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MMSA MEDICAL EDUCATION

Minima Medica

Mind Maps

JOURNALS BY THE MALTA MEDICAL STUDENTS' ASSOCIATION

2024

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FOREWORD MESSAGE

SCOME Officer '23-'24, Ms Martha Schembri

I am excited to launch the 2024 edition of MMSA's Minima Medica Journal! Since the start, Minima Medica has served as a platform for medical students, providing them with the opportunity to contribute to a peer-reviewed journal and take their first steps into the world of research.

This year's edition features five articles, each diving into different medical topics. Under the supervision of academics from the University of Malta and specialised Medical Doctors, the credibility of MMSA's Minima Medica Journal is reinformed, ensuring our publication remains of the highest standard possible.

I would like to thank Dylan Farrugia, the SCOME Publications Coordinator, whose dedication and coordination have been essential in bringing this year's edition to life. Dylan has managed every aspect of the process, from releasing article preparations to liaising with the peer reviewers and organising the MMSA research conference.

A special acknowledgement is also due to Elisa Psaila, the SCOME Assistant whose commitment to the standing committee has been extremely evident throughout the year. Additionally, MMSA's PRO, Denise Galdes and our PR Coordinator Keith Calleja also deserve recognition for their designs which have brought our journal to life.

Finally, I would like to thank the authors for their dedication and contributions. Their efforts in writing and submitting these articles have helped this publication grow. I also extend gratitude to the academics and doctors who have generously volunteered their time to review the submissions ensuring our journal is of the highest quality possible.

To every reader, whether a student, academic, or enthusiast, I invite you to immerse yourself in the contents of this journal. May it serve as a source of inspiration, offering insights into the wonders of the medical field.

Martha Schembri

Medical Education Officer

FOREWORD MESSAGE

SCORP Officer '23-'24, Ms Elyssa German

Hey, welcome to SCORP's 2024 edition of Mind Maps! This journal is dedicated to exploring topics that tend to be unrepresented in our medical curriculum. This includes mental health, neuroscience, bioethics and sociology of health and illness.

This year we are happy to publish two articles, both targeting different aspects of what our journal "Mind Maps" represents. These articles have been under the supervision of academics from the University of Malta as well as under our Editor, Dr. Claude Bajada. With his help, this allows us to give students the opportunity to write an article on their own initiative and obtain the skills and experience that are required to take on research independently in the future.

This journal would not be complete, without the work of Dylan Farrugia. In the MMSA term of 2023-2024, Dylan has served as SCORP's Mind Maps coordinator. His hard work and dedication have been essential in the creation of this journal as well as his innovative ideas for the research conference and the future of academic journal writing in MMSA.

I would like to acknowledge the hard work of my assistant Timothy Francis Borg, as he has taken an active role in this sector of SCORP, and I am excited to see how it flourishes in the next term. Additionally, MMSA's PRO, Denise Galdes and our PR Coordinator Keith Calleja without their help, we wouldn't be able to present to you today this cohesive design that reflects our author's hard work.

Lastly, I want to express my appreciation to the authors for their commitment and valuable contributions. Their hard work in crafting and submitting articles has significantly contributed to the advancement of our publication.

As we embark on this journey together, may "Mind Maps" continue to inspire curiosity, foster collaboration, and allow students to create their own understanding of the key concepts of vast overlap between neuroscience and human action and outcome.

Thank you to everyone who has been involved,

Elyssa German

SCORP Officer 2023-2024

FOREWORD MESSAGE

Editorial by Mr Dylan Farrugia, SCOME & SCORP Publications Coordinator '23-'24

In today's digital era, where information is readily accessible a few clicks away, the foundational role of science in medicine may sometimes be overlooked. The ease of finding quick answers has led to questions about the value of expertise. However, research and publishing, which are the cornerstones of science, offer more than just superficial answers available at one's fingertips.

While one might assume that medical education, with its extensive curriculum, may not be the ideal environment for fostering research skills, this is far from the truth. Developing the ability to ask pertinent questions and systematically investigate to find rational answers is a transferable skill essential for future medical professionals. The capacity to gather data and critically evaluate solutions is equally crucial.

The MMSA's student-run medical journals Minima Medica, and Mind Maps, for another year have provide students with perhaps their first opportunity to submit work and undergo a peer-review process. These platforms not only introduce students to professional academic endeavours but also ignite their interest in future research. This year's articles spanned diverse medical fields, from cardiology and psychiatric disorders to public health and neurodegenerative conditions, as well as chronic infection effects and ethical considerations in modern medicine. I hope these articles have not only sparked the authors' curiosity but also engage the readers. Research reveals not just what we know but also what remains to be discovered, inspiring us to continue our quest for knowledge for the betterment of humanity!

In my final remarks, I would like to express my gratitude to MMSA for entrusting me with the roles of publications coordinator for both SCOME and SCORP. Throughout this learning journey, I had the pleasure of collaborating with a dynamic group of enthusiastic, like-minded individuals. Without their contributions, this endeavour would not have been possible. Special thanks to SCOME and SCORP officers Martha Schembri and Elyssa German for their unwavering support, as well as assistants Elisa Psaila and Timothy Borg. I also extend my appreciation to the PR team, Denise Galdes, Keith Calleja, Leah Tanti, and Rohanne Spiteri for their assistance with posters and publication layout. Dr. Claude Julien Bajda deserves recognition serving as editor

for Mind Maps. My heartfelt thanks to the peer reviewers who generously provided feedback to the students who submitted articles to this year's Minima Medica edition, namely Prof. Chamaine Gauci, Dr. Paul Herrera, Prof. Pierre Mallia, and Dr. Rachel-Anne Xuereb. Lastly, a big thank you to the main contributors of this project who out of their own initiative, dedicated time and effort to write and submit articles for this year's editions of Minima Medica and Mind Maps: Erica Busuttil, Peter Calleja, Michaela Fenech, Karl Livori, Mireille Pace, Alan Sultana, Katya Saliba, and Ruby Sciriha Camilleri.

Dylan Farrugia

SCOME & SCORP Publications Coordinator 2023-2024

Foreword Message

Editorial by Dr Claude Julien Bajada, Mind Maps Editor '24

In this second edition of the Mind Maps journal, we enhance our commitment to academic rigour by introducing a peer review process that includes both an academic and two student reviewers for each article. This approach not only diversifies the evaluation but also provides a practical learning experience in peer review. Featured in this issue are comprehensive reviews of Emotionally Unstable Personality Disorder in clinical practice and the roles of astrocytes in Alzheimer's and Parkinson's Diseases.

As medical students progress in their studies, the common advice is to "publish articles" to bolster prospects for specialty training programs. While publishing is a valuable milestone, it represents just one facet of the extensive scientific endeavour. Research encompasses the formulation of pertinent questions, mastery of relevant methodologies, integration of findings into the existing body of knowledge, execution of experiments, and ultimately, the dissemination of results. Balancing this intricate process with medical education is challenging. However, our faculty supports numerous research groups involved in every stage of this cycle, providing students with opportunities to engage directly with cutting-edge scientific work. To further enhance this engagement, we encourage the formation of student-led societies that can act as conduits between students and research groups, fostering a community of collaboration and innovation.

The faculty has also recently introduced an intercalated year designed specifically to nurture these crucial research skills. This addition to our curriculum is tailored to immerse students in statistical analysis, and laboratory techniques; skills that are becoming increasingly vital as the landscape of medicine evolves.

True medical expertise requires standing at the cutting-edge of knowledge, a position attainable only through active research participation. For future medical practitioners, the development of analytical skills is indispensable.

As you delve into the pages of Mind Maps, let it serve as a reminder of the pivotal role research plays in our collective pursuit of medical innovation and knowledge. Let this journal inspire you to explore, question, and contribute to the medical field, shaping your future and that of global health.

