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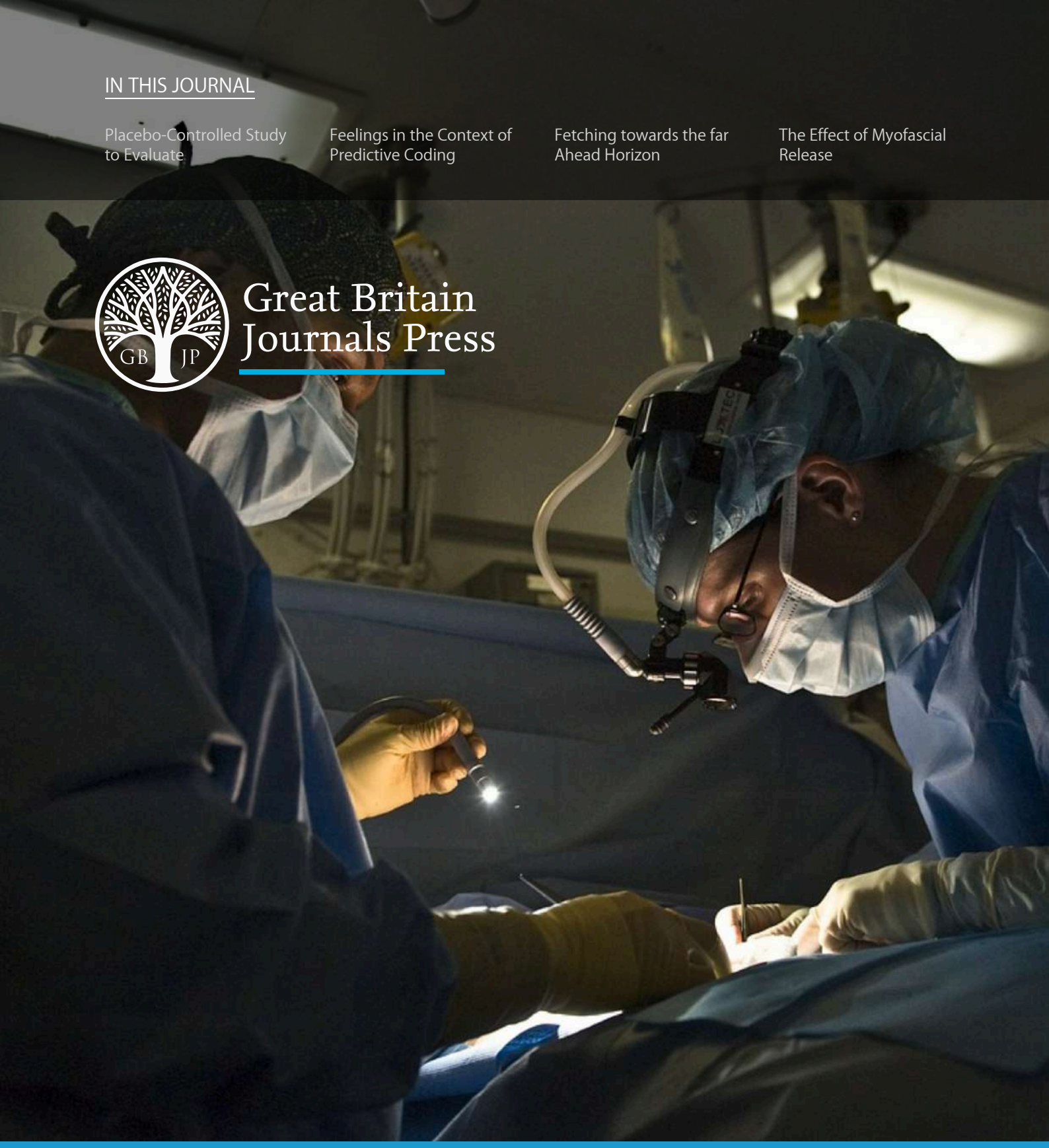

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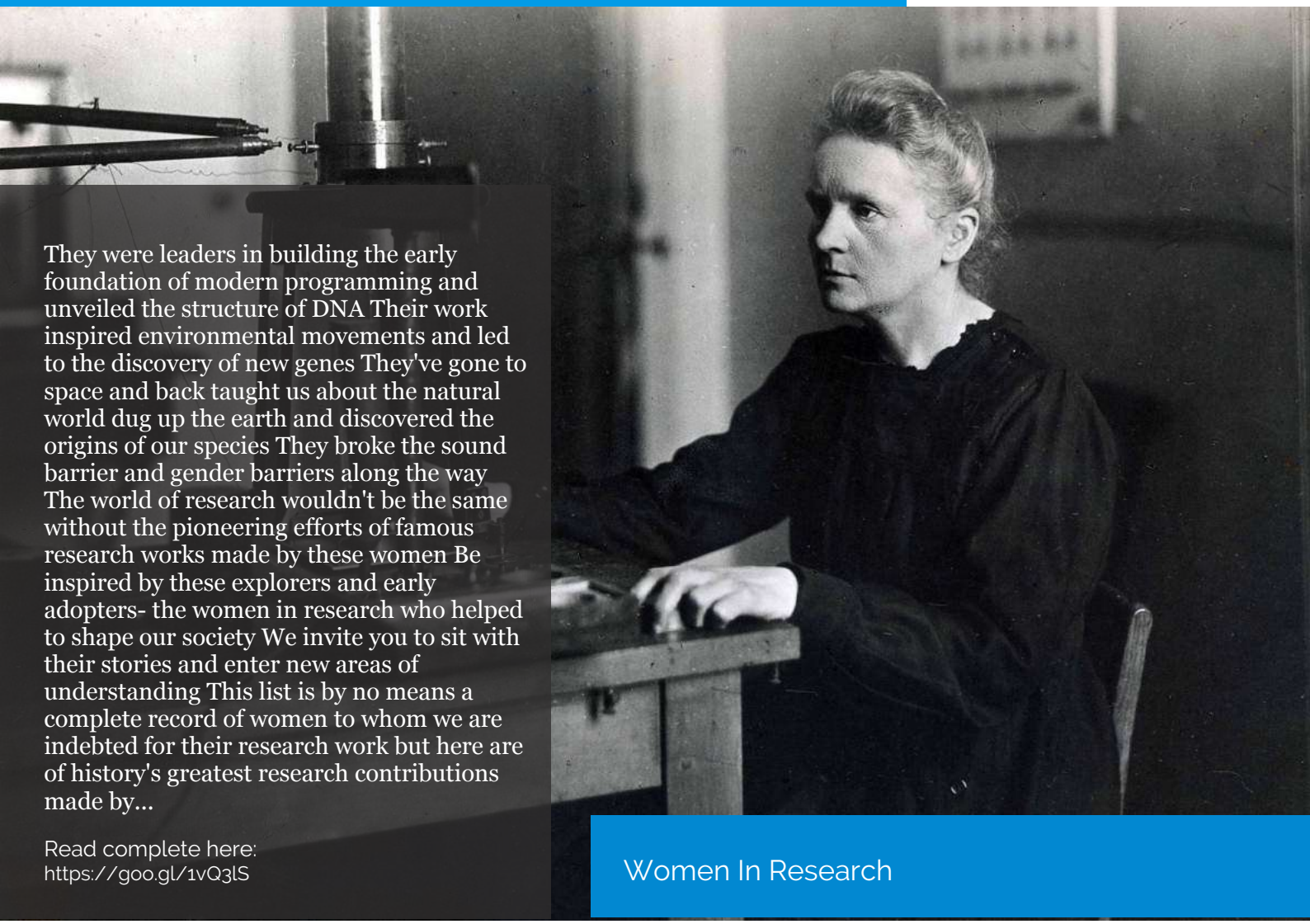

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of our species They broke the sound barrier and gender barriers along the way The world of research wouldn't be the same without the pioneering efforts of famous research works made by these women Be inspired by these explorers and early adopters- the women in research who helped to shape our society We invite you to sit with their stories and enter new areas of understanding This list is by no means a complete record of women to whom we are indebted for their research work but here are of history's greatest research contributions made by...

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Hyaluronic acid and Recombinant Enzymes Pbserum Low for the Treatment of Sagging Body Skin

Ana Toro, Carlos Lloreda, María Cristina Cuello, Diana Forero & y Jorge López-Berroa

Universidad del Norte

ABSTRACT

Body flaccidity is one of the most significant physical concerns today. Flaccidity manifests as weakened, rough skin with a noticeable loss of tone and elasticity, deviating from the aesthetic ideal. The causative factors are both intrinsic, such as the natural aging process, and extrinsic, including stress, alcohol, and sun exposure, among others. Women are the gender most prone to flaccidity and are more vulnerable to societal and media messages, leading these physiological changes to have a negative impact on their body image perception and psychological well-being.

Keywords: skin flaccidity, sagging skin, hyaluronic acid, enzymes, collagenase, recombinant.

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Hyaluronic acid and Recombinant Enzymes Pbserum Low for the Treatment of Sagging Body Skin

Ana Toro[α], Carlos Lloreda[σ], María Cristina Cuello[ρ], Diana Forero[ↀ] & y Jorge López-Berroa[¥]

ABSTRACT

Body flaccidity is one of the most significant physical concerns today. Flaccidity manifests as weakened, rough skin with a noticeable loss of tone and elasticity, deviating from the aesthetic ideal. The causative factors are both intrinsic, such as the natural aging process, and extrinsic, including stress, alcohol, and sun exposure, among others. Women are the gender most prone to flaccidity and are more vulnerable to societal and media messages, leading these physiological changes to have a negative impact on their body image perception and psychological well-being.

Here, we present a clinical, open-label study, involving 18 patients, who were treated for their flaccidity areas with Low 1.5 HA pbserum, a cocktail of recombinant enzymes, collagenase, lipase, and lyase, together with high molecular weight hyaluronic acid (HA). Our study showed that Low HA 1.5 pbserum significantly improved body flaccidity after 36 days of treatment. It was effective against skin flaccidity in 92 % of patients.It also improved firmness in 92 % of women and reduced fat in 84 %. We also measured the patient satisfaction and 93% of women were satisfied with the treatment. The product was well tolerated, permitting a good quality of life.

Keywords: skin flaccidity, sagging skin, hyaluronic acid, enzymes, collagenase, recombinant.

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I. INTRODUCTION

Body flaccidity stands out among physical concerns for individuals. This condition manifests as weakened, rough, and sagging skin, marked by a noticeable loss of tone and elasticity, deviating from the aesthetic ideal. It is particularly prevalent in areas such as the buttocks, thighs, inner legs, and arms.

The main cause of skin flaccidity is the natural aging process. Intrinsic genetic programming leads to a chronological decline in collagen and elastin production, muscle mass, and hydration[1]. Additionally, extrinsic elements accelerate cellular deterioration and aging, even among young people, by generating free radicals. Such conditions manifest in stress, smoking, and sun exposure. Ultraviolet A and B radiation specifically harm collagen and elastin fibers in the dermis, causing weakening and contributing to photoaging.Reactive oxygen species, resulting from oxidative cell metabolism, significantly influence both intrinsic and extrinsic processes [2]. Other factors preceding sagging include sedentary lifestyles, resulting in muscle mass loss; protein-deficient or sugar-rich diets that glycosylate and stiffen collagen; rapid weight loss; and prolonged exposure to hot water, which induces relaxation of skin tissues [3-5].

Women are the gender most prone to flaccidity. Apart from the inherent thinness of women's skin compared to men's, they often encounter various life situations that compromise the integrity of dermal fibers. For example, during pregnancy, the skin undergoes significant stretching, leading to

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postpartum abdominal flaccidity. Hormonal fluctuations serve as additional triggers for sagging, including changes during menstruation, pregnancy, and menopause. It is well-established that hormonal deficiencies, specifically in estrogen and androgen levels along menopause, contribute to collagen degradation, dryness, reduced elasticity, epidermal atrophy, and skin wrinkling [6].

Women are also more vulnerable to societal and media messages, experiencing strong expectations to maintain youth and thinness, especially during middle age, between 30 and 60 years old, and aging woman [7,8]. The physiological changes accompanying normal aging can distance these women from the perceived 'ideal' image, potentially increasing body dissatisfaction [7,9]. Flaccid skinmay prompt significant rejection. This can lead to a reassessment of body image and, more critically, contribute to severe emotional disorders such as depression or associated anxiety disorders [7,10].

In aesthetic practice, there are limited therapeutic alternatives for addressing skin flaccidity. Our study aims to assess the clinical efficacy of a novel product, Low HA 1.5 pbserum intradermal injection, for the treatment of sagging body skin. Additionally, we evaluate the clinical tolerance and safety of the product, together with patient satisfaction.

II. MATERIALS AND METHODS

2.1 Study design

This study was conducted as a clinical, open-label and interventional trial, carried out in 5 Colombian medical centers, with a sample of 18 patients, who were their own control. Subjects could be of either sex, aged between 18 and 80 years, and with body flaccidity. In the patient information sheet, they were warned of the possible adverse or unpleasant reactions of the product and their reversibility.

2.2 Product and Administration Schedule

The product studied was Low HA1.5 pbserum (supplied by pbserum Proteos Biotech S.L.) which consists of a 1.5 ml syringe of 0.1% sodium hyaluronate, obtained from *Streptococcus equi subsp. zooepidemicus*. A vial contains 3 recombinant bacterial enzymes: collagenase PB220, lipase PB500 and lyase PB72K; lyophilised and in different proportions. There is a vial of saline solution. The enzymes were reconstituted with the sodium hyaluronate, and the amount of saline solution required for the area to be treated. Once the enzymes are completely dissolved, they are collected with the syringe and injected into the flaccid body skin zone.

The product was administered intradermally with superficial and deep injections,according to the standard dose per area of 1ml in every 2 cm. The assessment of skin flaccidity was carried out using the Flaccidity Scale (Table 1)

Patients were administered Low HA1.5 pbserum once a week for 3 weeks: V1 Basal (day 0), V2 (day 7) and V3 (day 14). The degree of flaccidity was assessed before each injection. A final evaluation of the flaccidity was carried out15 days after the last injection: V4 (day 29).

2.3 Patient Satisfaction

Patient satisfaction measured at the last visit (V4), using a survey composed by three parts: (I) Overall appreciation and organoleptic characteristics, with a numerical scale from 1 to 7, where 1 is "I strongly dislike" and 7 is "I really like". (II) Efficacy, with a numerical scale from 1 to 5, where 1 is "Strongly disagree" and 5 is "Strongly agree". And (III) Quality of life and dermatology, with the Dermatology Life Quality Index (DLQI) scale.

Table 1: Flaccidity Scale Depending on the Body Area

Area	Scale	Definition
Arms	0	Normal
	1	Adiposity with good skin tone
	2	Loose, hanging skin without severe adiposit
	3	Loose, hanging skin with severe adiposity
Breasts	0	Normal
	1	Ptosis grade 1 or 2 or severe macromastia
	2	Ptosis grade 3, or moderate volume loss, o constricted
	3	Severe lateral roll and/or severe volume lo with laxity
Back	0	Normal
	1	Single fat roll or adiposity
	2	Multiple skin and fat rolls
	3	Ptosis of rolls
Abdomen	0	Normal
	1	Redundant skin with rhytides or moderate adiposity without overhang
	2	Overhanging pannus
	3	Multiple rolls or epigastric fullness
Flank	0	Normal
	1	Adiposity
	2	Rolls without ptosis
	3	Rolls with ptosis
Buttocks	0	Normal
	1	Mild to moderate adiposity and/or mild to moderate cellulite
	2	Severe adiposity and/or severe cellulite
	3	Skin folds
Mons	0	Normal
	1	Excessive adiposity
	2	Ptosis
	3	Significant overhanging below symphysis
Hips/lateral thigh	0	Normal
	1	Mild to moderate adiposity and/or mild to moderate cellulite
	2	Severe adiposity and/or severe cellulite
	3	Skin folds

III. STATISTICAL ANALYSIS

A descriptive statistical analysis of the results of the quantitative biometric variables at different experimental times was performed, including basic descriptive parameters (central tendency and variation) that reliably exposed the distribution of the main variable at each time. The Wilcoxon Signed Rank test [11]was used for the evaluation of the response variable Flaccidity Scale, with the aim of evaluating the clinical response of the product throughout the experimental times (V1 Basal, V2, V3, V4). The effect of the product on the values of the main variables in the statistical analyses is interpreted with reference to the initial time (V1 Basal). The Wilcoxon Signed Rank Test used in the study for data analysis are present in the wilcox. test function of the stats package of the R software. For multiple biometric measurements over time, random effects at the level of each individual have been taken into account, allowing the intercept of the models to vary randomly between individuals in the trial. The significance value established for all statistical tests in the study was $p<0.05$.

IV. RESULTS

All patients who participated in the study were women aged between 26 and 59 years, with a mean age of 46 ± 11 years, a mean weight of 61.67 ± 7.99 kg and a mean height of 162.50 ±7.51 cm. Of the 18 women who started the study, 13 completed it. The demographic data are shown in table 2.

Table 2: Demographic Data of the Sample

Patient	Demographic data			
	Sex	Age	Weight (kg)	Height (cm)
1	Woman	26	57,0	153
2	Woman	61	76,0	167
3	Woman	28	75,0	172
4	Woman	45	63,0	172
5	Woman	56	66,0	152
6	Woman	56	51,0	162
7	Woman	52	73,0	173
8	Woman	34	62,0	154
9	Woman	36	67,0	178
10	Woman	52	53,0	159
11	Woman	52	55,0	159
12	Woman	36	60,0	160
13	Woman	42	52,0	158
14	Woman	53	58,0	163
15	Woman	42	71,0	167
16	Woman	44	59,0	158
17	Woman	58	55,0	156
18	Woman	59	57,0	162
Average (SD)	100 % Woman	46,22(±10,84)	61,67(±7,99)	162,5(±7,51)

4.1 Flaccidity Scale

Throughout the treatment, the higher flaccidity categories decreased, and the lower categories increased, from 6 patients in scale 3 at V1 to 2 patients at the end of the treatment (V4) (Table 3). As a percentage, the scale 1 was 17 % at V1 and became 46 % at V4 (Fig. 1). The statistical analysis showed that Flaccidity Scale changed significantly at the last visit compared to previous visits. The confidence interval established was 95% and the counter statistic was less than 0.05 (Table 4). In figure 2 and 3 we see the visual changes in the abdominal part in two of the patients.

Table 3: Sum of the Patients with the Same Punctuation in the Flaccidity Scale along the Visits

Flaccidity Scale				
.	V1 Basal	V2	V3	V4
Grade 1	3	4	7	6
Grade 2	9	12	10	5
Grade 3	6	2	1	2
TOTAL	**18**	**18**	**18**	**13**

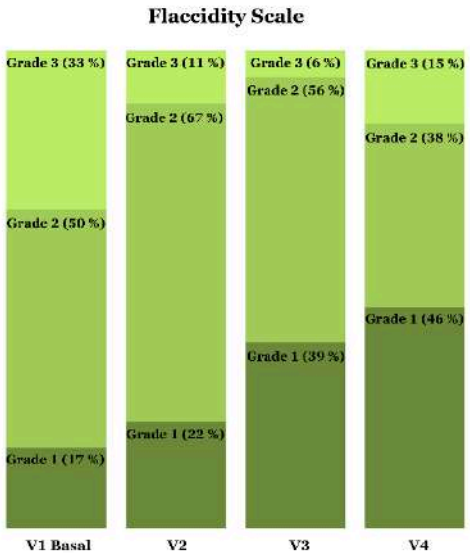

Figure 1: Percentage of Patients in each Scale along the Visits

Table 4: Wilcoxon Signed Rank Test Calculated in each Visit

WILCOXON SIGNED RANK TEST (Flaccidity Scale)				
.	V1 Basal	V2	V3	V4
V	-	10	15	21
p Value	-	0,07	0,053	0,03
Significance	-	NS	NS	S

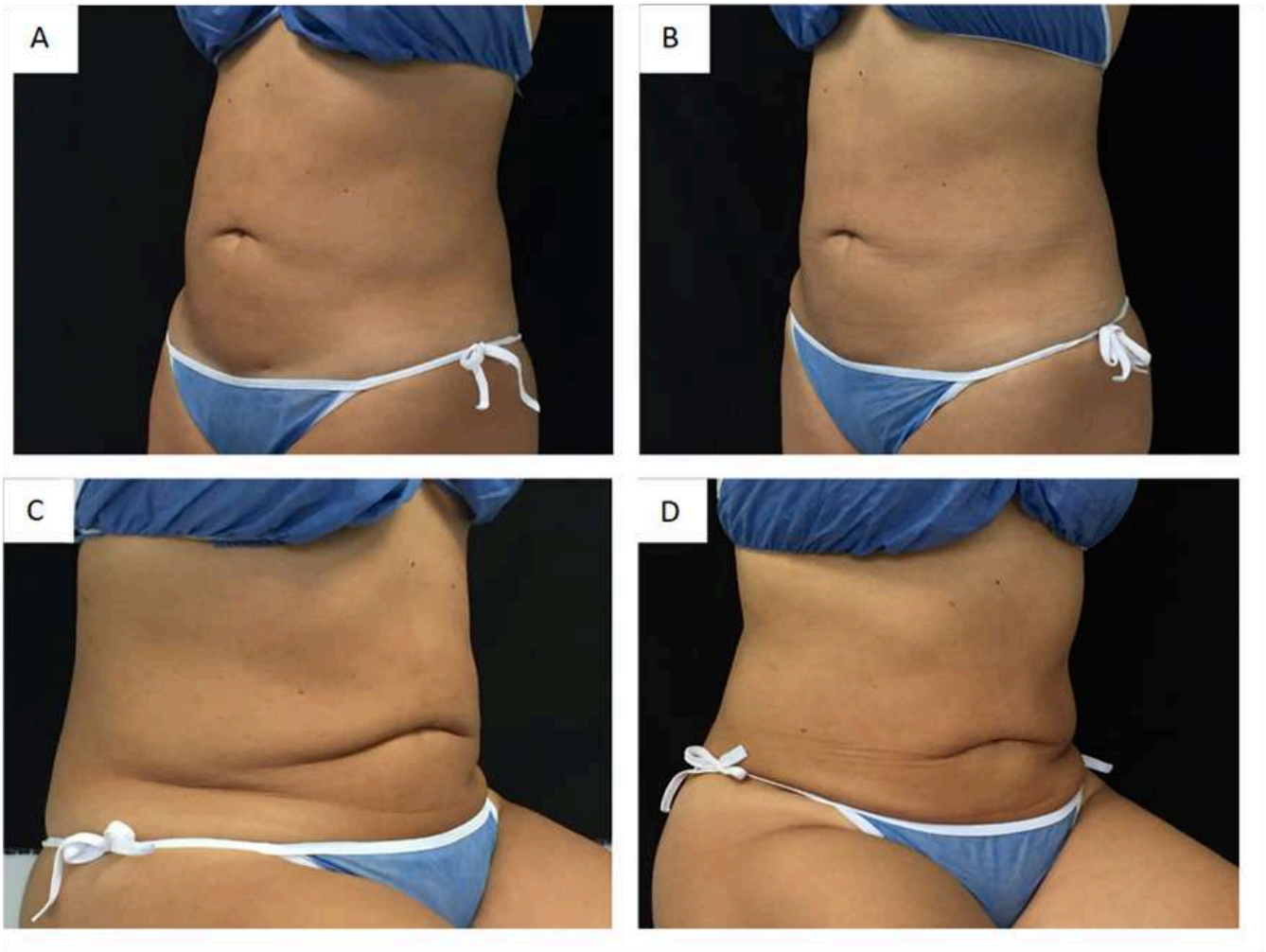

Figure 2: Patient with Abdominal Flaccidity Treated with Low 1.5 HA Pbserum. A and C Before, and B and D after the Treatment

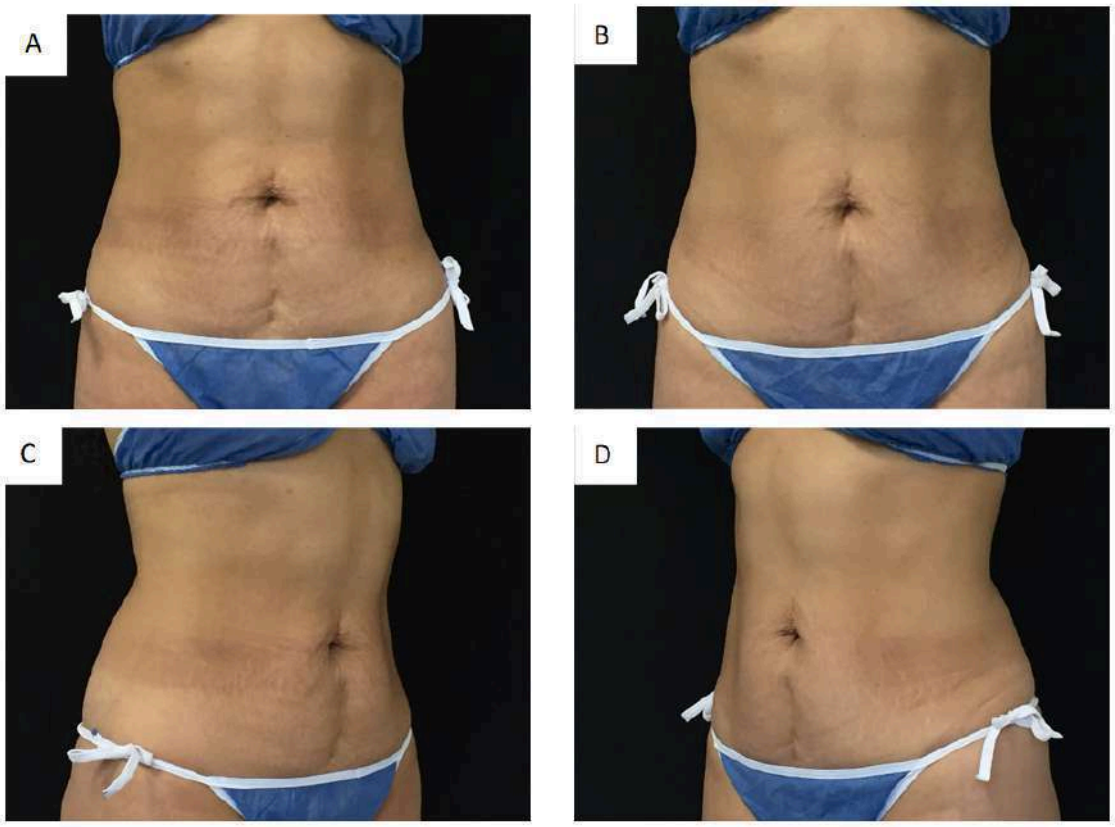

Figure 3: Patient with Abdominal Flaccidity Treated with Low 1.5 HA Pbserum. A and C Before, and B and D after the Treatment

V. PATIENT SATISFACTION

5.1 Overall Appreciation and Organoleptic Characteristics

Sixty-seven percent of patients liked the treatment very much compared to 33% who liked it moderately.

Regarding the organoleptic characteristics, 69% of the patients liked the appearance of the treatment (Fig. 4 A) very much. Twenty-two percent liked the aroma of the product very much and 67% neither liked nor disliked it (Fig. 4 B). Forty-five percent of the patients liked the extensibility of the product on the treated area very much and 36% liked it moderately (Fig. 4C). Regarding the sensation of the product on the skin:9 % liked it very much, 18% liked it moderately, 9% neither liked nor disliked it and 27% disliked it moderately (Fig. 4 D).

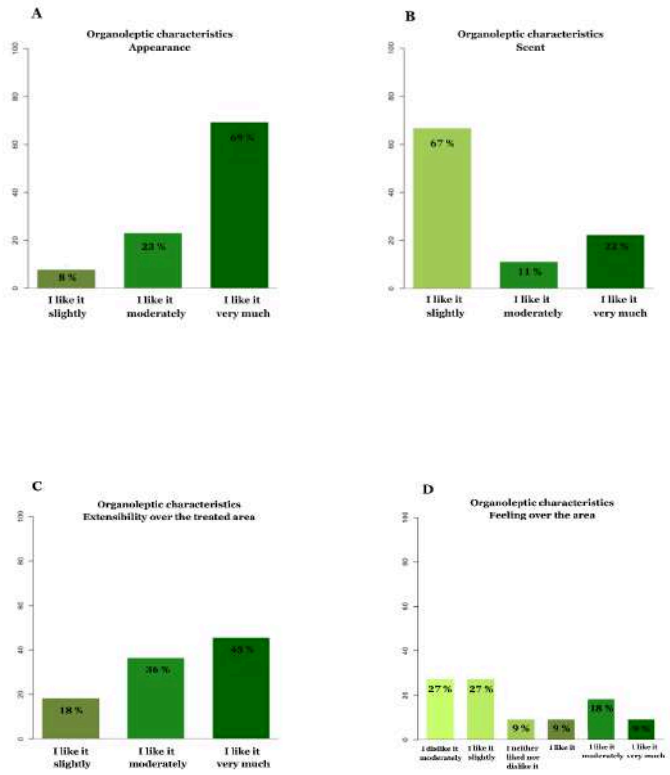

Figure 4: Organoleptic Characteristics Appreciated by the Patients. A) Appearance. B) Aroma. C) Consistency. and D) Feeling Over the Zone

5.2 Efficacy

Regarding the product's efficacy in reducing the degree of flaccidity, 54% have seen their flaccidity reduced and 38% of the patients totally agree with the reduction (Fig. 5 A). About the statement "The use of the product caused fat loss", 46% agree with it and 38% of the patients strongly agree with it (Fig 5 B). And with respect to the improvement of the degree of firmness, 54% agree with this statement and 38% strongly agree (Fig 5C).

