The Massachusetts male aging study proves that erectile dysfunction effects more than 50% of men aged 40–70 years, and by 2025, the numbers of men affected is expected to rise from 140 million to more than 300 million worldwide.

Gene therapy Phase I clinical trials could provide suffers of erectile dysfunction with a 6-month treatment

The current market for erectile dysfunction (ED) treatment is dominated by sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®), and recent reports, courtesy of Spectra Intelligence, claim that the market for sexual disorders is currently worth US$1.7 billion. Serious side effects such as priapism, which is a painful erection lasting for over 4 h, can occur with current treatments.

The Phase 1 gene therapy study was conducted at the Albert Einstein College of Medicine in New York and and led by Professor Arnold Melman. "Men could be much more spontaneous with their sex life with this therapy," explains Melman, "With all other therapies, you have to take a pill or give yourself an injection or something else beforehand."

Eleven patients with moderate to severe ED related to diabetes or cardiovascular disease and aged between 42 and 80 years, were given a single dose of corpus cavernosum injection of hMaxi-K. The hMaxi-K is a naked DNA plasmid that carries cDNA for the human slowpoke gene (*hSlo*), which is responsible for development of the α-subunit present in human smooth muscle Maxi-K channels. The Maxi-K, or potassium ion channels, are opened in response to the plasmid, which allows potassium ions to flow out of the cell, making it hyperpolarized. This allows the cell to relax, with the net effect of muscle relaxation. When the muscle relaxes, the penis is better able to fill with blood and maintain an erection.

The patients were administered varying doses of the gene and monitored for 24 weeks. Clinical evaluation tests proved the safety and tolerability of the new treatment. The international index of ED was measured, and validated by patients' partner responses.

Melman stated "the therapy lasts for a long time and may work synergistically with Viagra or Cialis." He further added "The great thing about this therapy is that it allows for spontaneity and works well in aging and diabetic models." Melman also believes that this relaxation of the smooth muscle cells could be effective in treating overactive bladder disease by stopping the spasms that cause the condition.

Previous gene therapy has been met with problems as the vectors used have caused side effects and complications, but this treatment is thought to be different because of the small number of cells that need to be targeted and because the plasmid does not integrate with human chromosomal DNA already in the cells. A single dose can last up to 6 months, which allows for spontaneity and eliminates the patient's need for on-demand drugs. "This is an exciting field of research because current treatments for men with ED, whether pills or minimally invasive therapies, must be used on demand, thereby reducing the spontaneity of the sexual act" added Melman.

The efficacy of the gene therapy is still unknown as no control groups were used. Melman said "While this Phase I safety trial was not designed to provide efficacy answers, one patient in each of the higher-dose groups reported clinically significant and sustained improvements in ED and there have been no adverse effects. The promising results proving the safety and viability of the treatment warrant further trials and more research into the genes used to control overactive bladder disease. The research is due to be published later this month.

Source: Melman A, Bar-Chama N, McCullough A *et al.*: hMaxi-K gene transfer in males with erectile dysfunction: results of the first human trial. *Hum Gene Ther.* (2006) [Epub ahead of print].

Pilot study of gamma-knife radiosurgery for medial temporal lobe epilepsy looks promising

Gamma-knife radiosurgery (GKS) is an alternative to open surgery for mesial temporal lobe epilepsy (MTLE), the common cause of epilepsy and, like open surgery, its safety has been questioned. "While acknowledging that open surgery is an effective treatment for MTLE," said M Quigg who led the study, "there remain risks involved with the procedure." Quigg explained "The question that a patient and a doctor have to discuss is whether the open brain surgery, which results in immediate freedom of seizures, is a better option than nonsurgical treatment with a delay in freedom of seizures." Patients with MTLE underwent the procedure and were followed up for 24 months. Seizure diaries were kept and viewed at 3-month intervals. Seizure-free status was obtained when the patient had not suffered a seizure for 6 months. GKS may offer a safe and effective alternative to standard open surgery for unilateral MTLE. There are also signs that high-dose GKS may be more effective than low-dose, without additional morbidity.

Source: Quigg M, Barbaro NM, Laxer KD *et al.*: Study of gamma knife radiosurgery for mesial temporal lobe epilepsy. Presented at the *American Epilepsy Society Annual meeting*, December 4, 2006.

Priority Paper Alerts

Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial.

Siddall PJ, Cousins MJ, Otte A *et al.*: *Neurology* 67(10), 1792–1800 (2006).

This study evaluated a 12 week, randomized, multicentre trial of patients receiving either flexible-dose pregablin 150–600 mg/day, or placebo. Existing stable pain therapy was maintained. The end point mean pain score and key secondary end points, such as pain responder rates, sleep interference, mood and global measurement of change, were assessed. The study concluded that the mean end point pain score was lower in those treated with pregablin, and efficacy was observed as early as 1 week, and maintained. Pregablin was also associated with improvements in disturbed sleep, anxiety and a global improvement at end point.

