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ANALEPTIC APPLICATIONS OF PEPTIDES

Bharat Kwatra[1], Juvaria Zafar[2], Mahima Choudhary[3], Nashat Akhtar[4], Tanya Golani[5]
University of Debrecen[1], Aligarh Muslim University[2], The University of Melbourne[3], University of Hyderabad[4], University of Glasgow[5]

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Corresponding author: Bharat Kwatra
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Abstract
Bioactive peptides are protein parts which positively affect the capacities and states of living creatures. Peptides have demonstrated a few helpful properties for human wellbeing, including antimicrobial, antifungal, antiviral, and antitumor exercises. These mixes are delivered by practically all types of life. Notwithstanding, they are delivered in restricted amounts in nature. Subsequently, scientists have attempted to integrate bioactive peptides to contemplate their properties and applications in different zones. This review delivers a concise portrayal of the applications utilized by peptides: Triptorelin Acetate, Thymosin Alpha 1, Leuprolide acetate, Liraglutide, Desmopressin Acetate, Teduglutide, Pramlintide, Oxytocin, Calcitonin, Octreotide and Triptorelin.
Keywords: Triptorelin Acetate, Thymosin Alpha 1, Leuprolide acetate

Introduction

Peptides speak to an exceptional class of drug mixes, atomically ready between little particles and proteins, yet biochemically and remedially particular from both. As characteristic flagging atoms for some physiological capacities, peptides present an open door for restorative intercession that intently mirrors common pathways. Surely, a few peptide drugs are basically "substitution treatments" that add back or supplement peptide hormones in situations where endogenous levels are lacking or missing.

The use of peptides as therapeutics has advanced over the long run and keeps on developing with changes in medication improvement and treatment standards. Peptides separated from characteristic sources, for example, insulin and ACTH, if life-saving meds in the primary portion of the twentieth century. At the point when succession explanation and compound union of peptides got possible during the 1950s, manufactured oxytocin and vasopressin additionally entered clinical use. As toxins of arthropods and cephalopods got perceived as mother lodes of bioactive peptides, detachment of common items from outlandish sources turned into a famous system for distinguishing new expected therapeutics. The genomic time considered the ID and atomic portrayal of receptors for some significant endogenous peptide hormones, and industry and the scholarly community started to seek after novel peptide ligands for these receptors.

Methodology:

Papers on the peptides considered were selected on the basis of sample population size involved in the paper with respect to sample population size involved in the clinical trial library created by Cochrane libraries and databases for clinical trials, further student's t-test was applied on both the sample size to shortlist the papers.

Discussion:

TRIPTORELIN ACETATE 1–4

One Sample T-Test for Triptorelin acetate

One Sample T-Test			
Sample size	t	df	p
	-3.744	3	0.033

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 252.

Triptorelin Acetate in Early Pregnancies

Triptorelin acetate is a synthetic gonadotropin releasing hormone agonist (GnRH-a) which has a glycine substituted by D-tryptophan at 6th position. This substitution prevents triptorelin acetate from getting degraded by the enzymes. There are two doses of Triptorelin available- a short acting dose of 0.1mg and a long-acting dose of 3.75mg. This is used in IVF-ET (in-vitro fertilization embryo transfer) in couples affected with infertility. Triptorelin acetate increases the chances of pregnancy by desensitizing the pituitary prior to human menopausal gonadotropin stimulation resulting in premature LH surges and increase in number of oocytes development. Studies suggest that there are two protocols of GnRH-a. One with short effects which begins with the start of menstruation and a long protocol which starts at the luteal phase of the previous menses. Studies show that long protocol has proved to be beneficial however the risk of getting pregnant during the treatment can be a risk.

This study reported four cases of uneventful pregnancy in women undergoing IVF. Of four cases, three delivered normal babies and one experienced a first trimester miscarriage. In all the cases, treatment with triptorelin

acetate during IVF was performed. Also, in one of the successful pregnancies two female twins were born. A follow up of 18 months to 6 years was done in case of successful deliveries. These pregnancies can also be due to the natural chances of getting pregnant during infertility. Therefore, it makes it difficult to conclude that Triptorelin acetate was responsible for the pregnancy outcomes. Various studies have been conducted to clear this confusion around the use of triptorelin acetate during pregnancies due to its potential risks and side effects involved but it is advisable for the doctor to conduct pregnancy test during the treatment with IVF and Triptorelin acetate so as not to miss inadvertent pregnancies and stop Triptorelin administration immediately.

Triptorelin Acetate with Laparoscopic Surgery on Patients with Endometriosis and Infertility

Endometriosis is another common disease whose incidence is increasing every year. Its symptoms include pain and infertility which causes great stress among the affected people. Though the cause of infertility in patients with endometriosis is unknown, a lot of treatment methods have been proposed to correct this problem. Laparoscopic surgeries are successful as they provide relief to the patients from the pain. However, this surgery cannot remove all the lesions and due to the hormonal effects, the chances of recurrence is increased. To overcome this, combination of laparoscopic surgery with GnRH agonists seems to be a possible therapeutic strategy. Triptorelin acetate can inhibit the Luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, promoting apoptosis of endometrial cells that causes the lesions. Triptorelin acetate also upregulates the formation of T-lymphocytes thus providing immune responses that can kill these lesion causing cells. These effects of Triptorelin acetate are consistent with the outcomes in this study as compared to group B (gastronome) and C (mifepristone). In conclusion, combination therapy of Triptorelin acetate with laparoscopic surgery is a successful strategy for treatment of endometriosis and has better effects than gastronome and mifepristone.

Triptorelin Acetate in Assisting Pregnancy in Infertile Women

Infertility is a rising problem in the world. Studies show that 25% of the couples in China are infertile at their reproductive age. Various techniques are being evolved to overcome this of which in vitro fertilization-embryo transfer (IVF-ET) is the most successful. However, to successfully undergo IVF-ET, a lot of challenges need to be overcome including adverse events, embryo quality and more.

Triptorelin acetate has the ability to regulate the levels of hormones like FSH and LH. It is a gonadotropin releasing hormone agonist (GnRHa) and thus can be used in assisted reproduction. However, studies have shown that the use of Triptorelin acetate can cause allergic reaction and increased blood glucose level. It also possesses the risk of causing ovarian hyperstimulation syndrome (OHSS) which is one of the known complications in IVF-ET. This study aims to compare Triptorelin acetate with cetrorelix acetate which is another widely used GnRH for their efficacy in assisted reproduction.

This study aims to compare the effects of Triptorelin acetate and cetrorelix acetate in assisted pregnancies. It involves 182 women undergoing in-vitro fertilization-embryo transfer (IVF-ET). 91 women received Triptorelin acetate (group A) and 91 received cetrorelix acetate (group B). When using IVF-ET, a sudden increase in LH levels is observed before the follicular maturation. This LH surge can be inhibited by using GnRH agonists like Triptorelin acetate which thus helps in increasing the pregnancy rate. However, cetrorelix acetate has better ability to reduce estradiol (E2) and follicle stimulating hormone receptor (FSHR) levels. FSHR increased levels is associated with infertility and thus explains why group B has a greater number of oocytes and embryos. Although Triptorelin acetate is also used to prevent OHSS, cases of OHSS were seen in group A showing its insignificance in inhibiting OHSS. This study shows that cetrorelix acetate is more efficient than Triptorelin acetate for assisted pregnancies.

Triptorelin Acetate in Treatment of Central Precocious Puberty (CPP)

CPP is characterized by the appearance of secondary sexual characters in girls before the age of 8 or start of menses before the age of 9. The idiopathic form of CPP is caused by the maturation or the hypothalamic pituitary gonadal axis. A lot of biochemical and laboratory evaluations form the criteria for the diagnosis of CPP. However, increased levels of LH, bone age of the non-dominant wrist, BMI, and pubertal stage are some of the major criteria. Triptorelin acetate (TPA) and pamoate (TPP) have shown efficacy and safety in clinical trials for the treatment of CPP. This study aims to compare the effectiveness of Triptorelin acetate and pamoate in treatment of CPP.

During the first year of treatment, a significant decrease in LH values were found in both the groups with greater reduction in TPA group. Also, estradiol was now in their prepubertal values. BMI was increased in both the groups with no significant differences. Bone age was reduced in both the groups equally. Breast growth and public hair development also declined in both groups equally. Ovarian volume, uterus length and endometrium lining were found to be decreased too but the decrease was much greater in the TPA group. During the second year, a significant decrease in the LH value was observed with no difference in both the groups while the estradiol value remained at prepubertal stage.

Triptorelin acetate is already being approved for the treatment of CPP. In this study, the comparison of Triptorelin acetate and pamoate shows that TPP has more suppressive effects in treatment of CPP. This was because

during the first year TPP group showed great reduction in LH value but after 24 months there was no difference in reduction of LH values in both the groups. However, TPA shows significant reduction in ovarian volume and endometrial thickness and these results are better than TPP. Other measurements in terms of treatment with TPP and TPA were similar in both the groups with no significant differences. The ability of TPP to reduce LH levels in patients with CPP more significantly suggests that it can be used in patients with higher LH values or those who started the treatment late and have more progressive disease. In conclusion, both TPP and TPA have shown efficacy in treatment of CP

THYMOSIN ALPHA-15–7

One Sample T-Test for Thymosin Alpha 1 Acetate

One Sample T-Test			
Sample size	t	df	p
	-3.262	3	0.047

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 348.5.

Efficacy of Thymosin Alpha 1 Acetate in Japanese Hepatitis B Patients

Hepatitis B infection is a worldwide problem affecting millions of people. It is also associated with liver cirrhosis and hepatocellular carcinoma. Treatment options are designed in order to inhibit viral replication and induce long term remission. Interferon therapy, lamivudine and adefovir are currently used for the treatment of hepatitis-B. However, these treatments though efficient show relapse in most cases once the therapy is stopped. Thymosin alpha-1 is a 28 amino acid long peptide that has proven immunomodulatory function and helps in T-cell maturation and production. It has shown its efficacy for treatment of hepatitis B in various studies. This study aims to evaluate dose dependent efficacy and safety of T**α**1 in treatment of hepatitis B patients.

T**α**1 is a synthetic peptide which is extracted from bovine thymus. It is used for the treatment of viral infection due to its ability to inhibit viral replication by secretion of interferon alpha and interferon γ and cytokines. It also induces T-cell maturation thus boosting immune responses. With its ability to block apoptosis and its antiviral properties, its use in treatment of viral diseases has increased. Various studies have shown the efficacy of T**α**1 in treatment of viral and immunological diseases with successful results. Interestingly, it is effective not only during the treatment, but its efficacy also increases gradually after the treatments.

In this study, a total of 316 HBV-DNA patients with abnormal alanine aminotransferase (ALT) levels are included in this study. They were divided into two groups with dosage 0.8mg and 1.6mg for 24 weeks and a follow up period of 48 weeks post treatment. T**α**1 has shown clinical efficacy in treatment of HBV. No differences were found between the two dose groups. However, for those having advanced infected 1.6mg dose was more effective.