Dr Claude Julien Bajada

Mind Maps Editor

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JOURNALS BY THE MALTA MEDICAL STUDENTS' ASSOCIATION

Childhood Vaccination in the 21st Century: Vaccine Hesitancy and Immunization Rates

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Abstract

The main focus of this review is to analyse global vaccination in children in the 21st Century, which type of vaccines are available, their benefits and reasons by parents that could lead to vaccine-hesitancy. There are different ways that vaccines work including live attenuated, inactivated, toxoid vaccines, viral vectors and mRNA vaccines. People's willingness to receive recommended, safe, good quality, and effective vaccines has been challenged for the last few decades. Vaccine hesitancy arises in parents due to fears based on myths. Mainly they fear side effects and mandatory vaccine policies. The available vaccines that are present on the market according to WHO include Diphtheria, Hepatitis, Heamophilus influenzae type B (Hib), Human Papillomavirus (HPV), Measles, Meningococcal meningitis, Mumps, Pertussis, Pneumococcal disease, Poliomyelitis (Polio), Rotavirus, Rubella, Tetanus, Tuberculosis, and Varicella, COVID and seasonal influenza vaccine. Resulting from their beneficial effects, WHO data shows that, in 2021 and 2022, there was a 12% rise in vaccination rates. However, myths continue to worry parents including potential allergens, toxicity, autism related to the Mumps Measles, and Rubella (MMR) vaccine, cases of Immune Thrombocytopenic Purpura (ITP), and safety of combined vaccines. These misconceptions are reviewed in detail in this work.

Keywords: Vaccines, disease prevention, children

Introduction

Dr. Edward Jenner discovered vaccines 200 years ago. The innate immune system, composed of physical barriers, phagocytes, inflammation, and endocytosis, detects pathogens using PRRs. (1) APCs eliminate pathogens through opsonization and engulfment, while macrophages and dendritic cells activate the adaptive immune system. (2,3)

The adaptive immune system is pathogen specific and develops throughout the person's life, it has immunologic memory which allows for quick elimination of a pathogen during a subsequent infection. The APCs express MHC II on their surface; this binds to TCRs which activates T cells.

Once T cells are activated, they differentiate to CD8+ cytotoxic cells or CD4+ helper cells. Through clonal expansion, cytotoxic cells produce effector cells which prompt the apoptosis of the target cells. Once the pathogen is no longer detected the majority of these cells die off, but some are retained, resulting in immunologic memory. The helper T cells cannot destroy the infected cells themselves but through the release of cytokines they can direct other cells to do so. Helper T cells secrete cytokines which results in B cell multiplication and maturation.

B cells can recognize antigens, and they do not need APCs because of the presence of antibodies on their surface. When B cells are activated, they proliferate

and differentiate into memory B cells and plasma cells. The plasma cells are the cells which secrete antibodies. Once an antibody binds to the surface of a pathogen the pathogen is destroyed through competent activation, opsonization, phagocytosis or neutralisation. The plasma B cells will undergo apoptosis when the pathogen is eliminated. The antibodies secreted by the plasma cells remain in the circulation as protection against that pathogen. Memory cells also remain in the body's circulation as part of immunogenic memory. (2) The different types of vaccines are explained in the following sections.

There are now multiple vaccines available including; live attenuated vaccines, inactivated vaccines, subunit vaccines, toxoid vaccines, viral vector vaccines and mRNA vaccines (5,6). Live attenuated vaccines are weakened live pathogens to prevent serious illnesses in healthy patients, replicating and initiating an immune response upon entry. Inactivated vaccines, made of dead pathogens inactivated by chemicals or heat, require more antigens than live attenuated vaccines for effectiveness, triggering an immune response. (6)

Subunit vaccines are made up of antigens, adjuvants, and a delivery system. The components alone are not capable of producing an effective immune response on their own and thus, adjuvants are needed. Adjuvants create an immune reaction through the activation of dendritic cells by binding to PRRs to create antigens. These vaccines are considered to be very safe. The adjuvants and antigens create an immune response as described above. (6,8)

Toxoid vaccines are made from bacterial toxins, particularly those endotoxins which produce disease after the infection. The endotoxin is purified and inactivated or suppressed to render them harmless when used in vaccines. (6) The body's immune system will create antibodies and antitoxins to combat the toxin that is introduced by the vaccine. (9)

Viral vectors induce an immune response through antigen expression and cytotoxic T lymphocyte response, leading to cellular and humoral responses. These vaccines do not require adjuvants and have a long-lasting immune response, reducing the need for booster doses, especially when replicating viral vectors are used. (10, 11)

mRNA vaccines are versatile, used not only for pathogen protection but also as immunotherapies and cancer treatments, particularly during the SARS-CoV2 pandemic. (12) The exogenous mRNA has an immunostimulatory effect, because it has the ability to function as immunoadjuvants since it is pathogenic in origin. (13)

Numerous vaccines have been developed and countries need to make a decision which vaccines are offered to the public. Cost-effectiveness is a key factor in US and UK decisions. (1) For Malta, the national vaccination schedule which offers vaccines to the population free of charge is based on policy determination based on the epidemiological and cost benefit criteria. Malta's national immunisation schedule for children aged 0-16 is shown in table 1. (4)

Age	Vaccine
From 8 weeks	DTaP – Hib-IPV-HepB (6 in 1) 1 PCV 1Men B 1
3 months	DTaP-Hib-IPV-HepB (6 in 1) 2 Men ACWY (1)
4 months	DTaP-Hib-IPV-HepB (6 in 1) 3PCV2 Men B 2
12 months	PCV3 Men B (3)
13 months	MMR1 Men ACWY (2)
18 months	DTaP-Hib-IPV-HepB (4)
3-4 years	MMR2
12 years	HPV1
12 years + 6 months	HPV2 (for both girls and boys)
14-16 years	dT-IPVMen ACWY (3)

Table 1: Maltese national immunisation record

Methodology

Research Search

Google Scholar and Pubmed were the main search engines used to find relevant articles for this review. 'Vaccinations', 'children', 'rates', 'parents', 'disease', 'benefits', and 'myths' were used in different combinations in order to retrieve the most appropriate information for this review. The WHO website was also used.

Inclusion Criteria

The initial inclusion criteria was aimed at including articles from the last 10 years however, this was extended to include articles as far back as 2008 after careful review to determine their relevance. On account of the writers only being fluent in Maltese and English only articles that were written in English were included to avoid errors in the process of translation. In order to thin out the articles aimed at identifying the most apposite articles the titles, followed by the abstracts were read. Of those which were the most relevant the full text was reviewed.

Data Extraction and Synthesis

The data which was deemed most pertinent was extracted from the different studies that were reviewed. Contrasting and similar views were discussed.

Discussion and Review

What causes vaccine hesitation in patients?

Parents often refuse vaccines due to various reasons, including past experiences, side effects, 'natural' living, perceptions of other parents, interactions with healthcare providers, information sources, challenges, preferences, distrust in health system players, and mandatory vaccine policies. (15)

2.1 Fear of side effects:

Parents fear long-term adverse effects of vaccination, including asthma, allergies, fever, fuzziness, seizures, multiple sclerosis, articular rheumatism, and neurodevelopmental disorders, with autism being the most common concern. (16)

Parents are concerned about the impact on their children's undeveloped immune system and the chemicals entering their bodies, including mercury, formaldehyde, aluminum, animal DNA, thimerosal, and human tissue. They argue that not everyone is the same therefore everyone will be affected differently. (15) A 2018 study found that a third of participants experienced side effects, making them reluctant to take more vaccines, while half believe it's safer not to exceed three types simultaneously. (17) Some parents, despite not being anti-vaccinators, may skip or delay vaccinations due to concerns about side effects reported by a small proportion. (18)

2.2 Information Sources, Challenges, Preferences

Misinformation on the internet often leads to vaccines' negative reputation, as it is often presented in a clear and simplistic manner, making it difficult for doctors to counteract. (17)

People with lower socio-economic backgrounds tend to have different reasons for not vaccinating their children. Parents tend to vaccinate their children for diseases that they are more familiar with. Some parents think that as the disease no longer is of such high recurrence, their children would be protected through herd immunity. (19)

Parents are worried about MMR and autism, Hep B, and multiple sclerosis. (19)

Vaccine-Preventable Disease

A vaccine-preventable disease is one for which an effective preventive vaccination is available. (20) Vaccines have significantly reduced the incidence and even eradicated smallpox. (21) Successful vaccination programs have significantly reduced morbidity and mortality rates from diseases such as

measles and hepatitis B. They were successful in the eradication of smallpox and in the progress of elimination of polio. (22) Furthermore, in 2012, the World Health Organisation estimated that vaccination saves 2.5 million lives each year. (23)

3.1 Classification and examples of available vaccines

The WHO classifies these vaccines into 'Available Vaccines'; vaccines that are already accessible, and 'Pipeline Vaccines'; vaccines and/ or monoclonal antibodies that are still under discovery or development in the pharmaceutical industry. Table 3.1 lists available vaccines and summarises information regarding their administration. (24)

