in turn could influence neurotransmitter activity (Klawansky et al 1995)

STIMULATION METHODS

Medical signal generators typically employ constant currents in order to ensure the correct electrical dose is delivered. This is important as the skin conductivity varies widely under different circumstances according to its location, underlying blood flow and skin secretions (conductivity is increased by the watery sweat but reduced by the oily sebum).

These generators deliver a series of interrupted pulses of a given duration which are typically monophasic or biphasic rectangular pulses. The term Hertz (Hz) is used in the electrostimulation literature to describe the repetition rate or number of pulses per second. The average current intensity produced by modern devices is zero thus eliminating burns and electrolytic effects which can cause tissue damage.

The devices are typically battery operated (although desk top and mains versions are also available). Electrostimulation is commonly given by 5cm x 5cm electrodes as these are thought to be optimal (small electrodes are thought to run the risk of increasing current density with the possibility of burns, and larger ones could exhaust the batteries too quickly). Most devices offer specific electrical parameters, and a range of fixed frequencies, but recently a programmable device has become available which allows much more choice over the electrical parameters for treatment.

The presence of sensation in peripheral nerves indicates that the stimulation is causing the peripheral nerves to fire. Different electrostimulation techniques are associated with different levels of sensation:

Table 5: Sensation Associated with the Different Electrostimulation Techniques

Sensation	**Examples** (and comments)
Maximum level of comfortable tolerance	TENS, AL-TENS (works best at this level which maximises the gating effect on pain)
Comfortable level of stimulation	NET
Adjusted to be just below sensory threshold	NEAP, EST
No sensation	SPES, MET (well below level of perception)

Electrostimulation of different frequencies and intensity (current amplitude) can elicit responses in specific groups of nerves. The various classes of afferent nerves that can be excited preferentially by electrostimulation as in table 6 below.

	Table 6: Classes of Peripheral Nerve Fibres Stimulated at Various Amplitudes and Frequencies (**x**mA refers to the minimum amplitude (in mA) required to produce sensation, for example 20**x**mA is twenty times the minimum current amplitude) (Chung *et al* 1984, Li *et al* 1976)		
	Aβ	**Aβ + Aδ**	**Aβ + Aδ + C**
Frequency (Hz) of Stimulation	1-1200 Hz Aβ fibres begin to fire at an amplitude of xmA that is just sufficient to produce sensation. Aβ fibres have short refractory periods (0.4-1.0 ms)	1-80 Hz at an amplitude of 10-20xmA, both Aβ and Aδ fibres respond.	1-2 Hz at an amplitude of 20-60xmA, C-fibres are recruited (for a brief period C-fibres can respond at 100Hz, but the continue to respond only to ≤2Hz. as their refractory period is 2ms)
Current Amplitude (intensity)	1-2 xmA Aβ fibres begin to excited at an amplitude of xmA. At 2xmA all of them are firing	Aδ fibres begin to fire at an amplitude of 10xmA and by 20xmA all are firing	C-fibres begin to be excited at 20xmA and all are recruited at 20xmA
Minimum Pulse Duration to Trigger Action Potentials (at 0.2mA current)	6μs is the minimum pulse duration for an electrical stimulus to trigger action potentials in Aβ fibres	The minimum pulse duration is > 600μs for an electrical stimulus to trigger nerve action potentials in Aδ fibres	The minimum pulse duration is > 600μs for an electrical stimulus to trigger nerve action potentials in C-fibres
Effects of Stimulation of these Types of Nerve Fibres	Aβ fibres respond rapidly to a wide range of sensations including such innocuous events as movement & touch. They are designed to be the sensing aspect of the body	Recruitment of Aδ fibres is indicated by a mildly painful, pricking sensation, or sharp pain. Aδ fibres are probably designed to transduce high intensity mechanical stimulation, noxious cold, and non-noxious warm to initiate 'first pain' responses. Chung *et al* 1984 showed that Aδ stimulation inhibits spinal cord interneurons particularly wide dynamic range neurons lying in the spinothalamic tract	Stimulation of C-fibres (unmyelinated nerve fibres) causes persistent severe dull or aching pain, but initially require a high level of noxious mechanical or chemical stimulation or be subjected to excessive heat or cold – all those effects that threaten tissues. In the spinal cord, although inputs from both Aβ and Aδ can suppress C-fibre input, C-fibre input cannot suppress itself (Bowsher 1998)