Other conventional treatments like interferon alpha demonstrated the same efficacy as T**α**1 in a clinical trial. However, the chances of relapse in case of interferon alpha were found to be decreasing post treatment. This was not the case in T**α**1 treatment where after the treatment, the rate of HBV-DNA clearance and HBeAg clearance had the tendency to increase. Lamivudine is another therapy for treatment of hepatitis B which demonstrated great resistance to viral replication in the clinical trials. However, 90% of the patients experienced recurrence of HBV post treatment. Additionally, some also developed resistant mutations for lamivudine. Such mutations were not reported in any case of T**α**1 treatment. A comparison of combination therapies of interferon alpha with T**α**1 and Lamivudine with T**α**1 in HBeAg- negative chronic hepatitis B patients showed that 74% and 54% of patients had sustained response at week 26 respectively. However, 18 months post treatment, the sustained response was found to be 70% in T**α**1 plus interferon alpha and 20% in T**α**1 plus lamivudine. Further investigation is required to confirm this. Finally, T**α**1 therapy has clinical efficacy in treatment of HBV patients.

Effect of Thymosin Alpha-1 on Inflammatory Autoimmune Diseases

Thymosin alpha 1 is a natural peptide formed of 28 amino acids. It is derived from the N-terminus of prothymosin-alpha cleaved by legumain (a lysosomal asparagine endopeptidase). Both legumain and T**α**1 are found widely in the same tissues suggesting that they are involved together. T**α**1 plays an important role in regulating immune responses in various diseases. They are thus used for the treatment of various infections and diseases that involve immune cells imbalance.

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE) differ from each other clinically and in symptoms. However, these three involve immune disbalanced which causes further organ and tissue damage. This study analyses subjects with Pa, PsA and SLE in comparison to controls to detect any correlation between these diseases and serum T**α**1.

This study was conducted to understand the role of malfunctioning of T regulatory cells in case of autoimmune and inflammatory diseases. T**α**1 are natural peptides that occur in our body and are associated with immune responses. The study shows that T**α**1 levels in serum of females are lower than in males. This correlates with previous studies that show that females have more intense antiviral action leading to easy virus clearance but if this response is excessive it can lead to autoimmune diseases. This supports the fact that prevalence of autoimmune diseases is higher in females than in males.

Also, serum T**α**1 levels in HC is much lower than the patient group showing T**α**1 level are lower in patients with autoimmune diseases. The value of T**α**1 in serum varied among patients' groups suggesting that though they may seem superficially similar to one another, they have different clinical, laboratory, molecular and morphological differences. The study warrants further investigation.

Effect of Thymosin Alpha Acetate Acute Liver Failure

Acute liver failure (ALF) is a chronic heterogenous disease which is characterized by liver function damage and multiple organ failure. Nearly 60-70% of the ALF affected patients die after contracting the disease. The main cause of this disease is associated with misbalance of pro-inflammatory and anti-inflammatory cytokines. The only treatment which is considered as a successful option is liver transplant. However, liver transplant has its own limitations including high cost, graft shortage and risk to the life of the donor. Thymosin a 1 (T**α**1) is a synthetic peptide that is known for its immunomodulatory characteristics. It helps balance pro-inflammatory and anti-inflammatory cytokines and also promotes the maturation of T-lymphocytes. This study evaluates the efficacy of Ta1 in a rat model of D-galactosamine hydrochloride (D-GalN)/lip polysaccharide (LPS) induced ALF by quantifying T**α**1 induced pro-inflammatory and anti-inflammatory effects, and expression of B-cell lymphoma 2 (Bcl-2) and Bcl-2 associated X protein (Bax) associated with apoptosis of hepatocyte. It involved 88 mice which are divided into two groups. Group A with 25 rats divided into control group (CG- 2ml saline), model group (MG- D-galactosamine and lips polysaccharide) and treatment group (TG- T**α**1 0.03mg/kg). In group B, 64 rats were divided into CG, MG and TG group and rats were sacrificed at 3,6,9 and 12 hours

Treatment with T**α**1 improved survival rates, decreased alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL) and tumor necrosis factor alpha (TNF-**α**) plasma levels, and increased IL-10 levels in ALF rats. This suggests that they reduced liver damage caused during ALF. Pro-inflammatory TNF-**α** reduces survival rates in ALF. Treatment with Ta1 reduced pro-inflammatory TNF-a in TG and MG suggesting improvement in survival. IL-10 is a key cytokine that has the ability to inhibit the production of proinflammatory cytokines that causes inflammation and tissue damage. In this study, TG has higher levels of IL-10 which inhibits excessive immune response and prevents cells from undergoing apoptosis. The immunomodulatory role of T**α**1 is beneficial for the treatment of ALF. This is pilot study in rats and needs to be confirmed using clinical trials.

Effect of Thymosin Alpha 1 on the Growth of Lung Cancer Cells

The incidence of cancer is increasing with time of which lung cancer has a high mortality rate. Various treatment methods have been developed to treat lung cancer. Thymosin alpha 1 (T**α**1) is a 24-amino acid containing polypeptide found in the thymus. It is considered as an immunoregulatory compound as it upregulates the production of CD4 + T cells and CD8 + T cells. It is used in the treatment of various autoimmune diseases and immunodeficiency diseases. The interaction between the immune cells and immune factors can help in inhibiting the growth of tumors. Studies show that CD4 + T cells release reactive oxygen that can inhibit tumor production. T**α**1 helps in maturation of T cells and also enhances immune response. By presenting antigen at the time of tumor production, it can help activate the immune response and tumor inhibition. T**α**1 is generally used in modified forms or in combination with other drugs. This is because it has antitumor properties in which it can also attack the body's normal cells along with tumor cells. This study combines T**α**1 with RGDR which is an Arg-Gly-Asp sequence found specific to integrins. Integrins are adhesion molecules that can bring about adhesion and bidirectional signaling across the cell membrane. Integrin **α**vβ3 is highly expressed on the surface of cancer cells and has an RGD recognition site. The C-terminal of the RGD sequence has a motif that binds to neuropilin-1 which is also expressed on the surface of tumor cells. **α**vβ3 integrin plays an important role in different stages of cancer development including metastasis, angiogenesis and invasion. Binding T**α**1 with RGDR using GGGG linker forms a T**α**1-RGDR polypeptide. This study aims to evaluate the antitumor activity of T**α**1-RGDR in lung cancer.

The histochemistry and IHC results show that T**α**1-RGDR has increased infiltration of CD4 and CD8 cells into tumor tissues than T**α**1. Also, the necrosis was severe in T**α**1 and T**α**1-RGDR. The tumor weight in human cell line tumors after 11 days was found to be highest in PBS. Ta1-RGDR had lower tumor weight than T**α**1. Additionally, the tumor inhibition rate in this case was also higher in T**α**1-RGDR than T**α**1. The necrosis in this cell line was found to be more severe in T**α**1-RGDR than T**α**1. CD31 antibody which is associated with vasculature growth was found to be more in T**α**1-RGDR than T**α**1 suggesting increased down regulation of vasculature. In terms of fluorescence intensity and coverage, T**α**1-RGDR had better coverage of tumor and higher intensity than T**α**1 suggesting that it targets the tumor cells better than Ta1. This study suggests targeting tumor cells using T**α**1-RGDR is more efficient than T**α**1 alone. Previous studies also show the limited use of T**α**1 due to its lack to target cancer cells

Does Thymopentin Treatment Affect Maturation of Bone Marrow Dendritic Cells?

Thymopentin is a synthetic peptide obtained from a fragment of thymopoietin. It has the same activity as that of thymopoietin and has the structure Arg-Lys-Aap-Val-Tyr. Thymopentin has been approved as a drug in China due to its immunologic role. Various studies have now proved the benefits of Thymopentin in immune regulation in immunodeficiency, autoimmune and cancer like diseases. This study focuses on the role of thymopentin in maturation

of bone marrow dendritic cells (BMDCs). Dendritic cells of the immune system are those cells that patrol the body looking for antigens. They convert these antigen into small pieces and present them to T cells for further immune response. This activates a cascade of immune response. The study analyzes the role of Thymopentin in maturation of these dendritic cells.

Thymopentin plays a key role in immune responses and thus is used for the treatment of various immune related diseases. It also acts an adjuvant in promoting immune response to vaccination and is involved in regulation of innate and adaptive immune responses. In this study, Thymopentin showed to play a key role in maturation of BMDCs by reducing the number of phagosomes, increasing key molecules like CD40, CD80, CD83, CD86 and MHC-II which play an integral role in activation of T-cells. Also, it improves IL-12 and TNF-**α** which amplifies the intensity of T-cell responses. Additionally, IL-12 and TNF-**α** while maintaining the stability of Th1 responses also causes the release of IFN-gamma and TNF-beta which initiate further immune responses forming a loop of immune reactions against the foreign antigen. This study though confirms the role of Thymopentin in maturation of BMDCs, further investigation is required to understand how it helps in maturation of BMDCs in detail.

TP5-iRGD has Better Targeting to Tumor Cells than TP5 Alone.

Thymopentin also called thymopoietin pentapeptide is a synthetic peptide that has shown to have immune modulating effects. It is used as a treatment for cancer due to its anti-cancer and immunomodulating properties. Most of the anti-tumor drugs fail to target the tumor cells resulting in drug resistance and their minimal efficacy. Thymopentin sometimes fails to penetrate deep into the cancer cells and this requires other effective means for their delivery so that their anti-tumor potential can be used properly. In this study, thymopentin is combined with iRGD which is a synthetic RGD produced to enhance the delivery of RGD to its target. RGD is a tripeptide of arginine-glycine-aspartic acid (Arg-Gly-Asp) which binds to the receptor sequence on the avb3 integrin which are highly expressed on the surface of cancer cells. Many studies have utilized this property of RGD to target tumor cells. Endostatin was combined with RGD to target tumor cells. However, the linear RGD peptides have a very short half-life while cyclic RGD peptides have better stability and thus higher half-life in plasma. iRGD first targets avb3 integrins, cleaving to generate truncated CRGDK/R motif which is followed by binding to neuropolin-1 (NRP-1) which is found on the surface of cancer cells. Thus better targeting of tumor cells. In this study iRGD is combined with thymopentin to evaluate their activity as an anti-tumor agent.

Effect of TP5 and TP5-iRGD on the survival of the cancer cells were observed at different concentrations. The growth of the cancer cells was inhibited in both the groups however the inhibition percentage of TP5-iRGD was significantly much higher than TP5 at every concentration. These results suggest that combining TP5 with iRGD increased the anti-proliferative activity of TP5 in all cancer lines. TP5-iRGD also inhibited the growth of tumor cells in vivo and this inhibition was significantly much higher in TP5-iRGD than TP5.

Furthermore, the extent of necrosis, lymphocytes infiltration and CD86 expression was higher in TP5-iRGD treated cells than TP5 treated ones. TP5 acts as an anti-tumor agent by its properties like T-cell differentiation, activation of CD4+ and CD8+ lymphoid cells, activation of NK cells and tumor growth reduction. In summary, it is a potent anti-tumor agent, and its antitumor property is enhanced upon binding with iRGD.

Role of Myristic Acid-modified Thymopentin in Immunoregulation

Thymopentin (TP5) is synthetic pentapeptide which is used for the treatment of immunodeficiency disease as it regulates the immune system functions by activating T-cell, NK cell and macrophage. Additionally, TP5 are capable of maintaining the CD4+/CD8+ ratio in immunologically deficient patients. However, the half-life of TP5 is very less because of poor membrane permeability and extensive enzyme degradation which limits the use in therapeutics.