Table 3.1

Disease	Vaccine Administration
Diphtheria	The Diphtheria-Tetanus-Pertussis (DTP) vaccine, administered alongside tetanus and pertussis, is recommended to be given in three doses at 6 weeks of age, followed by three booster doses at 2 years, 4-7 years, and 9-15 years. (27)
Hepatitis	The World Health Organization only recognises Hepatitis A and B vaccines. Hepatitis A vaccination is recommended for children aged one year and older, while Hepatitis B vaccination is recommended for infants within 24 hours of birth. The WHO recommends all healthcare workers receive the Hepatitis B vaccine to prevent the disease in healthcare environments. (28)
Haemophilus influenzae type B (Hib)	The WHO states that Hib conjugate vaccines should be added to all routine infant immunisation programmes worldwide. (29)
Human Papillomavirus (HPV)	There are six licensed HPV vaccines, three bivalent, two quadrivalent, and one nonavalent, protecting against infection with types 16 and 18, responsible for 70% of cervical cancer cases. Adolescent girls aged 9-14 are the primary target group. The WHO recommends a one- or two-dose schedule for girls, young women, and older women, and two doses for immunocompromised or HIV-infected patients. The WHO Position on HPV vaccines (December 2022), suggests the following vaccination schedule: 1. For girls and women between 9 - 14 years and 15-20 years, a one- or two-dose schedule is recommended. 2. For women older than 21 years, two doses given six months apart are recommended. 3. For patients who are immunocompromised or HIV-infected, a minimum of 2 doses should be given. (30)
Influenza	The development of vaccines against the influenza virus with pandemic potential, as well as seasonal influenza vaccines that provide short and long-term protection, are highly prioritised by the WHO. There are several licensed vaccines against seasonal influenza. The WHO has pointed out groups of individuals that are linked with a higher risk of complications from contracting a seasonal influenza infection. These groups include children aged 6-59 months, pregnant women, healthcare workers, the elderly, and people who have chronic medical conditions. (31)
Measles	It is recommended that all children should receive two doses of the measles vaccine, either by itself or in combination with the MR, MMR, or MMRV vaccines and should be included in all national immunisation programmes. (32)
Meningococcal meningitis	Meningococcal meningitis vaccines, used to control outbreaks, are being replaced by polysaccharide-protein conjugate vaccines. WHO recommends including them in high-scale vaccination programmes in high or intermediate endemic countries. (33)
Mumps	Effective vaccines against mumps have mostly been combined with the MMR vaccine and included in national immunisation programmes. (34)
Pertussis	DTP vaccines are a three-dose primary series that significantly lower the risk of severe pertussis throughout infancy. It is recommended that the first dose should be taken at 6 weeks of age, followed by subsequent primary doses that should be given at a 4–8-week interval. A booster dose is ideally administered at two years of age, further booster doses may be indicated later in life. (35)
Pneumococcal disease	Three pneumococcal conjugate vaccines are available. These target 10 or 13 of the most common serotypes. The integration of PVCs in childhood national immunisation programmes globally is recommended by the WHO. (36)
Poliomyelitis (Polio)	The Polio vaccine offers lifelong protection against poliomyelitis. There are six available vaccines: Inactivated, Trivalent, Bivalent, and Monovalent. These vaccines protect against different types of poliovirus. (37)

Poliomyelitis (Polio)	The Polio vaccine offers lifelong protection against poliomyelitis. There are six available vaccines: Inactivated, Trivalent, Bivalent, and Monovalent. These vaccines protect against different types of poliovirus. (37)
Rotavirus	There are four oral rotavirus vaccines available. These are Rotarix™, RotaTeq™, Rotavac™, and RotaSiil™ and are live, attenuated rotavirus vaccines. The WHO recommends that these vaccines are to be included in all national immunisation programmes, particularly in South Asia, Southeast Asia, and sub-Saharan Africa. The first dose should be administered shortly after 6 weeks together with the DTP vaccine. (38)
Rubella	Rubella vaccines are usually given in combination with MR, MMR, or MMRV. The WHO recommends that all countries should introduce a rubella-containing vaccine in their immunisation programme. (39)
Tetanus	The most economical way to prevent maternal and neonatal tetanus and injury-related tetanus, is the administration of the Tetanus Toxoid Containing Vaccine. The WHO-recommended schedule is three primary infant vaccines followed by three booster doses at 12-23 months, 4-7 years, and 9-15 years, although different national schedules exist. TTCV is available as a single-antigen vaccine, as well as in combination vaccines to protect other VPDs. (40)
Tuberculosis	The Bacille Calmette-Guerin (BCG) vaccine, widely used in developing countries, protects over 80% of neonates and infants against meningitis and TB, particularly in children included in national childhood immunization programs. (41)
Varicella	There are several vaccine formulations of the live attenuated vaccine available. These are based on the Oka VZV strain and can be available as a single antigen or in combination with measles, mumps, and rubella vaccines. (42)

Benefits of Vaccination

The positive effects of vaccination can be noted on three different levels: the individual, the community, and the socio-economic levels. (43)

4.1 Benefits at the Individual Level

Individuals of any age can benefit from vaccines. Booster doses given during adolescence and adulthood protect against diseases for which vaccines were given in childhood, as they help preserve immunity. (44) Vaccination in individuals with chronic conditions may reduce the risk of complications. For example, the influenza virus increases the chance of an acute cardiovascular event in individuals with existing chronic conditions. However, those individuals who are immunised against influenza have a much lower risk of experiencing an acute cardiovascular event. (45). Hence vaccines reduce the chance of complications of the infectious disease.

4.2 Benefits at the Community Level

The main benefit of vaccination in the community is in reaching herd immunity. Herd immunity is the result of high levels of vaccination among the general population, which hinders disease transmission to unvaccinated individuals. Taking measles as an example, herd immunity is reached when vaccine coverage levels are higher than 95%, this has only been achieved in four European nations. (46) Another advantage is the fact that effective vaccination programmes contribute to a decrease in the use of antibiotics and hence lower the spread of antimicrobial resistance. For example, a 64% decrease in antibiotic prescriptions for respiratory infections was associated with the administration of the influenza vaccine in Ontario, Canada. (47)

4.3 Benefits at the Socio-Economic Level

Vaccination at all ages delivers economic benefits. These include reduced consumption of medicines and shorter hospital stays. For working individuals, vaccination can be cost-saving if one includes the cost of lost productivity. (48)Vaccination during one's lifetime is considered to be affordable. In Europe, the estimated amount to give around 17 vaccines throughout life is €4000, which costs less than other approaches at the population level. (49) Vaccines have an impact on school attendance in children. For example, school vaccination programmes in the US have resulted in lower absenteeism rates during influenza season. (50) Moreover, immunisation programmes lower the risks of outbreaks in schools. A study carried out by the University of Minnesota in 2002 concluded that

introducing varicella to the immunisation programmes of schools significantly reduced varicella outbreaks in school environments. (51) In adults, vaccination, not only prevents disease but also improves quality of life by increasing productivity and self-reliance. (52)

Vaccination Rates

Vaccine	Countries with vaccines on schedule, no. (%)	Coverage, %						
		Global	WHO Region					
			AFR	AMR	EMR	EUR	SEAR	WPR
BCG	155 (80)	87	80	87	90	93	91	92
DTPcv (1)	194 (100)	89	80	90	91	97	93	94
DTPcv (3)	194 (100)	84	72	83	84	94	91	93
HepB-(BD)	103 (53)	45	18	65	32	42	58	80
HepB (3)	190 (98)	84	72	83	84	91	91	93
Hib (3)	193 (99)	76	72	83	84	93	91	32
HPV, first	130 (67)	21	33	68	2	37	5	5
HPV, last	130 (67)	15	22	52	0	32	3	3
MCV (1)	194 (100)	83	69	84	83	93	92	92
MCV (2)	188 (97)	74	45	76	78	91	85	91
PCV (3)	157 (81)	60	68	78	55	83	58	23
Pol (3)	194 (100)	84	71	82	85	94	91	91
RCV (1)	173 (89)	68	36	84	42	93	92	92
Rota, last	120 (62)	51	51	74	58	31	68	4

Table 5. 1: shows the rates of vaccinations in the year 2022. (53)