Electrostimulation at a simple level can therefore be thought of as a system of treatment that aims to stimulate afferent nerves in order to elicit their normal effects:

Table 7: Classification of Electrostimulation by Types of Nerve Fibres Stimulated
(**x**mA refers to the minimum amplitude (in mA) required to produce sensation, for example 20**x**mA is twenty times the minimum current amplitude)

	80-1200 Hz (high frequency)	**2-80 Hz** (intermediate frequency)	**1-2 Hz** (low frequency)
1-2 xmA (low amplitude)	Low amplitude & high frequency (TENS) **Only Aβ fibres stimulated**		
10-20 xmA (intermediate amplitude)		Intermediate amplitude & intermediate frequency (Electroacupuncture and AL-TENS) **Both Aβ + Aδ fibres stimulated**	
20-60 xmA (high amplitude)			High amplitude & low frequency (It is painful to stimulate C-fibres so this is rarely used therapeutically) **All Aβ + Aδ + C fibres stimulated**

PENETRATION OF CURRENT INTO TISSUES

With electrostimulation, the maximum current density and sensation tends to occur in tissues in the immediate vicinity of the electrodes and only a proportion of the applied current reaches deeper tissues. Thus, when choosing a comfortable level of stimulation, the patient is first guided by sensations arising from peripheral nerve stimulation in the skin immediately below the electrodes. The current is normally adjusted so that it is comfortable (not painful) or just above or just below the sensory threshold. The figures in Table 8 below are approximate, as the depth of penetration of an oscillating current is increased by frequency, amplitude and voltage.

Table 8: Amount of Currents Detectable at Various Depths Below a Surface Electrode using TENS (Wells et al 1977)

Depth below skin (cms)	**Percentage of surface current detectable (%)**
1	80.0
2	64.0
3	51.0
4	41.0
5	33.0
6	26.0
12	6.5

In addition to the use of electrical parameters that simulate the natural firing parameters of the nerves (as described in table 6 and 7 above), there are a number of other electrostimulation techniques which also elicit physiological changes in the human body. For example if the intervals between each electric signal are less than the refractory periods of axons that require stimulation, action potentials in the nerves may still be generated by modulating two high frequencies to provide a low frequency stimulation either by interference or interruption, as described below:

Table 9a: Techniques that Result in Neuronal Firing

The higher the frequency, the more readily the current will penetrate the body as tissue impedance tends to fall as the frequency is increased, which may be especially useful if penetration into the brain is intended

Type of Stimulation	Method
Interference form of modulation	A low frequency 'beat' or interference signal is produced by interference between two high frequency (e.g. 4 kHz and 3.8kHz) signal generators that are coupled together. Thus a frequency of 200Hz (4 minus 3.8kHz) stimulates Aβ fibres lying in deep tissues (Kuzin *et al* 1963)
Interrupted form of modulation	Intermittent 4ms trains of typically 166kHz current is applied to the head via one frontal cathode and two posterior anodes on the mastoid processes. Each 4ms train is repeated typically at 77 or 100 times per second (Transcutaneous Cranial Stimulation or TCES, Stinus *et al* 1990)
High frequency without modulation	Surprisingly sensation still occurred with two 4 kHz signal generators even when there was no interference frequency (Palmer *et al* 1999). This is thought to be possible as at different moments in time there will always be some excitable axons present capable of firing

Table 9b: Techniques that do NOT Result in Neuronal Firing

Electromagnetic field created between two electrodes. Electricity conducted by means of ions within the body. High voltage pulses penetrate tissues better and may be used in order to reach the spinal cord which is roughly 5cm below the skin surface.

Type of Stimulation	Method
High voltage	High voltage (>100V) pulses are used, but to avoid causing pain they are made very brief in duration (typically 4μs) such that action potentials tended not to be produced. These pulses given over the spinal cord have been shown to cause widespread analgesic effects in the body and also central effects in terms of improved mood. This technique is called Transcutaneous Spinal Electroanalgesia or TSE (Macdonald and Coates 1995, Towell *et al* 1997).