Various studies have been conducted to develop the long acting TP5 with the help of micro and nano particles. although these particles have their own drawbacks. Therefore, to overcome the limitations of micro and nano particles, albumin binding strategies have been introduced. In this strategy the half-life extended by binding of TP5 with the circulating albumin through fatty acid, thus reduces the batch-to-batch variation. In this study myristic acid is used that is interconnected to the C terminal of TP5

The bioactivity and half-life of TP5-MA was analyzed on various aspects. It was shown that TP5-MA has more hydrophobic effect than TP5. Also, the results suggest that TP5-MA has stronger binding affinity by 4 folds than TP5. Furthermore, TP5-MA is more stable than TP5 which will increase the half-life . Moreover, it was also seen that production of TNF-alpha was undisturbed by TN5-MA. There was no cytotoxic effect produced by TP5-MA and the metabolic effect was increased as compared to TP5.Finally, the results show that TP5-MA can maintain a better ratio of CD4+/CD8+.

Improvement in Cardiac Health of Chronic Heart Failure Patients When Treated with Synthetic Thymopentin Immunomodulator

Most people suffering from heart diseases experience chronic heart failure (CHF) as the final outcome of the disease. In older patients, the risk of getting CHF is more due to the weak immune system in old age. Studies show that immune responses like T-cell activation and inflation of immune cells play an important role in progression of

CHC in patients. Thymopentin is a synthetic peptide which is also an immunomodulator by function. It promotes activation of T-cell response and T-cell maturation. This study will look into the effect of Thymopentin on older patients with CHF as a therapy.

Before the treatment, the levels of TNF-**α** and IL-1β (Th1 type) were found to be increased and IL-10 (Th2 type) was decreased. TNF-**α** can have a negative impact on heart ventricle as it activates nitric oxide synthase which increases the production of nitric oxide which leads to decline in myocardial contractility. It also induces cardiac hypertrophy, induces myocardial necrosis and cardiomyocyte apoptosis. Also, the reduction in IL-10 levels leads to a decrease in the protective effect of anti-inflammatory cytokines. This disbalance of Th1/Th2 type response is stabilized by Thymopentin as it decreases levels of TNF-**α** and IL-1β and increases levels of IL-10 in the CHF test (CHFT) group. Thus, restoring immune function.

BNP and hsCRP levels are associated with severity of heart failure which was found to be decreased in the CHFT group. The study shows that overall the heart function was improved after the treatment with thymopentin. Though the study has some limitations based on limited modulatory effects noted, not inclusion of myocardium pathological changes, it shows thymopentin is successful in improving cardiac function in CHF patients.

LEUPROLIDE ACETATE 8–12

One Sample T-Test for Leuprolide Acetate

One Sample T-Test			
Sample size	t	df	p
	-60.336	3	< .001

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 1355.

Leuprolide acetate – a promising treatment for central precocious puberty.

CPP is a rare disease (1:5000 to 1:10000) characterized by the early onset of secondary sexual characteristics in females who are ≤ 8 years of age and in males ≤ 9 years of age. The analogs of leuprolide have resulted in reductions in gonadotropins and sex steroids to prepubertal levels in children with CPP. Leuprolide acetate is a synthetic nonapeptide that is a potent gonadotropin releasing hormone receptor (GnRHR) agonist which suppresses gonadotropin secretion of luteinizing hormone and follicle-stimulating hormone that subsequently suppresses gonadal sex steroid production. The 62 patients were treated for 3.5 to 24.9 months and leuprolide acetate was directed in doses ranging from 4 to 50 µg/kg/day. Treatment with leuprolide suppressed the peak LH response to LHRH and the basal and LHRH-stimulated peak FSH levels. The clinical response was such that menses stopped in each of the 11 postmenarcheal patients during leuprolide therapy and menses did not begin in any of the premenarcheal patients although transient withdrawal bleeding did occur in 17 patients after 5 to 21 days of therapy. The most common side-effect experienced by 12 of the patientswere erythema at the injection site (5 patients) which was resolved spontaneously, and none was sustained with continued daily therapy. Plasma gonadotropins, testosterone in male patients and estradiol in female patients were significantly suppressed, as was growth rate but no firm conclusions can be made about the rate of skeletal maturation, overall growth in height, or adult height. The ultimate goal of LHRHa treatment is to restore normal growth potential while allowing puberty to occur at a timely age with subsequent normal reproductive potential. Side effects were minimal and long-term safety has not yet been established, however leuprolide appears to be an effective long-term therapy for central precocious puberty.

A double-blind Placebo controlled study of leuprolide acetate in patients with Functional Bowel Disease.

Functional bowel disease, also known as irritable bowel syndrome, is characterized by spasms within the colon wall that are recognized with symptoms such as abdominal pain and cramping, nausea, constipation or diarrhea. It was concluded that patients with moderate to severe functional bowel disease might benefit from therapy with a gonadotropin-releasing hormone (GnRH) analog like leuprolide acetate which is 15 times more potent than native GnRH and causes what is referred to as "downregulation" of pituitary gonadotropins, with inhibition of sex-hormone production in humans.

For the double-blind, placebo-controlled phase of the study, 30 women enrolled who were between the ages of 20 and 52. After completing the first phase, the subjects were offered the opportunity to continue receiving leuprolide acetate for an additional 40 weeks under an open-label protocol. 26 of the patients enrolled previously were elected to continue leuprolide acetate therapy and were entered into the open-label, long-term phase. The initial, double-blind study began with a two-week, no-treatment lead-in period, during which the patient's gastrointestinal symptoms were evaluated. All subjects had total symptom scores of ≥15 for unexplained nausea, intermittent vomiting, early satiety or anorexia or both, bloating and distension, and unexplained abdominal pain before and after eating. After the double-blind phase was completed, the method of administration and dosage of leuprolide acetate were changed. The average final dosage for all patients was found to range from 1.0 to 1.5 mg daily. During the double-blind phase, there were significant reductions in individual symptom scores for nausea and abdominal pain ($P < 0.01$) and for vomiting, bloating, and early satiety ($P < 0.05$) in the leuprolide-treated group. After the patients were into the open-label phase and under higher

doses of leuprolide, even greater improvements in symptom scores were apparent. For the subjects treated with leuprolide from the beginning, the overall assessment score at baseline was 7.9 ± 0.4. After 52 weeks the overall

assessment score had declined even more, to 2.6 ± 0.6 ($P < 0.0001$).

In the double-blind, placebo-controlled portion of the study it was concluded that the 3.75-mg depot form of leuprolide acetate significantly improved the symptoms of nausea, vomiting, abdominal pain, bloating, and early satiety ($P < 0.05$) over a three-month period. The adverse side effects are increased and at lower dosages. Bone pain and significant edema were the commonly encountered complaints. Experience with men was found to be much more limited (10 male patients), those who were treated had responded favorably to leuprolide acetate therapy. However, the continued use of leuprolide acetate to effective dosage and over longer periods of time produced even more striking and significant changes in symptoms and quality of life.

Effect of leuprolide acetate and tibolone in patients with severe premenstrual syndrome

Leuprolide acetate is a synthetic nonapeptide that is a potent gonadotropin releasing hormone receptor (GnRHR) agonist used for diverse clinical applications. GnRH agonists (GnRH-a) actuate a condition of hypogonadotropic hypogonadism by down-managing pituitary GnRH receptors. Tibolone, a synthetic compound was found to be a useful drug for add-back supplementation during GnRH-a treatment as an alternative to estrogen–progestin therapy as it has the advantage of improving libido and mood.

The clinical trial started with 30 female patients aged 23-29 years, all subjects were suffering from severe PMS for more than a year and had good general health as determined by medical history, physical and pelvic examination, blood count, and complete blood chemistry. Prior to being viewed as qualified for the study, all women went through 2 successive menstrual cycles of clinical assessment by daily rating of their symptoms on a well-validated analog scale. The visual analog scale was used to define 12 symptoms or signs: 4 positive psychological symptoms, 5 adverse psychological symptoms and 3 physical signs. The intensity of each symptom or sign was expressed as a score ranging from 0 to 10 on a 10-cm-long graded scale. After the two pretreatment cycles, all subjects were randomized and got depot leuprolide acetate at a dose of 3.75 mg IM. The main vial of LA was directed during the early follicular stage (third day of the cycle). Tibolone was directed orally at a dose of 2.5 mg/d, and oral placebo tablets were given at the dose of one per day. The length of the treatment was set to be two cycles that is, 2 infusions of leuprolide acetate. During treatment, all patients were asked to daily rate their symptoms on the same visual analog scale used in the pretreatment cycles. The efficacy of treatment was evaluated by comparing the mean severity of each symptom and sign during the 7 days before menstruation in the second

pretreatment cycle and the last 7 days of treatment.

The only side effect reported by the patients was hot flushes. Group A patients reported a significantly ($P<0.05$) lower incidence of hot flushes than group B. On comparing the last 7 days of treatment with the last 7 days of the cycle before treatment, the mean visual analog scale scores for each of the symptoms in patients of both the groups had improved significantly.

In the current investigation, we saw in all patients a measurably huge decrease in the mean scores for PMS after 2 months of treatment. Therefore, this study shows that tibolone controlled in association with GnRH-a doesn't decrease the restorative impact of these medications in women affected by PMS. Accordingly, tibolone given in association with GnRH-a may give long-term clinical treatment for women with PMS.

Leuprolide acetate- a potential peptide in the treatment of prostate cancer.

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in men. There are disease markers such as prostate specific antigen (PSA), Gleason score and tumor volume which partially predict patients which have the probability to progress to metastatic disease. LHRH analogues were identified for the treatment which effectively suppress testosterone in prostate cancer patients. LHRH agonists have the advantage of decreased morbidity and mortality from cardiovascular complications and the added advantage of being reversible. LHRH analogues are not orally active, and thus require parental administration. In order to deliver leuprolide acetate more effectively a subcutaneous extended-release formulation, Eligard® 7.5 mg, has been developed which uses the Atrigel® delivery system. The effectiveness of Eligard 7.5 mg formulation was demonstrated in clinical trials where a mean testosterone suppression of 6.12 ± 4.3 ng/dl was achieved with 97% of the patients being suppressed to < 20 ng/dl. LHRH agonists initially induce an increase in testosterone for ~ 1 week i.e., testosterone surge and then suppressing testosterone to <50 ng/dl on average in 21 days. This increase can invoke a 'disease flare' response that increases bone pain, spinal cord compression and urinary symptoms in ~ 10% of Stage D2 patients. The flare response is usually controlled by the administration of an androgen-receptor blocker like flutamide, bicalutamide or nilutamide which competes for the androgen receptor and attenuates the effects of the transient testosterone increase.

When a multi-center, open-label, fixed-dose investigation of six doses of Eligard 7.5mg/month was conducted in 120 patients, it was observed that with the first injection, the serum LH increased rapidly but then fell below baseline by day 10. After the second injection LH levels were barely detectable (mean: 0.1 ± 0.1 mU/ml). 112 of 119 patients were at castrate levels by day 28 and by day 42, all the patients achieved medical castration with 97% ≤ 20 ng/ml. All the patients on completion of the study-maintained castrate testosterone levels and had a mean testosterone of 6.12 ± 4.3 ng/dl at 6 months.

When a second multi-center, open-label, 6-month study of two fixed-doses of Eligard 22.5 mg every 3 months was conducted in 117 prostate cancer patients (Stage A – D). Right after the initial injection, LH increased during week 1 and then decreased below normal during weeks 2 – 4. After day 28, LH levels were barely detectable. In response to the LH spike, serum testosterone peaked on day 2 and then fell to castrate levels. 116 of 116 of the patients by day 35 had levels of ≤ 50 ng/dl.