Vaccine	WHO region coverage							
	Countries with vaccines on schedule, no. (%)	Global	AFR	AMR	EMR	EUR	SEAR	WPR
BCG	156 (80)	84	78	81	88	92	85	89
DTPcv (1)	194 (100)	86	80	86	89	97	86	91
DTPcv (3)	194 (100)	81	71	80	82	94	82	90

HepB-(BD)	111 (57)	42	17	59	33	43	51	78
HepB (3)	190 (98)	80	71	80	82	91	82	90
Hib (3)	192 (99)	71	71	79	82	81	82	29
HPV, last	116 (60)	12	21	38	—	27	2	2
MCV (1)	194 (100)	81	68	84	82	94	86	91
MCV (3)	183 (94)	71	41	75	77	91	78	91
PCV (3)	154 (79)	51	66	74	54	82	29	19
Pol (3)	194 (100)	80	70	79	83	94	82	90
RCV (1)	173 (89)	66	35	84	42	94	86	91
Rota, last	118 (61)	49	52	69	57	34	61	2

Table 5. 2: show the rate of vaccination in the different regions of WHO in 2021 (54)

Table 5.2 shows that WHO countries 80% had this vaccine as part of their national immunisation schedule. From the year 2021 to the year 2022 there was an overall increase in the rate of vaccination. In the case of the BCG vaccine, the increased demand for the vaccine was causing a shortage. Nowadays, the idea of targeted therapy in which only high-risk groups are vaccinated is becoming more popular, especially in Europe. The reasons for this vary, the most common being low risk of exposure and a risk-benefit trade-off. Despite all this, the rates of vaccination are still highest in Europe (53, 54, 55).

With regards to diphtheria, tetanus and pertussis vaccines the tables 5.1 and 5.2 show that the rate has either remained high or increased. This vaccine is found on the national immunisation record of every WHO country. This trend can be observed for the polio vaccine and the first dose of the measles vaccine. The third dose of the measles vaccine was found in the national immunisation schedule for 97% of the countries. The highest rate of immunisation for these vaccines is in the European region of WHO (53, 54).

With regards to hepatitis B, a birth dose is given in countries where the child has a high chance of being infected. This is why the rates of hepatitis B-BD is so low compared to other vaccines and why it is only on the national immunisation schedule for only 57% of the WHO countries. This is followed by 2 other hepatitis B immunizations as the schedule for hepatitis B is in three doses. The third dose of hepatitis B is found in 98% of the WHO countries. The rates of vaccination for hepatitis B have also seen an increase from 2021 to 2022. The highest rate of hepatitis B birth dose and third dose were in the West Pacific region (53, 54, 56).

The third dose of the human influenza B virus is found on the immunisation record of 99% of WHO countries. From the year 2021 to the year 2022 there was an increase in the rate of immunisation. The highest rate of immunisation in 2022 was in Europe (53, 54).

The immunisation rate for HPV was the highest in the American region. This vaccine is only found in 67% of the national immunisation schedules (53). The pneumococcal vaccine is in the national immunisation schedule of 81% of WHO countries. The rate has increased from 2021 to 2022 with the highest rate in 2022 being in Europe (53, 54). The rubella vaccine is 89% of the immunisation schedules. The rates of vaccination have also increased from 2021 and the highest immunisation rates were in the European region. The rotavirus vaccine is listed in 62% of countries. The highest rate of immunisation was in the American region (53, 54).

In 2020 the WHO published an immunisation agenda, this agenda is aimed at lowering the morbidity and mortality of vaccine-preventable disease, hence improving the rate of immunisation (57).

Debunking Myths

In the following, vaccine myths will be discussed and evidence will be used to debunk them.

Potential allergens in vaccines

The MMR vaccine contains certain traces of antibiotics, such as neomycin and gelatin, both of which can cause anaphylactic reactions. MMR is therefore contraindicated in patients who suffer from anaphylactic reactions. MMR vaccine is derived from the chick embryo fibroblast tissue culture and therefore people who are allergic to egg proteins could be affected. Patients who suffer from these reactions should test for immunoglobulin. (58)

In conclusion these reactions are of a rare side effect however it is true that some vaccines can cause certain adverse reactions. (58)

Are vaccines toxic?

Aluminium, a neurotoxin, is used in vaccines to induce long-term memory of target antigens. However, it is not recommended to exceed the recommended dose. Hepatitis B vaccine contains 0.6mg of aluminium, equivalent to the dietary intake needed. Formaldehyde is used in vaccines with 1mg, lower than normal human body levels. These substances are added to adjust the vaccine's pH, preventing toxic doses. (18)

In conclusion no vaccine can be released unless certified within the therapeutic range and therefore no vaccine is toxic. (18)

Autism

The alleged association of autism with MMR is a widespread myth. This association raised concern due to a now rejected publication from 1999 in a Lancet journal that is still quoted today. Nevertheless many studies were conducted which have rejected this alleged association. (59) Figure 1 shows the first studies that were reported to compare the trends of autism in relation to the MMR vaccine. (60)

As seen in figure 1, the first study was conducted throughout 1979-1998. When the trends of autism were compared before and after the administration of MMR there seemed to be no sudden increase in autism cases. This study was based in the UK. In California another study focused on cohorts born between 1980-1994, and looked at the annual trends of autism and MMR coverage were compared and there was no correlation present. In Yokohama and Japan, children born between 1988-1996 were studied. Here the findings were that Autism increase persisted after the MMR vaccine was withdrawn. (60)

In 1988-1999 in the UK, General practitioners conducted a study in patients who were 12 years and younger, unlike other studies in which the patients were younger. In this study there was the first reported diagnosis of autism. The incidence of autism increased while MMR vaccination remained the same. (60)

A recent study suggests that there might be a slight possibility in children that are at high risk for Autism, that is their siblings are Autistic. The study concluded that there was no correlation between the MMR vaccine itself and autism. (60)

Many other studies were conducted in the UK, Atlanta Georgia, Japan, Denmark and the US. Studies were of different natures including retrospective cohort and case control. In all of these studies, there was no correlation between MMR and autism. (60)

Even though these studies all seem promising, we need to bear in mind that they still have their limitations as they rely on population-level data that could be changed by different factors which are at their exposure. (60)

Is a young immune system capable of handling vaccines?

Parents worry about the amount of vaccines their kids are receiving in such a short time period. Even though many vaccines have been added, these vaccines have had different immunological changes, that is, immunogenic proteins have decreased. Therefore less effect on the immune system is present while still protecting children from disease. (65)

In conclusion, Parents worry vaccines may be too much for their children's immune systems, but infants can handle daily challenges, making vaccines less immunologically challenging than daily challenges and therefore vaccines can be given at this age. (65)

Study	Design	Years	Population	Comparison	Outcome(s)	Finding(s)
41	Ecological and case series	1979–1998	Children in eight UK health districts born during 1979–1992, including 498 cases of autism	Trends in incidence before and after introduction of MMR vaccination to the United Kingdom in 1988	Annual trends in autism cases Temporal clustering of autism onset or developmental regression	No sudden increase in autism cases after introduction of MMR vaccination No temporal clustering after vaccination
43	Ecological	1980–1994 birth cohorts	California kindergartners	MMR coverage and autism occurrence	Annual trends in autism cases	No correlation between level MMR coverage and large increase in autism cases
44	Ecological	1988–1996 birth cohorts	Yokohama, Japan, children up to age 7 years	ASD incidence before and after termination of MMR vaccination program	Annual trends in ASD incidence	ASD incidence continued to increase after withdrawal of MMR vaccination
42	Ecological	1988–1999	UK general practice patients 12 years and younger, with a focus on boys 2–5 years of age	Time trend analysis of MMR vaccination coverage and autism incidence	First recorded diagnosis of autism	Autism incidence increased fourfold while MMR vaccination was steady at >95% in boys 2–5 years
45	Ecological	1987–1998 birth cohorts	Schoolchildren in Montreal, Canada (N = 27,749)	PDD time trends relative to trends in MMR vaccination	PDD (n = 180), including autism	PDD rates increased while MMR vaccination coverage decreased
46	Case control	1987–2001	UK general practice patients born in 1973 or later Cases (n = 1,294) Controls (n = 4,469)	MMR vaccinated versus unvaccinated	First recorded diagnosis of PDD, with subgroup analysis of first diagnosis of autism (n = 991)	MMR vaccine was not associated with an increased risk of autism or other PDDs
47	Case control	1986–1993 birth years	Atlanta, Georgia, schoolchildren 3–10 years old in 1996 Autism cases (n = 624) School-matched controls (n = 1,824)	Age at first MMR vaccination	Autism and autism subgroups	The distribution of ages at MMR vaccination was similar in the cases and controls
48	Case control	Not stated (includes years before and after 2004 when MMR was included in the Polish vaccination schedule)	Children 2–15 years old in a region of Poland Autism cases (n = 96) Controls (n = 192)	Vaccinated versus unvaccinated with MMR or single antigen measles vaccine	Diagnosis of autism First symptoms of autism	No increased risk of autism found in any of the comparisons including after single antigen or MMR vaccines
49	Case control	1984–1992 birth years	Yokohama, Japan Cases diagnosed with ASD by 1997 ASD cases (n = 189) Matched controls (n = 224)	MMR vaccination	ASD	No increased risk of ASD associated with MMR vaccination
50	Retrospective cohort	1991–1998 birth cohorts	Children in Denmark (N = 537,303)	Vaccinated versus unvaccinated	Autistic disorder (n = 316) Other ASD (n = 422)	Risk of autistic disorder or other ASD was not increased by MMR vaccination