Long-term benefits of botulinum toxin type A (BOTOX) in chronic daily headache: a five-year long experience.

Farinelli I, Coloprisco G, De Filippis, Martelletti P.J: *Headache Pain* (2006) [Epub ahead of print].

Botulinum toxin type A (BTA) is suggested for the treatment of primary headache chronic forms. of both tension-type headache, and migraine. In this study, the dosage was 100 U and the fixed sites-fixed doses (FSFD) protocol was used. The results from 1347 patients from 2001–2005 were expressed. Number of headache days per month was studied in relation to the amount of injections administered. The study concluded that some patients observed 23 headache-free days a month and the treatment was said to be well tolerated and safe. BTA appears to be an efficacious new therapeutic choice of treatment in the prophylaxis of chronic daily headache.

Drug insight: testosterone preparations

Srinivas-Shankar U, Wu FC: *Nat. Clin. Pract. Urol.* 3(12), 653–665 (2006).

This is an overview of current and past applications of testosterone preparations in clinical use, from testicular and hypothalamopituitary diseases, to possible use of testosterone in nonclassical situations, such as male contraception, late-onset hypogonadism, HIV erectile dysfunction and female hypoactive sexual disorder. This review includes details on the chemistry, mechanism of action, and metabolism of testosterone. Also discussed are the pharmacokinetics, advantages and disadvantages of various formulations and a summary of the various preparations currently available.

Study shows Avandia® is more effective than metformin in treating long-term blood sugar control in Type 2 diabetes

Rosiglitazone maleate, a thiazolidinedione marketed as Avandia® (GlaxoSmithKline), has demonstrated its capability to reduce the risk of monotherapy failure in patients with Type 2 diabetes. The drug proved to be 32% more effective than metformin and 63% more effective than another oral glucose-lowering medication, glyburide.

The research involved a double-blind, randomized, controlled clinical trial involving 4360 patients recently diagnosed with Type 2 diabetes treated for a median of 4 years. The results were based on the time taken until monotherapy failure, which is the progressive loss of blood sugar control, and was defined as the presence of a fasting level of glucose over 10 mmol/l. Blood sugar control is lost due to increased insulin resistance, and a drop in the function of β-cells. Monotherapy failure was observed at 5 years in 15% of the patients treated with rosigiltazone, 21% with metformin and 34% with glyburide. These results were presented at the 19th World Diabetes Congress of the International Diabetes Federation, Capetown, South Africa, 3–7 December 2006.

Rosiglitazone was associated with side effects, such as weight gain and edema, unlike either metformin or glyburide, but had fewer gastrointestinal events than metformin and less hypoglycemia than glyburide. The potential risks and benefits of using each drug and the cost of treatment need to be considered when treating patients with Type 2 diabetes.

Source: Kahn SE, Haffner SM, Heise MA *et al.*: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* (2006) [Epub ahead of print]

Prolonged dose of chemotherapy might reduce the risk of heart problems caused by anticancer drugs

Treatments such as daunorubicin and doxorubicin, anthracycline drugs used to treat solid tumors and leukimeas, although successful at controlling cancer, are known to case heart damage. Recent research has indicated that rates of heart failure among patients receiving anthracycline drugs appeared to be significantly lower when the drug was administered via an infusion lasting 6 h or more.

Patients had the same chance of survival and tumor shrinkage whether they received the long or short therapies, the scientists found.

The study, conducted at the Emma Children's Hospital in the Netherlands, involved 557 patients and reduced the risk of heart failure by around 75% compared with patients receiving a quicker infusion.

Recent work suggests many childhood cancer survivors suffer from enlarged hearts and prematurely hardened arteries due, at least in part, to their chemotherapy.

Recent reasearch produced alarming results, indicating dramatic heart damage and blood vessel risk in some survivors just 10 or 15 years after treatment. If this damage is avoided, children will be less likely to suffer from heart defects in later life.

This treatment may be of use in patients who are already at high risk of heart damage or who will be receiving a high dose of the drug throughout treatment. For children, the few studies available did not appear to show any benefit for longer treatment, but furthur findings will enable doctors to see if there is a potential benifit in slower dosing of anthracycline therapy.

Source: van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Different dosage schedules for reducing cardiotoxicity in cancer patients receiving anthracycline chemotherapy. *Cochrane Database Syst. Rev.* (2006) [PubMed - in process].

Hormone therapy for early prostate cancer provides effective long-term results

A retrospective review of patients with localized and locally advanced prostate cancer has recently been published. The aim was to evaluate the efficacy of primary hormonal therapy and predict long-term prognosis in these patients. The review, published in the *International Journal of Urology*, claims that hormone therapy, with early or advanced prostate cancer, can result in positive long-term outcomes.