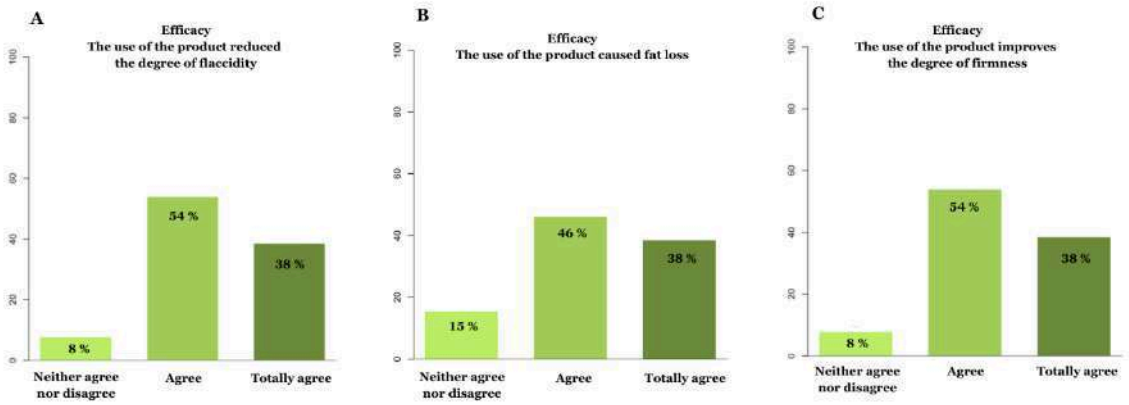

Figure 5: Patient Perception of the Product Efficacy in terms of: A) Flaccidity Improvement B) Loss of fat. C) Firmness Improvement

Overall, 62% rate the product as satisfactory and 31% as very satisfactory. And 67% of patients would use the product again and 17% are likely to use it again.

5.3 Quality of life and Dermatology

Eighty-five percent of patients did not show any unpleasant symptoms and those who did show a symptom, this was mild and transient burning at the time of application. Regarding whether patients had experienced itching, pain, or stinging, 100% had not experienced any of these symptoms in the last 7 days.

We wanted to assess whether the treatment could have influenced certain day-to-day activities and how they had felt their skin during the last 7 days using the DLQI scale. Sixty-two percent of patients had not felt uncomfortable or self-conscious because of their skin, the rest had felt only a little uncomfortable. Seventy-seven percent of the patients had no problems with shopping or housework and 15% saw no relationship between the treatment and this activity. For choice of clothes, the treatment had no influence at all for 85% of the patients but had a lot of influence for 8% of the patients. For social or recreational activities, 69% of the patients had no problems at all and 8% of the patients considered that they had a lot of problems. For sport, 85% said they had no difficulty at all, 8% had quite a lot of difficulty and 8 %did not see a link between treatment and sport.

VI. DISCUSSION

Concerns related to body flaccidity rank among the primary aesthetic worries prompting individuals to seek improvement through aesthetic clinics, aiming to enhance their physical appearance and emotional well-being. Nevertheless, it remains a challenging approach, given the limited availability of effective non-invasive therapies. Various techniques, including radiofrequency systems, lasers, infrared treatments, and specific collagen stimulators, have been explored [12-17]. However, their outcomes are at times statistically insignificant or require an extended period to see results. The quest for more therapeutic alternatives is crucial to strive for optimal and timely outcomes.

Sagging is a process in which different components of the skin can be affected. One of them is loss of skin moisture. This phenomenon is evident in skin aging, driven by hormonal changes [6]. HA emerges as a pivotal molecule that significantly influences skin moisturization. This is a glycosaminoglycan with the property to bind and retain water molecules [18, 19]. This capacity confers the functions of hydration, lubrication, space filling and the vehicle to cell migration [20]. It has been reported that, over time, one of the most dramatic changes that occurs in the skin is the progressive reduction of HA and its polymers [21, 22]. Due to all these aspects, there are currently on the market different HA fillers indicated to fill space and eliminate wrinkles on the face and neck.

Another manifestation of skin flaccidity may arise from the potential accumulation of fat. It is widely recognized that hormonal changes can result in alterations in adipocyte deposits [23]. In addition, accelerated weight loss increases the ratio of fat to protein in the skin[4]. Consequently, this fat is not adequately supported and, as a result, we observe sagging skin with loss of tone.

The most significant characteristic defining chronologically aged skin and photoaging is the reduction of fibrillar proteins, specifically types I and III collagen [24, 25]. On one hand, collagen-degrading matrix metalloproteinases are up-regulated. And on the other hand, a sustained down-regulation in collagen synthesis appears in photodamaged and chronological skin aged. Mechanisms underlying the loss of collagen synthesis are still under research. Some studies demonstrated that in severely photodamaged skin, the presence of fragmented or damaged collagen in the dermis inhibited collagen synthesis [26, 27].

Our study showed that Low HA 1.5 pbserum significantly improved body flaccidity after 36 days of treatment. It was effective against skin flaccidity in 92 % of patients.It also improved firmness in 92 % of women and reduced fat in 84

%. As for the overall sensation of the product in the skin, 54 % expressed dissatisfaction. It is understandable because the administration is through several intradermal injections. In general, ninety-three of women were satisfied with the treatment. The product was well tolerated and permitted to have a good quality of life in terms of DLQI scale.

One of the main components of Low HA 1.5 pbserum is high molecular weight HA. The superficial injections of high molecular weight HA helped to reconstitute the water level of sagging skin and to fill space to provide firmness and thus improve the appearance of the affected area. In addition, Low HA 1.5 pbserum has recombinant enzyme technology; it is composed of collagenase, lipase and lyase in different proportions. The lipase is an enzyme that helps to eliminate fat through metabolic processes[28]. In our study, the lipase could help to reduce excess sebum and localized fat but also would be a stimulator of lipid metabolism inside the adipocyte. Lipase and lyase improve the delivery of the other ingredients inside the skin. Collagenase is an enzyme inside the extracellular matrix, which has the function of regenerating collagen fibers in the dermis[29]. This fact could be promoted by degrading the damaged collagen. The result would be the production of new elastin and collagen, which would help to improve the appearance and texture of the skin, giving a firming effect.

We found some limitations in our study. Firstable, we had a small sample, which limits the treatment of the data and the statistical analysis. We currently only possess pictures of the abdominal region; it would be valuable to obtain images from other areas of the body. We only have treated women; it would be interesting to see the behaviour of the product in men skin. The study was carried out in one country, Colombia, thus the patients were Latin-Americans, which could skew the results according to race. While considering these aspects, through this study we offer a new efficacious and safety alternative based on high molecular weight HA together with recombinant enzymes technology for the treatment of sagging skin.

VII. CONCLUSIONS

Low HA1.5 pbserum, HAand recombinant enzymes technology, could be a good alternative therapy to the skin flaccidity. More studies should be done to get more rigorous data.

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Conflict of Interest

Dr. Toro, Dr. Lloreda, Dr. Cuello and Dr. Forero have no conflict of interest to declare. Dr. López Berroa is an employee of the company Proteos Biotech S. L. and he receives a salary for this purpose.

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Author Contribution

Dra. Paris contributed to the management and treatment of the patient, and the writing of the article. Dr. López Berroa contributed by advising on the indications for the treatment with the enzymes and supervising the manuscript.

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Dr. Mandyam Rangayyan Roopashree & Dr. Neelam Yadav

ABSTRACT

Introduction: As healthcare sectors are complex, it's difficult to handle the process involved in the management. Healthcare costs are increasing, so it is important to increase efficiency as well. Assessing appointment schedules and Turnaround time will help to analyze the workflow of the MRI department and optimize the processes.

Methods: The methods used were cross-sectional, prospective, descriptive, quantitative analysis, and qualitative methods. The patients for the study were selected through random sampling techniques and in-person data gathering was performed.

Results: Data was collected, and charted on an Excel tracker sheet, and in-depth analysis was performed. The tracker sheet included various study parameters like Registration Time, Waiting before changing, Changing Time, Waiting before Case history, Case History, Waiting before the scan, and MRI Scan Time. The data analysis included the average turnaround time for MRI i.e. from registration to scan was 1 hour 14 minutes.

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Discussion: The reasons that were causing the delay in the MRI department were enumerated. Reasons like carrying any metal object in the department, first preference for emergency patients, nature of the examination, and movement of the patient during the scan were studied in depth.

Application: This study provides the pattern that was supposed to be followed for scheduling patient appointments in the MRI department and to optimize the turnaround time for the patient. The possible reasons were causing a delay in the process of the MRI department by observing the current practices in the MRI department including the infrastructure, and staffing.

Keywords: optimization, turnaround time, quality, appointment schedule, efficiency.

I. INTRODUCTION

An MRI (Magnetic Resonance Imaging): One of the most common scanning techniques that are used in health care is Radiology and the Radio-diagnosis modality is Magnetic Resonance Imaging. MRI scanning is utilized in the staging of disease, medical diagnosis, and follow-up of cases without radiation exposure to the body. The received information is processed through the computer and an image is produced. The image obtained gives a detailed resolution that can detect changes that are minute and small changes in the body structure can be identified. MRI with contract plays an important role in enhancing image resolution. Contrast agents like Gadolinium are used in some of the procedures to enhance image accuracy [1, 2].

Preparation and procedure for an MRI scan:

The patient is instructed to remove all metallic objects from the body before proceeding with the MRI scan. As the patient lies in the close atmosphere in the MRI machine, the patient is expected to be still for accuracy. The patient is informed to breathe normally and stay calm and relaxed. Throughout the process of scanning, a continuous interaction is kept with the MRI technician. The patients are informed that throughout the scan there will be loud, repetitive clicking noises. In some cases, contrast injection might be needed to enhance the images. The

scanning time for an MRI varies as per the body parts involved [2].

History of MRI:

Nuclear Magnetic Resonance (NMR) is the spinning atom effect, which was first noticed in the late 1930s. Dr. Raymond Damadian 1971 discovered that MRI is beneficial for the diagnosis in the medical field. The whole-body MRI scanning was built and in the year 1977 was named Indomitable [3].

About the MRI department of the Tertiary care hospital:

Location:

- The MRI department is located on the first floor of the hospital. MRI scanning procedures are done on this floor.
- Reports are collected on the Ground floor (from the reports section).

Layout:

The layout of the hospital includes:

1. MRI machine room- 2
2. Console room-2
3. Consultant radiologist room- 2
4. Nursing Station
5. Changing room
6. Bed
7. Sofa

Machine:

1. There are 2 MRI machines (Magnetom Spectra) along with 2 console rooms.
2. The machine is 3 Tesla with automatic protocol.
3. SYNGO software is used for processing.

Manpower allocation:

Table 1: Manpower Allocation of the Mri Department of the Tertiary Care Hospital

Sr. No.	Personnel	No. of Personnel	Shift Timings
1	Consultant Radiologists	2	8:00 AM-4:00 PM, 9:00 AM-5:00PM
2	Resident duty doctors	4 (2-2)	8:00 AM-6:00 PM, 12:00 PM-8:00 PM
3	Nurses	3	8:00 AM-4:00 PM, 10:00 AM-6:00 PM, 2:00 PM-10:00 PM
4	MRI Technicians	7 (3-3-1)	8:00 AM-4:00 PM, 2:00 PM-10:00 PM, 11:00 PM-7:00 AM
5	Health care Assistants	3	7:00 AM-3:00 PM,11:00 AM-7:00 PM,1:00 PM-9:00 PM
6	Office attender	1	9:00 AM- 6:00 PM

The appointment scheduling process in the MRI department:

- Appointment is scheduled according to the slots available in the EHIS (Enterprise Healthcare Information System).
- Medium of appointment scheduling:

1. At the nursing station of the MRI department.
2. At the radiology reception of the imaging department.
3. Through call centers.

- There are fixed slots for EHC and IPD patients i.e. from 5:00 P.M.-7:00 P.M.
- By 10:30 AM EHC slots are confirmed or released for other patients.
- Receptionists make two calls to the OPD appointment patients one day prior at 9:00 AM and 1:00 PM to confirm their visit for the MRI scan.

Reports:

- Reports are dispatched to the patient the next day of the scan after 5 pm on the ground floor at the dispatch counter.
- Cases are diagnosed by the radiologist and they give the notations of impressions and

confirmed diagnosis on Dictaphone which is further typed and reviewed by them.
- CD is also given along with the reports.
- IPD patient reports: The morning patient gets the reports on the system by the end of the day.
- For evening patients, a provisional report is updated on the system the by end of the day.

II. AIMS AND OBJECTIVE

Aim:

- Study of appointment Scheduling pattern of the MRI department
- Analysis to optimize Turn Around Time.

Objectives:

- To study the appointment scheduling pattern of the MRI department and further analyze it.
- To study the Turn Around Time (TAT) of the MRI department.
- To study the reasons for the delay in the MRI department.
- To study the infrastructure and physical facility of the MRI department.
- To study the staffing pattern of the MRI department.

III. REVIEW OF LITERATURE

The Article proposes two approaches namely Online and Offline for scheduling the appointment, depending upon the availability of a batch of patients waiting for it. The author also discusses the benefits and cons of each of the alternatives. A comparison of this alternative is to provide insights into work efficiency and effectiveness. It also describes the work distribution and equity and optimization of resources. This also provides input on work discrimination power [4].

The author of the article demonstrates the functionality of types of stages in the scheduling process. He bifurcates the scheduling process into two categories of systems.

1. Single Stage, where the patient queues for a single level of the process.
2. Multistage, where the queuing includes stages like registration, examination, and checkout [5].

The study included data from 904 outpatients. He concluded based on the study that lack of education and low awareness regarding the instruction process were the key reasons [6]. Based on the study conducted to analyze the importance of turnaround time in radiology, it was been observed by the authors that, “Routine MRI studies are performed on weekends and the report is interpreted on a weekday[7]. With the available data that is analyzed, the conclusions can be drawn by optimized MRI results saving the time of 5 minutes 28 seconds per patient [8]. Improving the turnaround time is the objective to make the MRI process more efficient and effective. The author states that having a planned operation with the use of new technology by implementing interoperability within the departments can reduce the turnaround time for the patient[9]. After conducting the study on appointment patterns for patient scheduling, it is observed that continuous improvement of the performance of the diagnostic services and be enhanced by minimizing the cancellation probability. By summating all the capacity of the clinic and by increasing the clinic's overall performance, it can be compared with only a 5% cancellation probability [10]. After conducting the study for the scheduling process of patients for tests, the results show that multi-appointment scheduling problems are becoming increasingly popular. Multi-appointment scheduling problems in hospitals are currently gaining progressively more momentum in the academic literature [11]. As Lin states, “To summarize, this article addresses the following questions for a multiphase and multi-server queueing system with stochastic factors to optimize the (weighted average) objectives of patient waiting time, resource over time, and waiting room congestion”[12]. Hans Lugnegård, product manager for Sectra's Diagnostic Imaging Suite said "Achieving quick report turnaround times requires an efficient RIS/PACS solution with closely integrated tools, such as speech, intelligent display protocols, 3D visualization, and other clinical applications," [13]. The importance of the MRI scan has increased in

the healthcare and medical departments. How powerful a magnetic field along with strong radio waves helps to take clear and detailed pictures of the human body organ. This supports the detection of any abnormalities in the organs and thus saving the life [14]. The article discusses the advancement of MRI implementation in medical studies. Concepts such as MRI scanning for Lungs have now become possible and have helped doctors in the treatment of many diseases. FDA clearing 7T MRI system has added an advantage for detailed neurological diagnosis [15]. Using MRI scan scheduling effectively to reduce process time is the main objective to attain efficiency. Many factors like the sudden and randomly arriving emergency patients, and reasonable slaking time slots provide better performance. It is important to reserve the slot time for these emergency cases and revise the turnaround time. Setting an appropriate time for every individual scan becomes crucial in managing the time [16]. In the radiology department, quick attendance and delivery of reports always improve the patient's psychological suffering in a place where emotional and physical torture has occurred[17]. By understanding the patient turnaround time which is directly propositional to the quality of services rendered to minimize the turnaround time[18]. Most of the patients demand efficiency and timeliness in service delivery of medical care because of manual entry of appointment schedule and the situation is irritating due to long waiting hours at the health care services set-up. There is a need for an integrated healthcare system that will provide efficient care for the benefit of patients. By offering an online appointment system, the system can be improved to provide access to health care services[19]. The model followed: Patient service times are determined and the slot times are considered that be equal to appointment slot allocation. Accordingly, the nature of the problem is combinative, which is used. Given the combinatorial nature of this problem, they use a lateral thinking approach to solve it. This work very much improves by providing a united optimization framework for general problems and by developing algorithms to solve them efficiently [20]. There are tangible quality elements such as patient waiting times and waiting room congestion. A well-designed and properly structured appointment schedule will minimize the waiting times for the patients. Online appointments and scheduling when incorporated can minimize patient dissatisfaction due to long waiting times[21]. The appointment schedule will have gaps when it is underutilized as of the doctor's time[22]. Patient satisfaction is enhanced with the initiation of treatment[23]. Various studies define waiting time and access time in various manners and ways[24]. Argues that sufficient staff makes sure that patients are not rescheduled or booked for later dates due to the staff taking offs and duty leaves. This is another factor that contributes to the long waiting time[25].

IV. METHODOLOGY

a) *Place of study:* Kokilaben Dhirubhai Ambani Hospital, Mumbai

b) *Population:* Patients scheduled for an MRI scan appointment.

c) *Unit of study:* The study included 167 waiting patients who were scheduled for an MRI Scan and the MRI department of the tertiary care hospital. Patients were selected for the study through Random sampling.

d) Variables:

- Patient footfall (expected inflow)
- Type of scan
- Scan time

e) Parameters of the study:

- Registration Time
- Waiting before changing
- Changing Time
- Waiting before Case history
- Case History
- Waiting before the scan
- Scan Time.

f) *Data collection:* The data for the study was collected through observation and EHIS.

g) *Method:* Observation, cross-sectional, prospective, Quantitative method, and Qualitative methods were used.

h) *Tools used:*

- Microsoft Excel
- Enterprise Healthcare Information System (EHIS) i.e. the HMIS of the hospital was used for reference, under the supervision of the management of the MRI department.

i) *Reliability of data:* In-person data gathering.
j) *Period of study:* The study was done for 23 days i.e. from 4th June to 26th June 2019.

Analysis:

A. Data Collection
B. Data Presentation and Data Analysis

1. *Data collection:* The project was conducted in the MRI department of a tertiary care hospital located in Mumbai city. The duration of the study was from 4th June to 26th June 2019 for a period of 23 days. The turnaround time was calculated for MRI procedures by random sampling. The study included 167 patients from the MRI department, were Outpatient Department, the Inpatient Department, Accident and Emergency, Executive Health Checkups, and Walk-in patients. A tracker sheet was devised for recording the time taken by each patient at different points in the process.

Process:

The data were collected at different stages i.e. the time required at different stages was noted:

- When the patient was registered
- When the history was documented
- When the patient is asked to change
- When the scan is performed.

The waiting time was noted at different points (before history, before the change, before the scan)

Process Flow For Opd, External, And Ehc.

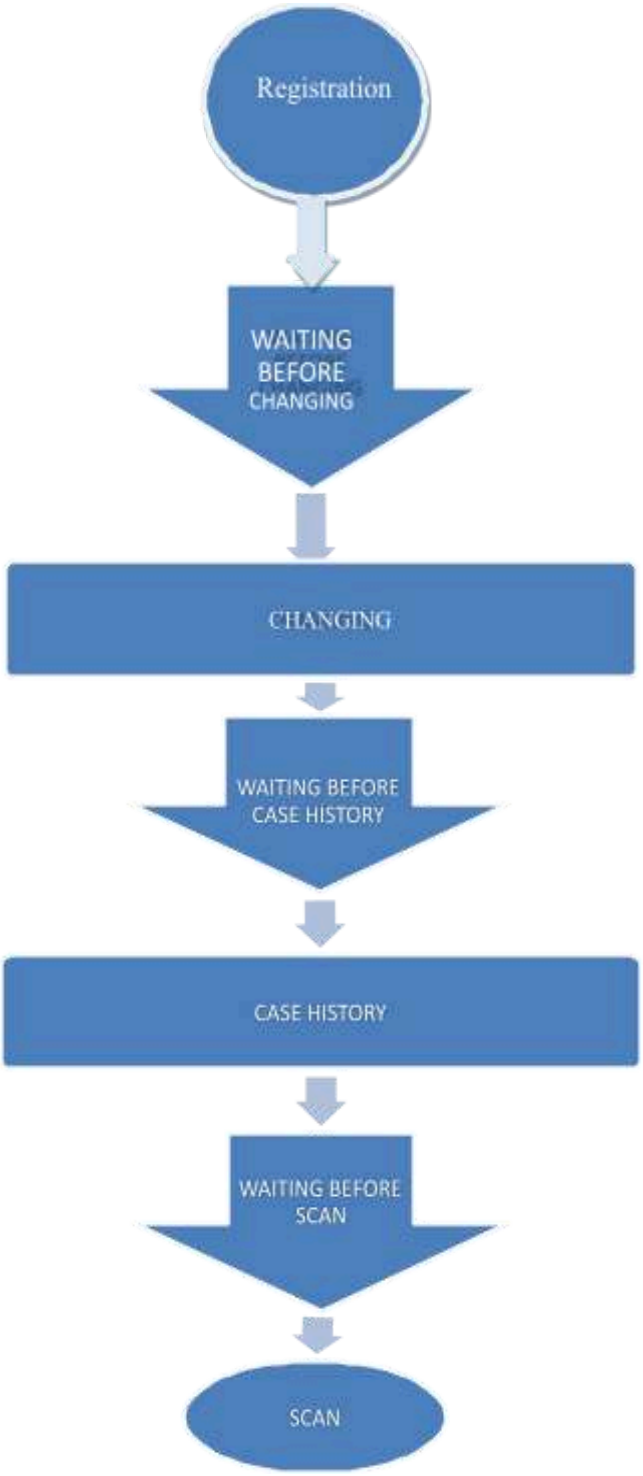

Figure no. 1: Process flow for OPD, External, and EH

Process Flow for in-Patient Department and Accident and Emergency.

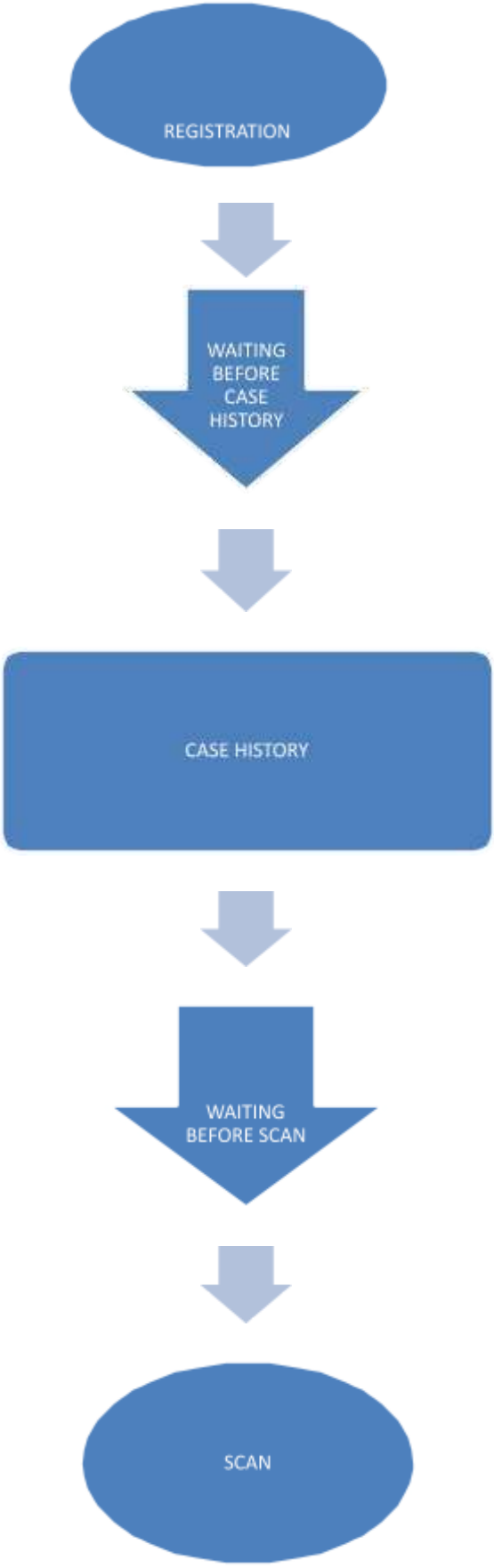

Figure no. 2: Process flow for In-Patient Department and Accident and Emergency

A. Data Analysis and Data Presentation.

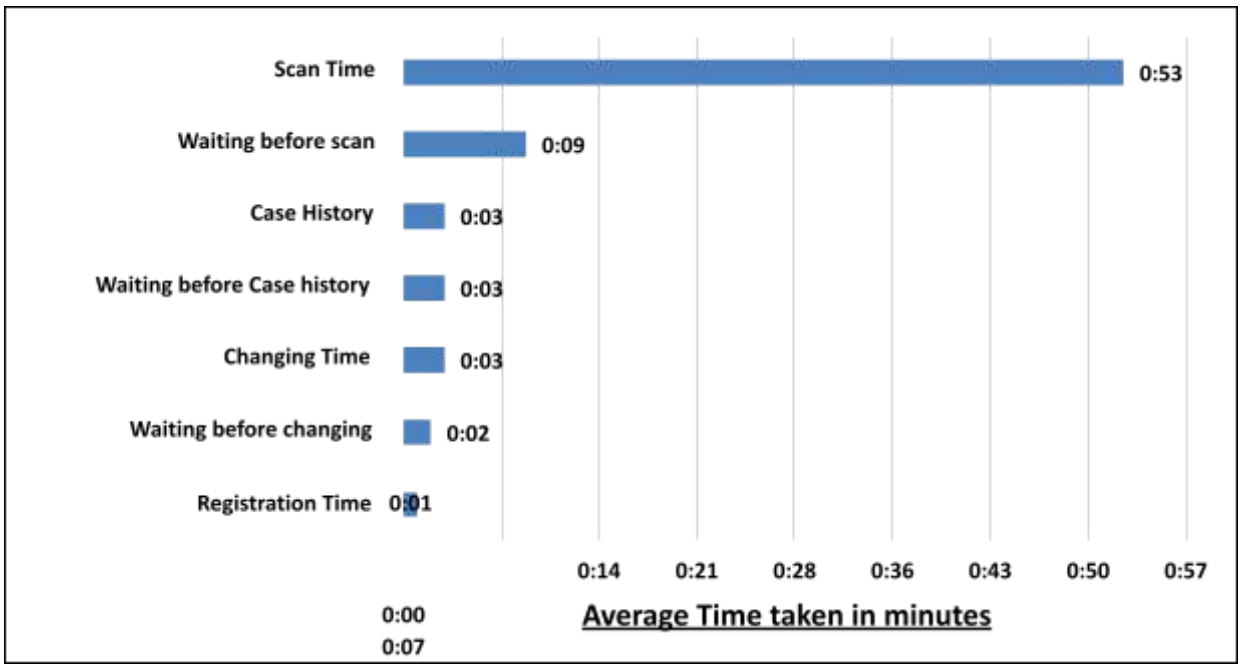

Figure.no. 3: Average Time Taken for MRI OPD Scan

Table 2: Average Time Taken for MRI OPD Scan

Process	Average Time Taken in Minutes
Registration Time	0:01
Waiting before changing	0:02
Changing Time	0:03
Waiting before Case history	0:03
Case History	0:03
Waiting before scan	0:09
Scan Time	0:53
Total time	1:17

Data Interpretation: The above graph shows the average total time required to complete the whole process for MRI OPD patients from registration to scan completion i.e. Turnaround time is 1 hour 17 minutes.