Figure 6.1 The first ecological studies to compare MMR and autism (60)

In 2014, a meta-analysis was performed to confirm that there is no relation whatsoever between the MMR vaccine and the onset of Autism. (61) The CDC specifically recommends MMR vaccines under the title 'Understanding MMR Vaccine Safety.' (62)

In conclusion, there are many proofs of the lack of association between the two, however, unnecessary hesitancy still persists. (61)

Are vaccines safe to combine?

For years, evidence supports this strategy. Different types of lymphocytes in vaccines can respond to different antigens simultaneously. Nowadays, newer drugs with smaller antigen numbers and purified properties are better for the immune system (18)

COVID-19 Vaccination in children and parent hesitancy

Children infected with COVID-19 experienced milder clinical symptoms than adults. However, a significant number of cases of inflammatory manifestations after infection, such as multisystem inflammatory syndrome in children (MIS-C), were noted. (66)

Both European and U.S. agencies approved the use of the BNT162b2 mRNA COVID-19 (Pfizer-BioNTech) vaccine for use in children aged 5-11 years as a two-dose series and as a booster dose in children aged 12-15 years by February 2022.(67) In a global crisis during the COVID-19 pandemic, vaccine hesitancy and refusal was a barrier to vaccine administration, especially in children. Parents were concerned about possible side effects of the COVID-19 vaccine, and some even stated that the vaccine can alter human genes. A strong relationship was noted between parents' attitudes towards vaccinating children against COVID-19 and their children's overall vaccination status. Almost half the number of parents who held the belief that COVID-19 vaccines are safe had vaccinated their children whereas only one-fifth of parents who do not believe that COVID-19 vaccines are safe vaccinated their children. (68)

Multiple studies have proved that COVID-19 vaccination protects children. For example, in Israel, around 200, 000 children participated in an observational study. Rates of COVID-19 infection according to vaccination status in children (5-10 years) and adolescents (12-15 years), for two weeks when the omicron variant was dominant in Israel, were studied. Rates of COVID-19 infection in children who received the two doses of the BNT162b2 mRNA COVID-19 vaccine where more than two times lower than children of the same age who received one dose. (69) Therefore, the BNT162b2 mRNA COVID-19 vaccine protects children against severe complications of infection and hospitalisation. (70)

Conclusion

Vaccines have repeatedly been shown to cause a reduction in the incidence, morbidity, and mortality of many diseases. The importance of vaccines in public health is highlighted in the fact that they are an affordable measure to lower disease rates and improve the quality of life of a population. Several misconceptions about vaccines exist due to a lack of understanding of how they work. Myths surrounding vaccines lower vaccination rates and as a result, the benefits of vaccines are less felt, both on the individual and population level. This will put the global health systems into jeopardy as it will lead to a comeback of diseases we today have the tools to prevent. Therefore, patient education, training of health care workers and evidence-based information are of main importance in vaccination programmes, to dispel misinformation, improve immunisation rates and protect public health.

Declarations

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List of Abbreviations

Abbreviation	Definition
AFR	African region of WHO
AMR	American region of WHO
APCs	Antigen-presenting cells
BCG	Bacille Calmette Guerin vaccine
DTaP	Diphtheria, tetanus and acellular pertussis
DTP	Diphtheria, tetanus and pertussis
EMR	Eastern Mediterranean region of WHO
EUR	European region of WHO
Hib	Human influenza B vaccine
HPV	Human Papillomavirus

ITP	Immune Thrombocytopenic Purpura
MCV	Measles containing vaccine
MHC	Major histocompatibility cells
MMR	Measles, Mumps and Rubella
MMRV	Measles, Mumps, Rubella and Varicella
MR	Measles and rubella
PAMPs	Pathogen Associated Molecular Patterns
PCV	Pneumococcal vaccine
PRRs	Pattern recognition receptors
RCV	Rubella vaccine
RIG-1	Retinoic acid inducible gene 1 like receptors
SEAR	South East Asia region of WHO
TCR	T cell receptors
TLR	Toll like receptors
TTCV	Tetanus Toxoid Containing Vaccine
VPDs	Vaccine Preventable Diseases
WHO	World Health Organisation
WPR	Western Pacific region of WHO

Authors' Contribution

Michaela Fenech paid contributions to the following sections: 'Vaccine-preventable diseases', 'Benefits of Vaccination' and 'COVID-19 vaccination in children and parent hesitancy'.

Erica Busuttil paid contributions to the following sections: 'Introduction', 'Methodology' and 'Vaccination Rates'.

Mireille Pace paid contributions to the following sections: 'What causes vaccine hesitation in parents' and 'Debunking myths.'

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Artificial Intelligence In Healthcare: Balancing Automation And Human Oversight

Authors: *Peter Calleja and Manuel Fenech*

Abstract

Artificial Intelligence (AI) endeavors to replicate human cognitive functions, heralding a transformative era in healthcare. This evolution is propelled by the increasing abundance of healthcare data and the rapid advancements in analytic techniques. This article delves into the present landscape of AI within healthcare, exploring its diverse applications and contemplating its future trajectory, with keynotes on current policies, disadvantages, advantages and ethical conundrums it brings to the field. AI's versatility is demonstrated through its application to a spectrum of healthcare data such as computer vision and providing suggestions. Within the realm of healthcare, AI is prominently deployed in key disease areas such as cancer, neurology, and radiology. This article further delves into the possibilities of AI applications in detection and diagnosis, treatment strategies, as well as outcome prediction and prognosis evaluation (as a tool for the physician). Despite these advancements, challenges persist in the practical implementation of AI in real-world healthcare scenarios. This article brings up original ethical arguments supported by other experts in the field who share the same concerns particularly about accountability. In conclusion, the hurdles and considerations necessary for effective deployment of AI solutions in healthcare as well as arising limitations are discussed; primarily through updating policies, adding new ones or working around already established ones.

Introduction

The document detailing the EU's policies on AI in healthcare defines AI as: “when a machine is able to mimic human intelligence or even surpass it to perform a given task such as prediction or reasoning”. However, in this report, the focus is on one subfield of AI that is dominant in the healthcare area, namely machine learning and convolutional neural networks. AI is a tool to assist humanity or replace them in certain fields if more capable (2). It can suggest, predict and perform tasks with a more efficient structure, but with the obvious consequences of losing the human touch, sometimes risking data breaches or privacy issues to doctors or patients' information. Therefore, the aim of this article is to discuss truths and misconceptions about AI to influence medical professionals and students to educate themselves about the subject and show its pros and cons to the field.

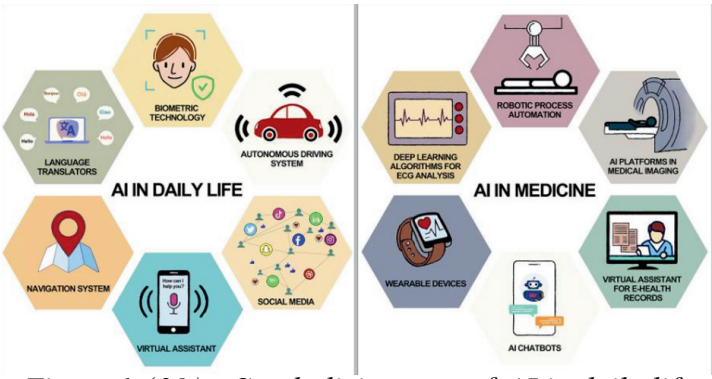

Figure 1 (30) : Symbolizing uses of AI in daily life and within healthcare.