At the end of 6 months all 111 patients completing the study were at castrate testosterone levels with 104 of 111 below the NACN guideline of ≤ 20 ng/dl. LHRH agonist depot formulations have become the preferred method of testosterone suppression because of their decreased cardiovascular complications, reversibility and patient preference. Eligard 7.5 and 22.5 mg clinical trials showed that > 99% of the patients initially achieved suppression and > 94% of patients had testosterone levels of < 20 ng/dl at 6 months.

LIRAGLUTIDE13–16
One Sample T-Test for Liraglutide

One Sample T-Test			
Sample size	t	df	p
	-1.885	2	0.200

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 45.83.

Liraglutide: New Perspectives for the Treatment of Type 2 Diabetes.

The complex nature of the pathophysiology of type 2 diabetes makes treatment difficult. In patients with Type 2 diabetes mellitus, the incretin effect is greatly weakened, and it is assumed that this may contribute to the incapability of these patients to adjust their insulin secretion to their needs. The impact of GLP-1 on food intake and body weight is of significant importance and of great interest in the expected treatment of Type 2 diabetes mellitus, where obesity is a significant concern.

Data from a randomized, double-blind, parallel- group trial included 165 patients with Type 2 diabetes mellitus directed higher doses of liraglutide- 0.65, 1.25 or 1.9 mg for 14 weeks and confirmed that liraglutide is capable of decreasing FPG levels between 2.7 mM (0.65 mg) and 3.4 mM (1.25 and 1.9 mg) on average when compared with placebo. In the same study, a decrease in levels of HbA1c of ≤ 1.7 percentage points was noted and ~ 50% of the patients with Type 2 diabetes mellitus managed to reach the goal level of < 7% in HbA1c set by the American Diabetes Association (ADA) when receiving the 2 highest doses of liraglutide (1.25 and 1.9 mg) compared with only 5% in the placebo group. In the highest liraglutide dose group (1.9 mg), change from baseline in body weight was -2.99 and -1.21 kg compared with placebo.

It can be concluded from the trial data and literature available that Liraglutide or GLP-1 analogues have established lasting improvement on HbA1c levels, weight reduction and improved β-cell function in patients with Type 2 diabetes mellitus. No effect of gender or age has been seen with respect to the pharmacokinetics of liraglutide. This agent is presently in Phase III clinical development.

Liraglutide in Type 2 Diabetes: Weight Management and Glycemic Control

Liraglutide is the first glucagon-like peptide-1 receptor agonist (GLP-1 RA) based on the human GLP-1 sequence, with potential weight loss benefits, approved for the treatment of type 2 diabetes (T2D) mellitus. The major risk factor for type 2 diabetes (T2D) are classified as overweight or obese, and it is highly helpful if they lose as little as 5% of body weight, which may improve glycemic control and cardiometabolic markers, reducing the risk of obesity-related problems such as cardiovascular diseases (CVD).

In this trial, long-term efficacy of Liraglutide 1.2 mg or 1.8 mg in a Southern Italy population of subjects affected by Type 2 Diabetes were analyzed and studied. 40 consecutive diabetes patients were taken in for the study, who were also classified as overweight or obese, were treated with Liraglutide for a minimum follow-up of 60 months, either alone or in combination with other antidiabetic drugs.

A total of 40 diabetic subjects completed 5 years of treatment with Liraglutide: 20 with 1.2 mg/day dosage and 20 with 1.8 mg/day dosage and a significant weight loss was observed in the patients where body weight decreased from 92.1 ± 20.5 Kg to 87.3 ± 20.0 Kg ($p < 0.001$), with a mean reduction of 5.0 ± 7.0 Kg. Additionally, the weight loss observed during the first 6 months of therapy was maintained throughout the 5-year study period. Nevertheless, encouraging effects on several markers of cardiovascular disease (CVD), additions in the 5- and 10-year risk for the first atherosclerotic cardiovascular event were documented, as four incident cases of myocardial infarction were recorded.

The results of the current study demonstrate that prolonging treatment of obese and overweight T2D patients with Liraglutide up to 1.8 mg/day for 5 years, in combination with one or more oral glucose-lowering agents, is effective at inducing and sustaining weight loss.

Liraglutide: A Potential Peptide for the Treatment of Polycystic Ovary Syndrome

Polycystic ovary syndrome is an unpredictable and heterogenous jumble involving various organ frameworks and extraordinary molecular pathways with strong epigenetic and natural impacts. Polycystic ovary syndrome is firmly connected with obesity, particularly abdominal obesity, albeit numerous people with PCOS have a higher amount of subcutaneous fat compared with controls.

Preclinical data have demonstrated that both GLP-1 and

glucose dependent insulinotropic polypeptide significantly suppress many progestogenic enzymes and factors, and moderately increase FSH expression in granulosa cells, suggesting a possible role in the treatment of hormonal dysregulation seen in PCOS. Liraglutide accomplished huge improvements of glucose also, fat dysregulation in preclinical and clinical investigations of overweight or obese people, patients with prediabetes, also, patients with T2D.

Clinical Studies of Liraglutide Therapy in PCOS.

Table 1: Prospective clinical studies of women with polycystic ovary syndrome (PCOS), in which liraglutide (LIRA) and metformin (MET) were administered: main results

Study population	Study design	Main results
36 obese women with PCOS, who were pretreated with MET for 6 months and have lost less than 5% of body weight were analyzed.	12-week prospective open-label study. Participants were randomized to receive LIRA 1.2 mg daily (n = 11), MET 1000 mg twice daily (n = 14), or combined LIRA 1.2 mg daily and MET 1000 mg twice daily (n = 11)	Women in the combination arm achieved on average a 6.5 ± 2.8 kg BW reduction compared with 3.8 ± 3.7 kg in the LIRA arm and 1.2 ± 1.4 kg in the MET arms. Menstrual frequency was not significantly changed
44 drug-naïve obese women with PCOS (mean BMI: 37.2 ± 4.5 kg/m2)	12-week prospective open-label study. Participants were randomized to receive combined LIRA 1.2 mg daily and MET 1000 mg twice daily (n = 22) or LIRA monotherapy in a daily dose of 1.2 mg. In the combination arm, all participants were treated with MET for 2 weeks before the administration of LIRA. One participant discontinued the study	Participants in the combination arm lost a median of 6.2 ± 2.4 kg compared with 3.8 ± 3.5 kg in the LIRA arm (p = 0.024). Significant reductions for total and free T and androstenedione levels, as well as significant increases in SHBG (p < 0.001), were described in the combination arm. However, only SHBG and free T significantly changed in the LIRA monotherapy arm. No alterations of LH or FSH levels were found. A significant reduction in androstenedione levels were shown in the combination arm when compared with the LIRA arm (2.3 ± 2.9 nmol/L vs 0.0 ± 2.3 nmol/L, p = 0.029)
32 obese women recently diagnosed with PCOS (mean BMI: 39.5 ± 6.2 kg/m2)	12-week prospective open-label study. Participants were randomized to receive LIRA 1.2 mg daily (n = 17) or MET 1000 mg twice daily (n = 15). 28 participants completed the study (14 women in each arm) and their data were analyzed	In a subgroup of our participants with severe obesity and insulin resistance and a higher OR of the metabolic syndrome, LIRA was more effective than MET. LIRA promoted a significant increase in LH levels and no essential change in total T levels. On the contrary, MET a caused a significant LH reduction, as well as a significant decrease in total T levels. No significant menstrual frequency changes were found in either group
41 obese drug-naïve women with PCOS (mean BMI 38.6 ± 6.0 kg/m2)	12-week prospective open-label study. Women were randomized to receive LIRA 1.2 mg daily (n = 14), MET 1000 mg twice daily (n = 13), or ROF 500 mg daily (n = 14)	An average BW reduction of 3.1 ± 3.5 kg (p = 0.006), 2.1 ± 2.0 kg (p = 0.002), and 0.2 ± 1.83 kg (p = 0.735) was achieved with LIRA, ROF, and MET, compared with baseline, respectively. Free T, SHBG, androstenedione, and DHEAS levels were not changed significantly. Menstrual frequency increased in all treatment arms and was slightly greater in patients treated with ROF
28 obese women with PCOS (BMI 38.3 ± 5.4 kg/m2)	LIRA 3 mg daily (n = 14) was compared to the combination of LIRA 1.2 mg daily and MET 1000 mg twice (n = 14) daily for 12 weeks	Participants in the combination arm lost an average of 3.6 ± 2.5 kg compared with 6.3 ± 3.7 kg in the LIRA high-dose arm (p = 0.062). Androstenedione and free T reductions tended to be greater, but not statistically significant, in the combination arm compared with

		the monotherapy arm. In the high-dose LIRA arm, a significant increase of SHBG levels was reported (p = 0.018)
28 obese women with PCOS (mean BMI: 36.7 ± 3.5 kg/m2)	12-week prospective open-label study. 27 participants were finally analyzed: 13 received the combination of low-dose LIRA 1.2 mg daily with MET 1000 mg twice daily and 14 MET monotherapies. The IVF protocol was offered to all women who completed the medical treatment after a 4-week washout period	Women in the combination arm lost 7.51 ± 3.89 kg compared with 6.99 ± 6.02 kg in the monotherapy arm. Only the HOMA-IR reduction was significant in the combination arm (p = 0.04). In both arms, a significant increase in SHBG levels was found compared with baseline. Pregnancy was achieved in 69.2% of women in the combination arm and 35.4% in the monotherapy arm after 1 year. The PR per ET was significantly higher in the participants in the combination arm (85.7%) compared with 28.6% in the other group (p = 0.03)

AC abdominal circumference, BMI body mass index, BW body weight, DHT dihydrotestosterone, ET embryo transfer, FSH follicle-stimulating hormone, HOMA-IR Homeostasis Model Assessment
of Insulin Resistance, IVF in vitro fertilization, LH luteinizing hormone, OR odds ratio, PR pregnancy rate, Ref. reference, ROF roflumilast, SHBG sex hormone-binding globulin, T Testosterone,
VAT visceral adipose tissue.

The major adverse effect of liraglutide administration in women with PCOS was found out to be nausea. It was more common when liraglutide was given at the maximum dose of 3 mg daily. When liraglutide was administered in a daily dose of 1.2 mg combined with metformin; nausea appeared to be less common, which may be due to the lower doses of liraglutide. Significant reductions in androstenedione levels were found when liraglutide was combined with metformin, compared with liraglutide monotherapy, suggesting the importance of combining these two medications. Larger and longer, well-organized, multi-centered, double-blind placebo-controlled trials, with rigorous designs and more post-interventional monitoring, are crucially anticipated to explore the efficacy and safety of liraglutide, in overweight and obese women with PCOS, and to clarify the benefit/risk profile of its use.

DESMOPRESSIN ACETATE17–20

One Sample T-Test for Desmopressin Acetate

One Sample T-Test			
Sample size	t	df	p
	-30.011	3	< .001

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 790.