OPTIMISING ELECTRICAL PARAMETERS

In a broad sense the electrical parameters chosen for treatment are to a large extent determined by the need to avoid painful stimulation, the degree of tissue penetration required, and the electrical dose to the neurons in the deeper tissues. However a number of more specific factors may also be important in order to ensure the most therapeutically effective response such as intensity, wave-shape, pulse frequency and polarity (with monophasic pulses) where the positive electrode is attached to the nondominant hemisphere i.e. positive electrode to right side in a right handed person (Patterson et al 1993). It has also be observed that changing the pulse frequency by as little as 10Hz may change an apparently effective treatment into an apparently ineffective one (Grinenko et al 1988), and thus that the clinical efficacy of a treatment may be dependent on the device accurately and reliably producing the signal frequency chosen (Patterson et al 1993). In China, Han *et al* 1991 observed that at 2Hz met-enkephalin was increased, while at 100Hz it was reduced; however at 100Hz a modest rise in dynorphin was found. This led to the idea that maximal endogenous opioids would be released by combining the two frequencies, with stimulation at 2Hz for a few seconds to be followed by 100Hz for a similar period of time – known as the dense-disperse mode of electrostimulation. A wide range of other hormonal and neurotransmitter substances have also been shown to be affected by different stimulation frequencies in animals, including cortisol, serotonin, noradrenaline (Capel et al 1982b, Patterson et al 1993, 1994), and in humans to affect dopamine, serotonin and monoamine oxidase A and B levels (Grinenko et al 1988).

CONTROLLED STUDIES IN MAN

A huge amount of literature is available on electrostimulation as a treatment in both humans and animals. The authors therefore decided to confine their search to studies involving treatment by electrotherapy in humans using only skin electrodes (electrostimulation) as it is this technique currently practiced in the Trust. Research involving needles alone (manual acupuncture) and electrical stimulation of needles (electroacupuncture with needles) was excluded. The published literature was searched for original articles involving patients with a drug dependency or drug problem using Medline, BMJ, and Cochrane libraries, searching the web as well as examining review articles. The treatment of alcohol, illicit drugs and prescribed addictive drugs were included, but not nicotine addiction (a Cochrane review on smoking cessation which included electrostimulation has already been published which found no clear evidence for effectiveness, White et al 2002). Papers thought likely to be of category I and II evidence (see below) were obtained wherever possible and then reviewed by all the authors and assigned an evidence rating. Only category I and II evidence was then reviewed and included in table 11. These papers were also searched for other relevant articles.

The classification of papers into specific evidence categories was taken from the methodology of the North of England Evidence-Based Guideline Development Project undertaken by the Centre for Health Services Research, University of

Newcastle upon Tyne and the Centre for Health Economics, University of York. These categories are:

Ia: Evidence from meta-analysis of randomized controlled trials
Ib: Evidence from at least one randomised controlled trial
IIa: Evidence from at least one controlled study without randomisation
IIb: Evidence from at least one other type of quasi-experimental study
III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

In addition the literature was searched for review articles on the use of electrostimulation for the treatment of anxiety, depression, sleep problems and cognitive dysfunction. Tables reviewing these studies from these summary papers are given below (tables 12 to 15). It is of note that these summary tables involve several studies including addiction patients. In addition some of the studies are included in more than one of the tables.

The methodological quality of these category I and II studies is not reviewed here. However in general it appears that there were methodological problems with most of these studies. A number of studies and reviews are written by authors with a commercial interest in specific electrostimulation devices (e.g. Smith & O'Neill 1975, Kirsch & Smith 2004), and their methodological quality appears to be below those performed by independent authors. A Cochrane review is soon to be published on electrostimulation for the management of opioid withdrawal, which has been available in protocol form only until now (Auriacombe 2001), and this article will no doubt review the methodology. Other Cochrane reviews of acupuncture for opioid dependence, and auricular acupuncture for cocaine use are also at the protocol stage.

The outcome of the 32 category I and II studies are briefly summarised in table 10 below):

Table 10: Summary of Controlled Studies of Electrostimulation (ES) in Addiction Patients
(based on table 11 below)

Drug of choice	Total Number of Studies	Studies in Favour of ES	Studies Against ES	Non-Conclusive	% in favour of ES
Alcohol	11	8	2	1	72%
Opiate	13	11	1	1	84%
Hypnotics	1	1	-	-	100%
Cocaine	1	1	-	-	100%
Marijuana	1	1	-	-	100%
Polysubstance	5	3	1	1	60%
Total	32	25	4	3	78%

The reasons for the conflicting findings are not clear, but may relate to the wide variation in electrical parameters, techniques of application and patient groups used.