Artificial Intelligence as a Tool

One fundamental aspect of AI's role as an assistant in healthcare is its proficiency in processing and analyzing vast datasets at speeds beyond human

capability (11)(7). Neural networks, a subset of AI, excel at recognizing intricate patterns and correlations in data, making them invaluable in tasks such as medical imaging analysis, diagnostic support, and treatment planning. This augmentation of analytical capabilities can significantly alleviate the burden on healthcare professionals, allowing them to focus on nuanced decision-making, patient interactions, and more complex aspects of care. The sophisticated neural network systems, modelled after the human brain, are adept at processing vast amounts of data and identifying patterns that might elude the human eye, for instance in lung cancers (15).

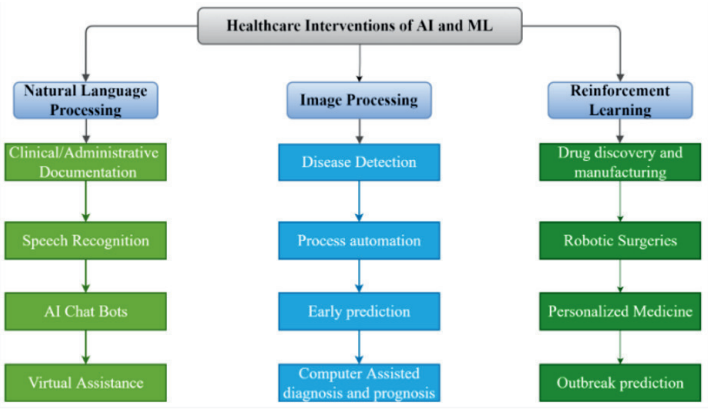

Figure 2 : representing the applications of AI and Machine Learning in Medical Infrastructure (25)

If AIs use is to provide assistance or suggestions to the matter at hand, it can provide a more accurate diagnosis or provide alternatives to the physician's diagnosis. Here arises an issue as perhaps, clinicians become too reliant on the suggestions of AI using it as a first hand authority on the diagnosis. This can lead to inexperienced new doctors who cannot handle practical issues without the assistance of AI and are negligent of the patient, as harm was caused by a breach of duty. The learning curve will be steeper because newer doctors are not receiving enough firsthand experience to develop efficiently in their practice. This can be seen affecting other fields where education and growth is a major part of development, (13).Furthermore, giving AI too much responsibility can easily lead to malpractice issues, as the doctors aren't intuitive enough to work independently. Healthcare professionals bring essential qualities to the table, such as empathy, intuition, and a holistic understanding of patient needs, which AI, as a tool, currently lacks. . The human touch in healthcare remains irreplaceable, encompassing the ability to interpret subtle cues, provide emotional support, and engage in complex decision-making that considers not only clinical data but also individual patient circumstances. Since AI lacks these human qualities, it cannot work independently, and the doctors, as argued cannot work independently on it, thus some form of education or training on the subject matter is required. It is crucial to acknowledge that AI systems are not immune to errors, and their reliability might be compromised, especially in situations where inexperience in handling these technologies comes into play.

Another ethical consideration revolves around the informed consent of patients regarding the use of AI in their healthcare. As AI systems become integral in decision-making processes, ensuring that patients are adequately informed about the role of AI in their care becomes paramount. Striking the right balance between leveraging the benefits of AI and upholding ethical standards is essential, if it is a tool we must treat it as such. Multiple tests are normally performed to confirm a diagnosis using a variety of tools, this concept mustn't change if AI is incorporated into the procedure of diagnosing. Furthermore, we must consider the patient's right to be informed about all the diagnostic tools being used.

One notable distinction between AI and human practitioners is the nature of responses, particularly in patient interactions. While AI can provide consistent and authentic responses, it may lack the intuitive understanding and emotional intelligence that humans inherently possess. Research indicates that AI, despite its advancements, struggles to accurately detect human emotions and lies, raising concerns about its ability to discern when patients may not be entirely forthcoming. (14). As mentioned previously this further proves it cannot

be used as a sole means of diagnosis along with why it cannot replace the human physician, people are needed to identify psychological inferences that people express. That being said, AI has been proven to have increased or equal success rates in diagnosing and monitoring such as in studies conducted by Bardhan et al (15) and Zhang et al (16). (refer to figure 3).

though theoretically plausible, practically infeasible as an occurrence, due to legal and ethical concerns about AI (1)(18).

The integration of AI in healthcare holds immense promise, with applications ranging from diagnostic support to administrative efficiency. Balancing the benefits of AI with informed consent and mitigating

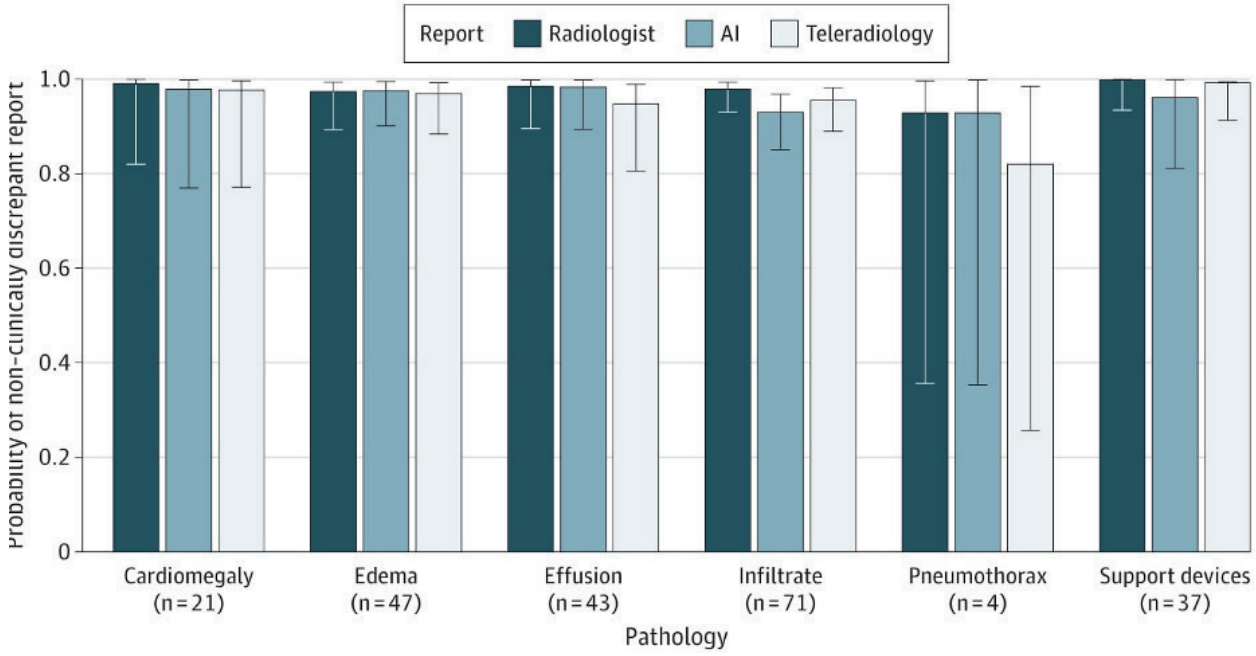

Figure 3: Probability of Non–Clinically Discrepant Report Across Pathologies (31); The probability of producing a non–clinically discrepant report (ie, Likert score ≥3) for each read type across subsets of studies with a given abnormality. Error bars designate the upper and lower confidence limits of the probability estimate. The number below each label indicates the study count for that subset.

The question of whether AI can transcend its role as a tool in healthcare is a subject of ongoing research and ethical scrutiny. Some argue that AI when integrated with robust research methodologies, has the potential to evolve beyond its tool status (20). However, ethical considerations loom large in this discourse, necessitating a careful balance between technological advancements and the preservation of patient rights and safety. From a utilitarian standpoint if AI is to provide greater quality care and more efficient quality care taking less time technically it ought to transcend its role. It raises the dilemma that it will make many professions obsolete and automated, including healthcare roles and as such AI is given human qualities i.e. the responsibility to make ethical decisions in medicine;

the risks of malpractice require a comprehensive approach. Furthermore, the nuanced differences between AI and human practitioners in patient interactions underscore the need for ongoing research and ethical frameworks. As we delve deeper into the realm of AI in healthcare, navigating these complexities becomes imperative to harness the full potential of these technologies responsibly.