Treatment with Desmopressin Acetate to Reduce Blood Loss after Cardiac Surgery

The hemorrhagic response to Cardiac Bypass surgery may stem from mild fibrinolysis, unnaturalized heparin, reduced number of platelet fibrinogen receptors, etc. The effects of DDAVP were studied (double-blind, prospective, and randomized trial) on 72 patients undergoing heart surgery. The patients were divided into two groups, one experimental and one control (n=35 each). Blood samples were obtained using an arterial catheter before the operation, right after the bypass but before Protamine administration, post-protamine administration, 90 minutes after DDAVP administration/ Placebo administration, and 24 hours after the operation. Parametric data were analyzed by Student's t-test while nonparametric data were analyzed by Mann-Whitney rank-sum test. The consistency of proportional data was studied by chi-square test (corrected for continuity) or by Fisher's exact test. patients who received DDAVP had less blood loss in the operating room, 12 hours after the operation, and in the 12th through the 24th hours after the operation. Out of the 22 patients in the placebo group who had a Von Willebrand factor of less than 1.8 U per milliliters, 10 of them ended up losing more than 2 liters of blood within the first 24 hours of the operation (including the operation). However, of the 15 patients who had a preoperative Von Willebrand factor of less than 1.8 U per milliliters in the experimental group (received DDAVP), only one person lost more than 2 liters of blood. Desmopressin affected the Von Willebrand factor in a more pronounced manner if it was less than 1.8 U per milliliters to begin with.

DDAVP needs to be tested in other cardiac surgical procedures in order to identify its efficacy; it can then be used for patients who begin to bleed out excessively.

Nocturnal Enuresis: Treatment using Desmopressin Acetate

Nocturnal enuresis is a common condition that can cause substantial psychological distress in children with the condition. By eight to ten years of age, nocturnal enuresis has significant costs in terms of self-esteem, inconvenience, and peer standing. Desmopressin acetate (DDAVP) is a synthetic analogue of human arginine vasopressin (ADH). DDAVP was used in 59 patients with nocturnal enuresis over a five-year period. 40 boys and 19 girls, 8 to 20 years of age made up the study group. Initially a dose of 5 µg of Desmopressin Acetate was given intranasally at bedtime to all the children and if the initial 5 µg dose was found to be unsuccessful after a period of two weeks, the dose was increased to 10 µg.

The result of this trial was concluded that dose levels of 10 µg or less produced suitable results in 81% of patients. During treatment, 54% of the children achieved dryness every night and 38% had a decrease in the number of wet

nights per week. Only 8% of the patients had no improvement on DDAVP. A satisfactory result was well-defined as complete nighttime dryness or a reduction in the number of recorded wet nights. DDAVP is effective in the large subgroup of patients with nocturnal enuresis with abnormal ADH secretion patterns. Therefore, DDAVP can be recommended as an effective and satisfactory alternative to other forms of treatment of nocturnal enuresis in children eight years of age and older.

Desmopressin Acetate in Cardiac Surgery: A double-blind, randomized study

This paper was published after the research of Salzman and his colleagues which talks about the effects of DDAVP. The need for decreasing blood loss has gone up in the wake of communicable diseases. This was a double-blind, prospective, randomized trial in which 83 patients (undergoing primary open-heart surgery) were allocated to the placebo group (n=43) or the experimental DDAVP group (n=40). The DDAVP was subjected intravenously. The contents of the bottle were administered after Heparin Reversal had been documented and Protamine had been infused. Blood loss was measured with the help of intraoperative suction collections and postoperative chest tube drainage for 24 hours. Student's t-test did a statistical analysis of data, besides chi-square tests. No significant difference was noted between the two groups, except the PTT (Partial Thromboplastin Time) which was significantly longer in the placebo group. No other significant differences were noted between the placebo and experimental group for the overall time difference up to 24 hours postoperatively. No consequential benefit could be derived from the application of DDAVP, except for two areas. The chest tube drainage was less within the first four hours (post-operatively) in men who had been administered with DDAVP. The chest tube drainage is more than usual, as compared to other studies because 50% of the patients were undergoing antiplatelet therapy at the time of the experiment. The study concluded that in general, DDAVP doesn't cause less postoperative blood loss or the transfusion requirements after an uncomplicated cardiac surgery.

Desmopressin Acetate in Percutaneous Kidney Biopsy

Percutaneous kidney biopsy is essential in the diagnosis of primary and secondary kidney diseases. Accurate clinical, chemistry, and renal ultrasound evaluation before and 24 hours after kidney biopsy is necessary to check for bleeding complications. Desmopressin has been used as a haemostatic agent in patients undergoing surgery at major risk of bleeding and in post biopsy bleeding complications in patients undergoing ultrasound-guided percutaneous native kidney biopsy. This was a phase 4, single-center, double-blind, randomized, controlled study in patients with kidney disease receiving ultrasound-guided percutaneous biopsy of the native kidney. A total of 162 patients (88 men and 74 women) were enrolled; 80 were allocated to desmopressin acetate treatment, and 82, to the placebo group All eligible patients in the experimental group were treated using desmopressin acetate subcutaneously, dosage of 0.3 µg/kg 1 hour before the kidney biopsy. The control group was treated with placebo subcutaneously, 1 mL of saline solution.v36 patients who experienced a bleeding complication, the hematoma was significantly smaller in the desmopressin group than in the placebo group. There were no differences in values for hemoglobin, coagulation parameters, estimated GFR, or blood pressure after the biopsy procedure between the experimental and control groups. Furthermore, no change in post biopsy hemoglobin levels was seen in either group. No adverse events and side effects of the drug were recorded on the report form. Results stated that desmopressin administration in patients with preserved kidney function and absence of coagulation disorders significantly reduced the risk of bleeding complications after kidney biopsy procedures, mainly hematoma formation. Thus, it is obvious to recommend mandatory use of desmopressin in patients with bleeding disorders. In high-risk patients, the use of other procedures, such as trans jugular renal biopsy or laparoscopic kidney biopsy, also may decrease hemorrhagic complications.

TEDUGLUTIDE (21–24)

One Sample T-Test for Teduglutide

One Sample T-Test			
Sample size	t	df	p
	-0.462	3	0.675

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 41.86.

Teduglutide to Revert the Damage Caused by Chemotherapy-induced Mucositis

Gastrointestinal mucositis is one of the most common side effects of chemotherapy characterized by nausea, anorexia, diarrhea, bacterial infection, loss of electrolyte-balance and can be lethal in severe cases. The epithelial lining of the intestinal tract has potential stem cells that divide rapidly and continuously and cure the intestinal damage present, if any. About 32 cells are able of crypt regeneration and GLP-2 enhances the proliferation rate and increases the crypt and villi size. The GLP-2 analog, Teduglutide, helps in enhancement of the adaptive process. Administration of this drug helps cure the damage and disease caused by the chemotherapy in cancer patients.

10-12 weeks old male mice were used, CD1 as the reference model and BDF1 for the experimental irradiation purpose. Three groups of BDF1 mice received subcutaneous injection of either GLP-2 or Teduglutide or saline (control) at 12-hr intervals for a range of 4 to 14 days. Irradiation was induced in BDF1 mice every morning and 4 days later it was sacrificed. The number of regenerated crypts were counted for each mouse and a crypt survival curve was generated.

In BDF1 and CD1 mice, GLP-2 administration increased the height & area of crypts by 11% & 24% and 7% & 15% respectively whereas after Teduglutide injection the number increased to 25% & 30% in the former and 5% & 14% respectively. The villus height changes were to 8% and 15% after GLP-2 injection and 23% and 36% after

Teduglutide injection in BDF1 mice whereas the numbers in CD1 mice stood at 15% & 12% and 17% & 12% after GLP-2 and Teduglutide administration respectively. When Teduglutide was administered 14 days prior to irradiation, a significant change in crypt survival curve was observed.

Teduglutide can reverse the damage caused to intestinal tract in colitis, enteritis and the chemotherapy-induced mucositis in cancer patients. An irradiation prior treatment of Teduglutide was evidently more effective in crypt survival rather than a post-irradiation treatment or a combination of both.

Teduglutide: A Treatment for Short Bowel Syndrome

Short Bowel Syndrome (SBS) displays characteristic symptoms like weight loss, diarrhea and nutrient malabsorption. This condition results when there is less than 200cm of functional small bowel. The gut hormones, like glucagon-like-peptide-2 (GLP-2), cholecystokinin, neurotensin, insulin, gastrin and GH, help in the post-resection adaptation process. Among these, GLP-2 works efficiently as a therapeutic agent for curing the SBS. The circulating Dipeptidyl-peptidase IV (DPP IV) inhibits the GLP-2 activity in intestine, so analogs of GLP-2 i.e. Teduglutide are administered to the SBS patients to prolong the half-life of the GLP-2. This drug shows resistance to DPP IV enzymes and thus possesses therapeutic potential.

Clinical trials have been done for this drug. A range of 2.5-10 mg dose administration was tested in a set of individuals in Phase I study. In phase II study the patients were divided into two groups: (i) ones with 50% or more colon continuity and (ii) ones with end-jejunostomy. To the former set of patients, subcutaneous teduglutide at 0.03 or 0.10 mg/kg/day while to the latter 0.03, 0.10 and 0.15 mg/kg/day was injected for 21 days. In another set of phase II study, SBS patients with jejunostomy but no colon continuity was given subcutaneous Teduglutide at concentrations of 0.03, 0.10 or 0.15 mg/kg/day for 21 days. These patients depended on parenteral fluids or nutrition. Jejunal biopsies were conducted at the end of 21 days and on day 42 also.

Phase I trial: Peak plasma conc. of the drug was seen after 3 hours of administration. Phase II trial: the significant findings include (i) increased absolute and relative wet weight absorption, (ii) decreased fecal wet weight and (iii) increased urine production. In participants with end-jejunostomy, the drug induced an increase in the (a) small bowel villus height, (b) mitotic index and (c) crypt depth.

The success of Teduglutide dependent treatment of SBS brings light and hope on the drug as a treatment for it. The drug administration is found to be safe as no adverse effects reported in patients. However, additional trials and data are required to optimize the dosage of the drug and to check the appearance of any side effects.

Effect of Renal Impairment on Teduglutide Pharmacokinetics

Teduglutide is given to SBS patients for rapid adaptation of the intestine like, increasing the crypt proliferation, the mucosal surface area and the villus height. This drug is resistant to the inhibitory effect of the DPP IV and significantly reduced the need for PN in many patients for a few days. In humans, the kidneys are mainly involved in the clearance of teduglutide. Thus, pharmacokinetic (PK) analysis of this drug was done and the impact of renal function and age on teduglutide clearance was investigated.

Three groups of people with renal impairment were given teduglutide with the parallel administration of the same drug to the next three groups of elderly, healthy people with normal renal function. The age range involved in this study was 18-75, male and female, with a BMI range of 18-34 kg/m2. The renal function marker i.e. creatine clearance (CC) was tested for each group. Trial setup: (I) Screening (day -28 to -2), (II) Check-in (day -1), (III) SC injection of 10mg/mL of Teduglutide (day 1), (IV) Check-out (day 2), and (V) Follow-up (for 7 to 9 days). Blood samples were collected prior to dose administration and at various different time intervals after the dose administration to check the blood plasma level of the drug.

In the patients with end-stage renal disease, the plasma concentration and exposure extent were 2.08 and 2.59 times higher than that seen in the healthy individuals. Plasma clearance of the drug is found to be higher in the healthy ones. Therefore, it is clear that the exposure to teduglutide increased with increase in the stage of renal impairment. The mean CC was lower in the healthy individuals (91 mL/min) compared to the non-healthy ones (106 mL/min). No death and no serious or significant side-effect for the drug was observed hence, the drug is announced safe to be administered.