CONCLUSIONS

The published studies in each of the conditions reviewed are largely in favour of electrostimulation. Although methodological problems with the studies exist, the evidence presented suggests that electrostimulation generally produces positive outcomes for the patient and is therefore a promising treatment that is worthy of further investigation.

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Table 11: 32 Controlled Trials of Electrostimulation in Addi
(table derived from original literature and Mayor 2005)

Author	Study Design & Evidence Category	Participants & Diagnosis	Patient Groups	Device and Electrical Parameters	Durat
Smith 1982*	Randomized controlled trial double blind 1b	100 Alcoholics with brain dysfunction tested within 10 days of detoxification	ES (N=50) Control (N=50)	100 Hz/msec, 0 to 1.5mA Neurotone 101 "Ear stethoscope" electrodes at maxillo-occipital juncture	Stimulat for 40mi for 15 successiv days
Krupitsky et al 1991*	Randomized double blind placebo controlled trial 1b	20 Alcoholics with affective disorders. All abstinent for at least 3-4 weeks	ES (N=10) Control (N=10)	70-80 Hz and 4-7 mA, epicutaneous electrodes on forehead and behind ears	30 min/d 4 weeks
Ellison et al 1987*	Randomized double blind trial 1b	16 Opiate addicts for withdrawal	ES (N=8) Control (N=6) (2 drop-outs)	Limoge current	48 Hours
Ellison et al 1987*	Randomized double blind trial 1b	11 Opiate addicts for withdrawal	48 Hours (N=6) 24 Hours (N=5)	Limoge current	48 and 2 hours
Elmoghazy et al 1989*	Randomized single blind trial 1b	125 Opiate addicts for withdrawal	Active(N=39) Placebo(N=29) Half drop out	50-300 Hz and pulse duration of 30 msec. neuro stimulator device surface electrodes over each mastoid bone	7 days
Gossop et al 1984*	Controlled clinical trial IIa	24 Opiate addicts for withdrawal	ES (N=12) Methadone (N=12)	70Hz for heroin, 90 for methadone, 400 for opiate and benzo, 0-35 volts, load 5kohm, NET, flat adhesive	10 days, continuo first 6, n

				electrode on mastoid	intermitt
Han et al 1994*	Controlled clinical trial IIa	212 Opiate Addicts DSM-III-R for withdrawal (high dropouts)	Control, 2 Hz, 100 Hz, 2/100Hz (N=13-16) each	Various frequencies, 10-20mA. Han's acupoint nerve stimulator, electrode on hand and other forearm	30 min/d 10 days
Gariti et al 1992*	Randomized double blind placebo controlled trial 1b	18 Opiate & 25 Cocaine dependent DSM-III-R for withdrawal	Active, Placebo	10-2000 Hz, 0.22 ms, 0.6 to 4.3mA, Electrodes placed behind ears	10 days continuo first 6 da intermitt next 4 da

Table 11 (cont): 32 Controlled Trials of Electrostimulation in A
(table derived from original literature and Mayor 2005)