Table 1: List of principles identified in the literature and those proposed by the UK National Screening Committee Artificial Intelligence task group (27) - Disclaimer: this is a sample of the original table.

	Identified in the literature	Further considerations proposed by the UK National Screening Committee Artificial Intelligence task group
Population	The test set should represent the whole spectrum of pathological and normal findings encountered in the target population as well as the key demographics	The dataset should be representative of the real screening population, including the full age and ethnic diversity of the UK population; it should be sufficiently large to represent women with varying levels of risk and have uncommon events such as rare breast pathologies and varied mammographic features
Population	The test set should be multi centred	No further comment
Reference standard	Mislabelling should be minimised (ie, misclassification)	The choice of an appropriate reference standard to avoid mislabelling will also depend on its intended clinical pathway (eg, replacing a human reader, triage, or add on); screening programmes aim to detect disease early and are subject to additional sources of bias that can affect the choice of a reference standard such as lead time bias, length bias, differential verification bias, and overdiagnosis
Population	The test set should account for technical variations in image acquisition, including image quality	For breast cancer screening, the test set should include films of mixed technical quality (eg, compression, exposure factors, filters, and positioning; including technical repeats, and number and types of views); when AI is proposed as the first reader of multiple readers in a screening programme, the threshold of technical recalls due to an inability to process the data for AI scrutiny can then be compared with the existing rates of technical recalls for that programme; with respect to image quality, there could be a systemic issue in the use of retrospective test sets if they are only taken from the final set of images from clinical practice; knowing how many times the image was taken (ie, a clinician could not read the image, so it was re-taken until it could be read) could be difficult; this issue should be taken into account when test sets are being considered

Accountability

In the Deontological ethics of Immanuel Kant, emphasis is placed on treating everyone equally as detailed by principles and the intentions of the legislator and legislated. Medical practitioners follow Kantian principles. In essence, the application of Kantian ethics to AI raises questions about the compatibility of Kantian principles with the intricacies of AI systems and the nuances in assigning responsibility for their actions. For example, who is to blame when using a software, is

it the programmer or the clinician who made use of it or the AI itself?

Where do we or how do we assign blame or accountability? Whose competence is it; doctors' or programmers'? The World Health Organisation (WHO 2023) identifies 6 core principles in relation to AI being:

1. Protecting human autonomy
2. Promoting wellbeing, safety and public interest
3. Ensuring transparency, explainability and intelligibility
4. Fostering responsibility and accountability
5. Ensuring inclusiveness and equity
6. Promoting that AI is responsive and sustainable.

Besides this, there are policies in EU law that regulate AI to reduce errors (18), but errors are possible. Exploring this, the ethical repercussions of blaming the AI for mistakes? By stopping the use of the program, by utilitarian principles; if it was beneficial to 1000 people but harms 1 therefore 999 people are missing out on the benefits. Thus it is ethical to perform said action as it does bring the greatest benefits to the greatest number of people. Furthermore, to assign blame is to assign a level of autonomy to the AI, implying it is aware and self-conscious. The software cannot be treated as a human being, it being a hardware or software error, not a malpractice issue.

Looking at human inputs, for example, the programmer and software company, it can be said their responsibility lies in ensuring they have released the safest and most reliable product according to the laws on AI creation and EU Liability for AI document. They aren't responsible for the level of reliability assigned to the AI. AI is a tool to assist in healthcare, not replace the physicians' responsibility to their patients. If it is a tool, then AI cannot be blamed. Who inserted the program or is responsible for ensuring its continued efficiency could be to blame as perhaps they neglected their responsibilities. The doctors' blame would be case-dependent, the AI predicts and gives suggestions but human input is necessary for a multitude of reasons. AI bases its actions on statistical analysis and objective functions (32), thus when receiving false information, it will base its diagnosis on the "untrue" statement. The software-based AI cannot detect underlying intent, it is the physicians' job to diagnose based on the information and cannot be replaced by an AI. Here lies the risk of doctors becoming too dependent on the AI's predictions, agreeably this is incompetency on the doctors' side, it is the same as trusting Google searches as a 100% accurate diagnosis.

If the technology exists must it be used? One example is using AI to perform surgeries, due to many sceptical beliefs on AI, most would disagree with its use even if it might have a higher success rate in for example identifying organs as shown in the study by Hashimoto et.al (11). Though AI is used for many things, even the autopilot on a plane, our lives are in the hands of AI often, what is so different about using it for surgical procedures? Perhaps it's a psychological belief that medicine is done by medical professionals and other entities shouldn't interfere, as to not give AI more power and stick to an AI alignment mentality where we treat medicine as a function of humans even if AI might help. Patients and doctors still aren't fully comfortable using AI in healthcare situations (19) , discovered at least 50% aren't willing to let AI be used in their treatment, due to the ethical issues of loss of autonomy and AI power.

It would be unethical for AI to replace humans in this field but to think of the money saved by reducing tedious work and saving time for physicians to focus on more important things (20). Tedious work such as filing, bookkeeping and records can be quickly and easily done by software. A major issue is the fear of data being breached (21), causing loss of autonomy and private details if a breach were to occur, AI does formulate said information into databases where if leaked, hospitals and clinicians would lose valuable patient data. This issue is that if clinicians were initially too

reliant on said AI providing information, a consequence of this would be that medical professionals would be lost when faced with situations without AI assistance.

Mislabeling is a common mistake in hospitals yet has catastrophic effects not only on the significant waste of resources but also on the trust put into the healthcare professionals as late diagnoses are given or misinformation is believed (28). This is easily avoidable when using AI whose rate of making these mistakes is far less, at an accuracy that is markedly higher. Evidence from research done in a study published in the journal Nature (22), found that AI algorithms were able to identify cancer in mammograms with an accuracy of 99%, compared to 85% for human radiologists. It must be noted that when trained versus not trained some studies have found no significant difference in AI improving quality of care even when physicians are trained to use them. AI alone indubitably has made strides even when compared to human specialists, yet is still likely to make a mistake as it is not perfect and this is why a consultant is necessary to affirm the AI's hypothesis.

The integration of AI in healthcare brings forth intricate ethical challenges that extend beyond conventional solutions, necessitating an adaptive approach. Continuous education and conditioning for healthcare professionals are important towards their understanding of the evolving world of AI. Ethical considerations encompass safeguarding patient rights and safety, requiring robust guidelines for data confidentiality, informed consent, and addressing biases in AI algorithms. Simultaneously, instilling a sense of self-responsibility within the medical community emphasizing practitioners' role as stewards of patient well-being. Balancing technological innovation with human-centred care calls for collective efforts from medical professionals, policymakers, and technology developers.

Solutions and Problems

In recent years, the integration of Artificial Intelligence (AI) in healthcare has garnered significant attention and sparked numerous debates (18)(24). One of the primary challenges faced is the lack of education among healthcare professionals regarding the effective use of AI technologies. Addressing this issue is crucial for the successful implementation of AI in healthcare settings. Research studies, such as the one conducted by Topol EJ, et al (3), emphasize the need for targeted programs to educate healthcare professionals on AI applications and provide comprehensive training. These programs not only enhance the understanding of AI systems but also aim to mitigate the problem of user error associated with inexperienced users interacting with these advanced technologies.

User error in the context of AI in healthcare can have serious consequences, underscoring the importance of proper training. A study by Sujan et al (4), identified instances of user error in the interpretation of AI-generated diagnostic recommendations. However, the study also highlighted that with adequate training, the incidence of errors significantly decreased. This supports the notion that education and training are pivotal in reducing errors, ensuring the accurate interpretation of AI-generated insights, and ultimately improving patient care.

The impact of training on patient care is a critical aspect that cannot be overlooked. A study by Rajkomar et al (5), explored the application of deep learning algorithms in healthcare and found that, when used by well-trained healthcare professionals, AI technologies contributed to improved diagnostic accuracy and treatment recommendations. Patients, in turn, expressed greater confidence in the care provided by healthcare professionals who had undergone specialized AI training. This underscores the positive correlation between proper training, reduced user error, and enhanced patient confidence.