Therefore, it is confirmed that kidneys function in elimination of this drug and a dosage of 10 mg teduglutide is safe for subcutaneous administration in patients with moderate to high renal impairments.

Intestinal Failure Remedy: Teduglutide

Intestinal Failure (IF) is characterized by absorption deficit of the intestine as only a few 200cm of the intestine remain functional. Such individuals are dependent on intravenous fluid administration or parenteral nutrition (PN) to maintain their weight and health. In PN-dependent IF patients, the administration of GLP-2 enhanced the crypt-cell proliferation, villus height and mucosal surface area. However, the circulating DPP IV in the intestine inhibits the activity of GLP-2 so, its analog Teduglutide can be used, as it is resistant to the inhibitory effect of the DPP IV. Subcutaneous administration of both Teduglutide and a placebo in IF patients has shown significant changes in the intestinal mucosal cell architecture and composition.

Two groups of patients were given either placebo or teduglutide (at two different concentrations i.e. 0.05 and 0.10 mg/kg/day) subcutaneously for 24 weeks and at the time of endoscopy, two mucosal biopsies were immersed for isolation of mucosal DNA or RNA. Small intestinal villus height, crypt height and mid-villus width were measured for the samples. Mucosal protein, RNA and DNA were quantified. Glass slides representing the samples from large or small intestines were prepared for histological analysis and dysplasia condition, abnormal changes in the intestinal architecture, was checked for them.

After 6 months of both placebo and teduglutide treatment,

no dysplasia feature is observed in any of the biopsies after the extensive histological analysis done. Instead, Crohn's disease and eosinophilic colitis are observed at a low frequency. The small bolus villus height significantly increased in teduglutide treated patients for the conc. administered. No overall significant change in mucosal DNA and protein concentration but, significant changes in cellular RNA concentration in both small and large intestine is observed in teduglutide treated patients. Mean crypt depth and mean villus surface area significantly increase in both small and large intestine with higher dose of the drug only.

Teduglutide is thus an effective drug for the treatment of IF. It is a potential reparative agent for the intestine as it helps in rapid adaptation of patients suffering from this disease as it significantly increases the villus height, mucosal area and also by enhancing the crypt cell proliferation.

PRAMLINTIDE (25–29)

One Sample T-Test for Pramlintide

One Sample T-Test			
Sample size	t	df	p
	-1.532	3	0.223

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 415.8.

Pramlintide in Bone Density Regulation: Future Research Scope

Amylin secreted by the pancreatic β-cells helps reduce the PP levels by delaying gastric emptying. In DM-1, this hormone is deficient. It shares homology of 47% and 13% with calcitonin gene related peptide (CGRP) and calcitonin respectively and it is this homology that accounts for its role in bone metabolism and bone density regulation. Along with calcitonin, this hormone inhibits osteoclasts by reducing the PTH-stimulated bone resorption and reduces the motility of osteoclasts by elevating cytosolic cAMP levels. Its deficiency in DM-1 patients can cause low bone density and increase fracture probability in them. Pramlintide is administered to DM-1 patients to investigate its role in bone metabolism.

Patients, male and female, having a history of at least five years of DM-1, were a part of this study and received subcutaneous injection of Insulin and Pramlintide (30µg) respectively. This was carried out for 12 months. The levels of HbA1c, PTH, serum-calcitonin, amylin, bone density, urinary cross-links and osteocalcin were determined before the pramlintide and a consistent check-up of these factors was maintained in the patients for data analysis.

There was no significant change in the HbA1c values before and after the study. Bone density was not much significantly changed. At the beginning of the study, bone density was 1.19 ± 0.17 gm/cm2 and at the end it was 1.2 ± 0.7 gm/cm2 i.e. a non-significant improvement was observed in the participating individuals

Due to application of pramlintide at such low concentrations, not much of a change in bone reabsorption was observed. Thus, this topic is open to research and many unknown facts are yet to be dug. This experiment can be redone with different higher concentrations of pramlintide like 60µg, 90µg and 120µg in order to collect more data.

Investigation of Pramlintide Levels in Fetus for Safety

DM-1 is a chronic disease and once diagnosed with it, one has to take medication for it throughout their life. So, there is a possibility that some women might conceive while already being diabetic. Thus, it is necessary for us to check if the drug Pramlintide can cross the placental barrier and can cause any harm to the developing fetus.

Placenta of women was obtained following vaginal or cesarean delivery. It was then kept in saline for separating the uterus and perfused with a heparinized drug-free media. Various factors were calculated, viz, maternal-fetal match, transport fraction (TF), clearance (Cl) and clearance index (Ci) with the help of radioactive antipyrine (14C) for control as it can rapidly diffuse with minimal metabolism rate. Ci represents the drug clearance in the maternal perfusate relative to that of antipyrine. Ci = 1 indicates rapid clearance of the drug from maternal perfusate and a 40% maternal to fetal transfer. After the system was determined, perfusion with pramlintide was done to the maternal perfusate. It is known from the literature available that insulin cannot cross the placental barrier, so it is used as a control. These were performed in duplicates.

The mean Ci value for Insulin was 0.02 and was constant throughout the experiment. The Ci value of Pramlintide was found to be less than or equal to 0.05. The ratio of fetal to maternal concentration of pramlintide was calculated after determining the mean concentrations of the drug in both maternal and fetal perfusates. The ratio was found to be less than or equal to 0.006 in all the sets of the experiment. Thus, from the ratio obtained, we can say that there is very low probability for the transfer of pramlintide across the placental barrier and hence it ensures the safety of the drug.

It was already established that insulin cannot cross the placental barrier and through this experiment it was seen if the case is the same of pramlintide. From the data obtained it is clear that the drug does not cross the placental barrier and very low concentration was observed in the fetal perfusate and this was maintained throughout the series of experiments performed in both the lab animals. So, it can be concluded that the drug is safe for consumption for women and is very unlikely to cause any harm to the developing fetus during the gestation period.

Treatment of Diabetes Mellitus with Amylin Analog: Pramlintide

Diabetes Mellitus (DM) Type 1 and 2, both are one of the most common disease conditions seen in today's world. The three blood glucose tests: Fasting (F), Post-prandial (PP) and Oral glucose tolerance test, are significant predictors of cardiovascular diseases (CVD). Pramlintide (FDA approved, 2005) is an amylin analog that lowers PP glucose in both DM-1 and DM-2 conditions. Amylin is a neuroendocrine hormone co-secreted with insulin. Normally, amylin is secreted every 4 to 6 minutes but an impairment is seen in both DM types. It serves the

following functions: (i) slow gastric emptying and decreased food intake, (ii) reduced PP glucose (iii) enhance glycogenesis, (iv) Arg-induced PP glucagon secretion, and (v) weight loss. However, on account of its low solubility and self-aggregation, it is not possible to isolate and purify Amylin, so its analog Pramlintide is used as a drug to treat DM-1 and 2 in doses of 60µg and 120µg respectively.

651 volunteers received subcutaneous injection of placebo for 28 days before breakfast, lunch and dinner alongside insulin. Following this, they received subcutaneous injection of either placebo or pramlintide (60 or 90µg) three times daily for 52 weeks. All of them self-monitored blood glucose daily. Electrocardiograms, HbA1c and weight were assessed throughout the study.

Significant reduction in HbA1c levels is seen in the patients who received pramlintide compared to the placebo group. At week 52, the weight of the individuals, who received pramlintide + insulin therapy, reduced whereas in the other group, placebo + insulin, an increase was seen. The drug is found to be safe as it does not trigger any cardiovascular, renal or hepatic impairment.

It can be said that pramlintide, alongside insulin therapy, can help maintain weight and improve the glycemic conditions in DM-1 patients as pramlintide reduces HbA1c levels beyond that achieved by insulin alone.

Aβ Induced Impairment Restoration using Pramlintide in Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. The hallmark of this disease is deposition of amyloid β-protein (Aβ) in the cortical and limbic parts of the brain. As these portions are essential for the memory and cognition in an individual, formation of Aβ plaques at these sites lead to gradual memory loss. Both human-Amylin (seen in diabetic patients) and Aβ bind to the AMY3 receptor and can exhibit toxic effects. Pramlintide can reverse the neurodegenerative effects of Aβ by virtue of its interaction with the AMY3-receptor and improved memory in them.

Sets of experiments performed: (I)effect of amylin and Aβ on hippocampal long-term potentiation (LTP), done using 8-12 months old mice, and (II) testing influence of Pramlintide on LTP, done using mice overexpressing APP (Amyloid Precursor Protein, precursor of Aβ). Before external induction of LTP, normal responses were monitored for 10 mins. Brain was removed after decapacitation, then sections were cut in the hippocampus and the slices were kept for an hour in the artificial-CSF chamber. The slices then, one-by-one, were transferred to a submerged glass-bottom recording chamber. Constant perfusion with artificial-CSF was done at the rate of 2mL/min at 30oC and the field excitatory post-synaptic potential was recorded from the hippocampus area with the help of Pt/Fe electrode.

Pramlintide administration alone does not affect the LTP, but h-amylin depresses it. The application of this drug improves the depressed LTP in these mice and is reduced at the hippocampal Cornu-ammnois 1 (CA1) site. These results indicate that an impaired hippocampal LTP can be rectified by pramlintide application but the basal synaptic deficit at CA1 site cannot be rescued.

Pramlintide is a neuroprotective drug as it functions as an AMY3-receptor agonist. An improvement in memory and cognition is seen in mice. A potential therapeutic use of this drug may be lacking in AD due to presence of blood brain barrier and its poor solubility at physiological pH but, the restoration of Aβ induced LTP depression ensures its use as a treatment for AD like other h-amylin receptor antagonists.

OXYTOCIN

One Sample T-Test for Oxytocin (30-35)

One Sample T-Test			
Sample size	t	df	p
	0.827	3	0.469

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 76.75.

Oxytocin in Schizophrenia: A Therapy in Psychiatry

Schizophrenia is a disabling disorder affecting a small fraction of the population. Research done so far points towards oxytocin being an effective therapeutic agent. In schizophrenia patients, correlation between peripheral oxytocin and neurobehavior is seen which draws attention towards its therapeutic role. Oxytocin receptors relevant to schizophrenia have been located in parts of the brain like substantia nigra, solitary tract nucleus, lateral septal nucleus, central nucleus of amygdala (CeA) and parts of the basal ganglia.

Subjects diagnosed with Schizophrenia were enrolled in this double-blind placebo-controlled study. In addition to their regular antipsychotic medication, they received intranasal oxytocin for three weeks and intranasal placebo for another three weeks daily. 1st week, oxytocin dosage was 20IU and thereafter it was 40IU, twice daily.

At the end of three weeks, oxytocin manifested positive and negative symptoms scale ($p<0.001$) compared to placebo. It exhibits antipsychotic properties and this fact validates the preclinical study. Also, when given twice daily for three weeks, the drug is well-tolerated. Further study with larger sample size, longer treatment with different dosages is needed for a better understanding of the disease and this drug.

Borderline Personality Disorder and its Cure with Oxytocin

Borderline personality disorder (BPD) is a complex psychiatric disorder. Such patients have a fear of abandonment and have trust issues with their primary caregiver. They tend to misinterpret others' words and emotions and can show tantrums and are more susceptible to attempt suicide. Oxytocin downregulates amygdala responsiveness, which is hyper-responsive in BPD patients, and so it can help improve the cognition, which is the care symptom of BPD.