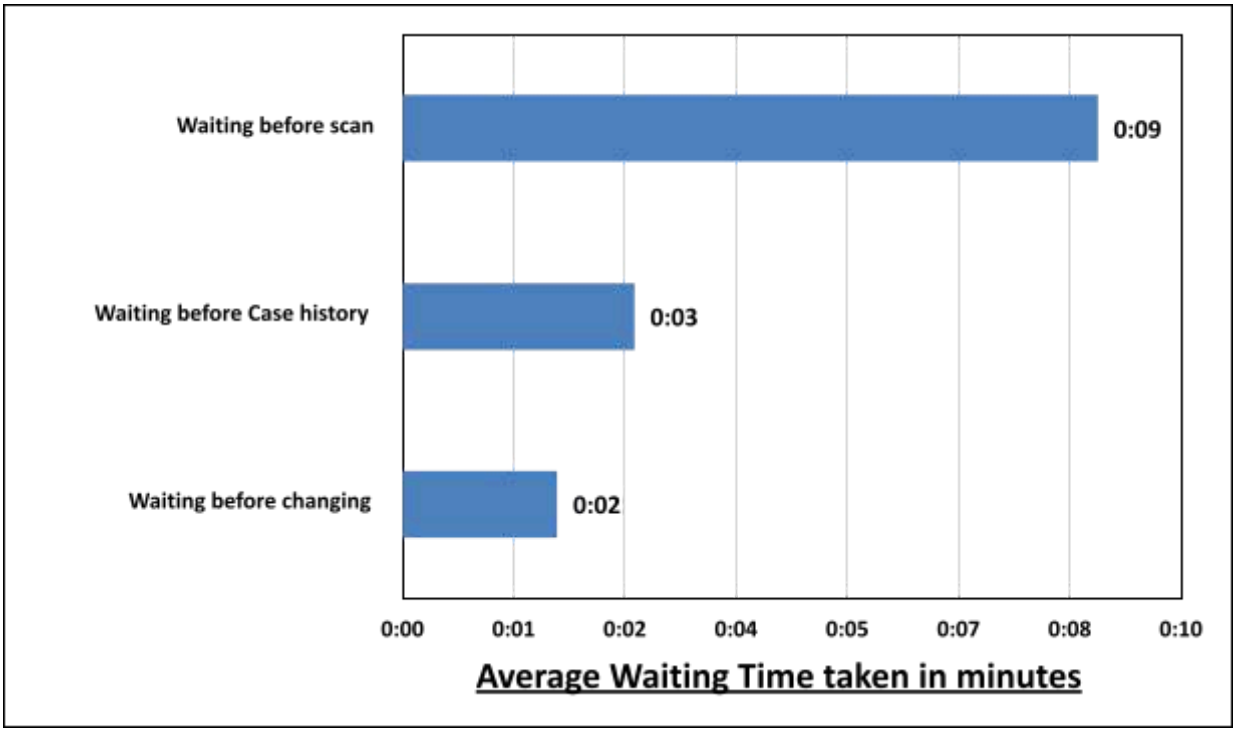

Figure no. 4: Average Waiting Time at Different Points for MRI OPD

Process	Average Waiting Time Taken in Minutes
Waiting before changing	0:02
Waiting before Case history	0:03
Waiting before scan	0:09
Total waiting time	0:14

Table 3: Average Waiting Time at Different Points for MRI OPD

Process	Average Waiting Time Taken in Minutes
Waiting before changing	0:02
Waiting before Case history	0:03
Waiting before scan	0:09
Total waiting time	0:14

Data Interpretation: The above graph shows that the average waiting time for MRI OPD patients is the highest before the scan i.e. 9 minutes and the shortest is before changing i.e. 2 minutes and the total waiting time is 14 minutes.

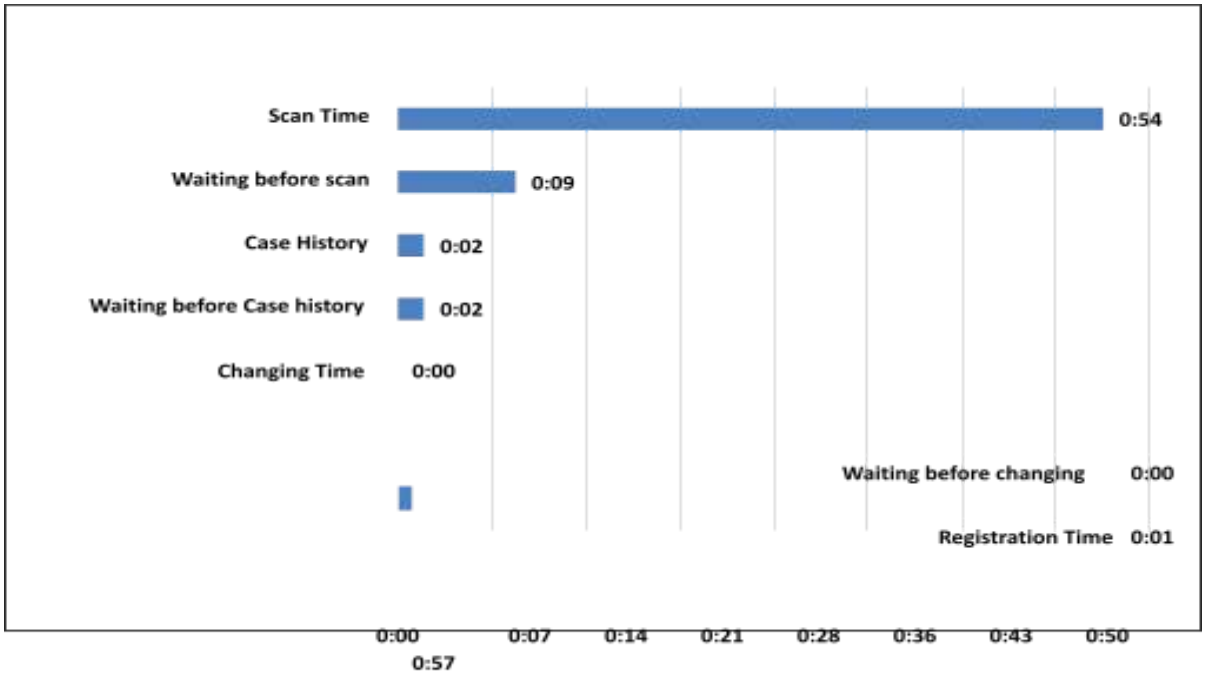

Figure no. 5: Average Time Taken for MRI IPD Scan

Table 4: Average time Taken for MRI IPD Scan

Process	Average Time Taken in Minutes
Registration Time	0:01
Waiting before changing	0:00
Changing Time	0:00
Waiting before Case history	0:02
Case History	0:02
Waiting before scan	0:09
Scan Time	0:54
Total time	1:09

Data Interpretation: The above graph shows the average total time required to complete the whole process for MRI IPD patients from registration to scan completion i.e. Turnaround time is 1 hour 9 minutes.

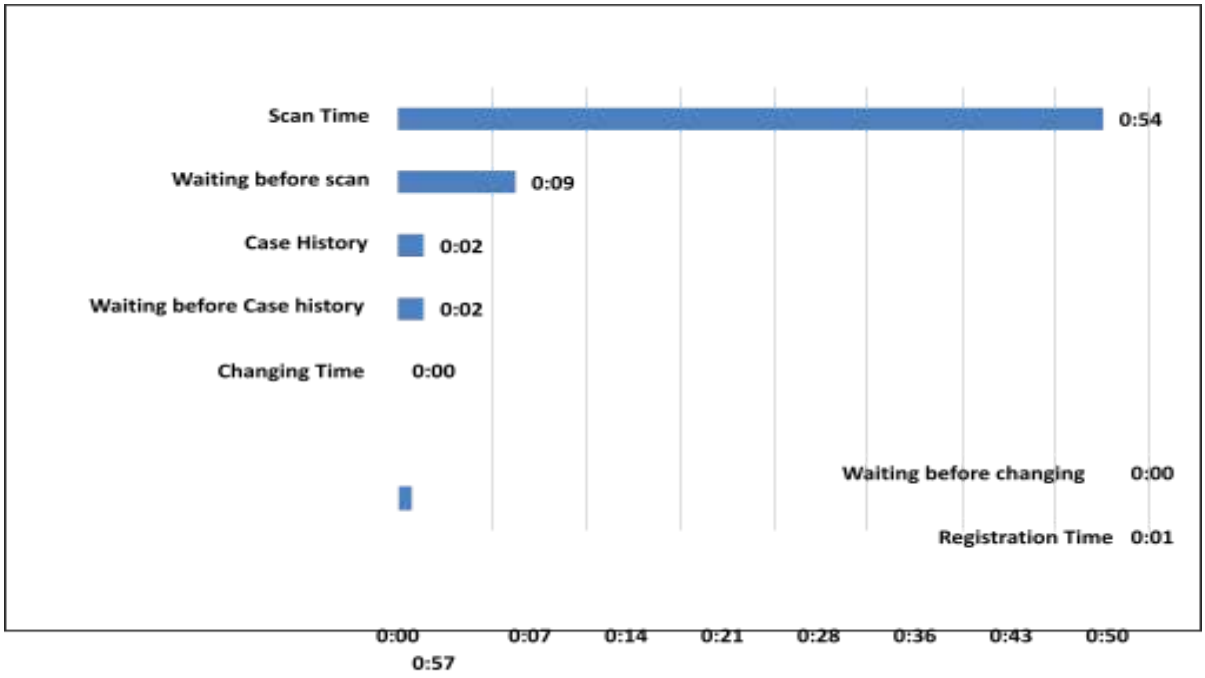

Figure no. 6: Average Time Taken for MRI IPD Scan

Table 5: Average Time Taken for MRI IPD Scan

Process	Average Time Taken in Minutes
Registration Time	0:01
Waiting before changing	0:00
Changing Time	0:00
Waiting before Case history	0:02
Case History	0:02
Waiting before scan	0:09
Scan Time	0:54
Total time	1:09

Data Interpretation: The above graph shows the average total time required to complete the whole process for MRI IPD patients from registration to scan completion i.e. Turnaround time is 1 hour 9 minutes.

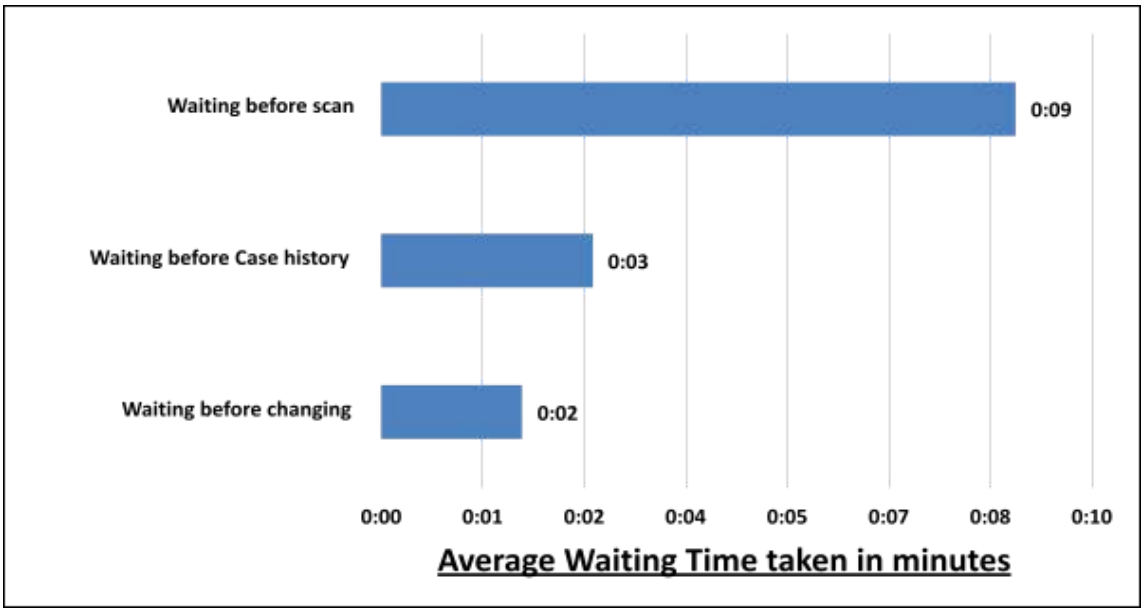

Figure no. 7: Average Waiting Time at Different Points for MRI IPD

Table 6: Average Waiting Time at Different Points for MRI IPD

Process	Average Waiting Time taken in minutes
Waiting before changing	0:00
Waiting before Case history	0:02
Waiting before scan	0:09
Total waiting time	0:11

Data Interpretation: The above graph shows that the average waiting time for MRI IPD patients is the highest before the scan i.e. 9 minutes and the shortest is before changing as IPD patients need not change before the scanning. The total waiting time for MRI IPD patients is 11 minutes.

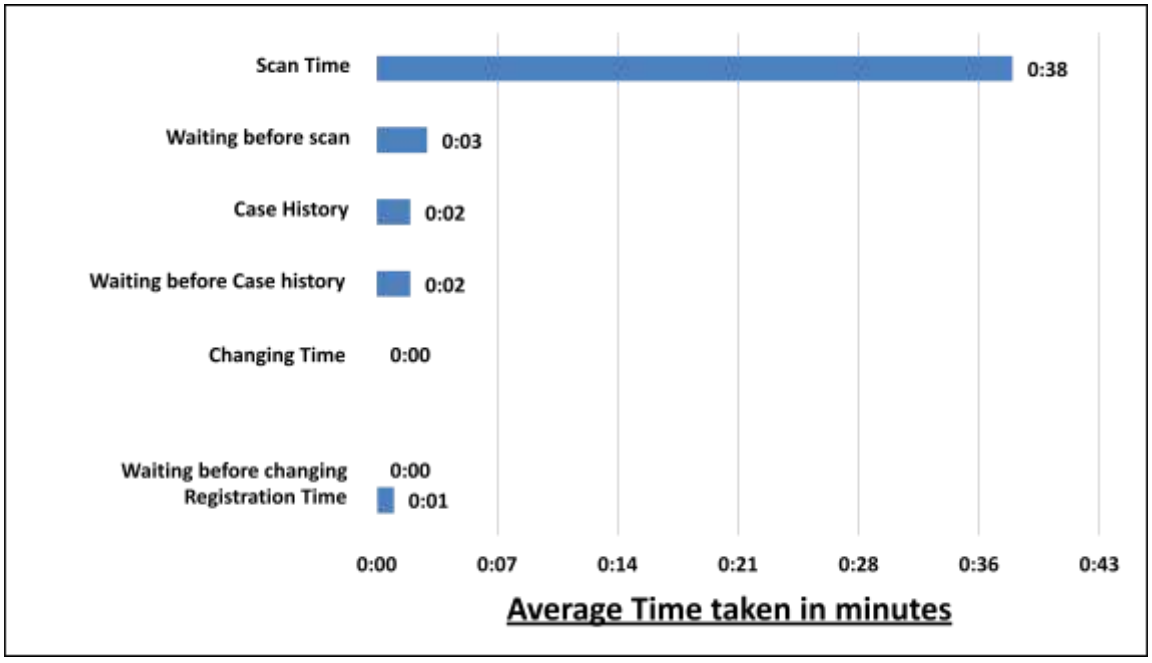

Figure no. 8: Average Time Taken for MRI A & E scan

Table 7: Average Time Taken for MRI A & E scan

Process	Average Time taken in minutes
Registration Time	0:01
Waiting before changing	0:00
Changing Time	0:00
Waiting before Case history	0:02
Case History	0:02
Waiting before scan	0:03
Scan Time	0:38
Total time	0:48

Data Interpretation: The above graph shows the average total time required to complete the whole process for MRI OPD patients from registration to scan completion i.e. Turnaround time is 48 minutes.

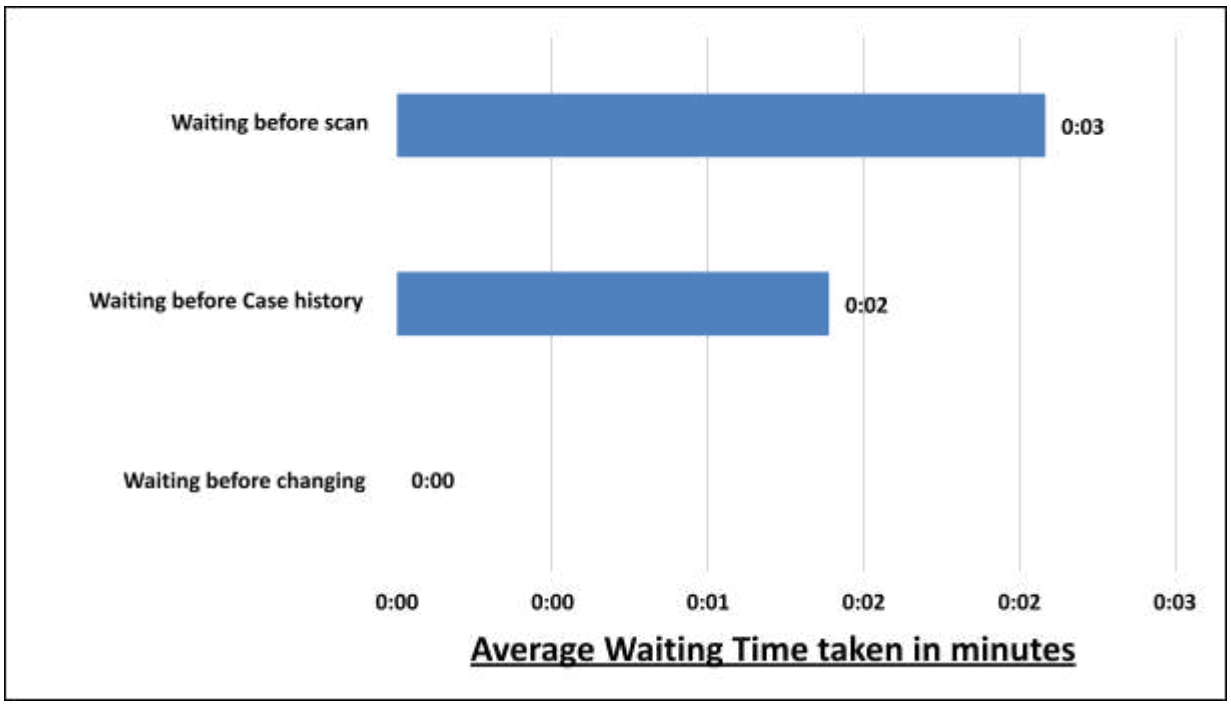

Figure no. 9: Average Waiting time at Different Points for MRI A & E

Process	Average Waiting Time Taken in Minutes
Waiting before changing	0:00
Waiting before Case history	0:02
Waiting before scan	0:03
Total waiting time	0:06

Table 8: Average Waiting Time at Different Points for MRI A & E

Data Interpretation: The above graph shows that the average waiting time for MRI A&E patients is highest before the scan i.e. 3 minutes and the shortest is before changing as A&E patients need not change before the scanning. The total waiting time for MRI IPD patients is 6 minutes.

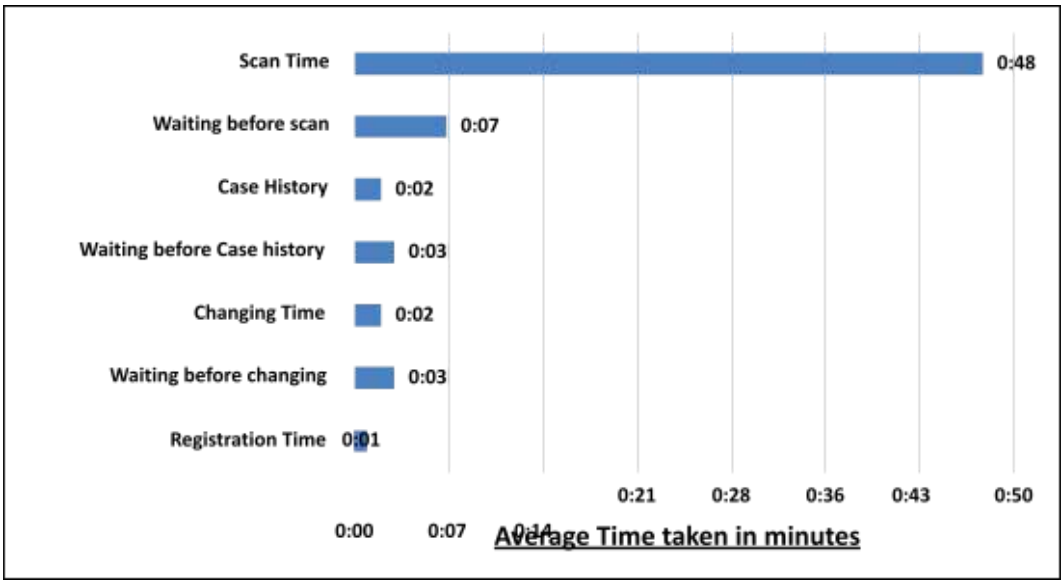

Figure no. 10: Average Time Taken for MRI Walk-in Scan

Table 9: Average Time Taken for MRI Walk-in Scan

Process	Average Time Taken in Minutes
Registration Time	0:01
Waiting before changing	0:03
Changing Time	0:02
Waiting before Case history	0:03
Case History	0:02
Waiting before scan	0:07
Scan Time	0:48
Total time	1:09

Data Interpretation: The above graph shows the average total time required to complete the whole process of MRI Walk-in patients from registration to scan completion i.e. Turnaround time is 1 hour 9 minutes.

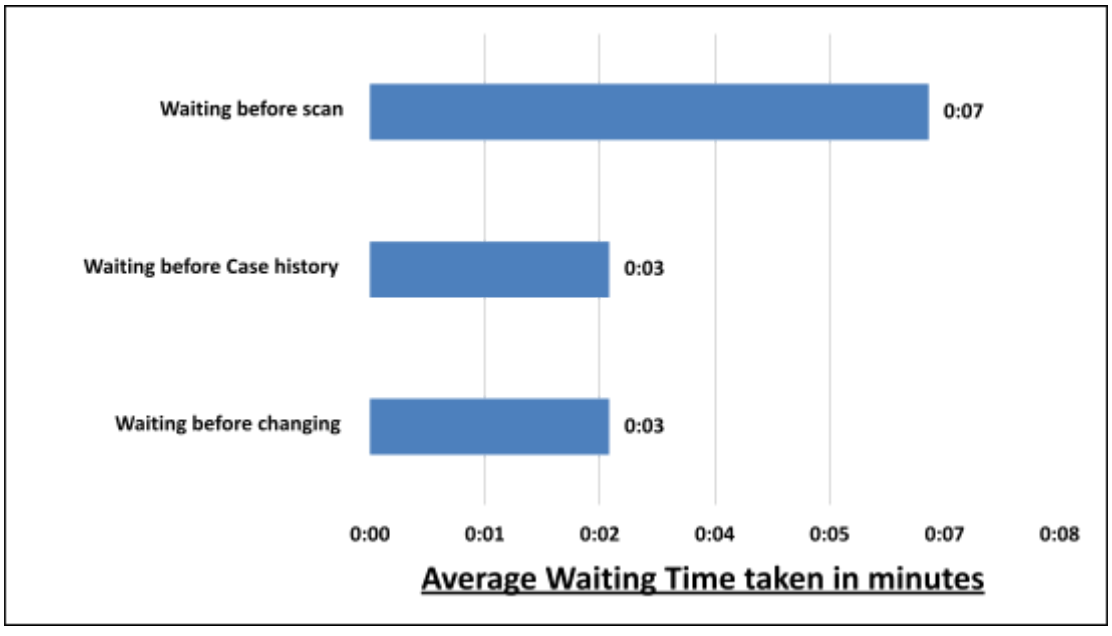

Figure no. 11: Average Waiting Time at Different Points for MRI Walk-in

Table 10: Average Waiting Time at Different Points for MRI Walk-in

Process	Average Waiting Time taken in minutes
Waiting before changing	0:03
Waiting before Case history	0:03
Waiting before scan	0:07
Total waiting time	0:14

Data Interpretation: The above graph shows that the average waiting time for MRI Walk-in patients is the highest before the scan i.e. 7 minutes and the shortest is before changing i.e. 3 minutes and the total waiting time is 14 minutes.

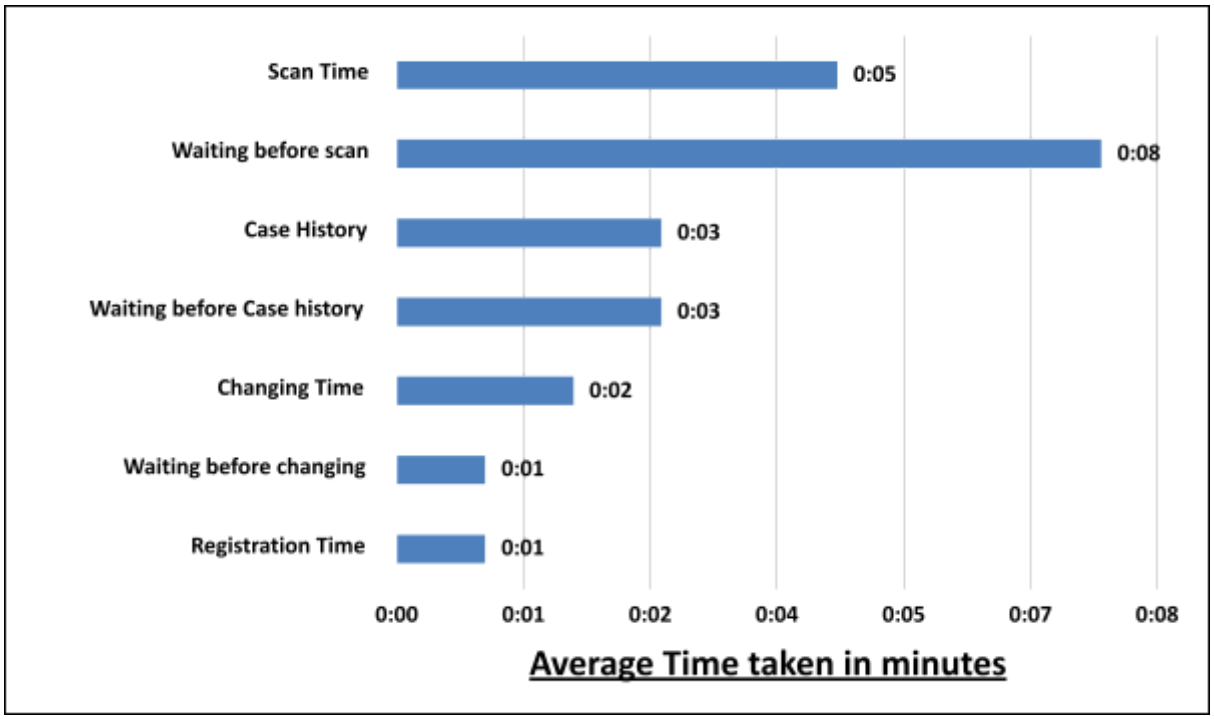

Figure no. 12: Average Time Taken for MRI EHC

Table 11: Average Time Taken for MRI EHC

Process	Average Time taken in minutes
Registration Time	0:01
Waiting before changing	0:00
Changing Time	0:00
Waiting before Case history	0:03
Case History	0:03
Waiting before scan	0:06
Scan Time	0:42
Total time	0:58

Data Interpretation: The above graph shows the average total time required to complete the whole process for MRI EHC patients from registration to scan completion i.e. Turnaround time is 58 minutes.

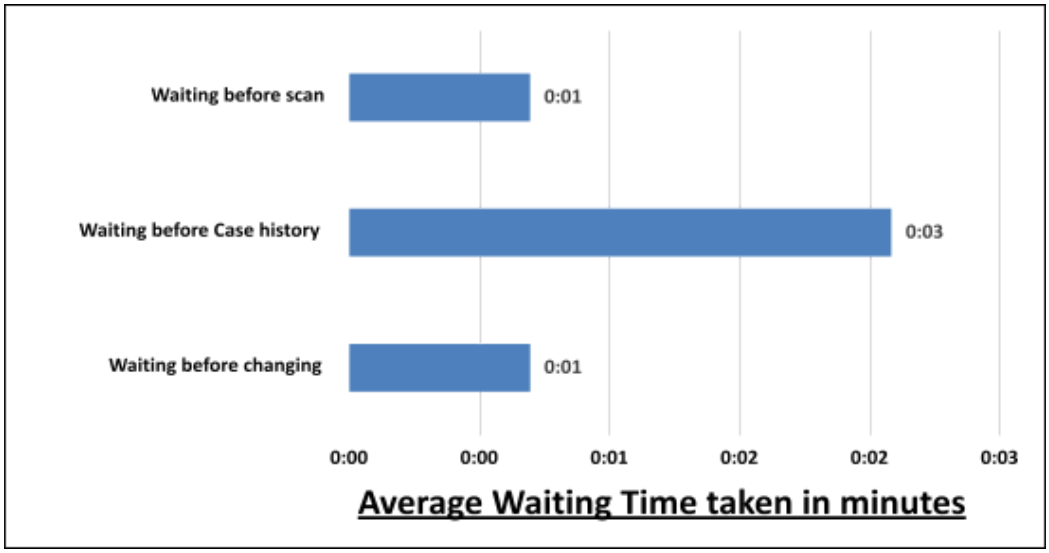

Figure no. 13: Average Waiting Time at Different Points for MRI EHC

Table 12: Average Waiting Time at Different Points for MRI EHC

Process	Average Waiting Time Taken in Minutes
Waiting before changing	0:00
Waiting before Case history	0:03
Waiting before scan	0:06
Total waiting time	0:09

Data Interpretation: The above graph shows that the average waiting time for MRI EHC patients is the highest before the scan i.e. 6 minutes and the shortest is before changing as EHC patients need not change before the scanning. The total waiting time for MRI IPD patients is 9 minutes.