Author	Study Design & Evidence Category	Participants & Diagnosis	Patient Groups	Device and Electrical Parameters	Durat
Gomez & Mikhail 1979*	Randomized trial single blind 1b	28 Opiate addicts admitted for methadone detox with anxiety and sleep problems	ES (N=14) Control-A (N=7), Control-B (N=7)	100 pulses per second, pulse duration 2ms, 0.4 to 1.3mA On forehead and mastoid	30 min / for 10 da
Tomsovic & Edwards 1973*	Randomized controlled trial single blind Ib	43 Alcoholics having sleep and anxiety problems	ES (N=20), Simulated (N=23)	Neurotone 101, 100 cycle/sec, wave 2msec on; 8msec off, 0-1.5 mAmp, Over orbit or mastoid	30 min sessions days
Schmitt et al 1984*	Randomized controlled trial double blind, 4:1 ratio 1b	60 Drug abusers, (60% primarily alcohol abusers) having brain dysfunction	ES (N=30) Sham (N=10) Control (N=20)	Neurotone 101, 100 pulses/second, Current: 0.0 to 1.0 mA "Ear stethoscope" electrodes behind each ear	15 daily minute treatmen
Rampes et al 1997*	Randomized controlled trial single blind 1b	59 Alcohol dependent or alcohcol abuser DSM-III-R for withdrawal	1: EA at addiction specific points (N=23) 2: EA at other (N=20), 3: control (N=16)	A square wave continuous electric current of 100 Hz (AcuMedic AM 3D model)	30 minut treatmen weekly f weeks
Schmitt et al 1986*	Controlled trial double blind trial IIa	60 Inpatient alcohol and/or polydrug abusers with anxiety	ES (N=30) Sham (N=10) Control (N=20)	Neurotone 101, 100 Hz, 20% duty cycle, <1 mA Electrodes behind each ear	15 daily, minute treatmen
Smith & Day 1977*	Controlled trial single blind trial IIa	227 Alcoholics with brain dysfunction, short term memory problems	ES (N=198) Control (N=29)	Neurotone 101, 100 Hz, 2 mS, 100 - 710 µA Electrodes below each ear	40 minut day, Mo through Friday, f weeks
Smith & O'Neill 1975*	Controlled single blind trial IIa	72 Alcoholic inpatients with affective disturbances	ES (N=24) Simulated (N=23) Dropout(N=25)	Neurotone 101, 100 Hz, 2mS, <1.5 mA Frontal and occipital electrodes	40 minut day for 1 days

Table 11 (cont): 32 Controlled Trials of Electrostimulation in A
(table derived from original literature and Mayor 2005)

Author	Study Design & Evidence Category	Participants & Diagnosis	Patient Groups	Device and Electrical Parameters	Durat
Bianco 1994	Randomized controlled trial double blind Ib	29 Inpatient polysubstance abusers with anxiety and depression problems	ES (N=11) Control (N=9) Sham (N=9)	LB 2000, 100 Hz, 2mS, <1.5 mA Electrodes behind the ears at the mastoid process	45 minut daily for days

Brovar 1984*	Controlled trial alternate allocation IIa	25 Cocaine abusers DSM III for withdrawal	ES (N=5) Refusers+controls (N=20)	Alpha-Stim 350, 0.5 Hz, 50% duty cycle, <500 µA, biphasic rectangular waves, Ear clip electrodes	20 minut twice a d the 5 day inpatient treatmen program
Overcash & Siebenthall 1989*	Controlled trial alternate allocation IIa	32 Marijuana users with diagnosed generalized anxiety disorder and substance abuse disorder	ES (N=16) Control (N=16)	Alpha-Stim 2000, 0.5 Hz, 50% duty cycle, <500 µA, biphasic rectangular waves Ear clip electrodes	
Braverman et al 1990*	Controlled trial IIa	13 Alcohol and/or drug abusers and 2 staff controls	ES (N=13) Control (N=2)	HealthPax, 100 Hz, 20% duty cycle, 1.0 mA, no dc bias, square waves, Electrodes at left wrist and forehead	40 minut ES betw pre and p ES BEA scans
Philip et al 1991	Controlled trial double blind (not randomized) IIa	21 Depressed (DSM-III) inpatients. All psychotropic drugs withdrawn (antidepressants, benzos, barbs, anxiolyics, neuroleptics)	ES (N=10) Placebo (N=11)	Diastim: 350 Hz, 0.7 mS, 1 - 1.2 mA, rectangular monophasic pulses, cathodes over orbits, anodes over mastoids	30 minut ES twice for 5 day

This article reviews the rationale for TMS in treating depression with a brief description of the basic principles underlying magnetic stimulation; a discussion of its putative mechanism of action; and its recommended treatment parameters. We then focus on the evidence base to support its use as both a monotherapy and adjunctive therapy for the acute and maintenance treatment of major depression. These data came from controlled trials comparing TMS to a sham procedure and naturalistic outcome studies for acute depression; studies directly comparing TMS to ECT for major depression; and open-lab Keywords: Internet addiction, review, behavioral addictions, prevalence, neuronal processes, treatment.Â Given the ubiquity of the Internet, its evolving nature as a modern tool of society, and issues surrounding its excessive use and abuse by a minority of people, Internet addiction (IA) has become an increasingly important topic for dedicated research agendas from several scientific fields including psychology, psychiatry, and neuroscience.