40 females diagnosed with BPD and 41 healthy females were a part of this double-blind placebo-controlled study. The participants received either 26IU of intranasal oxytocin or placebo spray. 45 minutes later, fMRI scanning was done. The emotional expression and eyes and mouth

fixation was noted and analyzed.

From the fMRI results, a reduction in posterior amygdala hyperactivation is observed. This reduced aggression in patients. Change in their facial expression and eye is quite evident. However, such a scenario is not seen in patients given placebo spray. Oxytocin administration may reduce social threat hypersensitivity.

The above studies suggest a dual mechanism of action of oxytocin in BPD patients i.e. involving amygdala and insular activity, both of which are related to BPD. Oxytocin not only just downregulates the Amygdala response but also increases insular response for negative stimuli. Thus, intranasal administration is suggested to help improve the conditions of these patients. Whether oxytocin application to these affected individuals would be absolutely safe or not, is yet not completely certain and needs further study.

Oxytocin Nasal Application: Autism Spectrum Disorder (ASD) Treatment

Studies have revealed that Oxytocin treatment aids to improve social interactions and communication skills in ASD patients, which are the main characters of this congenital disease and helps combat the repetitive nature of the patients making it a potential therapeutic agent. Recently, it has been observed that intranasal (i.n.) application of oxytocin efficiently delivers the drug to the brain via the olfactory nerve pathway. Nasal application also initiates rapid drug action and has shown no side effects. The motive behind this review is to get an understanding of i.n. application of oxytocin as a therapeutic agent for ASD treatment.

Intravenous (i.v.), intraperitoneal (i.p.) and i.n. administration of oxytocin was done to compare the efficacy of each application. Blood sample was collected from the portocaval vein. Following this, the brain was removed from the animal's body and washed. It was divided into three parts viz the occipital lobe, the frontal lobe and the olfactory bulb, each of which was weighed and homogenized with 100µL saline. Then acetonitrile was added, and it was centrifuged. The supernatant was allowed to evaporate and the concentration of oxytocin in the residue was measured. Degradation of oxytocin in the nasal cavity of mice was tested by perfusing oxytocin solution obtained from esophagus through a peristaltic pump. Stress was induced by keeping the mice in a transparent plastic cylinder for 2hr. Then a blood sample was collected to check the level of corticosterone (CCS) in plasma in both stress and non-stress conditions. The CCS level in the brain was also checked by LC/MS and the elution of both oxytocin and CCS was noted for peak values.

The conc. of oxytocin in the brain was found to be higher following i.n. administration with the concomitant decrease in plasma conc. whereas in case of i.v. and i.p. administration, plasma oxytocin levels were higher compared to that of in the brain. Moreover, the conc. of oxytocin in the olfactory bulb was higher than in the occipital or frontal lobe i.e. the DTP (Direct Transport Percentage) value of olfactory bulb (99%) was higher than the rest two after i.n. oxytocin administration. The oxytocin conc. in nasal perfusate first gradually decreased (90 mins) and then returned to initial concentration (180 mins) after perfusion. The stress indicator CCS levels in plasma under normal condition was 10-100ng/mL and after stress induction increased to 136-232ng/mL. This was reduced only after i.n. application of oxytocin and i.v. administration did not work in reducing plasma CCS level.

The results obtained from the plasma and brain level oxytocin following i.n., i.v., and i.p. administration clearly indicates that efficient delivery of the peptide to the brain can only be achieved after i.n. administration. The initial decrease in nasal perfusate conc. was not due to drug degradation but on account of temporal absorption. The higher conc. in olfactory bulb, after i.n. administration, indicates the presence of oxytocin receptors in the frontal cortex of the brain. In this transport system, the drug diffuses through the small pores in the cribriform plate from the nasal cavity to brain or CSF and this supports a direct-delivery mechanism to the brain. Thus, these results justify the effectiveness of intranasal application of Oxytocin and brings light to it being a potential therapeutic agent for treating ASD.

Intravenous or Intramuscular Oxytocin: Finding the More Effective Treatment for Postpartum Hemorrhage.

Postpartum Hemorrhage (PPH) is one of the leading causes of maternal mortality. Administration of Oxytocin in the third stage of labor is usually done to prevent PPH. It acts rapidly on the uterus after intravenous (i.e.) administration but it has a half-life of only 10 minutes, whereas intramuscular (i.e.) administration shows an effect after 3 to 7 minutes which is retained for 30 to 60 minutes. There has been much debate about which is a better option. So, through this article, this point was analyzed essentially i.e. to find the better method of oxytocin administration-intravenous or intramuscular. Women of 18 years or older at 37 weeks pregnant or more, aiming at vaginal delivery, were only allowed to be a part of this study. Women were randomly placed in two groups, one of which were given i.v. bolus of oxytocin and an i.m. bolus of placebo while the other received i.m. bolus of oxytocin and i.v. bolus of placebo, 1 min after the delivery. Also, blood samples were taken just when these women went into labor for analysis. After vaginal delivery the blood loss was measured by direct collection of blood i.e. gravitation method. These women were continuously monitored after the delivery to check for complications, if they arise. A full blood count was done a day after the delivery to check the hemoglobin levels.

The PPH is found to be lower in the i.v. group (18.8%) than in the i.m. group (23.2%) by 4.4%. Severe PPH is seen in only 4.6% if the i.v. group while in the other it is seen to be 8.1%. This result is statistically significant. Thus, the need for blood transfusion in i.v. and i.m. group is 1.5% and 4.4%. The side effects are not increased in the former group compared to the latter. From the study done and the results obtained, it is clear that the intravenous administration of oxytocin reduces the possibility of severe PPH, need for blood transfusion or intensive care of mother than the

intramuscular method of administration. So, intravenous administration of the drug is more efficient to prevent PPH.

CALCITONIN

One Sample T-Test for Calcitonin

One Sample T-Test			
Sample size	t	df	p
	-5.185	3	0.014

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 874.5.

Calcitonin in treatment of central giant cell granuloma

Central giant cell granuloma (CGCG) disease occurs in the mandible and maxilla of the mouth causing symptoms like pain, swelling, root resorption and tooth displacement. Calcitonin peptide inhibits the activity of osteoclasts and hence can be used in the treatment of this condition. It also inhibits multinucleated cells IN CGCG. Calcitonin nasal spray was proved to be effective for the treatment of this condition. Five patients with this condition treated with nasal calcitonin spray were considered for the study. The duration of the treatment lasted from 9 to 60 months. The patients took 200IU/spray twice daily. Ossification and complete resolution of the lesions was observed in radiographs of the patients. No major side effects were reported by the patients.

Calcitonin and its uses in treatment of neuro osteoarthropathy

Charcot neuro osteopathy (CNO) affects the architecture of bones in the foot. Currently only bisphosphonates have been used in the treatment of CNO. This paper explores the effects of calcitonin in treatment of CNO. This paper describes the effects of intranasal calcitonin in 32 patients suffering from acute CNO. A randomized control trial was conducted to study the effects calcitonin on bone metabolism for a period of 6 months. One group of patients were administered 200 IU of nasal calcitonin every day along with calcium supplements. The control group had to take calcium supplements. The study also included nine patients suffering from renal insufficiency.

The symptoms of the disease such as skin temperature bone turnover markers Type I collagen (1CTP) and Bone-specific alkaline phosphatase (BALP) were monitored monthly for the first three months and then every six months.

There was a reduction in bone resorption marker – 1CTP in the study group in comparison to the control group during the first 3 months of treatment. Statistically significant difference was also seen in the concentration of BALP in the study group after 3 months. Calcitonin works by acting on the osteoprotegerin/receptor-activator nuclear factor ligand system. Whereas bisphosphonates inhibit the action of osteoclasts. Studies also show that long term use of bisphosphonate suppresses the bone remodeling as well. Clinical trials with larger sample size should be conducted to study the effects of calcitonin.

Oral recombinant calcitonin for treatment of osteoporosis

Calcitonin is a naturally occurring peptide hormone. It is made up of 32 amino acids. It binds to the receptors of osteoclasts to inhibit their activity. This paper includes phase III clinical trial studies of oral Recombinant salmon calcitonin (rsCT) for the treatment of osteoporosis. The rsCT tablet was covered with an acid stable enteric coat to prevent it from dissolving in the stomach. 565 post-menopausal women suffering from osteoporosis were randomly assigned to three different groups, the first group received oral rsCT and placebo nasal spray. The second group received ssCT nasal spray and placebo tablets, and the third group received placebo nasal spray and placebo tablets.

The treatment was administered every day for 48 weeks and the patients were monitored after every 3 months. Condition of the disease was measured using bone density measurement, bone resorption biomarkers and fracture risk assessment. The efficacy of recombinant salmon calcitonin was monitored using criteria like bone mineral density (BMD) and bone resorption markers. The lumbar BMD improved significantly for the group taking rsCT in comparison to control and placebo groups. A reduction in bone resorption biomarkers was also seen in the patients taking oral rsCT tablets. Mild to moderate side effects like gastrointestinal were reported by women.

Calcitonin and osteoarthritis

Osteoarthritis is an autoimmune disease which causes the degeneration of both cartilage and bone. Nasal salmon calcitonin was used for the treatment of osteoarthritis. Calcitonin peptide can be used to increase the turn-over of both bone and cartilage as it has anti-resorptive properties. Calcitonin inhibits the activity of osteoclasts. Calcitonin induces the synthesis of collagen type II and proteoglycan. Reduced levels of estrogen also play a role in osteoarthritis. Hence, post-menopausal women with the age of 55-65 with good health were selected for this study.

This paper explores the effects of nasal calcitonin spray on 220 post-menopausal women suffering from osteoarthritis. They were administered with 200 IU nasal spray once every day. The feedback was collected using quality of life questionnaires by European foundation for osteoporosis. Knee radiographs were evaluated 1 year after the treatment and evaluation was conducted every 3 months.

Statistically significant improvement was seen in stiffness and knee pain after 3 months of treatment. Rescue analgesic intake was reduced by 60% by the end of 1 year. Oral form of salmon calcitonin is not currently available in the market. However, the results in this paper show that use of nasal calcitonin spray can lead to reduction in pain and stiffness. Several studies support the chondroprotective activity of calcitonin.

OCTREOTIDE

One Sample T-Test for Octreotide

One Sample T-Test			
Sample size	t	df	p
	-5.311	3	0.013

Note. For the Student t-test, the alternative hypothesis

specifies that the mean is different from 208.

Octreotide as a therapy for Sulfonylurea overdose in children

Sulfonylurea leads to hypoglycemia in children as it hyperpolarizes the beta cells in the pancreas, which causes more insulin secretion. Octreotide suppresses the secretion of insulin by pancreatic cells. From the cohort of 12 patients, the median age was 22 months. The number of hypoglycemic events before octreotide treatment were higher than after treatment with octreotide. Out of 121 patients 99 patients did not show any signs of hypoglycemia. 3 cases showed adverse side effects.

Previously, studies have been conducted in adults showing the superiority of octreotide in treating sulfonylurea poisoning. In a study conducted by Fassano et al, octreotide increased the levels of blood glucose and reduced the recurrence of the condition. Majority of the children only required one dose of octreotide. In 18% of children requiring more than one dose, the median was 5 hours (post treatment hypoglycemia).

Currently, octreotide is not approved by the FDA. It can cause side effects like injection site pain, brachy cardia, hyperglycemia, fluid retention. The cases studied for this review did not show any adverse effects of octreotide. This also suggests that octreotide is safe to use on children with age less than 6 years suffering from sulfonylurea.