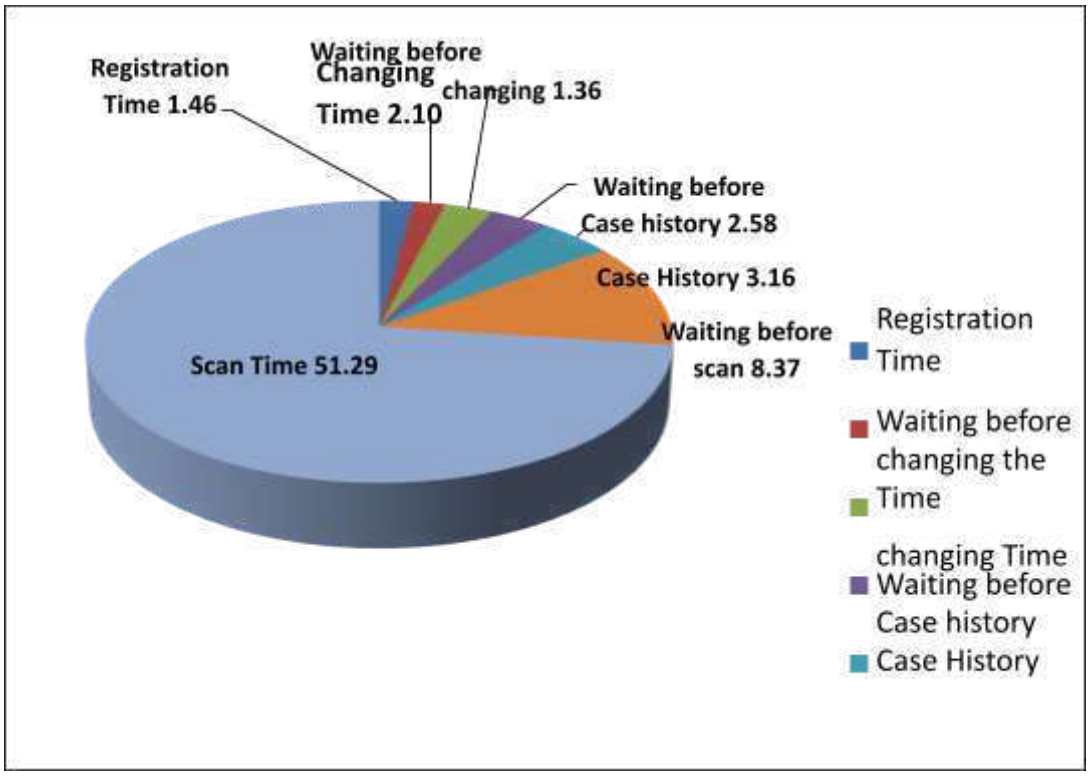

Figure no. 14: Average of Total Time Distribution (in minutes)

Data Interpretation: The above pie chart represents the average total time distribution in minutes. Delays mostly occur because of the long waiting time before the scan due to improper appointment scheduling.

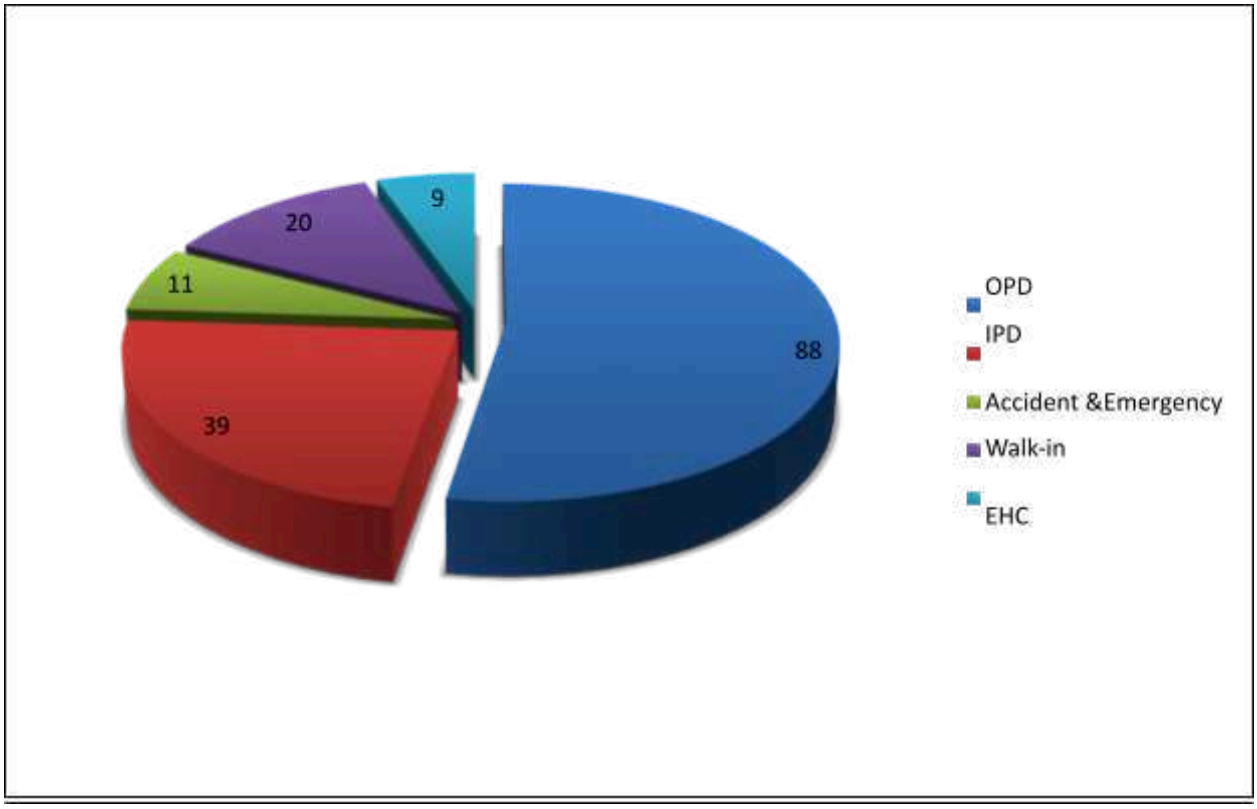

Figure no. 15: Number of Patients in Each Category

Data Interpretation: The above pie chart shows that the maximum number of patients are from the OPD followed by IPD then Walk-in then A&E and the minimum number of patients are from the EHC.

V. DISCUSSION

The average time taken by an OPD patient at every stage to complete all the processes i.e. from registration to MRI scanning. Knowing this average time for this entire process can be considered as an important factor while scheduling an appointment for an OPD patient and giving the slots accordingly.

The average waiting time is taken by an OPD patient before changing clothes, before case history, and before the scan. By knowing this we can check for places where there is more waiting and the reasons for this waiting so that the delays can be avoided or minimized. This will improve patient satisfaction.

The average time taken by an IPD patient at every stage to complete all the processes i.e. from registration to MRI scanning. Knowing this average time for this entire process can be considered as an important factor while scheduling an appointment for an IPD patient and giving the slots accordingly.

The average waiting time is taken by an IPD patient before changing clothes, before case history, and before the scan. By knowing this we can check for places where there is more waiting and the reasons for this waiting so that the delays can be avoided or minimized. This will improve patient satisfaction. IPD patients are not required to change clothes as they are already in hospital clothes and hence changing time is eliminated.

The average time is taken by an A&E patient at every stage to complete all the processes i.e. from registration to MRI scanning. Knowing this average time for this entire process can be considered as an important factor while

scheduling an appointment for an A&E patient and giving the slots accordingly.

The average waiting time is taken by an A&E patient before changing clothes, before case history, and before the scan. By knowing this we can check for places where there is more waiting and the reasons for this waiting so that the delays can be avoided or minimized. This will improve patient satisfaction. A&E patients are not required to change clothes as they are already in hospital clothes and hence changing time is eliminated.

The average time taken by a Walk-in patient at every stage to complete the process i.e. from registration to MRI scanning. Knowing this average time for this entire process can be considered as an important factor while scheduling an appointment for a Walk-in patient and giving the slots accordingly.

The average waiting time is taken by a Walk-in patient before changing clothes, before case history, and before the scan. By knowing this we can check for places where there is more waiting and the reasons for this waiting so that the delays can be avoided or minimized. This will improve patient satisfaction.

The average time taken by an EHC patient at every stage to complete the process i.e. from registration to MRI scanning. Knowing this average time for this entire process can be considered as an important factor while scheduling an appointment for an EHC patient and giving the slots accordingly.

The average waiting time is taken by an EHC patient before changing clothes, before case history, and before the scan. By knowing this we can check for places where there is more waiting and the reasons for this waiting so that the delays can be avoided or minimized. This will improve patient satisfaction. EHC patients are not required to change clothes as they are already in hospital clothes and hence changing time is eliminated.

The pie chart helps us to understand the average total time distribution in minutes at every stage in the process including all categories of patients. This gave an average turnaround time for all categories of patients.

The number of patients categorically. We understood the appointment scheduling for each category, the maximum time delays for each category and further what can be done to make processes lean category-wise using recommendations that follow.

Challenges:

The data collection from department MRI had to be specific and the turnaround time had to be measured appropriately. This required proper knowledge and awareness regarding the data collection and data analysis. There are sequences of events that require proper coordination. The challenge was to ascertain the job role of each and proper monitoring of the same.

The duration was very less and short. The data needed to be refined as per the requirements. There were delays mostly in the daytime only and not during the night timings. So data collected was not very significant at night times.

Limitations:

This study was conducted in a single department and one unit of the hospital.

- The study was conducted for 6 months duration.
- No other department or unit is involved in the data collection.

VI. CONCLUSION

A. The average turnaround time for MRI (from registration to scan) is 1 hour 14 minutes.

B. The following are the reasons leading to the delay in the turnaround time in the MRI department of a tertiary care hospital:

- If the patient carries any metal object in the department, they have to remove it before entering the scan room, which takes time.
- When the emergency patient arrives, they give the first preference. The appointment patients are made to wait for a long time as it causes delays in the entire procedure.
- Longer waiting times may also be experienced where the nature of the

examination requires immediate additional workup such as in the case of contrast studies.

- The appointment patient arrives late.
- IPD patient is transferred late to the MRI department.
- Last-minute adjustments due to the cancellation of the appointment patient.

VII. RECOMMENDATIONS

- OPD patients are to be communicated 20 minutes before their appointment time to complete the billing, changing, and case history process and avoid delay in the scan.
- Confirmation calls are to be performed by the nurses if the appointment patient does not reach 20 minutes early so that an alternate patient (IPD/EHC/A&E) can be scheduled in case of cancellation.
- One of the MRI rooms has been dedicated to OPD patients and another one to IPD, EHC, and A&E patients.
- As IPD, EHC, and A&E patients are already present in the hospital, they can be called 20-30 minutes before the completion of the previous scan (considering the Porter availability) to maintain a continuous flow of patients and minimize waiting time for the next patient.
- 1 porter can be assigned specifically to the MRI department.
- Considering 1 hour slot for 1 patient, on 2 MRI machines approximately 26-28 patients can be done per day. So by avoiding the delays, 2-4 patients can be increased each day.

Conflict of interest: NIL

Source of funding: NIL

Ethical clearance: Not applicable and not required. (As these do not involve any of the patient's information directly, ethical clearance is not needed).

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Feelings in the Context of Predictive Coding – Some Affective Psychology Reflections on the Human Form of Being

Lutz Goetzmann, Rainer Krause, Michael Meyer zum Wischen, Roxana Assadi, Barbara Ruettner & Adrian M. Siegel

ABSTRACT

Feelings play an increasingly important role in psychoanalysis and neuroscience. Following some general reflections, we introduce the concept of predictive coding or anticipatory simulation. Within this framework, feelings are a constructed judgements on inner simulative states. Both feelings and language have the task of investing inner states with meaning and rendering this meaning communicable. Feelings are conscious; they constitute the first form of phenomenal consciousness. This scientific approach can easily be formulated as part of Lacanian metapsychology. Thus, for instance, the Markov blanket can be understood as a function of the Real, and the theory of predictive coding sheds light on the characteristics of the Imaginary. Phenomena such as transference, countertransference or projective identification can also be better elaborated against this interdisciplinary backdrop.

Keywords: affects; predictive coding; simulation; markov blanket; RSI paradigm.

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ABSTRACT

Feelings play an increasingly important role in psychoanalysis and neuroscience. Following some general reflections, we introduce the concept of predictive coding or anticipatory simulation. Within this framework, feelings are a constructed judgements on inner simulative states. Both feelings and language have the task of investing inner states with meaning and rendering this meaning communicable. Feelings are conscious; they constitute the first form of phenomenal consciousness. This scientific approach can easily be formulated as part of Lacanian metapsychology. Thus, for instance, the Markov blanket can be understood as a function of the Real, and the theory of predictive coding sheds light on the characteristics of the Imaginary. Phenomena such as transference, countertransference or projective identification can also be better elaborated against this interdisciplinary backdrop.

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I. FEELINGS IN THE ENLIGHTENMENT

The concept of feeling took root in the German-speaking area over the course of the 18th century. This discovery of feelings was the foundation of individual experience, social communication and civic coexistence (Fleig 2019, p. 33). Like "taste" and "hearing", the term "feeling" was originally used to designate the external perception: Feeling belonged to the sense of touch (Fleig 2019, p. 34).[1] Throughout the Enlightenment, the concept of feeling underwent an expansion of psychological meaning: It became more focused on internal sensations and subjectivity. Thus, feeling migrated from the skin to the inner perception of the body. Although oscillation between external sensory perception and internal sensation remained thoroughly characteristic of developments in the 18th century (cf. Scheer 2001, p. 630), it was Kant in his *Critique of Judgement* (1790) who undertook to "consolidate and systematise the various approaches to reflection on feelings to combine subjective perception, reflection, and aesthetic feeling in his concept of aesthetic judgment" (Fleig 2019, p. 34). Kant differentiated aesthetic feeling from the previously prevailing understanding of feeling as an external sensory perception and elevated this feeling to a reflexive capacity (Scheer 2001, p. 648 ff.). At the same time, feelings shared between individuals were seen as the basis of sociality and sociability. Feelings have retained this key position in our culture to this day and have even gained importance in the humanities and sciences as part of an "affective turn" (Angerer 2019, p. 56). Here, psychoanalysis, and Lacanian psychoanalysis in particular, was accused of neglecting feelings. On the other hand, Lacan had proposed a differentiated theory of anxiety and further affects (in Seminar X, Lacan 2016 [1962/1963]). With this in mind, we want to incorporate the present-day scientific perspective on affects and predictive coding into a model based on the RSI paradigm

[1] The English word "feeling" has a longer history than the German term *Gefühl* and can be traced back as far as Shakespeare (ca. 1600) and Chaucer (ca. 1400) (Fleig 2019, p. 33).

with the registers of the Real, Symbolic and Imaginary (Lacan, 2021). We are convinced that developments in affective research concerning e.g. the construction of emotions (Feldman Barrett 2017, 2020), the Theory of Predictive Coding and the Theory of Prediction, Assumption and Simulation (Friston, 2013; Solms & Friston 2017; Solms, 2022, Feldman Barrett 2017, 2020) are outstandingly well suited to creating a bridge between psychoanalytic ideas and neuroscientific findings. We aim to develop a theory of feelings considering both sides of the coin – i.e. the ideal (psychoanalytical) side and the material (neuroscientific) side.

The ontological background to our reflections is as follows: Spinoza believed that spirit and matter are attributes of a single substance. This observation can also be found in Leibniz's theory of monads. Within the framework of such a "dual-aspect monism", Hegel distinguished between idea (spirit) and matter (nature); however, he understood spirit and nature as two sides of the same coin. Thus, this substantial coin encompasses both the Ideal (i.e., the Immaterial: the soul and the spirit), as well as matter (i.e., the Material: nature and the body (Hegel 2010, § 389). Nature encompasses mechanics and physics as well as our living body including the neuronal networks and excitations which are kick-started by hormones, minerals and neuropeptides. From the perspective of the Ideal, nature and the body are both the Outer and the Other. Nature and the body are ideas "in the form of Otherness" (Hegel 2010, § 247; Orman 2015, p. 523). We highlight this Hegelian trope because nowadays it plays an outsize role in the neurosciences regarding the Theory of Predictive Coding. Although matter is the sensorially Perceptible which is characterised by temporo-spatiality (Hegel 2010, § 261 Z), it can only be thought of in the registers of the Ideal.

From this idealistic perspective, only the Ideal is real – as if there were no reality but subjective reality. From a Lacanian perspective, this ideal side of materiality is composed of the dimensions of the Real (R), the Symbolic (S) and the Imaginary (I):

- The Real is the Non-Represented and Indeterminate; it is unconscious. Although it exists, it is non-existent for us, because it is non-represented.[2] Occasionally, the Real is equated with the Traumatic, but it should not be limited to it. On one occasion, Hegel (2010, § 401 Z) speaks in connection with the soul, which forms the deeper layers of the subjective mind, from simple sensations that he terms unconscious. We therefore describe the Real as the register of unconscious sensations. These sensations are distinguished from conscious or repressed-unconscious thoughts, which belong to the imaginary- symbolic register (cf. Soler 2016, p. 57). In this respect, the Real is everything Ideal that is not a thought. Sensations are translatable to the register of the Imaginary. Later on, they can be determined symbolically, i.e. linguistically.
- The Imaginary is the Sensory in the form of images, noises or sounds, smells and tastes, but also in the form of feelings and internally or externally perceived haptics. Feelings are also imaginary thoughts. Additionally, we expand the Imaginary by adding the dimension of the Atmospheric and the Phenomenal. We call feelings that spread in a space (i.e. that go beyond the boundaries of one's body) "atmospheric". The atmosphere is therefore the affective vibe in an architectural or scenic space. The Imaginary, and hence the atmosphere, are initially "phenomenal". "Phenomenality" means preverbal-conscious experience (in the sense of the Greek *φαινομεναι* – "something appears"). The phenomenon appears as a visual image, acoustic sound, smell, taste, tactile touching, feeling or atmosphere (cf. Demmerling 2021). Imaginary phenomena are characterised by

[2] The Real is also deemed to be the "impossible". This means that something is not only possible (*potentia*) but actually existent (*actus*). In this respect, the Real is "impossible". It does not belong to the realm of possibilities. "Impossible", however, also means that it cannot be thought of: Its representation is impossible. The Real eludes symbolisation. The "impossibility of the Real" means "it exists but cannot be represented".

their pure, nonverbal presence. They lose their phenomenality as soon as they are determined or named by the Symbolic, which is discursive-linguistic. The Real is the Pre-Phenomenal, and the Symbolic is the Post-Phenomenal. Thus, the Real exerts an effect on the Phenomenal, i.e. the Phenomenal is posited by this "pheno-real effect". The Pheno-Real is an effect, i.e. it is a fundamental condition of further thinking. It is the experiential core of thought.

- The Symbolic is the Linguistic, insofar as words (i.e. signifiers) convey a mental meaning or sense. The sound of the voice is just as imaginary as the graphic design of a letter. Words that contain a meaning or sense, however, belong to the register of the Symbolic. Words and their combinations are learned in childhood. Language then yields more complex, discursive word combinations such as laws. Linguistic signifiers can determine the Phenomenal. In this case, the linguistically determined Imaginary loses its phenomenality. We limit ourselves here to the point of view that the Symbolic is linguistic, and that the symbolic order is only effective within and through language (cf. footnote 15).

Figure 1: Summarises our reflections. It shows matter (M) and the three registers of the Ideal: the Real (R) as the Non-Represented, the Imaginary (I) as the Sensory in the form of images, sounds, smells, tastes, feelings and internally or externally perceived haptics, and the Symbolic (S) as language, words, signifiers; the Imaginary is expanded by the quality of the Phenomenal (Non-Linguistic) and Atmos- pheric (feelings in space and time). The line denotes a substance or structure - in any case, an underlying element from which the Material and Ideal arise (e.g. as thunder and lightning arise from electricity; cf. Solms, 2022, p. 302). Lacan (1998, p. 150 f.) describes matter as a *registre biologique*, i.e., as a biological order. In this respect, there is a material exterior that is the biological body and a material exterior that is the organic and inorganic world outside of this body. The biological register is the material side of the Ideal, i.e., of the Real, Imaginary and Symbolic:

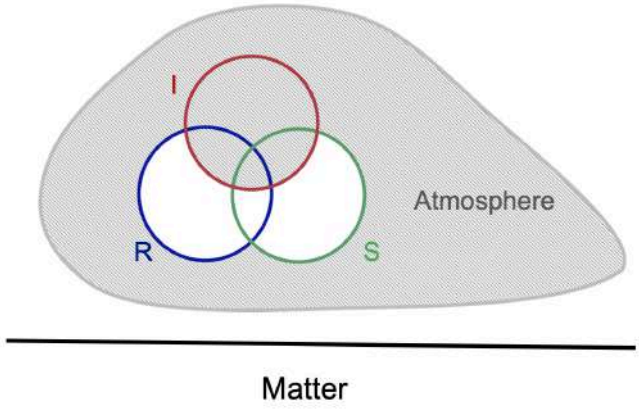

Figure 1: Matter (M), among other things in the form of the biological register, as well as the three registers of the Ideal: the Real (R), Symbolic (S) and Imaginary (I), with atmosphere as a feeling projected into space. The Phenomenal of the Imaginary or the Atmospheric is shaded

Let us now elucidate various psychology-of-affect findings and theories made available by the neurosciences and then relate these to the outlined psychoanalytical model.

II. WHAT ARE FEELINGS?

1.1. The question of essences and their physiological correlates

When we examine what feelings are from the perspective of empirical research, we discover the following points of view: feelings are states that

occur due to the influence of drives or cognitive processes. They are mainly conceptualised as reactions (Krause 2012, p. 179).[3] Freud (1895, p. 457) described affects as "valve-like discharge channels". Their function was to regulate the drives. Affects are expressed in the facial muscles or the voice (Krause 2012, p. 177). They are both perceived and responded to by others. In this respect, affective systems firstly form a sort of interface between various subsystems of the organism and the environment (Scherer, 2000). Secondly, affective development is divided into the ability to encode and decode affects. Tomkins (1962, 1963) proposes a corresponding taxonomy according to the social functions of the affects. The following types of affects exist: 1) social affects, such as mourning, joy, rage and shame; 2) information-processing affects, such as surprise and interest; and 3) distress affects, such as fear and disgust. Panksepp and colleagues defined seven basic emotions: SEEKING, LUST, CARE, PLAY, FEAR, RAGE/ANGER, SADNESS/PANIC (Panksepp 1998; Panksepp *et al.* 2016). These affective states trigger chains of action that are characterised by varying degrees of complexity: Flight and attack actions, for example, require very complex motor actions, while vomiting or spitting represent chiefly reflexive responses.

Lisa Feldman Barrett (2020, p. XV) thinks that a major upheaval is currently occurring in our understanding of feeling and spirit. In previous conceptions, it was assumed that every emotion had a specific and innate essence that differed from other essences. On a material level, certain areas of the brain were considered responsible for the origin of emotions. In addition, there was said to be a typical correlate in the body (in the form of a "fingerprint") common to all variants or instances of a specific emotion. This correlate supposedly expressed itself in one particular expressive behaviour (Feldman Barrett 2017; Feldman Barrett 2020, p. 158). By contrast, Feldman Barrett advocates the thesis that a single category of emotion could arise in various areas of the brain. She argues that many variants could emerge in terms of physical correlates. A specific facial expression (e.g., wide-open eyes meant to signal fear) would then instead be said to correspond to a cultural stereotype conveyed by videos, comic books or cartoons (Feldman Barrett 2020, p. 11). Furthermore, she asserts that bodily reactions to emotions are generally very similar to one other, so there are no bodily fingerprints of different emotions (Feldman Barrett, 2020, p. 13). Here, the argument of "many-to-one connectivity" is invoked (Edelman & Gally 2001; Mayr 2004; Marder & Taylor 2011; Clark-Polner *et al.* 2016; Siegel *et al.*, 2018): this primarily means the ability of different neuronal groups to elicit instances of the same category of emotion. The hypothesis is that an emotion forms a category consisting of highly variable emotional instances. Categories of emotion are therefore merely abstractions that need not necessarily exist in nature (cf. Clark-Polner *et al.*, Wilson-Mendenhall *et al.*, 2015). One can experience fear with or without activation of the amygdala (i.e. the brain region that is commonly considered to be the seat of fear). Rage may or may not be accompanied by elevated blood pressure (Feldman Barrett 2020, XII). Hence, a pattern described as sadness is not a specific brain state in the biological register. It is merely the statistical summary of a highly variable quantity of different variants.[4] In this respect, the brain contains core systems involved in generating numerous mental states: a core system can play a crucial role in thinking, remembering, deciding, seeing, or experiencing different emotions. For this reason, feelings should be understood as holistic constructions, i.e., constructions encompassing the entire brain and the body (Feldman Barrett 2017).

1.2 Assumption and Anticipatory Simulation

This theory of the construction of emotions refers to the idea that brain activity constructs anticipatory simulations, predictions or presuppositions, together with their corrected versions. We are speaking here of clear evidence

[3] We use the terms "feelings", "affects" and "emotions" synonymously. Usually, we speak of feelings. When we refer to authors that speak explicitly of affects or emotions, we use these terms (provided that they can be understood as synonyms).

[4] Moreover, the activation of a specific group of neurons does not always signify the same feeling, since cultural factors play an important role.

that what we see, hear, touch, taste or smell are simulations, i.e., predictions or presuppositions about the material Outside. These inner states are by no means simply reactions to stimuli. If someone sees an apple, their brain simulates the image, the taste or the scent of an apple. It uses just a few signals and combines these signals with knowledge about previous apples to construct a hypothesis about the apple on the outside. Simulations are presuppositions about what is happening outside of the brain. The brain applies such predictions to trigger a bodily activity, e.g., taking hold of the apple. If the brain were to react primarily, it would be constantly bombarded with a plethora of chaotic sensory impressions. Its capacity to react would not be able to keep the individual alive (Feldman Barrett 2020, p. 60). Moreover, brain activity that functioned primarily reactively would be far too metabolically complicated, requiring substantially more connections than it could maintain regarding its energy budget.[5]

Friston (2013; 2017, p. 69 ff.) describes the predictive coding (i.e., the coding of sensory signals to produce predictions) within the model of self-organising systems. For this description, he introduces four states:

1. Outer states (Ψ): These states encompass the outside of the material world which remains completely hidden from the individual. In our RSI model, the outer state is "matter", which we shall describe in greater detail below.
2. Inner states (R): These states are presuppositions (simulations) about the outside world, in the sense of presuppositions and retrospective assumptions arising after correction of the prediction error. In the RSI model, these inner states will be described as "imaginary thoughts".
3. Sensory states (S) mediate between the outer and inner world; in the RSI model, these states are real sensations.
4. Action states or motor activities (A) arise from presuppositions or retrospective assumptions. The action level should be added to the RSI model (in the broadest sense of Lacan's *acte*, see Lacan, 2024).

Friston (2013, 2017, p. 69 ff.) locates sensory states (S) and action states (A) within probability statistics operating with probability distributions (p) in the so-called Markov blanket. A Markov blanket separates the inside of the system from the material outside in the form of a mathematical object. Later, we will assign the Markov blanket to the real register, which contains unconscious sensations or sensory signals. These signals construct inner states (presuppositions, simulations) with recourse to conscious and unconscious memory content. The signals are therefore coded in the form of predictions. If the prediction error is large, a surprise effect will occur. This effect leads to an increase in entropy in the form of "free energy" (Friston 2012; Friston 2017, p. 78; Solms & Friston 2018). The presupposition or simulation is then checked by comparing it with further sensory signals (i.e. real sensations), using only those signals needed for the correction of the prediction error. Above all, such a selection saves a great deal of energy. All self-organising systems aim to decrease entropy enough for equilibrium (homeostasis) to be re-established at a deeper entropic level, e.g. as a result of a(n) (motor) action. In this way, through prediction and correction, the brain is constantly creating an ideal model of the world[6].

1.3 Emotional and Verbal Concepts

Simulative models can be judged emotionally and linguistically, i.e., with feelings and words.

[5] If the brain reacted to all light waves impinging on the retina and the retina's sensory signals were relayed via the thalamus to the primary visual cortex (V1), a vast number of neurons would be required to relay this information (Feldman Barrett 2020, p. 61)

[6] All brains fulfil the same core task: the efficient provision of resources for the body's physiological systems (Sterling & Laughlin 2015). This act of provision is termed "allostasis" (Sterling 2012). Whenever the brain predicts a movement, whether this is getting out of bed in the morning or taking a sip of coffee, the body's budgeting regions adjust the necessary budget. When the brain predicts that the body is going to need a boost of energy, these regions instruct the adrenals to secrete the hormone cortisol, whose primary purpose is to flood the bloodstream with glucose to provide the cells with immediate energy so that – for example - the muscle cells can expand and contract. Thus, the interoceptive network controls the body, takes stock of energy resources,

Through emotional judgment, the individual knows in a specific situation whether the situation is pleasurable or unpleasurable. A verbal judgement locates and anchors the simulated model in linguistic knowledge and enables the communication of these inner states to others.[7]

The evolutionary function of feelings lies in the evaluation of inner states that simulate the outer world (cf. Panksepp *et al.* 2016). Similarly, Ulrich Moser (2009, p. 59) argues that an affect or feeling indicates an (inner) situation. Here, we see the main task of feelings: to invest presuppositions and corrected assumptions with an emotional significance. Strictly speaking, feelings are judgements that assign an emotional importance to simulations or inner states. As we shall describe below, feelings are ideal and imaginary thoughts. They are imaginary thoughts that judge other imaginary thoughts. In terms of their regionality, they have no defined neurophysiological correlate, and may also express themselves differently (Feldman Barrett 2020, p. 31).[8] In contrast to Feldman Barrett's theory, we advocate the view that mimetic or vocal signs of affect have indisputably developed over the course of phylogeny, together with the knowledge of their significance. Because of this co-evolution of signs and their understanding, a baby, for example, can draw on an already phylogenetically preformed understanding. We would argue that this phylogenetically preformed affective understanding can be used in the current construction of feelings in the same way that the subject can draw on earlier experiences when constructing or simulating inner states.