Each year, approximately 27,000 men are diagnosed with prostate cancer in the UK alone, making it the most common cancer in men, as stated by the Office for National Statistics. Hormone therapy is designed to block testosterone from stimulating the growth of prostate cancer, which reduces tumor size and chances of metastasis.

In this study, 399 patients (63.5%) were treated with combined androgen blockade (CAB) and 229 patients (36.5%) were treated with castration monotherapy. A total of 628 patients around the age of 75 years who were diagnosed with stage T1c to T3 prostate cancer were treated with primary hormonal therapy. The patients were classified based on pretreatment prostate-specific antigen (PSA) levels, and Gleason score, which grades the two largest areas of cancer with a number from 1 to 5, grade 5 usually implies metastasis has occurred. The time until nadir PSA level (TnPSA) was also taken into account. To conclude if hormone treatment showed success, disease-specific and progression-free survival rates were investigated in all patients.

The treatment showed the disease-specific survival rate of all 628 patients was 89.1% after 8 years. Those who received the primary hormonal therapy demonstrated a good response, and patients with a PSA level of 20 ng/ml or less, those with a Gleason score of 7 or less and those who achieved their lowest PSA level within 6 months of treatment showed the greatest response to hormone therapy. Less than 1% of the patients in this group died after 8 years.

The researchers concluded that hormone therapy, especially CAB treatment, for treatment of patients with localized or locally advanced prostate cancer could provide effective long-term positive outcomes among cancer patients.

Source: Ueno S, Namiki M, Fukagai T *et al.:* Efficacy of primary hormonal therapy for patients with localized and locally advanced prostate cancer: A retrospective multicenter study. *Int. J. Urol.* 13, 1494–1500 (2006).

Combination therapy can improve outcome in patients with pulmonary hypertension

Pulmonary arterial hypertension (PAH) is a potentially fatal disease characterized by the progressive narrowing of blood vessels in the lungs, causing high blood pressure and strain on the heart. PAH usually leads to heart failure and effects approximately 20,000 people in the USA alone. The actual figure is estimated to be approximately 100,000 but, in many cases, PAH is misdiagnosed as asthma, chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF).

PAH has no known cause and is difficult to diagnose. Symptoms include shortness of breath following exercise, excessive fatigue, dizziness, fainting and weakness, with symptoms tending to worsen over time. Although it is more common in women, aged 21–40 years, it can affect men or women at any age.

The current treatments for PAH are usually administered individually. Iloprost is an inhaled drug, a synthetic compound that is structurally similar to prostacyclins, which enable vasodilatation in the lungs. It is classed as a synthetic prostacyclin (PGI2) analog. Another drug on the market is bosentan, a sulfonamide-derived, competitive and specific endothelin receptor antagonist that blocks the action of endothelin 1, an extremely potent endogenous vasoconstrictor and bronchoconstrictor, by binding to endothelin A and B receptors in the lungs.

The two drugs, which are of different classes, were studied in combination in a randomized trial to treat PAH. In the study, 32 patients diagnosed with PAH were treated in a double-blind trial. Inhaled iloprost (5 µg) or placebo was added to stable monotherapy with bosentan for 12 weeks. After 12 weeks, increases in exercise capability, reduction in clinical worsening and hemodynamic parameters, were assessed.

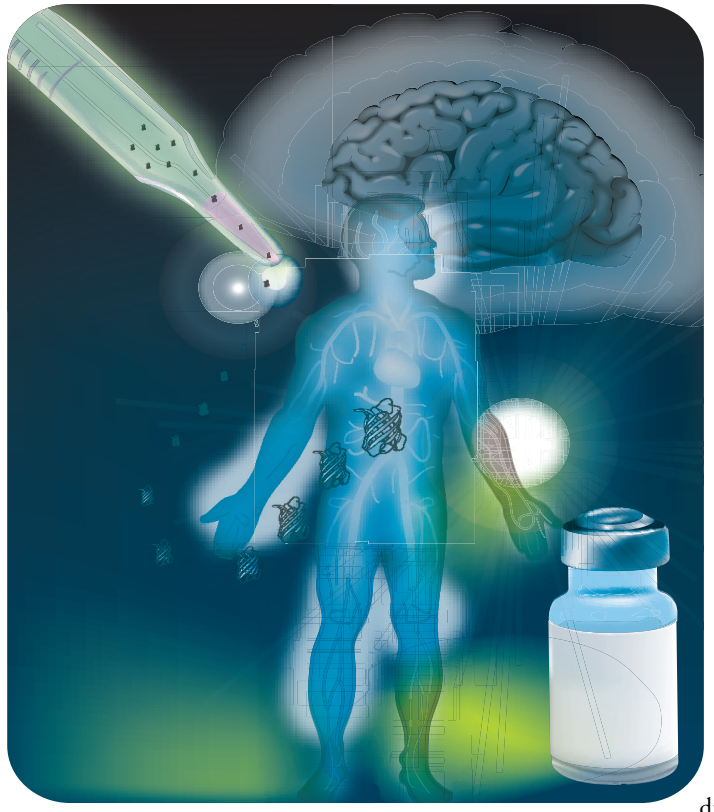
A total of 67 patients were treated during the 12-week study, and results indicated that time to clinical worsening was significantly increased in those who received the combination of the two drugs, with none of these patients meeting the criteria for clinical worsening. Of those who recived the placebo treatment, five reached the criteria for clinical worsening.