Prophylactic use of octreotide for asparaginase-induced acute pancreatitis.

Octreotide is a synthetic peptide and also an analog of somatostatin. Asparaginase drug is used to treat acute lymphoblastic anemia. However, use of this drug again and again causes recurrence of pancreatitis. This study evaluates the effects of using octreotide against asparaginase induced pancreatitis.

Pediatric data from both the hospitals was evaluated for patients with a medical history of asparaginase and octreotide. Seven patients who took asparaginase and octreotide were identified between 2008 and 2015. All the patients received a dose of 2.5-2.0 ug/kg/day of octreotide by intravenous fusion. The first dose of octreotide was administered 24 hours before asparaginase administration.

Octreotide treatment was administered throughout the course of asparaginase administration and given every day until 10 days after the last dose of asparaginase. 3 patients did not show any signs of recurrence of pancreatitis. 4 patients showed recurrence of pancreatitis. However, no severe side effects were observed.

Asparaginase hydrolyses asparagine to aspartic acid and ammonia, this leads to lower levels of asparagine in blood plasma. Since lymphoblastic leukemia cells acquire essential amino acids like asparagine from the outside environment, depletion in asparagine causes these cancerous cells to die.

Octreotide can be used for the treatment of pancreatitis as it reduces synthesis of pancreatic enzymes and pancreatic secretion. The 4 patients who showed recurrence of pancreatitis, the disease was rather severe in the recurrence stage. Octreotide was administered intravenously continuously. The dose amount requires research work. The sample size of the study should be increased. Only females suffered from recurrence of pancreatitis suggesting that gender can play a role in the effect of octreotide.

Uses of octreotide for treatment of recurrent gastrointestinal bleeding in patients with continuous flow left ventricular assist devices.

People with serious heart conditions and continuous flow left ventricular assist devices (CF-LVAD) usually suffer from gastrointestinal bleeding. Use of anti-thrombotic causes more blood related complications. Previously, octreotide has been used on patients not supported by LVAD and has shown positive effects and prevented recurrence of GI bleeding. In this study, octreotide was administered to patients who were supported by CF-LVAD.

The sample size of the study included seven people supported by CF-LVAD with recurrence of GI bleeding who took octreotide. Octreotide treatment was administered to the patients who were admitted to the hospital several times due to GI bleeding. Two patients received 20 mg dose subcutaneously every month. And the other five patients received 50 mcg dose subcutaneously two times a day. GI bleeding is very common in patients who are supported by CF-LVAD. The lack of pulse pressure in CF-LVAD supported patients can lead to AV malformations which can be the cause of bleeding. AV malformations can also lead to intestinal ischemia which leads to the production of vascular endothelial growth factor (VGEF). Somatostatin peptide is released by gastric and intestinal mucosa, pancreatic cells. Octreotide is a somatostatin analog and helps in management of GI bleeding. This analog acts via various pharmacological mechanisms like increase in vascular resistance, improvement in platelet aggregation and in inhibiting angiogenesis. Patients administered with octreotide showed a decrease in hospital admissions, blood transfusions and endoscopic procedures.

Octreotide for treatment of congenital and acquired chylothorax in babies

Chylothorax is a disease caused due to accumulation of lymphatic fluid in pleural space due to the leakage of thoracic ducts. The liquid is white colored and contains more than 1000 cells/mL. Chylothorax has low prevalence in new-borns. However, the mortality rate due to this disease is high.

This paper comprises of a systematic review of using octreotide in treatment of congenital and acquired chylothorax.

Out of 88 neonates, 60 babies had congenital chylothorax and acquired chylothorax. Drug administered one to three times a day. No significant differences were observed in birthweight or gender. Remaining 4 patients were administered octreotide via subcutaneous injections. Doses varied from 1 to 70 μg/kg/day. Patients with acquired chylothorax were administered with intravenous octreotide therapy for 16 days with a continuation of subcutaneous injections for 151 days. Patients with congenital chylothorax had a longer treatment time and higher dose.

Octreotide was successful in cessation of pleural effusion. The stooping of pleural effusion took place anywhere between 3 days to 28 days. Side effects were reported in 12 patients out of 84. In the congenital group, problems like hyperglycemia, bloody stools, pulmonary hypertension were reported. Side effects are mainly based on individual response of the patients.

Octreotide showed positive results in 47% infants included in this systematic review. With respect to this study it can also be said that octreotide was more effective in congenital chylothorax. However, babies suffering from this disease were exposed to higher doses for longer periods of time. Octreotide treatment was chosen as the last resort before considering surgical pleurodesis. .

Octreotide was proven to be a safe treatment for chylothorax in infants. Since this condition is rare, conducting clinical trials is not possible. Hence, proper record of the patients with time duration of medication should be noted.

TRIPTORELIN

One Sample T-Test Triptorelin

One Sample T-Test			
Sample size	t	df	p
	1.097	3	0.353

Note. For the Student t-test, the alternative hypothesis specifies that the mean is different from 149.29.

Endometriosis is a condition in which endometrial gland and stroma are present outside the uterus. Endometriosis mostly affects the pelvic region and the ovaries of females. This can lead to pain symptoms and infertility as well. Endometrial lesions can be removed by surgery. However, there are chances of its recurrence. This paper is a systematic literature review which summarizes the pharmacokinetics, pharmacological properties and clinical efficacy of triptorelin. Triptorelin was proved to be efficient and safe for use in the treatment of endometriosis. In this paper, both observational studies and random controlled trials data was taken into account.

GnRH-a is produced by substituting D-amino acid in position 6, thus increasing their affinity for the GnRH receptors. Triptorelin was synthesized in 1973, by substituting glycine 6 with D-tryptophan. Triptorelin can be administered subcutaneously or intravenously. The half-life of triptorelin is 10 times higher when injected subcutaneously. GnRH-a like Triptorelin are administered to the patients as the second line of treatment, when other drugs fail.

Subcutaneous injection of 100 µg of triptorelin causes a rapid surge of the compound in the blood levels which lasts for up to 6 hours. However, at 24 hours there were no traces of triptorelin in the bloodstream. Some of the side effects reported were vaginal dryness, headaches, decreased libido, sleeping disorders and increase in weight. Hot flushes were observed in 75% of the patients taking triptorelin. Reduction in bone mineral density was also reported by some. Some studies showed reduction in the size of endometria nodules. There was no comparison of triptorelin's safety and efficacy with other GnRH analogs.

Triptorelin: A Review of its Use as an Adjuvant Anticancer Therapy in Early Breast Cancer James E. Frampton.

Breast cancer therapies include chemotherapy, radiotherapy, endocrine therapy and targeted therapy. Adjuvant endocrine therapies are employed on patients with hormone receptive positive tumors. These therapies block the action of estrogen at ER in the breast cancerous cells. Some of the commonly used adjuvant endocrine therapies are – orally active aromatase inhibitors (AIs), ovarian function suppression (OFS) – this can be done with the help of gonadotropin releasing hormone agonist or surgical oophorectomy, oral selective ER modulator – tamoxifen. Triptorelin is a synthetic peptide and is used as a Gonadotropin releasing hormone antagonist (GnRHa). GnRHa suppresses the activity of ovaries and hence the production of estrogen reduces. Continuous use of GnRHa leads to postmenopausal state, where, estrogens are produced due to aromatization of androgens. Triptorelin was used with an aromatase inhibitor in women suffering from early stage breast cancer. Treatment of patients with triptorelin showed positive results in reduced levels of ovarian function suppression.

Leuprolide and Triptorelin in precocious puberty.

Triptorelin and leuprolide are two GnRH analogs and are used in the treatment of precocious puberty. This problem is caused due to activation of hypothalamic-pituitary – gonadal axis which increases the production of gonadotropin-releasing hormone (GnRH) and Luteinizing hormone (LH). This paper highlights the use of triptorelin to treat precocious puberty and its indirect effect on height of children. Inactivation of two GnRH regulator neuropeptides – kisspeptin and neurokinin B in the hypothalamus can lead to delayed puberty. Analogs can be administered intravenously or intramuscularly. In some cases it was also administered subcutaneously. However, it requires a high dose.

With the use of leuprolide, the suppression of LH was seen only after the 3rd month of administering 3.75 mg dose every 28 days. In several studies, the patients were administered 11.25 mg triptorelin for 3 months and 87.6% showed suppression of LH. Both the analogs are effective against Precocious puberty. Leuprolide showed side effects like site pain, redness and sterile abscess. Sleep disturbances, mood swings and memory loss was also reported. The most common side effect Triptorelin had was weight gain. Both the analogs are equally effective. Early diagnosis and treatment of the condition is essential.

Use of Triptorelin in treatment of prostate cancer.

Prostate cancer is a leading cause of death in men. Prostate specific antigen (PSA) and increase in age leads to increase in prostate cancer cases. Hormonal treatments for example-testosterone are used to manage the patients with metastatic prostate cancer. The main aim of androgen deprivation therapy (ADT) is decreasing testosterone concentration. This can be attained by surgical castration or non-surgical

castration.

The castrate testosterone concentration after removal of the prostate is < 20 ng/ dL. Triptorelin as a drug is almost 100% efficient in reaching standard castration testosterone levels. Triptorelin is essential for maintaining low levels of testosterone and increasing the overall survival rates of patients undergoing ADT.

In Poland, two sustained release formulations of triptorelin are available. Diphereline- 3.75 mg, 11.25 mg and 22.5 mg Deacetyl Depot- 3.75 mg dose. These formulations release triptorelin slowly and make the administration of the drug fairly easy. The triptorelin is surrounded in a microsphere for controlled release of the peptide. The sphere is made up of a biodegradable polymer made up of lactic and glycolic acid. The gradual decomposition of the material causes the slow release of triptorelin. cIn preclinical studies, administration of triptorelin not only decreased the testosterone levels but also caused apoptosis of some cells in the tumor. This mechanism of action by Triptorelin is that it activates tyrosine phosphatases, which in turn reverses the growth of the tumor cells.

In the studies conducted in 1990's , it has been observed in studies that men suffering from Pca when administered with Triptorelin show castrate levels of testosterone in the serum and decrease in LH levels. 50% of tumor mass shrinkage was also observed.

The efficacy of one month and 3-month Triptorelin formulation is almost equal. The sustained release formulations were tested on 14 men with Advanced PCa. After one injection, the castrate level of testosterone was obtained at mean of 22 days and remained the same for 3 months. In a study, surgical castration – orchiectomy was compared to one-month Triptorelin formulation. After one month of therapy, decrease in levels of testosterone was comparable. It was also observed that men treated with Triptorelin suffered less psychological burden. After 12 months, men administered Triptorelin had an average of 29% lesser testosterone levels.

CONCLUSIONS:

The view that peptides hold different properties as therapeutics, including appropriate pharmacokinetic profiles, low harmfulness and immunogenicity, and attractive solvency highlights, is extensively acknowledged. Since huge numbers of the old style impediments they have to go about as medication specialists are being overwhelmed by improving methods and alterations, the utilization of peptides and peptidomimetics as a helpful system is developing.

In spite of the fact that the utilization of these peptides in treatment is picking up footing, more exertion is expected to improve restorative potential. With additional investigations of the structures, associations, and elements of proteins , more peptides will be found and created. With this system, the utilization of these peptides could give great occasions to different treatments, outperforming a portion of the constraints of current treatments.

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