As far as verbal concepts are concerned, we should bear in mind that in the child's experience, speech represents nothing but a stream of sounds. Even the infant recognises certain regularities in this stream of speech, however, such as regularly occurring boundaries between specific phonemes. In this way, the child develops concepts that can be used to underpin the stream of sounds with a stable semantic structure: verbal concepts categorise the acoustic input, and the young brain, bathed in the speech of others, is busy building a collection of simple concepts of this type (Feldman Barrett 2020, p. 85). Thus, the child learns that a word heard from its parents pertains to specific inner states (Feldman Barrett 2020, p. 101). In this respect, verbal concepts can also be applied to feelings: emotional concepts are anchored by words which name these concepts. On the other hand, words also categorise various facial and bodily configurations that express the same emotion. Verbal concepts, of course, are also variable, malleable, and context-dependent. A car does not always merely serve the purpose of getting from A to B; it can also be associated with the concept of "status symbol" or "phallus". A concept drawn on to construct a simulation usually contains different information on an object – say, a bee. It includes not only information on the object itself, as "meaning", but also information stemming from other concepts having to do with the object (e.g. "meadow", "flower", "honey", "sting", "pain"), as "sense" (see Frege 1993, pp. 23-43). All this information is integrated into the target concept of "bee" (Feldman Barrett 2020, p. 28). Concepts can therefore also be combined. Combinatorics makes it possible to construct a potentially unlimited number of new concepts from already available ones. In this respect, the brain uses previous experiences organised in the form of concepts to determine simulations by meaning or sense (Feldman Barrett 2020, p. 104).

and simulates internal experiences (Feldman Barrett 2020, p. 70).

[7] Furthermore, the judgement enables the inner states to be categorised by emotional or verbal concepts. In a situation where a snake appears, I categorise the sensations as seeing the snake, feeling my heart pound, and running away. I have properly predicted these sensations and explained them with an instance of the concept of "fear". In this way, emotions are constructed. Note that the feeling is always a combination of valence and arousal represented by a point on the affective circumplex (Feldman Barrett 2020, p. 74). Verbal concepts are word concepts. Emotional concepts are feeling concepts. In any case, the prediction is formed by categorisations that use emotional and verbal concepts from previous experiences (Barsalou *et al.* 2003; Barrett *et al.* 2015).

[8] When someone is furious, they may scowl, frown, scream, laugh, or remain uncannily quiet. The heart rate can increase, decrease, or stay the same. A word describing a feeling (like "rage", for example) can determine numerous different instances (Feldman Barrett 2020, p. 35).

1.4 The Role of Entropy

The greater the prediction error, the greater the surprise effect due to further sensory data fed into the Markov blanket. This surprise effect causes an increase in entropy in the form of "free energy", i.e. an energy that is not bound by mental work or actions (Friston 2012; Friston 2017, p. 78; Solms & Friston 2018). A surprise effect arises when a newborn, faced with the helplessness of an immature organism, is forced to recognise the erroneousness of its simulations and preassumptions, which relate to a positive situation in the womb. In any case, the excessive energy causes an increase in entropy. Simulations themselves can probably lead to increased entropy, e.g. if the simulation draws on previous traumatic episodes or assumes a punishment before the fact (e.g., in the sense of castration). The aim of any self-organising system, however, is to decrease entropy until as low a homeostatic level as possible is achieved. Our organism has various options available to achieve this aim: The subject can act in such a way that its current sensations once more accord with the predictions (i.e. through an active state (e.g. the baby cries to be fed) or through flight (in a situation perceived as traumatic). Thus, the fulfilment of need, demand or desire serves to decrease entropy (cf. Evans 1996, p. 35 f. and p. 124 f.). Alternatively, the subject can attempt to create more accurate predictions (Solms & Friston 2018).

III. HUMAN FORMS OF BEING

3.1 Multimodal Imaginary Constructions and the Symbolic

As said before, Lacan's (2021) Borromean knot, which is meant to represent mental reality, consists of the three rings of the Real, the Imaginary and the Symbolic. For our reflections, the Imaginary is particularly important. It corresponds primarily to Freud's *Sachvorstell-ungen* ("thing-presentations") (cf. Freud 1915). These are thoughts possessing an immediate sensuous and sensory basis: visual images, acoustic sounds, but also tastes, smells, the feeling of being touched, and not least of all the affective feelings. As mentioned, an internalisation process – from "bein touched" to "feelin " – took lace during the Enlightenment, i.e. over the 18th century. Originally, *Fühlen* and *Gefühl* (the gerund and noun "feeling", respectively) referred to the sensory perception of the Outer. As part of bourgeois inwardness, "feeling" (the noun) mutated into the perception of inner sensory analysis. Unlike the Real, which is deemed unrepresented, the Imaginary is generally conscious (unless it is secondarily repressed).

However, the Lacanian register of the Imaginary can be far more readily conceptualised with the Theory of Predictive Coding. We assume that presuppositions on the outer world, which is hidden from the individual, are constantly being formed (Friston 2013, 2017; Solms & Friston 2018). Nothing is known about the Outer, but with the help of previous experiences and a handful of sensory signals that are stated on the Markov blanket, imaginary presuppositions as to what the Outer might be like are constructed. We suggest that the Real is a Markov blanket, or that, as a formalised mathematical issue, the Markov blanket represents a part of the register of the Real. Thus, the Imaginary is a presupposition that also refers to the subject's earlier experiences. It is a simulation, or as Lacan (2010) puts it, it is a semblance (perhaps in combination with words). In this respect, the Imaginary predicts how the outer world could be. This prediction consists of images, sounds, smells, taste, or the perception of a touch. Karl Friston showed the aetiology of visual thoughts using an experiment in which the face of Nefertiti was presented to experimental subjects. Subjects were able to construct the face from just a few sensory points – in particular, the eyes, brow, and mouth – by linking these points of sensation with additional information from their memory (Friston 2017, p. 86; Friston, Adams, Perrinet & Breakspear 2012). This simulation requires substantially less effort to be expended than the perception of the entire face would. *Figure 3* illustrates the experiment:

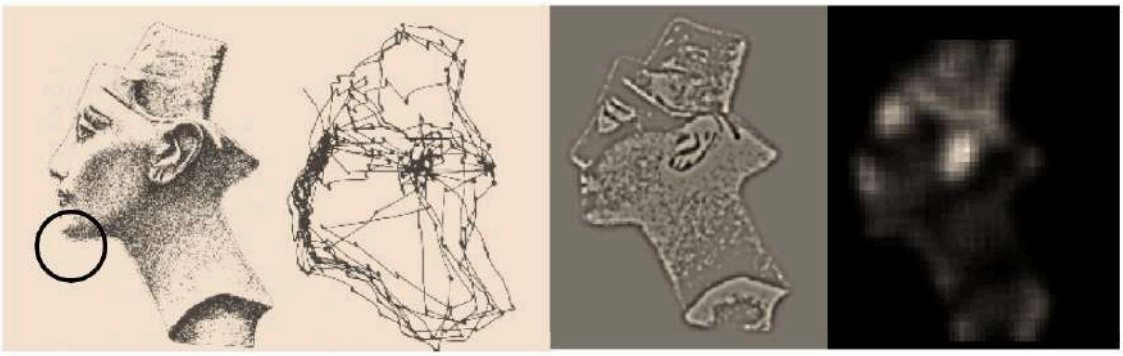

Figure 3: Saccades in the perception and construction of a face. The panels on the left show a stimulus (the face of Nefertiti) and the eye movements triggered by the stimulus. The panels on the right show the visual input after scanning the image. The size of the resulting field of vision relative to the visual scene is shown by the circle on the left-hand picture. The most important thing is for the prominent features of the image to include the ear, eye, and mouth. The position of these features and other spots (e.g., brow) appears to tally with the spots that attract the saccadic eye movements (Friston *et al.* 2012, p. 11).

In a further step, this simulated face is squared with the signals of the Markov blanket that point to a prediction error. Here too, not all data are processed. Because of the limited capacity of the brain, only those signals which are necessary for the correction are used.[9] The effect of these selected points of sensation on the – in this example – Visual-phenomenal can be described as the Pheno-real, that is, as the effect of the Real on the Phenomenal. Despite its fictional nature, semblance, i.e. simulation, is "the primary function of truth" (Lacan 2010, p. 37). Truth, one might say, has the structure of semblance. Thus, the truth of the Outer could be based on semblance, i.e. on the imaginary inner state that is possibly determined by words. We can only approach the truth of the Outer through predictions that are already accurate, or through predictions that become more accurate through correction of the prediction error. Hence, there is no truth of the Outer that is not based on semblance, i.e. the inner states.

Here, the salient point is that simulations can be judged both emotionally and verbally: initially, the simulation is judged with feelings of pleasure or unpleasure. This emotional evaluation takes place within a valence of feelings that can be positive or negative. A further evaluative dimension is the degree, i.e. the intensity or excessiveness of feelings (on the material side: the degree of arousal). In the case of trauma, the valence of the feelings is negative, and the arousal is excessive, with the result that the feelings must be secondarily warded off. In this respect, feelings are second-order imaginary thoughts that judge first-order imaginary thoughts.[10] Through this judgement, an imaginary simulation, i.e. an inner state, is invested with an emotional significance. Thus, there are two orders of the Imaginary:

1. The first order encompasses presuppositions in the form of predictive simulations, as well as retrospective assumptions arising from the correction of prediction errors. These are first-order imaginary thoughts: images,

[9] The stimulus-reaction paradigm thus only applies in so far as just a few signals are selected. It is not the stimuli but the simulations that are important. In the rivalry that persists between Pavlov and Freud (both of whom were trained in physiology laboratories), it is Freud and Lacan who would currently be likely to emerge as the scientific winners.

[10] The Kiel phenomenologist Hermann Schmitz (2014, p. 30) described feelings as "spatially poured atmospheres" extending beyond the boundaries of the individual's body as defined by the skin. In an imaginary space, an atmosphere is created through feelings projected into this space. A person perceives a feeling in himself, in his body, i.e. the atmosphere arising from a feeling or various feelings. The conscious feeling-judgement evaluating an inner state, however, also includes the space of the field of vision and the acoustic space of a voice. These imaginary spaces are likewise inner states that are judged atmospherically.

noises, sounds, smells, tastes and the perception of touch and movements. First-order imaginary thoughts arise from pheno-real effects that can be traced back to sensory signals or states on the Markov blanket. These imaginary thoughts are conscious or preconscious, i.e., potentially conscious (e.g. a sound that we pay no attention to, such as the ticking of a clock, or the chirping of birds). Imaginary thoughts (particularly images) can be secondarily repressed.

2. The feeling judges the simulation, i.e. the presupposition, the surprise effect arising from a prediction error and the corrected simulation, and invests it with an emotional significance. Because of this judging function, feelings are second-order imaginary thoughts. They are conscious.[11] By being conscious, feelings, with their features of valence and arousal, form the foundations of phenomenal consciousness. However, feelings occur primarily when semblance, i.e. the simulation, is plunged into a crisis, e.g. because of prediction errors or trauma-induced inner states. The role of feelings is to point to this crisis.

We now turn our attention to the Symbolic. In the symbolic register, the simulations are determined by linguistic significance (Lacan 2021). It is the Discursive-Linguistic and the structure implied by language. The register of the Symbolic contains the Freudian word-presentations (Freud 1915) that initially appeared in the form of acoustic perceptions, just as the birth of linguistic concepts is described as a categorisation of the stream of speech sounds (Feldman Barrett 2020, p. 85).

Here, the expression "concept" plays an important role: if a linguistically competent individual or a speaking being (cf. Soler, 2009) grasps a thought, then this linguistically composed thought is based on concepts, i.e. the content of such a thought is designated by the content of the corresponding concept (Newen 2003, p. 419). Concepts are abstract objects that are updated in connection with words or propositional statements.[12] Schiffer (2000, p. 9) described concepts as "pleonastic entities" which are not yet linguistic determinations. The concept is knowledge about something (e.g., what a tomato is). Hence, an emotional concept is based on the relatedness of feelings to one or more concepts. A linguistic concept, for its part, is based on the relatedness of words or propositional statements to concepts. Learned knowledge of the meaning of a simulation is thus connected with emotional or linguistic utterances: a concept can be articulated through a feeling or a linguistic proposition. Conceptual knowledge can therefore also be expressed emotionally (via a particular facial configuration) or linguistically. In this respect, the concept of the simulation conveys two forms of meaning: the objective meaning (denotation) and the emotional meaning (connotation) (Eckes 1991).

The Symbolic is thus the fact that there are words (verbal signifiers) whose dimension of meaning is the concept. These words can determine imaginary thoughts (Lacan 2006, p. 228 f.). Freud (1905, p. 120) said that a concept is a kind of *Vorstellungskreis* ("circle of ideas") which, as

[11] Lacan says in Seminar X: "I have tried on occasion to say what affect is not. It is not Being given in its immediacy, nor is it the subject in some brute, raw form. (...) On the other hand, what I have said of affect is that it is not repressed. Freud says this just like me. It is unfastened; it goes with the drift. One finds it displaced, mad, inverted, or metabolised, but it is not repressed. What is repressed are the signifiers that moor it" (Lacan 2016, p. 14).

[12] Kant was the first to distinguish between *Anschauung* ("sense perception") and *Begriff* ("concept"). He categorises these into concepts of *experience* or *understanding* (categories) and *reason* (ideas) (see Eisler 1961, https://www.textlog.de/eisler/kant-lexikon/anschauung; https://www.textlog.de/eisler/kant-lexikon/begriff). Sense perceptions originate from sensuality alone and concepts from reason alone. However, according to Kant, there are no concepts without sense perception and no sense perception without concepts. Sense perceptions without concepts (or, in Feldman Barrett's terminology, without categorisation through concepts) are blind. According to Kant, categories serve to help reason merge or synthesise the variety of sensory impressions into an insight. However, Kant maintains that where sensuousness combines with reason – i.e. where the concept is filled with content – is where a genuine insight is possible. Today one would not speak of a "genuine" insight. Instead, the theorists of predictive coding would speak of the greater or lesser probability of the assumption about the hidden Outer being correct.

knowledge, underlies a feeling or word. Feelings therefore invest a simulation with an emotional meaning, and words add a linguistic meaning. Lacan distinguishes here between the meaning and sense of a word or combination of words by adopting Frege's distinction between meaning and sense. The meaning of the word (or of the sign) relates directly to the object being designated (e.g., the car that we see or imagine): "The reference of a proper name is the object itself which we designate by its means" (Frege 1993, p. 26). By contrast, the sense of the sign relates to the "mode of presentation" of the object. Sense also considers further circumstances (Frege 1993, p. 24). In this respect, meaning is "*einseitig*" (illuminates a single aspect), while sense is "*allseitig*" (comprehensive). In ideal terms, the sense is "comprehensive knowledge". However, this comprehensiveness will never be possible; in terms of the sense, something always remains hidden (Frege 1993, p. 24). In contrast to Frege's position, we contend that it is not the object in external reality (since external reality is hidden from us), but rather the simulated, i.e. represented object that is given a meaning or sense through its linkage with language. With the help of verbal signs provided by the parents, the child initially learns the meaning of an idea about external reality. When an adult speaks to an infant, the infant learns that the word has a meaning relating to an idea. As the child matures, it will also learn something about the sense of the idea. Feldman Barrett (2020, p. 91) describes this process using the example of a car: in addition to simply being a car, it can also be a status symbol, a maternal sanctuary, or evidence of male potency. Both the meaning and the sense of a verbal sign can now be evaluated by feelings. Linguistic utterances categorise, stabilise and consolidate the internal imaginary states by investing them with meaning or sense. They make it possible to communicate these states to others. Both feelings and linguistic signifiers may also trigger a simulative reality, however. We hear the word "tomato" or "car" and simulate the corresponding reality: the taste of a tomato or the sound of an engine. This linguistic creativity reminds us in the broader sense of Lacan's idea (2006, p. 223) of "liberated speech", which would mean that signifiers themselves create a simulative reality. The slipping of the signifiers or the switch from one circle of ideas to the next (Freud 1905, p. 120) then evokes inner states, which can be classified either as fantasies or reality.[13] To summarise these aspects, we can say that inner states as well as feelings are invested with a meaning or sense by verbal concepts that are based on one or more conceptual circles of ideas. These verbal concepts are themselves capable of re-evoking inner states which point to something that might exist outside.

3.2 Intersubjective Simulation

Language comes from the Other – this is a fundamental Lacanian idea. Language comes from adults, who are representatives of the "Big Other" that conveys the culture, laws and ideology. According to Freud (1915), word-presentations are used to determine thing-presentations (i.e. imaginary simulations). The basis of all linguistic categories is thus imaginary: it is the tones and sounds that the baby hears. The baby can recognise and make a mental note of their structure (Feldman Barrett 2020, p. 85 ff.). It learns to register the sounds of others as words and to assign these words and word combinations to inner states that simulate the outer hidden world. Through the linkage with language, inner states are given a meaning or sense.[14] Of course, it is not just words but glances, touches or the sound of the voice that are conveyed by the Other. These partial objects are implanted on the Markov blanket (i.e. in the real Unconscious) in the form

[13] Regarding an expansion of Bion's "Theory of Elements", such simulations may be termed "gamma elements" (Goetzmann 2020).

[14] In essence, a symbolic order as structure is already introduced in the context of statistical learning, i.e. with the child intuitively gauging the probability that vocalisations occur together. From this point of view, the symbolic order that differentiates (cf. Lacan 2016, p.16) is not limited to the Linguistic. We shall, however, restrict ourselves to the argument that the Symbolic is primarily the Linguistic -Discursive, hoping through this emphasis to create a clear conceptual differentiation from the Imaginary. From this perspective, one should probably speak of an imaginary order that already makes differentiation possible e.g. in the experience of animals or even single-celled creatures (amoebas), which are able to differentiate sensory impressions.

of sensory states. In this way, the Other's expression of affect, which manifests itself in the voice or facial configuration, becomes the individual's organisational nucleus. It is this expression of the Other's affect that causes an imaginary simulation owing to the pheno-real effects and their translation (cf. Laplanche 2011, pp. 99-114; Laplanche 2017, pp. 108-114). As described, this simulation is judged emotionally by conscious feelings. In this way, the child is confronted with a whole host of parental affect utterances that can be described as "emotional scripts" and that are structured as follows:

1. The Other possesses an inner state that is judged emotionally. This emotional judgement is expressed in variable configurations of the voice, the facial muscles or tactile contact.
2. The subject receives affective signals via the Markov blanket and uses a selection of these signals as pheno-real effects. Taking into account further information from the memory, a presupposition or a corrected assumption concerning the message of the Other is simulated.
3. The subject judges this simulation in both emotional and verbal terms: in a first step, the mother simulates a happy baby face which she judges in an emotionally positive manner (delight, happiness). In a second step, the baby simulates the mother's happy face and judges this simulation in an emotionally positive way. If both the mother and baby smile, the reciprocal simulation is confirmed. Via repetition, an organisational nucleus forms in the child's psyche.
4. In this way, simulations are shared and states are synchronised. The contribution made by both the Other and the subject itself consists in the fact that the predictive simulation is supplied to a considerable, perhaps even overwhelming extent from their respective memories.[15]

Various transference errors can occur in this complex dialogue structure (cf. Krause 2016 a and b). Firstly, a decoding shortcoming on the part of the Other can be responsible for transference errors. In this case, the Other has an (e.g. alexithymic) perceptual defence against its own and others' affects. Secondly, decoding errors that are more affect-specific can also occur. An example of this would be that only states of rage are disregarded or reinterpreted in the form of another, more positive affect. Prediction errors that are inadequately corrected may also occur. In this case, a simulation is constructed by the subject which has little congruence with the emotional judgement of the Other. As Lacan says in Seminar X, many affects, such as guilt or melancholy, are the attempt to cope with this anxiety concerning what the Other wants. The feeling or affect is therefore both an imaginary and a symbolic construction which attempts to limit the extent to which the subject is overwhelmed by the Real. Feelings can thus form a protective shield. However, they can also unsettle and confuse the subject – for example, when it comes to the evaluation of traumatic states which increase the respective entropy to excessive levels. Lacan (2016, p. 13 f.) speaks of *l'embarras* ("distress") or *l'émoi* ("turmoil", "dismay") when faced with the demands and desires of the Other. We might also say, therefore, that feelings are thoughts that attempt to judge, grasp, and process threatening inner states.

3.3. In the Crosshairs of the Axes

How can we imagine the "interconnection" of these different processes intra and inter-individually? Lombardi (2022, p. 64) outlines a horizontal and vertical axis in the experience of the subject: the vertical axis denotes the transformation of an original, as-yet-unrepresented experience (for Bion, the experience O; for Lacan, perhaps the Real) into alpha elements, i.e. into imaginary states that are evaluated with

[15] Transference is then a simulation based on the predictive coding of just a few signals which are sent by the analyst. An overwhelming proportion of the simulation, however, arises through recourse to the memory, which contains experiences with previous people (e.g. the parents). Countertransference feelings are emotional judgements on presuppositions about the Other. We are dealing here with simulations based on (1) the current behaviour of the Other, (2) previous experiences in the relationship with this Other and (3) the memory content regarding previous experiences, e.g. from infancy.

emotional and verbal concepts. By contrast, the horizontal axis extends between the subject and the Other. The Other is located in a hidden outer world. Only the Markov blanket enables a mediating relationship between this outer world and the inner states of the subject. In the crosshairs of these two trajectories lies feeling. Thus, for example, in the case of the distress cry, a state referring to the unbearable absence of the Other is judged with the emotional concept of desperation.[16] This emotional judgement causes an action, i.e., an active state on the Markov blanket expressed as a desperate wailing. Feelings emerging in the crosshairs of these trajectories often serve the purpose of proximity-distance regulation (e.g. the feeling of disgust: see Krause, 2006).[17] Such feelings then appear in the crosshairs of the trajectories. Here, they establish the first forms of consciousness. In the crosshairs of intersubjectivity and transformation, therefore, imaginary thoughts together with their judgements cause the emergence of subjectivity. This early subjectivity will co-determine all further simulations. We therefore contend that the imaginary crosshairs will determine an individual's personality, i.e. their way of being over their entire lifespan, and that the earliest forms of their consciousness are essential imaginary organisational nuclei.

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[16] It is said that the earliest social feeling is that of desperation, which triggers a distress cry (Krause 2017, p. 255). The infant's wailing is intended to bring about renewed closeness to the object.[17]

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Oral Squamous Cell Carcinoma: Challenges in Treatment for Low- and Middle-Income Countries: Fetching Towards the far Ahead Horizon

Dr. Arushi

ABSTRACT

This perspective article discusses the origin of tobacco, its spread and the changes it produces in human body, most prevalent of which it is oral squamous cell carcinoma. Especially in low-and middle -income countries, where the use of tobacco is already trend setting and concomitant cases are also increasing, so some simpler measures should be needed to implement which can reduce the size of the lesion and the lymph node shrink from the original size so that it prevents not only the load of reconstruction, but might also lead to improved mortality outcomes.

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I. INTRODUCTION

The advent of human form of lives on this planet Earth commenced billions of years ago, deriving the ancestry from marine life which upon finding land life more alluring thrived towards it resulting in newer species evolution in continuum till the point various species of chimpanzees and orangutans progressed through various eras of evolution to finally form the first species of humans and hitherto newer evolutionary species inhabiting in the Cenozoic era is Homo *homo Sapiens*.

This species, being the most intelligent of all the ones that follows in line of its succession can be reasoned to the cortical development which not only had interconnecting neural pathways between different primitive parts of the brain, but is also the highest seat of intelligence, thereby controlling all the complex decision-making processes and the curiosity. While this cortical gray matter has enabled humans not only theirs, but also of other species improvement in their living style and harnessing nature through various complex technologies, booming both science and technology. However, the discovery that tobacco can be obtained from the leaves of genus Nicotiana, indigenous to North and South America propelled native people to use this extracted product for religious and cultural purposes. [(1)] By the time Columbus discovered tobacco in other countries, the natives started using tobacco in pipes, cigars, and snuff. Subsequently, Portuguese and Spanish sailors helped to spread different forms of tobacco to be used, around the world. [(2)] as a consequence of what we can observe today, is the widespread us of tobacco in various forms in smoked and smokeless forms.

There is a direct or an indirect influence of culture on tobacco use as some sharing an inherited factor later become nicotine dependent. Boys see their grandfathers or fathers smoking, so they start consuming it as a part of their ritual. [(3)] Smoking is seen as part of being a man and a sign of his male authority. In India, the reasons for its use and continual addiction and dependence have been shoved off citing off various reasons such as it relives worry, prevents bad breath and helps in gastrointestinal issues. [(4)] Despite all defensive reasons given by normal population to promote and defy their own usage of this product and dealing in its business since many decades, , no one can shut their eyes to the fact that tobacco used in any form, whether by any sex, contains as per present scenario, 2550 known compounds which have at least 43 carcinogens and some radioactive substances involving polonium 210.[(5)] Different systems of our body are interrelated and they influence the use of any such

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product which is likely to cause health hazards affects many such body functions. Nicotine is one such product which affects top-to-bottom irreversible changes in body functions.

What and Why it Concerns us?

As oral pathologists and healthcare professionals, a grown trend has been seen in usage of nicotine usage not only by adults, but by even younger kids and adolescents throughout the current geographically marked entire States and Union Territories of India**.** Its active ingredients, tar, nicotine, and nitrosamine, are potentially associated with oral cancer worldwide. [(6)] consequently, it has been to cause nearly 85% of all the cancer deaths reported.

What Is Oral Squamous Cell Carcinoma And Its Deficits?

Oral cancer is a squamous epithelial category of tumours afflicting any region of the oral cavity, pharyngeal regions and salivary glands. However, this tends to be used interchangeably with oral squamous cell carcinoma (OSCC), representing the most frequent of all oral neoplasms documented to an approximate case of 90% of all the oral tumours. [(7)]

One of the biggest flakes that is persistent with this tumour is the fact the initial changes in the oral mucosa are so innocuous, that the patient themselves neglect these changes or is unable to visualise them, only later stages may present with some sort of bearable pain which is also neglected by population of low-to-middle income countries .Even though they are advised beforehand about the premalignant lesions developing and are advised to stop the habits through various schemes and health awareness camps organised.

Because of its addictive properties and lack of proper follow-up for tobacco cessation programs, they continue to use these products till the point the mouth opening reduces or a large ulcer proliferative lesion can be seen developing in the oral cavity, hampering their daily nutrition intake.[(8)] The screening procedures here become a failure and the TNM staging used for staging can prove the tumour already progressed to an advanced stage, leaving the patient to either undergo extensive surgical procedure concomitant radio or chemotherapeutic procedures.

These procedures, although have been developed to decrease morbidity and increase quality-of-care, however due to lack of advance technologies and insufficient funding source/lack of access to medical health insurance policies, they are unable to get the standard medical care from tertiary hospitals, resulting in either incomplete removal leading to recurrence or the unesthetic appearance of their faces thereby increasing morbidity for their nutrition. Despite advances in surgery and radiotherapy, which remain the standard treatment options, the mortality rate has remained largely unchanged for decades, with a 5-year survival rate of around 50%. [(9)] At later stages of pression that is stage II and III TNM of OSCC, metastases will occur in cervical lymph nodes in almost 80% of patients. Cervical lymphadenectomy (radical neck dissection) is traditionally applied in these cases. [(10)]

As the entire lymphatics drain from the head and neck into the upper, middle and deep cervical lymph nodes, removal of these becomes the ulterior motive since the ways to detect cervical lymph nodes is mainly through clinical examination or Cone-Beam Computed Tomography (CBCT), still the sentinel lymph nodes are most of the times missed during investigative procedures, therefore surgeon is left with no choice but to remove the entire chain of the corresponding side lymphatics which is in itself a most extensive and morbid procedure. Contrary to many times. lymph nodes upon histological examination are found to be intact without any capsular invasion.

II. NOVELTY FOR THE CAUSE THAT CAN BE CONSIDERED

Several mechanistic studies have provided detailed insight into the mechanistic basis for Lymph node Metastasis. The ability of tumour cells to migrate and invade Lymph nodes is associated with expression of particular receptor proteins and cytokines, eventually culminating in

the evasion and/or suppression of normal immune function such that these malignant cells can thrive within the LN microenvironment. [11] since the lymph nodes invasion takes place through passage of large venules with ultimately the aggressive tumour cells turning to mesenchymal cells, so as to evade the immune defence mechanism.

One way to curb the lymphatics flow till the surgery commences or the investigations are taking place, sclerosing agents can be injected against which would not activate inflammatory cells, but also would initiate fibrosis thereby, preventing further of the squamous cells deeper into the lymph nodes, thereby might also encase the further seeding of the cells. These agents have been used since decades to treat varicose veins and are compounds like sodium dodecyl sulfate.

This would not only shrink the lymph nodes, but also would at least would decrease the surgical extensive procedures and might would lead to more activation of immune response upon introduction of another foreign agent.

III. CONCLUSION

Sclerotherapy might be useful in cases of oral squamous cell carcinoma cases of low and middle-income countries who cannot afford such long stays at hospitals and overwhelming financial surgical procedure and might help in reducing further spread of the tumour.