The scientists concluded that the study demonstrated that the addition of inhaled iloprost in patients with PAH with reduced exercise capacity on bosentan monotherapy is safe and efficacious. The treatment did cause syncope, a brief loss of consciousness, in a few cases, this was thought to be due to insufficient blood flow to the brain, and possibly an effect of bosentan treatment.

Source: Vallerie V, McLaughlin, Ronald J *et al.:* Randomized Study of Adding Inhaled Iloprost to Existing Bosentan in Pulmonary Arterial Hypertension. *Am. J. Resp. Crit. Care Med.* 174, 1257–1263 (2006).

Novel biomarker discovered that could aid Alzheimer's disease diagnosis

There is an increasing requirement for biomarkers in the diagnosis and prognosis of disease progression, more so in the case of Alzheimer's disease (AD) as clinicians are required to use their own clinical judgment to ascertain if AD or another form of dementia is present. Most cases remain uncertain until after autopsy. Erin Finehout, lead author of the new research explained "Typically, AD is not diagnosed until the disease has already caused some amount of dementia," she continued that "Having a chemical test available may allow patients to be diagnosed earlier in the course of the disease."



Approximately 4.5 million Americans are affected by AD, and this number will only increase as the average age of the population increases and the number of people suffering from the disease is expected to have tripled by 2050. Current treatments only temporarily alleviate the symptoms, such as loss of memory clarity, failure to recognize family members, anxiety and even aggression.

The biomarker was discovered by scientists from Cornell University (NY, USA) and Weill Cornell Medical College (NY, USA). They identified a panel of 23 protein markers in cerebrospinal fluid of patients suffering from AD. It is thought that this will enable doctors to identify patients with AD. The findings also show evidence for the practicality of biomarkers in clinical use, and it is thought that this new finding could distinguish whether symptoms are reflective of Alzheimer's, another dementia or normal aging.

"Our study is the first to use sophisticated proteomic methods to hone in on a group of cerebrospinal fluid biomarkers that are specific to autopsy-proven AD." Those postmortem tests confirmed that the panel is over 90% sensitive in identifying people with AD," said Kelvin Lee, Professor of Molecular and Cell Biology at Cornell. "Just as the human genome reflects the array of genes a person possesses, the proteome is the vast collection of proteins expressed by those genes," said Lee. The main theory behind the study was to identify proteins present in patients suffering from AD that were not present in AD-free patients.

The study combined cutting-edge proteomics technology with detailed imaging analysis and computational and statistical analyses. The techniques were used to simultaneously compare 2000 proteins present in cerebrospinal fluid of AD and non-AD patients in 34 age-matched autopsy-proven sufferers with 34 control subjects.

The 23 proteins identified, if present individually, are not likely to indicate the presence of AD but, when found together, could indicate a fingerprint specific to the disease. The proteins identified are associated with various pathological features, such as inflammation, plaque formation and synaptic dysfunction, which is an indicator of the diseases progression.

Norman Relkin, Associate Professor of clinical neurology and neuroscience at Weill Cornell claims that the biomarker has a 93% sensitivity to probable cases of AD and a 90% accuracy in avoiding false diagnosis.

It is thought that the progression of the disease can be tracked by observing the presence of the biomarkers. This also means that the effectiveness of experimental drugs can also be monitored; Relkin explained "In fact, we are now using this panel to study the effects of a promising new experimental treatment for AD called IVIg (intravenous immunoglobulin)...You might have a promising treatment for the disease, but how can you know for sure that it's impacting on the underlying pathology, rather than just easing outward symptoms as most of the drugs that we have now do," he continued.

The research will be published in the December online edition of the journal *Annals of Neurology*.

Despite their excitement over the new findings, the researchers stress that the results still need to be replicated in much larger populations, and currently there is a trial involving larger numbers of patients with AD, who will undergo spinal taps at brain imagine in an effort to support current research.

Source: D'Ascenzo M, Relkin NR, Lee KH. Alzheimer's disease cerebrospinal fluid biomarker discovery: a proteomics approach. *Curr. Opin. Mol. Ther.* 7(6), 557–564. (2006).