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The Effect of Myofascial Release and Cervical Traction on Pain, Range of Motion and the Neck Disability Index in Patients with Chronic Neck Pain: A Randomized Controlled Trial

Ho-Yong Shin, PT, PhD

ABSTRACT

Purpose: This study examined the effects of the myofascial release and cervical traction after applying conservative physical therapy to patients chronic neck pain.

Methods: Patients were randomly divided into two groups, namely myofascial release (7 subjects) and cervical traction (7 subjects). Each group performed their therapy 45 minutes per day, two times a week, for four weeks. Pain intensity was measured using the visual analog scale (VAS). Function was measured with the neck disability index (NDI). The cervical range of motion (CROM) was measured with a cervical range of motion (CROM) goniometer.

Keywords: cervical traction, chronic neck pain, NDI, myofascial release, VAS.

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Results: After four weeks of therapy, the VAS ($p < .05$) and NDI ($p < .05$) significantly decreased, and ROM significantly increased in both groups ($p < .05$). There were also significant differences between the two groups for these three measures, except for neck flexion and neck extension ($p<.05$).

Conclusion: Myofascial release and cervical traction are more effective than cervical traction alone for reducing VAS and NDI and increasing ROM in patients with chronic neck pain.

Keywords: cervical traction, chronic neck pain, NDI, myofascial release, VAS.

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I. INTRODUCTION

Working on a computer and using a smartphone is essential for modern people, and smartphone usage among adults in South Korea has increased dramatically over the past decade, from 53% in 2012 to 97% in 2022 [1,2]. While the ubiquity of smart devices provides convenience, it is also a major contributor to the rise in musculoskeletal disorders[3]. According to the Korea Health Insurance Review and Assessment Service, one in three Koreans visited a medical institution in 2019 for musculoskeletal pain and dysfunction, and the number of people diagnosed with musculoskeletal disorders increased from 12.85 million in 2009 to 17.61 million in 2019[4]. Neck pain is one of the most diagnosed musculoskeletal conditions in the last decade, with 67% of people experiencing it at least once in their lifetime [4,5].

Neck pain is generally defined as pain and stiffness in the back and sides of the neck region between the superior nuchal line and the first spine [6,7]. This neck pain can cause decreased neck function, shoulder pain, headaches, and chronic fatigue that interfere with normal daily activities [8]. In addition, neck pain has a poor prognosis even after treatment and management, with a high likelihood of recurrence and often leading to chronicity [9]. Chronic neck pain is caused by a variety of factors, including physical, social, and psychological factors, although the exact and probable cause of tissue damage is unknown [10,11].

Variety of physical therapy interventions, including therapeutic modalities, manual therapy, and exercise therapy, which utilize heat, electricity, ultrasound, and mechanical forces to

reduce pain and improve function in patients with chronic neck pain, are widely used in clinical practice [1,12,13]. Of these, cervical traction is often used to treat patients with neck pain [14]. Cervical traction stretches the spinal structures, removing compression and irritation of the nerve roots to relieve pain, stabilizing the patient and reducing muscle spasms [15]. Borman et al [16] showed significant improvements in pain and Neck disability index (NDI) with cervical traction in patients with chronic neck pain, Chiu et al [17] showed improvements in pain and range of motion with cervical traction in patients with chronic neck pain, and Romeo et al [18] reported that cervical traction combined with manual therapy or other physical therapy interventions was more effective than traction alone in improving neck pain.

In recent years, it has become increasingly popular as a treatment for neck pain as it has been used in many countries to treat various musculoskeletal disorders [19-20]. Myofascial release is a commonly used manual therapy method in clinical practice that relaxes and normalizes fascia, muscle, and other tissues by applying compression, stretching, and other forces to the fascia, and is effective in reducing pain and improving joint range of motion [21-22]. Previous studies have reported that myofascial release is effective in improving neck range of motion and pain in patients with chronic neck pain by reducing adhesions in painful tissues and improving blood and lymph circulation [23], and myofascial release has been shown to significantly reduce pain in previous studies of patients with chronic neck pain. In addition, short-term studies of myofascial release in patients with chronic neck pain have shown improvements in pain and neck dysfunction index [24-25].

Although various interventions and treatments have been applied to patients with chronic neck pain, most studies have focused on patients with combined neck pain and other symptoms, making it difficult to objectively evaluate the intrinsic effectiveness of treatments for patients with chronic neck pain. In addition, although the effectiveness of myofascial release and cervical traction in the treatment of chronic neck pain has been demonstrated in several previous studies, there is a lack of research on the combination of myofascial release and cervical traction in the treatment of chronic neck pain.

Therefore, this study aimed to investigate the effects of myofascial release combined with cervical traction on pain, neck dysfunction index, and range of motion in patients with chronic neck pain, and to provide evidence for future clinicians or patients with chronic neck pain to utilize in the treatment and management of chronic neck pain.

II. METHODS

2.1 Subjects

This study was conducted on 14 patients with chronic neck pain who voluntarily participated in the study after being fully informed about the content, purpose and objectives of the study, experimental procedures, and safety of the study. The subjects were those who complained of neck pain for more than 12 weeks, had a Korean version of the Neck Disability Index (NDI) score of 5 or more, and excluded those who had undergone surgery in the neck area, had neurological diseases, received injection therapy within the last 2 months, or had a neck fracture. The 14 participants were randomly assigned to the experimental and control groups by lottery. The experimental group received 10 minutes of myofascial release, 10 minutes of neck traction, and 25 minutes of general physical therapy for 45 minutes twice a week for 4 weeks, while the control group received 10 minutes of neck traction and 35 minutes of general physical therapy for 45 minutes twice a week for 4 weeks.

2.2 Assessment

Visual Analogue Scale

In this study, a Visual Analog Scale (VAS) was used to assess pain. The VAS is a patient's subjective rating of pain on a scale of 0 to 100 mm, with 0 mm representing no perceived pain and 100 mm representing unbearable, excruciating pain. The VAS has been shown to have very high test-retest reliability of r=.99 and inter-rater reliability of r=1.00 [26].

Cervical Range of Motion

In this study, the CROM (performance attainment associates, MN, USA) was used to measure the range of motion of the neck during forward flexion, backward extension, side bending to the right and left, and right and left rotation. The two inclinometers on the forehead and next to the head are gravity inclinometers to measure flexion, extension, and side bending to the right and left, and the third inclinometer is a magnetic inclinometer to measure rotation, which can only measure the rotation of the head relative to a magnet fixed to the torso to exclude trunk movement. The subject is seated and the examiner fixes the subject's shoulders and measures 1) Neck flexion, 2) Neck extension, 3) Neck right side bending, 4) Neck left side bending, 5) right rotation, and 6) left rotation in the following order: 1) Neck flexion, 2) Neck extension, 3) Neck right side bending, 4) Neck left side bending, 5) right rotation, and 6) left rotation. The last range was measured while the subject was actively performing the movement and did not induce pain (Fig.1.). To reduce error, the test was performed three times, and the average of the three measurements was used after one practice without the protractor [27-28]. The reliability of the instrument was found to be ICC=.87 for flexion, ICC=.90 for extension, ICC=.92 for left side bending, ICC=.92 for right side bending, ICC=.90 for left rotation, and ICC=.94 for right rotation [29].

Neck Disability Index

In this study, the degree of functional limitations in daily life due to chronic neck pain was evaluated using the Korean version of the Neck Disability Index (NDI) [30]. The Neck Disability Index (NDI) is a 10-item questionnaire developed to measure neck pain and dysfunction, and consists of items such as pain intensity, daily activities, leisure activities, concentration, work, driving, and sleep. For each of the 10 items, patients are asked to select one of six possible responses ranging from 0 (no pain or no dysfunction) to 5 (intolerable pain or complete dysfunction) [31]. The NDI score is calculated by summing the scores for each item, dividing by the total score, and multiplying by 100, with higher NDI scores indicating greater functional impairment due to neck dysfunction [32]. In interpreting the results, the original developer, Vernon, suggested that a score of 4 or less indicates no disability, a score of 5 to 14 indicates mild disability, a score of 15 to 24 indicates moderate disability, a score of 25 to 34 indicates severe disability, and a score of 35 or more indicates complete disability [28]. The reliability of the instrument is ICC=.90 [30].

2.3 Treatment Methods

Myofascial Release

Myofascial release was applied to the upper trapezius, levator scapulae, sternocleidomastoid muscle, and Suboccipital muscles. The method was applied as shown in Figure 2 and lasted for 10 minutes.

Cervical Traction

The cervical traction device used for the intervention was the Auto Trac AT-5 (Auto Trac AT-5, DMC, KOREA), which is used with the patient sitting in a chair with the band secured to the chin and occipital bone area. The traction force was 1/10th of body weight, 6-10 kg, and intermittent traction was applied for 10 minutes with 10 seconds of traction followed by 10 seconds of traction at 15-20% of the traction force (Fig. 3.).

General Physical Therapy

Hot pack, ultrasound, and interference current therapy were used in the intervention as general physical therapy. The experimental group applied 10 minutes of hot packs, 5 minutes of ultrasound, and 10 minutes of interference current therapy, while the control group applied 15 minutes of hot packs, 5 minutes of ultrasound, and 15 minutes of interference current therapy by adding 5 minutes each of hot packs and interference current therapy to equalize the treatment time with the experimental group.

2.4 Data Analysis

Data processing for this study was performed using the IBM SPSS Statistics Win. 26 Subscription statistical program. Chi-squared test and independent t-test were used to test the homogeneity of the two groups. The Shapiro-wilk

test was used to test for normality, and the Wilcoxon signed ranks test was used to handle pre-post comparisons of the dependent variables by intervention within groups due to non-normal distribution, and the Mann-Whitney U test was used to compare the amount of change in the dependent variables by intervention between groups. All statistical significance was considered at $p < .05$.

IV. RESULTS

4.1 Subject Characteristics

There were 14 subjects in the study, 7 in the experimental group and 7 in the control group, and the homogeneity test for gender and age showed no statistically significant difference ($p > .05$) (Table 1.).

4.2 Effect of Treatment on VAS

The experimental group's VAS scores were significantly different in the pre- and post-intervention comparisons ($p < .05$). The VAS scores of the control group showed a significant difference in the pre- and post-intervention comparisons ($p < .05$). The between-group comparison of the experimental and control groups showed a statistically significant difference in VAS scores ($p < .05$) (Table 2.).

4.3 Effect of Treatment on CROM

Neck Flexion

The mean angle of neck flexion in the experimental group was significantly different in the pre- and post-intervention comparisons ($p < .05$). The mean angle of neck flexion in the control group was significantly different in the pre- and post-intervention comparisons ($p < .05$). There was no statistically significant difference ($p > .05$) in the mean neck flexion angle between the experimental and control groups (Table 3.).

Neck Extension

The experimental group's mean neck extension angle was significantly different in the pre- and post-intervention comparisons ($p < .05$). The pre-intervention mean neck extension angle of the control group was significantly different in the pre- and post-intervention comparison ($p < .05$). There was no statistically significant difference ($p > .05$) in the mean neck extension angle between the experimental and control groups (Table 3.).

Neck right side bending

The mean angle of the neck right side bending in the experimental group was significantly different in the pre- and post-intervention comparisons ($p < .05$). The mean angle of the neck right side bending of the control group was significantly different in the pre- and post-intervention comparison ($p < .05$). The between-group comparison of the experimental and control groups showed a statistically significant difference ($p < .05$) in the mean angle of the neck right side bending (Table 3.).

Neck left side bending

The mean angle of neck left side bending in the experimental group was significantly different in the pre- and post-intervention comparisons ($p < .05$). The mean angle of neck left side bending in the control group was significantly different in the pre- and post-intervention comparisons ($p < .05$). The between-group comparison of the experimental and control groups showed a statistically significant difference ($p < .05$) in the mean angle of neck left side bending (Table 3.).

Neck Right Rotation

The mean angle of neck right rotation in the experimental group was significantly different in the pre- and post-intervention comparisons ($p < .05$). The mean angle of neck right rotation in the control group was significantly different in the pre- and post-intervention comparisons ($p < .05$). The between-group comparison of the experimental and control groups showed a statistically significant difference ($p < .05$) in the mean angle of neck right rotation (Table 3.).

Neck Left Rotation

The experimental group's mean neck left rotation angle was significantly different in the pre- and post-intervention comparisons ($p < .05$). There was no significant difference between the pre- and post-intervention comparisons for the control group ($p > .05$). The between-group comparison between the experimental and control groups

showed a statistically significant difference ($p < .05$) in the mean angle of neck left rotation (Table 3.).

4.4 Effect of Treatment on NDI

The mean NDI scores of the experimental group were significantly different in the pre- and post-intervention comparisons ($p < .05$). The mean NDI scores of the control group were significantly different in the pre- and post-intervention comparisons ($p < .05$). The between-group comparison of the experimental and control groups showed a statistically significant difference in NDI scores ($p < .05$) (Table 4.).

IV. DISSCUSSION

This study was conducted to determine the changes in pain, function, and range of motion following neck traction and myofascial release in subjects with chronic neck pain. Patients with neck pain exhibit changes such as decreased neck joint mobility, decreased muscle strength and muscle endurance, muscle fiber contractures, and joint adhesions due to pain [33, 34]. If neck pain becomes chronic, it leads to changes such as decreased kinesthetic function due to loss of proprioception in the neck, persistent muscle tension and fatigue, and neuromuscular lesions and inhibition, which can lead to discomfort and restriction of daily activities and limited range of motion in the neck, causing psychosocial problems [8, 11, 35].

In this study, a VAS was used to measure pain in patients with chronic neck pain. Both the experimental and control groups showed a significant decrease in pain from pre- to post-treatment ($p < .05$). This is consistent with the results of Bae et al [3], who showed a significant difference in pain by applying myofascial release to patients with chronic neck pain, and Kim and Kim [15], who showed a significant difference in pain by applying neck traction to patients with neck pain, and it is believed that myofascial release and neck traction reduced pain by reducing adhesions in pain-causing tissues and relieving nerve root compression and irritation. The study also showed a greater improvement in pain in the experimental group with myofascial release and neck traction compared to the control group ($p < .05$). Savva et al[36] showed a significant difference in pain in the experimental group that applied neck traction and manual therapy together compared to the control group that applied neck traction alone, and these results are similar to the results of this study, which showed that the combination of manual therapy and neck traction was effective in improving pain.

Chronic neck pain impairs neck motion and limits the function of the neck joints, which in turn leads to physical changes such as decreased range of motion, muscle fiber atrophy, decreased adaptability, joint adhesions, and abnormal posture [37]. In this study, neck flexion, extension, right and left side bending, and right and left rotation were measured using a neck goniometer. In both the experimental and control groups, there was a significant increase in range of motion in neck flexion, extension, right and left side bending, and left rotation from pre- to post-experiment ($p < .05$), with right rotation being significantly increased only in the experimental group ($p < .05$). The results of this study are similar to those of Kim and Lee [23], who showed a significant increase in range of motion after applying myofascial release to the trapezius, upper trapezius, and posterior cervical spine in 15 patients for 4 weeks, and Hong and Kim [38], who showed a significant increase in range of motion after applying neck traction for 4 weeks. The study also showed a significant difference between the experimental group and the control group in side bending and rotation ($p < .05$). This suggests that myofascial release induced a vaso-fluidic response in the tight fascia and muscles and atrophied muscles in patients with neck pain, altering the proprioceptive mechanisms of soft tissue, and that the relaxation of fascia and muscle tension helped to restore range of motion [39], and these results are similar to those of Moustaf and Diab [40], who reported that neck traction combined with other physiotherapy treatments was more effective in

reducing neck pain, dysfunction, and range of motion than neck traction alone.

In this study, the NDI was used to assess function in patients with chronic neck pain. There was a significant decrease in NDI scores from pre- to post-test in both the experimental and control groups ($p < .05$). It has been reported that neck pain and the NDI, which assesses neck dysfunction, correlate with each other and affect daily functioning [41]. Manuel and Ivan [24,25] showed improvement in pain and NDI by applying myofascial release to patients with chronic neck pain, and Jeon Jae-guk and Kim Myung-joon [39] showed a significant reduction in pain and neck dysfunction index by applying myofascial release for 5 to 10 minutes per session twice a week for a total of 4 weeks. In addition, Fritz et al [43] showed a significant difference in NDI and pain in the combined exercise and mechanical traction group, which is similar to the results of this study. This study also showed a greater improvement in NDI scores in the experimental group with myofascial release and neck traction compared to the control group ($p < .05$), which is similar to the results of Young et al [44], who reported that neck traction is a good treatment, but combining manual therapy and exercise with neck traction treatment helps to relieve pain and function, which may be related to the more significant reduction in NDI in the experimental group.

A systematic review by Hidalgo et al [45] reported that the combination of manual therapies such as physical therapy and myofascial release was more effective than either of them alone for patients with neck pain. Therefore, the combination of myofascial release and neck traction for patients with chronic neck pain seems to be an effective intervention. However, this study is limited by the small number of subjects and the lack of follow-up after the intervention, which makes it difficult to confirm the persistence of the intervention effect. Future studies should take these limitations into consideration and consider different approaches to applying myofascial release and neck traction to patients with chronic neck pain.

V. CONCULSION

To compare the effectiveness of an intervention program for patients with chronic neck pain, this study assigned patients to myofascial release and neck traction (experimental group) or neck traction (control group) and measured changes in neck pain, range of motion, and neck dysfunction index before and after a 4-week intervention. The conclusions were as follows Both the experimental group with myofascial release and neck traction and the control group with neck traction alone showed improvement in pain, range of motion, and neck dysfunction, but the experimental group showed better improvement in pain, range of motion, and neck dysfunction compared to the control group. Based on the above results, it can be concluded that myofascial release and neck traction are effective in reducing pain, range of motion, and neck dysfunction in patients with chronic neck pain, and it is recommended that myofascial release and neck traction should be combined as a more effective intervention method in the treatment of patients with chronic neck pain.

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Table 1: General Characteristics of all the Subjects

Variables	EG (n=7)	CG (n=7)	χ^2/t(p)
Gender (M/F)	3/4	4/3	.500(.626)
Age (yrs)	42.28±17.63[a]	43.00±10.59	-.092(.928)

M: Male, F: Female EG: Group that applied Myofascial release, Cervical traction and Preservation Physical Therapy, CG: Group that applied Cervical traction Preservation Physical Therapy, [a]Mean (㎜)±SD

Table 2: Comparison of Visual Analog Scale values between the Experimental and Control Groups (unit: score)

VAS	EG (n=7)	CG (n=7)	z	p
Pre	5.71±1.38[a]	5.00±1.15		
Post	3.42±1.71	4.00±0.81		
Diff	-2.28±0.75	-1.00±0.81	-2.660	.007*
z	-2.401	-2.070		
p	.016*	.038*		

[a]Mean (㎜)±SD, VAS: Visual Analogue Scale, EG: Group that applied Myofascial release, Cervical traction, and Preservation Physical Therapy, CG: Group that applied Cervical traction Preservation Physical Therapy, * : p < .05

Table 3: The Comparison of the Neck Range of Motion Angle Values Between the Experimental and Control Groups (Unit: °)

		EG (n=7)	CG (n=7)	z	p
NF	Pre	40.14±3.43[a]	36.42±3.15		
	Post	43.14±2.34	40.42±2.50		
	Diff	3.00±1.91	4.00±2.23	-.846	.456
	z	-2.214	-2.226		
	p	.027*	.026*		
NE	Pre	36.14±5.95	38.28±3.45		
	Post	39.42±2.87	42.14±3.13		
	Diff	3.28±3.55	3.86±1.57	-.388	.710
	z	-2.023	-2.384		
	p	.043*	.017*		
NRB	Pre	28.00±4.32	30.28±2.98		
	Post	36.00±3.91	32.71±2.81		
	Diff	8.00±3.82	2.43±0.97	-2.528	.011*
	z	-2.371	-2.388		
	p	.018*	.017*		
NLB	Pre	29.14±2.73	29.57±3.30		

	Post	34.28±3.77	32.00±2.38		
	Diff	5.14±1.34	2.42±2.29	-2.074	.038*
	z	-2.375	-2.226		
	p	.018*	.026*		
	Pre	47.14±6.89	46.00±6.21		
	Post	53.14±6.06	49.00±4.79		
NRR	Diff	6.00±2.16	3.00±2.00	-2.404	.017*
	z	-2.410	-2.214		
	p	.018*	.027*		
	Pre	46.28±7.38	46.42±6.39		
	Post	53.57±5.41	47.71±5.76		
NLR	Diff	7.29±3.89	1.29±2.28	-2.505	.011*
	z	-2.207	-1.380		
	p	.027*	.168		

[a]Mean (㎜)±SD, NF: neck flexion, NE: neck extension, NRB: neck right side bending, NLB: neck left side bending, NRR: neck right rotation, NLR: neck left rotation, EG: Group that applied Myofascial release, Cervical traction, and Preservation Physical Therapy, CG: Group that applied Cervical traction Preservation Physical Therapy, * : p < .05

Table 4: Comparison of the NDI values between the Experimental and Control Groups (unit: score)

NDI	EG (n=7)	CG (n=7)	z	p
Pre	18.85±5.33[a]	18.14±4.22		
Post	12.85±2.73	15.71±3.72		
Diff	-6.00±2.50	-2.42±0.78	2.849	.004*
z	-2.388	-2.456		
p	.017*	.014*		

[a]Mean(㎜)±SD, NDI: Neck Disability Index, EG: Group that applied Myofascial release, Cervical traction, and Preservation Physical Therapy, CG: Group that applied Cervical traction Preservation Physical Therapy, * : p < .05

Fig. 1: Cervical Range of Motion (CROM)

	Content	Photo
Upper trapezius myofascial release	With the patient in an upright position, the therapist's hands are crossed, with one hand on the nuchal ligament and the other on the acromion and the therapist gently compresses and then gently extends while holding the compression for 90 to 120 seconds.	
Levator scapulae myofascial release	With the patient in the upright position and the patient's head turned, the therapist applies and maintains to the transverse process of C1 and drives toward the superior angle of the shoulder blade for 90 to 120 seconds.	
Sternocleido mastoid myofascial release	With the patient in the upright position, the therapist palpates the cervical spine with the patient's head turned, gently compresses the cervical spine, and holds the compression while slowly traveling from the cervical spine toward the clavicle and sternum for 90 to 120 seconds.	
Suboccipital myofascial release	With the patient in an upright position, the therapist supports the patient's head with the palms of both hands and uses the tips of the index to ring fingers to gently compress the suboccipital region of the back of the head for 90 to 120 seconds, followed by a gentle pull toward the therapist for 60 seconds.	

Fig. 2: Myofascial Release

Fig. 3: Cervical Traction

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A Multicenter, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Long-Acting Injectable Formulation of Vanoxerine (Vanoxerine Consta 394.2 Mg) for Treatment of Amphetamine-Type Stimulant (ATS) Dependence

Sead Kadric M. D., Ph. D.

ABSTRACT

Objective: To determine efficacy and tolerability of a long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) for treatment of Amphetamine-Type Stimulant (ATS) dependent patients.

Design, Setting, and Participants: A 12 weeks, A multicenter, randomized, placebo-controlled trial conducted between November 2022--- December 2023, at 16 Hospital-based drug clinics, in the 15 countries. Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 Stimulant Use Disorder Amphetamine-Type (ATS). Of the 4000 individuals screened, 3300 (82.5%) adults were randomized, 1650 participants to receive injections of Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) given intramuscularly once in 12 weeks and 1650 participants to receive Placebo injections, given intramuscularly once in 12 weeks.

Keywords: vanoxerine consta, long-acting depot formulations of vanoxerine, stimulant (amphetamine- type substances/ATS) dependence, long- term delivery, PLGA polymers.

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Main Outcomes And Measures: The primary endpoints (protocol) were: Confirmed ATS abstinence (percentage ie. the number of patients who achieved complete abstinence during week 12). Confirmed abstinence or "ATS -free" was defined as a negative urine drug test for ATS and no self-reported ATS use. Secondary end points included number of days in treatment, treatment retention and craving.

The study also investigated, on 1650 participant the plasma concentration of Vanoxerine and 17-hydroxyl Vanoxerine. Safety was assessed by adverse event reporting.

Results: Of 1650 participants Vanoxerine Group (N=1650), mean (SD) age was 38.7 (9.8) years and 300 (18.2 %) were women. Of 1650 participants Placebo Group (N=1650), mean (SD) age was 39.5 (10.4) years and 300 (18.2 %) were women. 1650 individuals were randomized to receive injections of Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) and 1650 to receive injections of Placebo. 1749 participants (53.0%) completed the trial.

Primary endpoints: Confirmed ATS abstinence

Complete abstinence was sustained by 69 % (n=1138) of Vanoxerine patients (patients treated with Vanoxerine Consta 394.2 mg, long-acting depot formulations) compared with 36.7% (n=605) of patients treated with Placebo, during weeks 5–12. The difference was significant as evaluated using a Chi-square test ($\chi 2 = 672.34$, $P < .0001$).

Secondary endpoint: Craving

A statistically and clinically significant reduction in Stimulant ATS craving was observed with Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) vs. Placebo by week 4 (P=0.0048), which persisted every week through 12 (P<0.0001). Patients given Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) had a 85% decrease in craving from baseline to week 12. Patients given a Placebo had a 2% increase in craving from baseline to week 12.

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Secondary endpoint: Treatment Retention

Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) helped significantly more patients complete 12 weeks treatment (n=1138, 69%) compared with Placebo (n=605, 36.7%) ($\chi 2 = 635.53$, $P < .0001$). Patients on long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) had longer treatment retention than patients on Placebo.

Concentrations of Vanoxerine and 17-hydroxyl Vanoxerine in plasma

Analyses were made of 300 study sample. There was no statistically significant difference for plasma Vanoxerine concentrations between days 2 and 84 (p=0.416). The plasma concentration of Vanoxerine were 70.4 and 94.3 ng/ml and concentrations of 17-hydroxyl Vanoxerine were 10.5 and 13.2 ng/ml, respectively. Plasma levels of Vanoxerine remained above 70 ng/ml for approximately 12 weeks after administration of Vanoxerine, long-acting depot formulations (Vanoxerine Consta 394.2 mg).

Adverse reactions

Adverse events were similar in ATS -dependent patients treated with long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) vs. patients treated with Placebo.

Conclusions And Relevance: Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) was more effective then Placebo injection in maintaining short-term abstinence from ATS and should be considered as a treatment option ATS -dependent individuals.

Keywords: vanoxerine consta, long-acting depot formulations of vanoxerine, stimulant (amphetamine- type substances/ATS) dependence, long-term delivery, PLGA polymers.

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I. INTRODUCTION

In the last decades, an ever-growing prevalence of people who use ATS has been reported in various regions of the world [1-3]. According to the World Drug Report 2022, 34 million people used amphetamines in the year 2020 alone [2]. ATS use disorder (ATSUD) has turned into a major health issue globally, with an estimated age-standardized prevalence of 64.7 cases per 100 000 people in 2016 [1]. An estimated 52 million people worldwide used ATS such as amphetamine, methamphetamine and MDMA in the past year for non-medical purposes, second only to marijuana and more than heroin and cocaine combined[1]. In the United States and Europe, admissions to publicly-funded treatment programs for ATS-related problems showed an overall increase from 5.7% to 7.7% between 2010 and 2020[2].

ATS (Methamphetamine (crystal meth, crank, speed, tweek, glass, etc.) are a psychostimulants that is highly addictive and affects monoamine neurotransmitter systems [1]. Methamphetamine and related stimulants are the second most frequently used illicit drugs worldwide. It is estimated that more than 35 million people around the world use this class of substance [2–4]. ATS dependence is associated with a number of psychiatric disorders including depression and psychosis [5–7]. Furthermore, ATS use is accompanied with various medical consequences such as myocardial infarction, renal failure, cerebral hemorrhage, muscle damage, nasal and sinus damage and sudden death [8–12].

ATS abuse and dependence have become a major health problem imposing a great burden on the society [13–15]. In recent years, a dramatic rise in ATS use has occurred in many countries [16].

Despite the alarming prevalence and severe socio-medical consequences, there is still no established pharmacotherapy recommendation for the treatment of ATSUD. Although proven pharmacotherapies are available for alcohol and heroin dependence none exist for ATS dependence despite two decades of clinical trials primarily involving antidepressants, anticonvulsants, and dopaminergic medications. Clinicians

rely mainly upon psychosocial-based interventions, which are found to offer short-term efficacy and are accompanied by difficulties in implementation [17-19]. As current modalities have limited efficacy, recent studies indicate that more than 60% of the population receiving treatment for ATSUD relapse within the first 12 months with a small percentage in remission after 5 years [20].

Multiple groups have tried to establish a pharmacological treatment framework to improve the standard of care for ATSUD based on the available evidence [17,18, 21]. In most cases, however, the varying quality of primary studies, the heterogeneity of reported results and insufficient sample size have prevented authors from conducting a meta-analysis or issuing any official recommendations [19,22]. Nonetheless, in most of these studies, agonist therapy using prescription psychostimulants (PPs) possessed the strongest evidence of efficacy and has been discussed as the most likely class to have the potential for the treatment of ATSUD [18, 22, 23].

It has been argued that agonist therapy using PPs could potentially be a viable strategy in this population and reduce harms associated with ATSUD, with limited adverse events [23]. Of note, agonist therapy for opioid use disorder is a standard of care that has led to significant harm and mortality reduction. Such a widespread strategy for the treatment of ATSUD has not been established due to limited evidence [18, 22, 24, 25] and should be properly assessed; given many differences between stimulant and opioid use disorders, for example, there are often periods of stimulant high-dose binge use followed by cessation and withdrawal, while opioid users frequently try to maintain a desired level of opioid effect which is targeted by agonist therapy [26].

In the last decade, many medications have been used for treatment of methamphetamine dependence including modafinil, antidepressants, ondansetron, risperidone, aripiprazole, baclofen, topiramate, N-acetyl cysteine, naltrexone, and gabapentin, but none demonstrated consistent efficacy [2,10,13,26–33]. Some studies suggested sustained-release dextroamphetamine and methylphenidate as effective pharmacotherapy for methamphetamine (MA) dependence [34–38]. Given that methylphenidate antagonizes the effects of methamphetamine in vitro, some researchers have tried it as a potential candidate for treatment of methamphetamine dependence [39,40]. Some studies questioned the notion of replacement therapy for amphetamine dependence (a cochrane review) [44].

Prior clinical trials have investigated medications that target dysregulation among the various neurotransmitter systems affected by chronic MA use. Early studies documented some promise for bupropion as a treatment for MA dependence, (45-47) given its ability to increase intrasynaptic dopamine and possibly ameliorate MA induced DA dysregulation. However, later studies failed to replicate these findings, although bupropion reduced MA use in those with mild to moderate levels of MA use. (45-48) Other antidepressants, including fluoxetine, paroxetine, mirtazapine and sertraline, have also been investigated. (49-52) Of these, only mirtazapine significantly reduced MA use. (50) Antipsychotics (aripiprazole, risperidone), antiepileptics (topiramate, vigabatrin, gabapentin), and other agents (dextroamphetamine, odansetron, varenicline, baclofen, modafinil, N-acetyl cysteine+naltrexone, and the proprietary approach Prometa®) either failed to demonstrate efficacy or have yet to be studied in large placebo controlled clinical trials. (53-66). Although many compounds have been evaluated for the treatment of cocaine dependence, none has been approved for this indication. Psychosocial and behavioral therapy are currently the treatments of choice for ATS dependence [67].

An effective pharmacotherapy has long been sought to improve treatment outcomes, particularly since this disorder has a significant neurobiological basis. Effective pharmacotherapy to improve treatment outcomes has long been sought, especially since this disorder has a significant neurobiological basis. Mesolimbic dopamine is a key neurochemical mediator of rewarding behaviors, for example, eating and sex [68]. In vivo microdialysis studies have shown that extracellular dopamine levels increase in the nucleus accumbens of humans who engage in

rewarding behaviors, such as self-administration of ATS. The drug's ability to raise mesolimbic extracellular dopamine levels is believed to be critical to its abuse, and those drugs that inhibit dopamine reuptake, resulting in addictive and euphorogenic effects, are classified as “type 1 blockers” [69]. There is a constant and growing need for pharmacotherapies that allow for the treatment of more drug addicts than would otherwise be possible with non-pharmacological treatment modalities and that can be linked to more traditional treatment approaches, such as counseling and rehabilitation [70]. One pharmacotherapeutic approach is the development of a competitive antagonist of the ATS, i.e. a drug that will bind to the dopamine transporter, but will not inhibit dopamine reuptake [71]. Such an ATS antagonist would be expected to block the stimulus from increasing extracellular dopamine levels. However, the patient could overcome the inhibitory effect of the competitive antagonist of the stimulus by self-administering more of the stimulus. Another pharmacotherapeutic approach is the development of a noncompetitive antagonist of ATS. A noncompetitive antagonist of an ATS would be one that binds to the dopamine transporter with high affinity and slowly dissociates [72]. A non-competitive antagonist of an ATS would then allow for a sustained increase in extracellular dopamine levels, thus providing the addict with relief from dopamine-deficient stimulant cravings, while also inhibiting the stimulant from further elevating extracellular dopamine levels and increasing the likelihood of increased toxic side effects [7]. One such noncompetitive antagonist of ATS is the compound 1-[2-[bis(4-fluorophenyl) methoxy]e-thyl]-4-[3-phenylpropyl] piperazine, otherwise known as Vanoxerine. Vanoxerine is a selective dopamine reuptake inhibitor and is about 700 times more potent than cocaine in inhibiting dopamine reuptake in vitro. However, unlike cocaine, Vanoxerine inhibition of dopamine reuptake does not lead to addictive and euphorogenic effects and thus Vanoxerine is considered a "type II blocker". In addition, although cocaine and Vanoxerine produce equivalent motor stimulant effects, Vanoxerine must occupy the dopamine transporter to a greater extent than cocaine to produce equivalent behavioral effects. Similarly, although cocaine and Vanoxerine cause dose-dependent increases in extracellular dopamine when administered alone, cocaine causes a rapid and short-lived increase in dopamine, whereas Vanoxerine causes a low and sustained increase in dopamine [73].

There are currently no drugs available that effectively block the acute effects of ATS. We have shown that (1- [2- [bis (4-fluorophenyl) methoxy] ethyl] -4- [3-phenylpropyl] piperazine, known as Vanoxerine, acts as an ATS antagonist. The study presented here provides means that it blocks the acute effects ATS: ^]ethyl]-4-[3-phenylpropyl] piperazine (Vanoxerine) acts as an ATS antagonist [74] Vanoxerine has been used as a dopamine antagonist for the treatment of cocaine addiction and as a dopamine agonist for parkinsonism. acromegaly, hyperprolactinemia and diseases arising from a hypofunction of the dopaminergic system [75].

However, the method of the study using Vanoxerine and analogs thereof as cocaine antagonists was previously known. Methods are disclosed for treating cocaine addiction, acute effects of cocaine, and cocaine craving.

However, the use of Vanoxerine and its analogs as ATS antagonists was not known. Treatment methods can prevent intoxication with ATS and prevent relapse during and after treatment. Safe and effective means of counteracting drug abuse are needed. The studies disclosed herein provides a means for blocking the acute effects of such drugs [76]. By decreasing or limiting the "high" effect of dosing with euphoria producing drugs, the method of treatment can counteract ATS intoxication and prevent relapse into drug use during and after treatment. Although drug treatments for ATS craving are available, there are currently no drugs available which will effectively block the acute effects of ATS. The drug, Vanoxerine Consta®, presented in this study acts as a ATS antagonist. We believe that the ability of Vanoxerine Consta® to bind tightly to, and dissociate slowly from, the dopamine reuptake complex, is the underlying mechanism responsible for its ATS antagonist activity. It has

been demonstrated that Vanoxerine Consta® act as a cocaine antagonist for extended intervals, ranging from a few weeks to 3 months [77]. The present study provides sustained-release derivatives of hydroxylated analogs of substituted 1[2[bis(aryl)methoxy]ethyl]-piperazines known as Vanoxerine, pharmaceutical compositions comprising the same, and a method of using such sustained-release derivatives to bind the dopamine transporter to achieve a desired effect, such as antagonism of dopamine reuptake inhibitors, such as amphetamine and cocaine, or dopamine releasers or norepinephrine and/or serotonin reuptake inhibitors, such as ATS ((methamphetamine (crystal meth, crank, speed, tweek, glass, etc.)) [78]. Since it is believed that the inhibition of DA reuptake is thought to be the major neurochemical mechanism responsible for the addictive properties of cocaine, PCP, amphetamine and methamphetamine, these agents also interact with the reuptake carriers for serotonin and norepinephrine. The treatment of these addictions is also within the scope of our research wherein treatment effects the DA reuptake complex, since these drugs also bind tightly (reversibly or irreversibly) to the serotonin or norepinephrine reuptake carriers [79].

Vanoxerine Consta® is supplied as a microsphere formulation of Vanoxerine[80]. The active ingredient in Vanoxerine Consta ®— Vanoxerine is an antagonist of dopamine transporter (DAT1) with Ki value of 16.9nM. Vanoxerine, is a potent and selective dopamine reuptake inhibitor (DRI). Vanoxerine binds to the target site on the dopamine transporter (DAT) ~ 50 times more strongly than cocaine, but simultaneously inhibits the release of dopamine[81]. This combined effect only slightly elevates dopamine levels and block the rewarding effects of ATS. Vanoxerine is one of the most potent inhibitors of dopamine (DA) reuptake, binds persistently to the DA transporter, resulting in a modest increase in the extracellular levels of DA (ECDA) in the caudate nucleus, as well as an attenuation of the ability of ATS to elevate ECDA levels[82]. Vanoxerine blocker' the acute effects of ATS, and the effect occurs immediately after drug administration.Vanoxerine is chemically designated 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine [83].

Long-Acting Injection Vanoxerine Consta ® is a combination of extended-release microspheres Vanoxerine for injection. Vanoxerine is microencapsulated in 7011-18819 polylactide-co-glycolide (PLG). Over the years, several polymers have been evaluated for development of controlled release injectable formulations [84]. Of these polymers, one class of polymers has achieved significant commercial success in the pharmaceuticalmarket. The polylactide (PLA) and polylactide-co-glycolide (PLGA) class of polymers are biodegradable, biocompatible, and nontoxic and have a long history of use[85]. In vivo, they are hydrolyzed into metabolic products that are easily eliminated fromthe body. Initially approved for surgical use in humans they have since been used to formulate a wide range of therapeutic agents. PLGA polymers are well suited for controlled delivery of drugs via the parenteral route as they exhibit good mechanical properties and demonstrate predictable degradation kinetics. Notably, polymeric microspheres prepared using PLGA have been successful in ensuring sustained release of therapeutic agents for various drugs [86]. Several examples in literature discuss their effectiveness in providing targeted drug levels in vivo, for long periods of time. For this reason, they are popular as delivery vehicles for drugs where sustained release is desired for extended intervals, ranging from a few weeks to 12 months[87]. The success of PLGA polymers as delivery systems is due to the fact that polymer properties are well understood and can be customized to afford sustained drug release. For instance, selection of copolymers of various lactide: glycolide with variable molecular weights is an effective way to control polymer degradation rate and drug release. By changing the composition of lactide or glycolide in the copolymer, a wide range of degradation rates can be obtained. An increase in the more hydrophobic lactide moiety ensures a slower degradation rate of the PLGA polymer leading to extended duration of drug release[88].

Similarly, utilization of a higher molecular weight copolymer increases degradation times leading to prolonged drug release. Additional properties that

can be varied include polymer crystallinity and glass transition temperature. These physical and chemical properties have been well studied and characterized leading to predictable degradation kinetics of the PLGA polymer, in vitro and/or in vivo[89]. Upon in vivo administration of a PLGA based injectable depot, water interacts with the polymer and hydrolysis of the ester bonds commences. As the polymer degrades, its hydrophobicity decreases and the number of hydrophilic hydroxyl and carboxylic acid end groups in the matrix increases. An accumulation of hydrophilic acidic end groups has a two fold effect: (1) it increases the amount of water incursion into the polymer and (2) initiates autocatalysis of the polymer matrix. Therefore, polymer degradation and, consequently, drug release from PLGA is a very complex and dynamic process. The studie presented a report of the results of a 3-month double-blind phase in terms of the effectiveness and safety of Vanoxerine Consta® for the treatment of ATS dependence.

The results showed efficacy through an adequate and well-controlled study conducted at several locations in Austria, Bulgaria, Canada, Czech Republic, Germany, Portugal, Romania, Russian Federation, Republic of Angola, Republic of Korea, Republic of Serbia, Spain, Switzerland, Ukraine, UK and United States, with supportive evidence from their clinical pharmacology program.

During treatment with Vanoxerine Consta, ATS desire is reduced, abstinence is supported, and relapses and ATS consumption decreased. Also, supportive pharmacological studies have demonstrated the blocking of ATS effect over 84 days. The depot formulation of Vanoxerine used in the current study provided a safe, effective and long-lasting antagonism of the effects of cocaine.

Pharmacokinetic: Concentrations of Vanoxerine and 17-hydroxyl Vanoxerinein plasma.

Analyses were made of 300 study sample. The plasma concentration of Vanoxerine were 70.4 and 94.3 ng/ml and concentrations of 17-hydroxyl Vanoxerine were 10.5 and 13.2 ng/ml, respectively. Blood samples for pharmacokinetic analyses were collected at day 1, 4, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48,52, 56, 60, 64, 68,72, 76, 80 and 84 after the doses. Concentrations of the drug and its metabolite in plasma indicate the stability of intact analytes in analytical conditions, including hydrolysis. 84 days after the administration of Vanoxerine, the plasma concentration of Vanoxerine was at the lower limit of quantification. The maximum plasma concentration of the drug (Cmax) was 12 h after dosing Vanoxerine Consta 394.2 mg. There was no statistically significant difference between plasma concentrations of Vanoxerine and Central Dopamine transporter receptor occupancy by Vanoxerine between days 1 and 84 (medium limit of quantification).

The depot formulation of Vanoxerine used in the current study provided a safe, effective and long-lasting antagonism of the effects of cocaines.

II. METHODS

This randomized clinical trial received 3300 patients in a clinical setting for treatment with long-acting injection of Vanoxerine (Vanoxerine Consta 394.2 mg) given intramuscularly once in 12 weeks compared to Placebo injection given intramuscularly once in 12 weeks. The inclusion was discontinued on January 30, 2022, and the last patient monitoring was carried out on December 18, 2023. The study was approved by the State Committee for Medical and Health Ethics, State Medicines Agency and research ethics committees in the participating countries and hospitals. The monitoring study was conducted by publicly funded supervisory authorities in accordance with good clinical practice standards. The participants gave a written informed consent.

A 12 weeks, A multicenter, randomized, placebo-controlled trial conducted between November 2022--- December 2023, at 15 Hospital-based drug clinics, in the 16 countries.

Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 Stimulant Use Disorder Amphetamine-Type Substance. Of the 4000 individuals screened, 3300 (82.5%) adults were randomized 1650 participants to receive injections of

Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) given intramuscularly once in 12 weeks and 1650 participants to receive Placebo injections, given intramuscularly once in 12 weeks.

Of 1650 participants Vanoxerine Group (N=1650), mean (SD) age was 38.7 (9.8) years and 300 (18.2 %) were women. Of 1650 participants Placebo Group (N=1650), mean (SD) age was 39.5 (10.4) years and 300 (18.2 %) were women. 1650 individuals were randomized to receive injections of Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) and 1650 to receive injections of Placebo. 1749 participants (53.0%) completed the trial.

2.1 Participants and Setting

Patients were recruited from January 25, 2021 to January 30, 2022 by research staff from 16 hospital clinics and detoxification units in 15 countries. Eligible participants were ATS-dependent (according to DSM-IV criteria) men or women aged 18 to 50 years. Exclusion criteria were dependence on other drugs or alcohol or a history of seizures or brain injury, a sensitivity or previous adverse reaction to Vanoxerine, any medical, neurological, or psychiatric disorder that would make study compliance difficult or unsafe, first-degree relatives with early cardiovascular morbidity or mortality, and being pregnant or nursing. Participants were also excluded if they were prescribed medications that could interact with the study medication. (*Table 1)*

Table 1: Criteria

Ages Eligible for Study:	18 Years to 50 Years (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No
Inclusion Criteria:	Exclusion Criteria:
Written, informed consent	Current or history of a major psychiatric illness, other than drug dependence or disorders secondary to drug abuse
18 years of age or older	Meets DSM-IV criteria for dependence on any drugs other than amphetamine-type stimulants,
Meets DSM-IV criteria for current cocaine dependence	Physiologically dependent on alcohol and requires medical detoxification
Currently seeking treatment for cocaine dependence	Use of prescription drugs within 14 days prior to study entry
Currently Not uses cocaine, as determined by a self-report and a negative urine test for cocaine, within 30 days prior to study entry	Use of non-prescription drugs within 7 days prior to study entry
Good general health	If female, used an oral contraceptive, Depo-Provera, Norplant, or intrauterine progesterone contraceptive system, within 30 days prior to study entry
Normal electrocardiogram	Pregnant or breastfeeding
Noncustodial, stable residence and phone, plus 1 contact with verifiable address and phone	History of liver disease and evidence of hepatic failure
Significant other (eg, spouse, relative) willing to supervise compliance with the study visit schedule and procedures	Current elevated aspartate aminotransferase or alanine aminotransferase levels
Completing or recently completed up to 30 days of inpatient treatment for cocaine detoxification for at least 7 days	Participated in any other clinical investigation within 4 weeks prior to study entry
Able to provide written informed consent	History of any illness or behavior that, in the opinion of the investigator, might interfere with the study
Able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study	Family history of early significant cardiovascular disease or mortality

	Clinically significant medical condition or observed abnormalities (eg: physical exam, electrocardiogram (ECG), lab and/or urinalysis findings)
	Current major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would compromise ability to complete the study
	Known intolerance and/or hypersensitivity to Vanoxerine or polylactide-co-glycolide (PLG)

Women in reproductive age could not be pregnant or breast-feeding and agreed to use effective birth control. Participants were screened for psychiatric disorders and examined for severe somatic illness. Routine blood tests (complete blood cell counts, electrolytes, and levels of ALT/AST) and urinalysis were completed as part of usual treatment before study enrollment. Assessments added for the study included a detailed history of drug use and psychiatric interview to confirm current ATSdependence; urine testing for ATSand alcohol breath test; Addiction Severity Index; pregnancy test; monthly measurements of ALT and AST levels while receiving medication; cocaine craving (visual analog scale); Global Assessment of Functioning; Brief Psychiatric Rating Scale; and visual inspection of the site 5 to 7 days after implantation (*Table 2)*. Urine drug testing was performed at biweekly counseling sessions.

Eligible participants were referred to the detoxification unit after examination and inclusion. The study took place at the hospital facility, and all participants were discharged from the detoxification unit and are in the process of hospital treatment. Ethnicity is defined by the participants.

Table 2: Lifetime and Baseline Clinical Characteristics of Participants Randomized Into Treatment Groups

	long-acting Vanoxerine (Vanoxerine Consta 394.2 mg) (n=1650)	Placebo (n=1650)
Age in years	38.7 (±5.5)	39.5 (±4.6)
Men	1350 (81.8%)	1350 (81.8%)
Female	300 (18.2%)	300 (18.2%)
Marital status	No. (%)	No. (%)
Never married	841 (51%)	874 (53%)
Married/de facto	495 (30%)	511 (31%)
Divorced/separated	313 (19%)	264 (16%)
Race	No. (%)	No. (%)
White	1031(62,5%)	1047(63,5%)
Black	379(23%)	379(23%)
Others	239 (14,5%)	305 (18,5%)
Employment status	No. (%)	No. (%)
Student	396 (24%)	478 (29%)
Employed (full/part time)	709 (43%)	660 (40%)
Unemployed/pension	495 (30%)	495 (30%)
Duration of ATS dependence in years	10.8 (7.8)	11.9 (9.9)
Distribution of Duration of ATSDependence	No. (%)	No. (%)
<2 years	165 (10%)	165 (10%)
2-4 years	214 (13%)	231 (14%)
4-6 years	363 (22%)	379 (23%)
>5 years	907 (55%)	858 (52%)
ATScraving scale	20 (±2)	20 (±2)
Hepatitis C positive	214 (13%)	239 (14.5%)

2.2 Procedure and Outcomes

After detoxification, participants were randomly assigned (1:1) to commence either administration of injections of Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) given intramuscularly once in 12 weeks or administration of injections of Placebo given intramuscularly once in 12 weeks. Allocation to treatment group was computerized using a permuted block algorithm provided by the state monitoring authority and not stratified for site or sex. Following induction into either medication regimen, participants were asked to attend standard drug counseling, but no behavioral interventions could be initiated. At baseline (inclusion) and every 4 weeks thereafter, patients underwent a structured interview using the European version of the Addiction Severity Index covering drug use, physical and mental health, work, education, and criminal activity.

Primary outcome variables Confirmed ATS abstinence (percentage ie. the number of patients who achieved complete abstinence during week 12) or " ATS-free" was defined as a negative urine drug test for ATS and no self-reported ATS use. The twice a week UDTs were analyzed using specific chromatographic methods and calculated as the number of ATS-negative urine drug screens divided by the total number of attended tests (group proportion) in accordance with recently revised Cochrane guidelines. Missing UDTs were considered as testing positive for ATS in all participants. Secondary outcome variables were comparison of retention in the study, number of days in treatment, the degree of ATS craving (Minnesota Cocaine Craving Scale (MCCS): Composed of five items which correspond to intensity, frequency, duration of craving, changes in relation to previous week and craving response to medication), and mental health (Hopkins Symptom Checklist-25 of anxiety and depression, 25-100, with 25 indicating very low; 100, very high). Retention in treatment was defined as the number of days until dropout from study medication and by the number of patients completing the study at week 12.

Pharmacokinetic studies: The plasma concentration of Vanoxerine and plasma concentrations of Vanoxerine-3-O- glucuronide.

Analyses were made of 275 study sample. Blood samples for pharmacokinetic analyses were collected at day 1, 4, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48,52, 56, 60, 64, 68,72, 76, 80 and 84 after the doses.

2.3 Pharmacokinetic Studies Protocol

Blood samples were collected through an indwelling plastic cannula, inserted into a superficial upper arm vein, into tubes containing anticoagulant Li-heparin. They were drawn at given time points, centrifuged, and plasma was separated within 1 h of sampling. The plasma specimens were frozen at -20°C or colder until analyzed. Vanoxerine and 17-hydroxyl Vanoxerine were extracted from plasma with ethyl acetate. The organic layer was transferred to clean tubes and evaporated to dryness. The residue was reconstituted in mobile phase and aliquots were injected into a high-pressure liquid chromatography–mass spectrometry system. Two analyses were made of each study sample: determination of intact Vanoxerine and Vanoxerine-3-O-glucuronide, and determination of total concentration of the analytes. A set of plasma standards containing 40–120 ng/ml of Vanoxerine and 17-hydroxyl Vanoxerine in drug-free plasma was used to construct a calibration curve for each batch of plasma samples. Four quality control samples containing 40, 60, 80, and 120 ng/ml of Vanoxerine and 17-hydroxyl Vanoxerine were analyzed in duplicate in each batch of study samples. The interbatch precision (CV%) for Vanoxerine was from 4.3 to 7.3% and for 17-hydroxyl Vanoxerine from 4.3 to 10.8% . Total concentration was analyzed with calibration range from 25 to 150 ng/ml. Two spiked and two pooled control samples were analyzed in duplicate in each sample batch. The spiked control samples (40 and 120 ng/ml) were made by spiking drug-free plasma with Vanoxerine and 17-hydroxyl Vanoxerine solutions to contain known concentrations of the analytes. The pooled controls were made by pooling plasma of previously analyzed study samples. Concentra-

tions of Vanoxerine in plasma pools were 71 and 94 ng/ml and concentrations of 17-hydroxyl Vanoxerine 10.5 and 13.2 ng/ml, respectively. The spiked plasma controls indicated stability of intact analytes under analytical conditions. The interbatch precision (CV%) was from 2.8 to 6.8% for Vanoxerine and from 4.2 to 6.6% for Vanoxerine-3-O- glucuronide. Pharmacokinetic variables of Vanoxerine and 17-hydroxyl Vanoxerine were determined from the concentration–time data by the PCNONLIN software using noncompartmental methods. Peak concentration (Cmax), taken as the maximum observed concentration in plasma, and time to peak concentration (tmax) were observed. After injection of Vanoxerine Consta 394.2 mg, area under the plasma concentration–time curve from time zero to infinity (AUC) was calculated by the trapezoidal rule to the last observed concentration with extrapolation to infinity by dividing the last observed concentration by the elimination rate constant. The effect of minor deviations from the planned blood sampling times in the pharmacokinetic analysis was cancelled out by using actual sampling times in calculations.

2.4 Statistical Analysis

The target sample size was based on the width of the 95% CI for the hazard ratio (HR) of the difference between treatments (Vanoxerine vs Placebo), projecting relapse-free survival of about 50% for each medication after induction. On the basis of simulation results, the 95% CI width for HR decreases as the sample size increases by 120 per group to 720 per group (from a base of 400 per group) by 31%, 19%, 14%, and 11%, respectively. A preplanned interim analysis increased the overall target sample size from an initial 1000 participants to about 3300 participants to achieve a minimum sample of 1950 participants in the late randomisation group.

Sample size calculations indicated that 1950 participants would yield a similar (only slightly wider) 95% CI to the original sample size target of 1000 participants, and preserved the aim to achieve a precise estimate of the difference in relapses between groups. We analysed endpoints according to the intention-to-treat principle as part of the primary analysis and additionally among a per-protocol population.

The per-protocol population consisted of only those participants who were successfully inducted onto an initial dose of study medication.The primary outcome analysis was the construction of the asymptotic 95% CI for the HR of the difference between the treatment groups among the intention-to-treat population in the time-to-event (relapse) distribution with the earliest relapse day assessed at day 21. We administratively censored participants at week 12.

The binary baseline covariate of early versus late randomisation was examined for an interaction with treatment; this covariate was not significant (p>0·10), and thus dropped from the final model. Unadjusted Kaplan-Meier survival curves and the extended Cox model HRs compared relapse by group. We examined the proportional hazard assumption via the interaction of treatment and time. Logistic regression yielding odds ratios contrasted induction success and overall 12 week ATS relapse by group. We used Pearson's χ^2 or Fisher's exact tests, and logistic regression for analyses of dichotomous secondary outcomes. We used Cox models for time- to-event secondary outcomes and Wilcoxon rank-sum tests and mixed effects models for continuous outcomes. We considered missing urine samples to be ATS positive and contributed to the definition of a relapse event. Thus, treatment dropouts (who stopped contributing data) were scored as having relapsed, an assumption which is likely in this population. Adverse events were compared using Fisher exact test. Retention in treatment was assessed by a logrank test. The results at $P < 0.05$ were considered significant in all superiority analyses. The noninferiority analyses were assessed by 1-sided test at the same significance level. Statistical analyses were conducted by a study-independent statistician blinded to the names of the study medications. The analyses were performed in SPSS, version 24 (SPSS Corp) and SAS, version 9.4 (SAS Institute).

Pharmacokinetic parameters ($AUC_{\tau,\infty}$, C_{max}) were analyzed using repeated measures analysis of variance. Natural logarithm transformation was

used for these variables in order to achieve normality, if needed. No additional covariates were used in the statistical model. Time to peak concentration (t_{max}) of each period was analyzed using a Wilcoxon signed-ranks test. Terminal half- life ($t_{1/2}$) was analyzed using repeated measures analysis of variance or Wilcoxon signed-ranks test, depending on the distribution. The limit of statistical significance for all analyses was set at $p<0.05$, and 90% confidence intervals for the ratios of geometric means (Vanoxerine Consta 394.2 mg / Placebo, Placebo380 mg) were calculated. Safety variables were analyzed by descriptive statistics. Statistical analyses were performed with the SAS for Windows version 9.4 (SAS Institute).

III. RESULTS

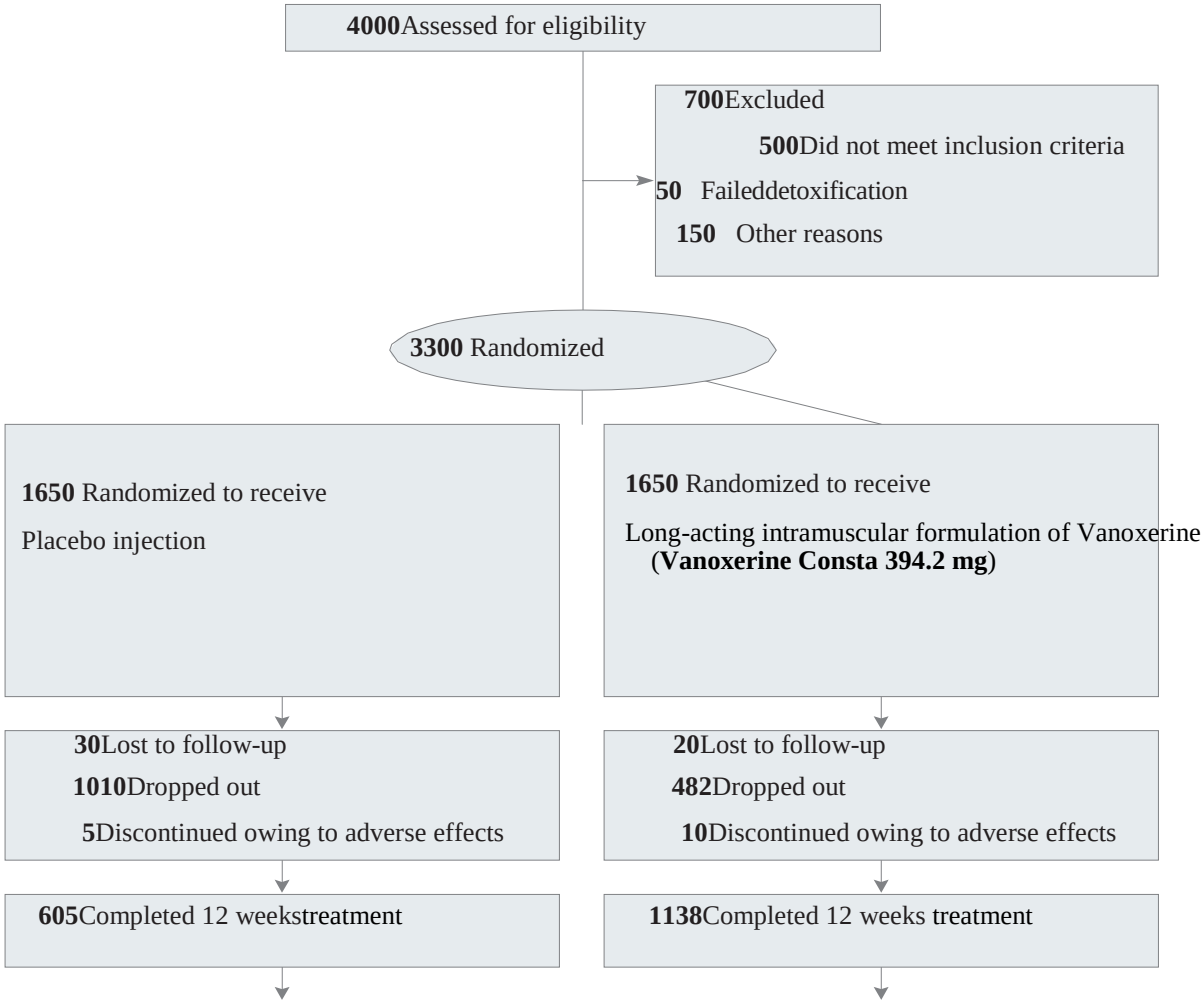


Figure 1: Flowchart for Inclusion of Participants

3.1 Patient Characteristics

Men and women displayed similar age distributions, 38.7 (9.8) and 39.5 (10.4) years, respectively), years of heavy ATS use (mean, 3.5 (±2.5) and 2.0 (±0.9) respectively and other social characteristics. 63% (±1) of the participants were white. 13 % (±1.5) participants tested seropositive for hepatitis C. *(Table 1, Table 2)*

3.2 Retention in Treatment

Among the 4000 participants assessed for eligibility, 3300 were included in the study and 1650 were randomized to treatment with Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) (n=1650, 50 %) or Placebo (n=1650, 50%) *(Figure 1).*

Reasons for exclusion of 700 individuals were not meeting inclusion criteria (500 [71%]), failed detoxification (50 [7.1%]) and other reasons (150 [21%]). Among the randomized participants, 3300 agreed to commence their medication: 1650 (50%) in the Long-acting intramuscular formulation of Vanoxerine group and 1650 (50%) in the Placebo group. Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) helped significantly more patients complete 12 weeks treatment (n=1138, 68.9%) compared with Placebo (n=605, 36.6%) ($\chi 2$ = 635.53, P < .0001) *(Figure 2)*. Of the Vanoxerine Consta 394.2 mg group that began the study, 68.9 % (1138 /1650) completed the full 12 weeks of treatment compared to Placebo group where 36.6 % (605 /1650) completed the full 12 weeks of treatment. Patients on long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) had longer treatment retention than patients on Placebo *(Figure 3)*.

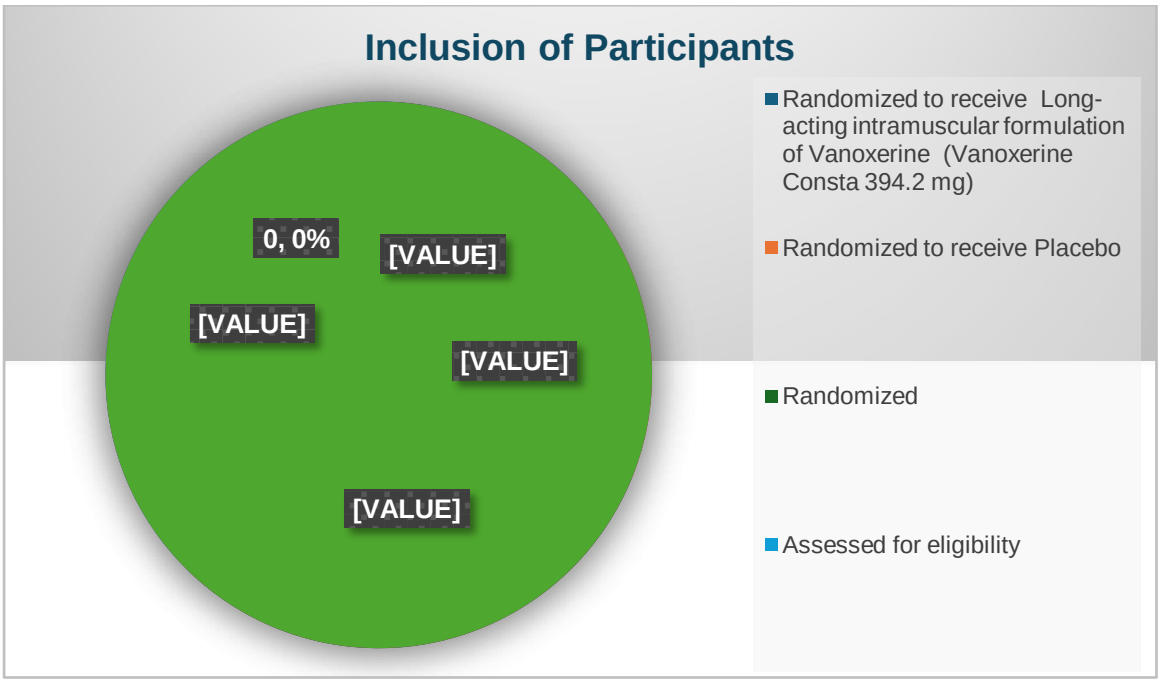
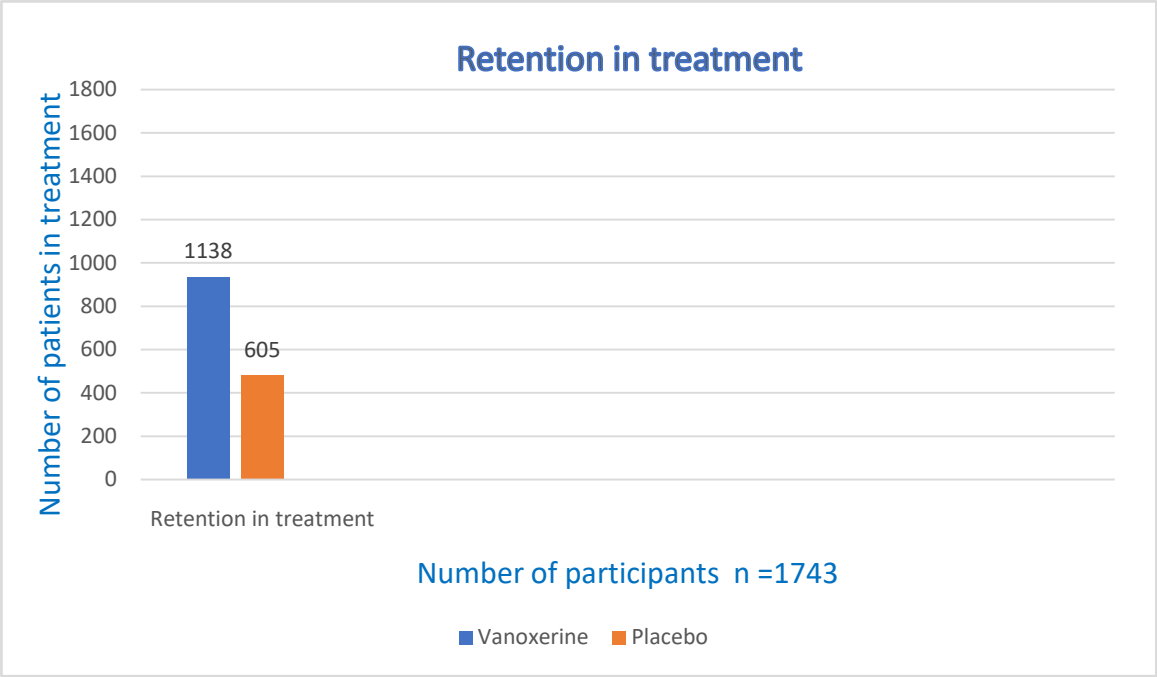
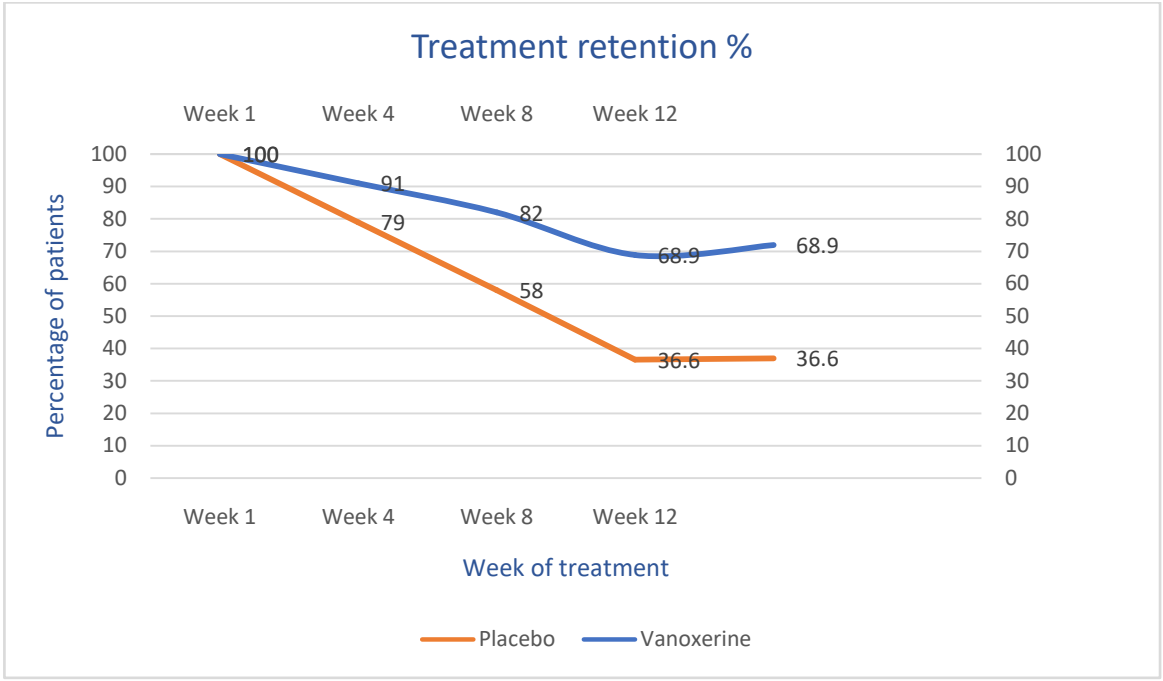


Figure 1: Flowchart for Inclusion of Participants



**number of participants in the treatment*

Figure 2: Retention in Treatment



**percentage of participants through the number of days in the treatment*

Figure 3: Survival Curves for Retention in Treatment

Primary endpoints: Confirmed ATS abstinence

Complete abstinence was sustained by 68.9 % (n=1138) of Vanoxerine patients (patients treated with Vanoxerine Consta 394.2 mg, long-acting depot formulations) compared with 36.6% (n=605) of patients treated with Placebo, during weeks 5–12 . The difference was significant as evaluated using a Chi-square test ($\chi 2 = 672.34$, P

< .0001) *(Figure 4)*. * (Percentage of cocaine-free patients through weeks 5-12). Confirmed abstinence or "ATS -free" was defined as a negative urine drug test for ATS and no self-reported ATS use. Assessing superiority of Vanoxerine Consta 394.2 mg treatment over the Placebo showed significant differences between the treatment groups in the proportion of negative UDTs (P < .0001). Treatment with Placebo was inferior to Vanoxerine long-acting depot formulations (Vanoxerine Consta 394.2 mg) regarding the group proportion of the total number of ATS -negative UDTs.

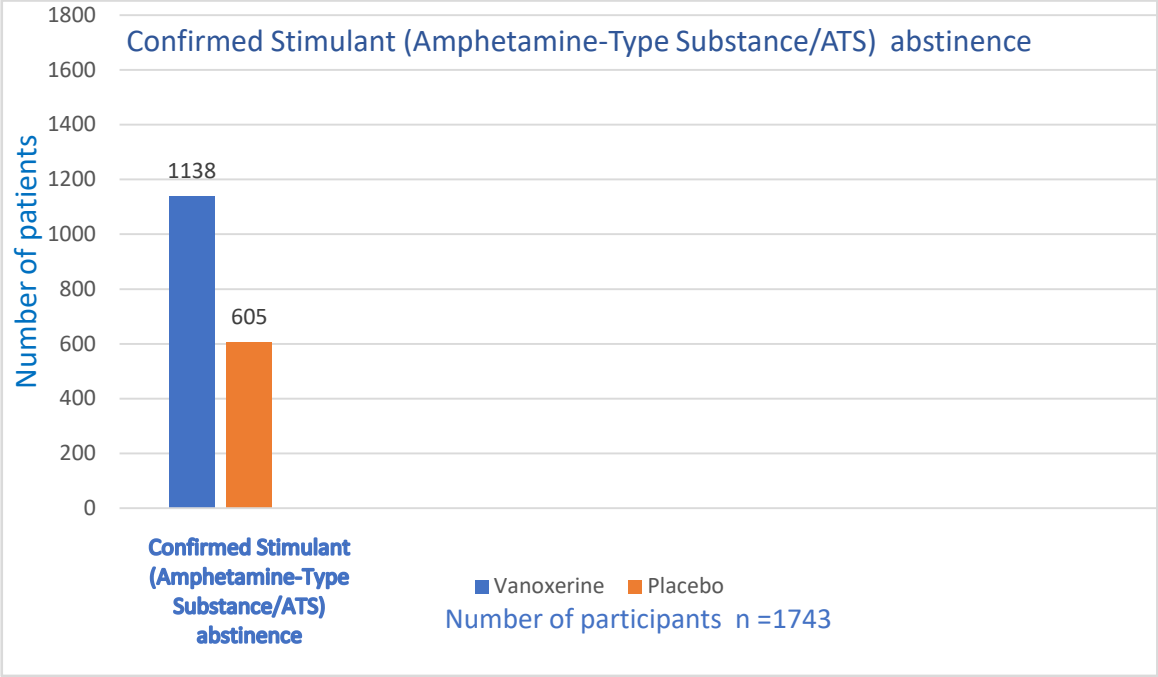


Figure 4: Confirmed Stimulant (Amphetamine-Type Substance/ATS) abstinence Secondary endpoint: Craving

Craving was reported weekly according to a Minnesota Cocaine Craving Scale (MCCS), composed of five items which correspond to intensity, frequency, duration of craving, changes in relation to previous week and craving response to medication (we used the first three items of the scale (none 0 to 10 maximum visual score analogue scale)).

Reduction in craving intensity was observedin baseline and every week to final evaluation, week 12. A statistically significant finding in this study was a decrease in craving intensity, frequency and duration of craving. A statistically and clinically significant reduction in cocaine craving was observed with Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) vs. Placebo by week 4 (P=0.0048), which persisted every week through 12 (P<0.0001). At all time points, participants receiving long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) reported significantly a decrease in craving intensity, frequency and duration of craving for cocaine than Placebo participants.

Patients given Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) had a 85% decrease in craving intensity , 70 % decrease in frequency and 85 % in duration from baseline to week 12. Patients given a Placebo injection had a 2% increase in craving from baseline to week 12.

Satisfaction with treatment was significantly higher among Vanoxerine Consta 394.2 mg, long-acting depot formulations) participants and they would also recommend their treatment to others to a higher extent compared with Placebo participants. The main clinical implication of this result is that Vanoxerine Consta seems to reduce craving, which is one of the main factors related to relapses in drug dependence.

Pharmacokinetic Assessments: Concentrations of Vanoxerine and 17-hydroxyl Vanoxerine in plasma.

Analyses were made of 300 study sample. Concentrations of the drug and its metabolite in plasma indicate the stability of intact analytes in analytical conditions, including hydrolysis, 84 days after the administration long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg). There was no statistically significant difference for plasma Vanoxerine concentrations between days 2 and 84 (p=0.416). The plasma concentration of Vanoxerine were 70.4 and 94.3 ng/ml and concentrations of 17-hydroxyl Vanoxerine were 10.5 and 13.2 ng/ml, respectively (*Figure 5*). Plasma levels of Vanoxerine remained above 70 ng/ml for approximately 12 weeks after administration long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg).

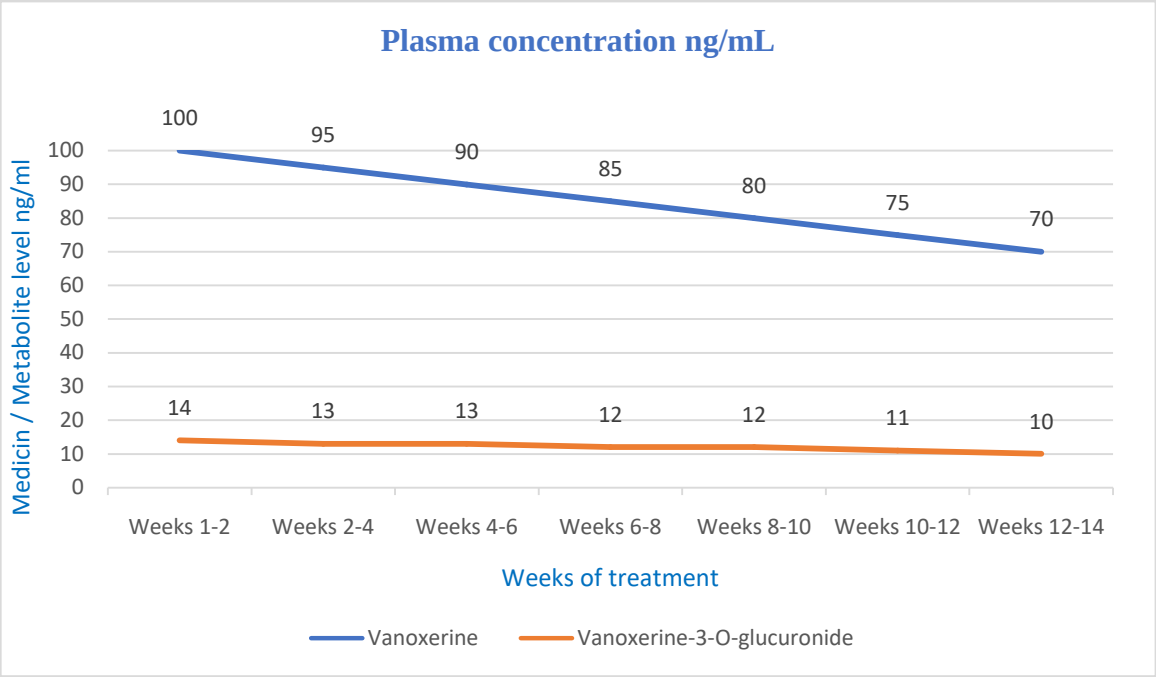


Figure 5. Plasma Concentration of Vanoxerine and Vanoxerine-3-O-glucuronide

IV. ADVERSE REACTIONS

Adverse events were similar in ATS -dependent patients treated with long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) vs. patients treated with Placebo (difference, 0.1 with 95% CI, −0.04 to 0.2; P < .001) *(Figure 7, Table 3)*.

Discontinuation rates due to adverse events were similar in ATS -dependent patients treated with Placebo vs. patients treated with Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg, (2%). Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) was generally well tolerated. It was not associated with increased levels of ALT or AST.

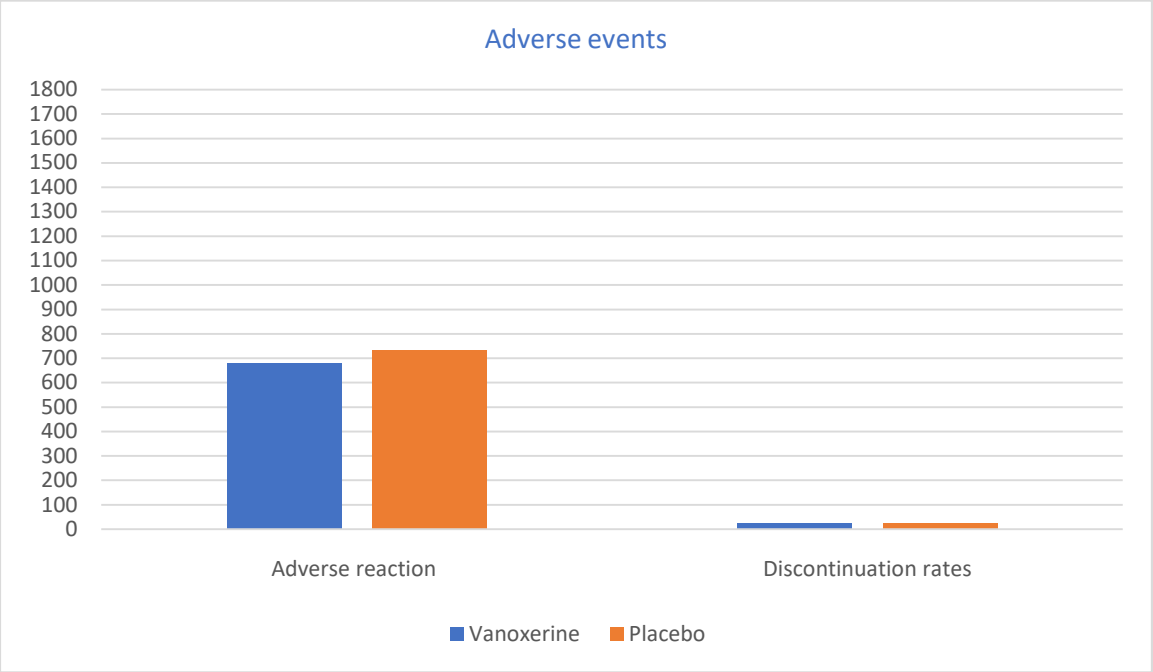


Figure 7: Adverse Events

There were no deaths, but 25 (1.51 %) Placebo participants and 24 (1.45%) Vanoxerine Consta 394.2 mg participants reported a serious adverse event. All made a full recovery but did not continue to participate in the study. Adverse reactions equally occurred in patients with Stimulants ATS dependence treated with Placebo and with Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) group.

Table 3: Adverse Events by Description

	long-acting Vanoxerine (Vanoxerine Consta 394.2 mg) (n=1650)	Placebo (n=1650)
Alanine aminotransferase increased	3 (0.18%)	3 (0.18%)
Aspartate aminotransferase increased	3 (0.18%)	3 (0.18%)
Gamma-glutamyltransferase increased	2 (0.12%)	2 (0.12%)
Back pain	110 (6.6%)	90 (5.45%)
Insomnia	115 (6.96%)	80 (4.84%)
Diarrhea	83 (5%)	66 (4%)
Hypertension	66 (4%)	50 (3%)
Injection site pain	132 (8%)	132 (8%)
Dizziness	66 (4%)	50 (3%)
Headache	50 (3%)	33 (2%)
Nervousness	50 (3%)	90 (5.45%)
Runny nose	0 (3%)	132 (8%)

V. DISCUSSION

To our knowledge, this is the first study comparing the effectiveness of long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) with Placebo injections (Placebo 380 mg,), the newest treatment for ATS dependent patients in many countries. Treatment with long-acting depot formulations of Vanoxerine

(Vanoxerine Consta 394.2 mg) was more effective then with Placebo in maintaining retention in treatment and craving for ATS. The main clinical implication of these findings is that long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) seems to be safe and effective then Placebo treatment for maintaining short-term abstinence from ATS in ATS -dependent individuals newly detoxified and/or discharged from inpatient treatment. Because we did not differentiate between ATS and other ATS-like formulations, our data appear to be clinically relevant to the growing number of individuals dependent on amphetamine-type stimulants.

Induction into treatment with long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) required full detoxification to a greater extent than into Placebo treatment. The modern instruction and guidelines for detoxification of ATS users turned out to be insufficient for study detoxification and frequently produced adverse effects related to withdrawal symptoms on induction of Vanoxerine Consta 394.2 mg, (long-acting depot formulations of Vanoxerine) and, to some extent Placebo. We therefore changed our detoxification strategy during the first year of the study in accordance with the most recent literature at the time of our study which reduced the number of new adverse events related to induction of treatment. Serious adverse events were equally distributed between the groups and were not directly related to the given treatment, which explains why there were no dropouts among participants reporting a serious adverse event.

Satisfaction with treatment and willingness to recommend their treatment to others were significantly higher among Vanoxerine Consta 394.2 mg, (long-acting depot formulations of Vanoxerine).

A clinically significant reduction in ATS craving was observed with Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) vs. Placebo. At all time points, participants receiving long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg) reported significantly less ATS craving and thoughts about ATS than did Placebo participants.

This finding makes it likely that the majority of participants were mainly motivated to receive the novel long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg). A treatment with long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) would be very effective in individuals with lower motivation for ATS abstinence.

There was no reported overdose in the study. This low rate may reflect the high motivation for treatment and good response to regular follow-up by the same study worker in this group of participants. In the present study, several participants used ATS after receiving the depot injections, but there was no evidence that attempts to override the blockade were successful, and no accidental or intentional ATS over-doses occurred. It is possible that the gradual dissipation of Vanoxerine from these long-acting injectable formulation (Vanoxerine Consta 394.2 mg) protected these patients from experiencing ATS overdose.

The results of the study also show consistency of release of Vanoxerine and on average level of Vanoxerine between 70.4 and 94.3 ng/mL over the 12, weeks life of the Vanoxerine Consta 394.2 mg. After the administration of long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg), mean Vanoxerine plasma levels ranged from 77 and 94 ng/mL. Across the 12-week study, plasma Vanoxerine levels tended to be fairly constant, with perhaps a slight decline during the twelfth week after drug administration. In general, many investigators agree that doses that maintain Vanoxerine plasma levels of approximately 70 ng/mL are sufficient for antagonizing the effects of high doses of cocaine agonists.

Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) was more effective then Placebo in maintaining short-term abstinence from ATS and should be considered as a treatment option for ATS -dependent individuals.

This study demonstrated that a long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) in conjunction with psychosocial treatment significantly reduced ATS use in a large geographically varied sample of treatment-seeking patients with ATS dependence. Long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) were well tolerated, few serious adverse events were reported, and there was no evidence of hepatotoxicity. Regarding tissue reactions around the site of injections, the formulation of depot Vanoxerine (Vanoxerine Consta 394.2 mg) used in the present study was well tolerated. In the 50 patients with injection site reactions, the severity was considered to be moderate, and all reactions resolved spontaneously over time.

In summary, the results from this trial, with one of the largest samples ever treated with a medication for ATS dependence, indicate that long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) is well tolerated and is associated with a significant reduction in cocaine use in ATS -dependent population. The long-acting formulation has the potential to improve intervention strategies for ATS dependence by providing a predictable pharmacological foundation for treatment. In addition to their utility for ATS dependence, long-acting formulations may prove to be an important treatment strategy for a variety of addictive disorders. The present results demonstrate that this long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) is safe, well tolerated, and effective in retaining patients in treatment. An increase in treatment retention is particularly important because it will allow clinicians sufficient time to engage patients in psychotherapy so that they can learn to make other psychological and social adjustments that support a life without amphetamine-type stimulants.

Table 4: Treatment Outcomes and Complications

Treatment outcomes	long-acting Vanoxerine (Vanoxerine Consta 394.2mg) (n=1650)	Placebo (n=1650)	Treatment efect
4000 Assessed for eligibility 3300 Randomized	1650 Randomized to receive Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2mg)	1650 Randomized to receive Placebo	1743 Completed 12 weeks treatment
ATS relapse patients weeks 4-12	31.1% (n=512)	63.4% (n=1046)	(P < .0001)
ATS -free patients weeks 4-12	68.9% (n=1138)	36.6% (n=605)	(P < .0001)
Retention in treatment	68.9% (n=1138)	36.6% (n=605)	(P < .0001).
Adverse reaction and adverse events	41.2% (n=680)	44.3 % (n=731)	(P = .04)

Contributors

Academic Research Department of AURUM Group, Ludgate Hill, London City, UK designed the study and wrote the protocol. All authors implemented the study protocol and contributed to data collection. Emmes Corporation coordinated the Data Safety Monitoring Board and study monitoring. Emmes Corporation had access to study data, and statistically analysed and interpreted the data. Sead Kadric wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Declaration of interests

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support from Aurum Pharmaceuticals, and consulting fees from Aurum Pharmaceuticals. All authors declare no competing interests.

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Role of the Funder/Sponsor

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication; however, Aurum Pharmaceuticals was allowed to comment on the manuscript before submission for publication.

Vanoxerine Consta 394.2 mg injection (long-acting intramuscular formulation of Vanoxerine) were donated free of charge by Aurum Pharmaceuticals.

The trial was conducted in hospital units at:

Klinik Parachute Vienna, Austria, Ayurva drug and alcohol addiction treatment clinic, Bulgaria, Clinical department of the Centre for Addictology, Czech Republic, Betty Ford Klinik GmbH, Germany,

Dianova Portugal International Addiction

Treatment Centre, Portugal, Clinica ALIAT, Addiction Treatment Center, Romania, Drug Addiction Treatment Center (Narcology), Russian Federation, Specialized treatment services for drug and alcohol addiction, Republic of Angola, Boramae Medical Center, Republic of Korea, Special Hospital for Alcohol and Drug Dependence, Republic of Serbia, The Narconon Center, Ukraine, Priory Addiction Treatment Centers, United Kingdom, Priory Clinic Canterbury, Priory Hospital North London, Drug and alcohol addiction treatment center Betty Ford, United States, Mayo Clinic drug and alcohol addiction, United States.

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