Despite the potential benefits of AI in healthcare, limitations stemming from existing policies can impede its widespread adoption. Policies are often in place to prevent ethical dilemmas and avoid a slippery slope effect. Addressing these limitations requires a careful examination of current policies and the development of solutions to overcome existing setbacks. Delving into the ethical considerations surrounding AI in healthcare suggests that a reassessment of policies is necessary to accommodate the evolving landscape of healthcare technologies (6).

The limitations of AI in healthcare are not solely confined to policy issues; they also extend to public perception and stigma. A study by Meskó et al (7), revealed that a significant portion of healthcare professionals harbour reservations about AI due to concerns about job displacement and a perceived lack of understanding of these technologies. This stigma can hinder the adoption of AI in healthcare settings (29). Acknowledging and addressing these concerns through targeted educational programs and awareness initiatives can contribute to dispelling myths and fostering a more positive attitude towards AI. (refer to figure 4)

Proposing comprehensive systems to address the challenges associated with AI implementation is imperative. This includes the development of programs to educate healthcare professionals, regular updates to software to enhance performance and security, and pretrial testing of AI applications. Additionally, incorporating educational modules to familiarize users with AI systems before deployment and restricting the use of AI to specific contexts where it serves as a tool to assist rather than replace human judgment are essential components of an effective strategy. These proposals align with the findings of research by Krittanawong et al (8), who emphasize the importance of a systematic approach to the integration of AI in healthcare to ensure its responsible and effective use.

The successful integration of AI in healthcare necessitates a multifaceted approach that addresses challenges related to education, policies, and public perception. Research studies provide valuable insights into the effectiveness of training programs, the impact on patient care, and the existing limitations and stigmas surrounding AI in healthcare. By leveraging these insights, healthcare systems can develop informed strategies to educate

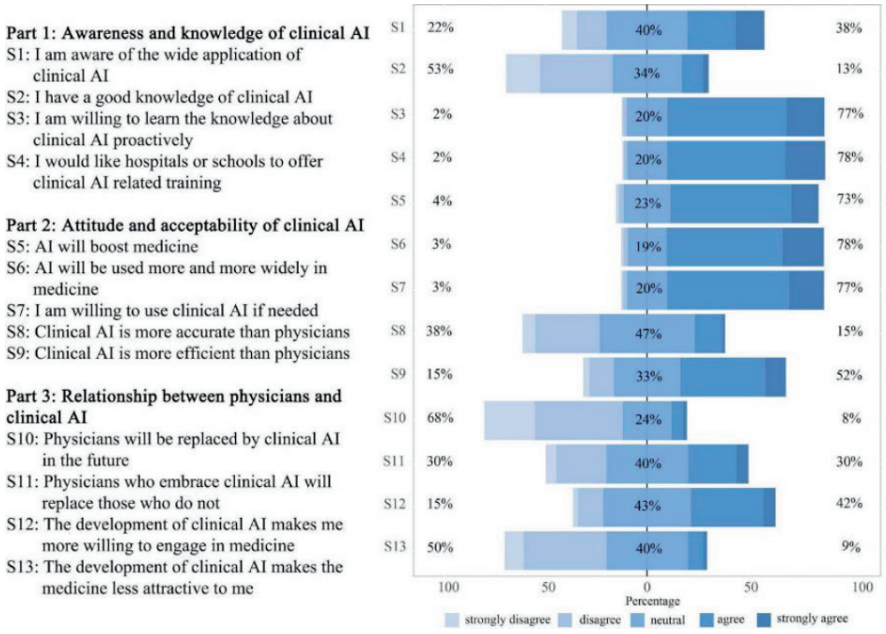

Figure 4: Medical students' perspectives on clinical AI, Statements 1 to 4 assessed respondent awareness and knowledge of clinical AI. Statements 5 to 9 assessed the attitude and acceptability of clinical AI. Statements 10 to 13 assessed respondent perception of the relationship between physicians and clinical AI. (29)

professionals, reassess policies, and foster a positive environment conducive to the responsible and effective use of AI in improving patient outcomes.

Conclusion

The goal of this article is to educate and aid medical professionals about the use, benefits and disadvantages of AI. The ethical repercussions of AI and the possibility of a slippery slope are discussed. This work took note of the current standing policies and the possibility of improving upon them in such a way that the possibility for overuse is acknowledged, with the aim of improving the medical community as a whole. With proper education and sufficient knowledge, healthcare professionals can ethically use AI. In such a manner as to overcome current issues of stigma against using AI and change future views and opinions such that every weapon in the arsenal within healthcare is used.

Declarations

Conflict of interest: N.A.
Ethical statement: N.A.

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Authors' Contribution

Peter Calleja (Medical Student at the University of Malta):
Main author to the article, primarily focusing on the writing of the article, recollection of information and ethical argumentation for and against AI.

Manuel Fenech (Student of Artificial Intelligence at the University of Malta):
Contributed to verification of facts, references. and provided essential definitions and points of view. Also assisted in writing parts of the article in the 'Solutions and Improvements'.

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Evolving Perspectives on Long COVID: Insights on Pathogenesis, Risk Factors, and Strategic Management

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Abstract

Long COVID is a medical condition that occurs when people experience symptoms that last long after they have recovered from acute COVID-19 infection. These symptoms can vary widely and impact multiple organ systems, with varying levels of intensity. Although the underlying pathophysiology is not yet well understood, it is believed to involve a complex interplay between the immune system, viral persistence, and other factors. Several risk factors can contribute to the development of long COVID, such as older age, pre-existing medical comorbidities, and the severity of the acute COVID-19 infection. Clarifying the underlying pathophysiology and risk factors associated with long COVID is important to develop effective prevention and management strategies. This review aims to summarize existing data on the pathogenesis and risk factors of long COVID, the challenges of diagnosing and managing long COVID and highlights the need for further research to improve our understanding of this complex condition."

Keywords: Long COVID, Pathogenesis, Risk factors, SARS-CoV-2, COVID-19"

Introduction

What is COVID-19?

When the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) pandemic in March 2020, it was not initially considered that the disease could have a chronic nature. The causative pathogen responsible for COVID-19 is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The pandemic has rapidly spread across the world and has resulted in more than 774 million confirmed cases and 7 million deaths as of 25th February 2024, according to the World Health Organization (WHO Coronavirus (COVID-19) Dashboard, n.d.). As of the latest available information in 2024, Malta has reported 71 cases and 1 death in the last 28 days to 25th February 2024. As more knowledge is being gained about this virus, we are also gaining a deeper understanding of the immediate and lasting consequences of contracting SARS-CoV-2.

The virus invades cells through the angiotensin-converting enzyme 2 (ACE2) receptor. Once inside the host cell, the virus replicates and matures, eliciting inflammation and immune cell activation (2). The ACE2 receptors can be found in various cells across the human body, such as the mucous membranes in the nose and mouth, lungs, heart, brain, digestive system, liver, kidneys, and spleen, as well as the cells lining the arteries and veins. This indicates that the virus can potentially harm multiple organs.

Fever, cough, sore throat, loss of taste or smell, body pains, and diarrhoea are among the symptoms of COVID-19. Recovery from mild cases typically takes 7-10 days, while severe/critical cases can take up to 3-6 weeks. The clinical severity of COVID-19 ranges from no symptoms to life-threatening illness (3).

What is Long COVID?

Long COVID refers to a condition where symptoms

persist or arise following an initial COVID-19 infection and cannot be attributed to any other medical condition (2). It is characterized by various symptoms, such as fatigue, shortness of breath, cognitive and mental abnormalities, headaches, muscle and joint pain, taste, and smell dysfunction, coughing, hair loss, sleep problems, wheezing, sputum, and cardiac and gastrointestinal issues (4). **Figure 1** highlights the multidimensional nature of long COVID, affecting various organ systems and some of its associated multi-organ manifestations.

Figure 2 illustrates the distinction between ongoing symptomatic COVID-19, which refers to patients experiencing symptoms 4 to 12 weeks after onset, and post-COVID-19 syndrome, which refers to patients whose symptoms persist for more than 12 weeks after onset.

Pathogenesis of Long COVID

The development of long COVID, with its persistent symptoms, is thought to result from a combination of inflammation and oxidative stress

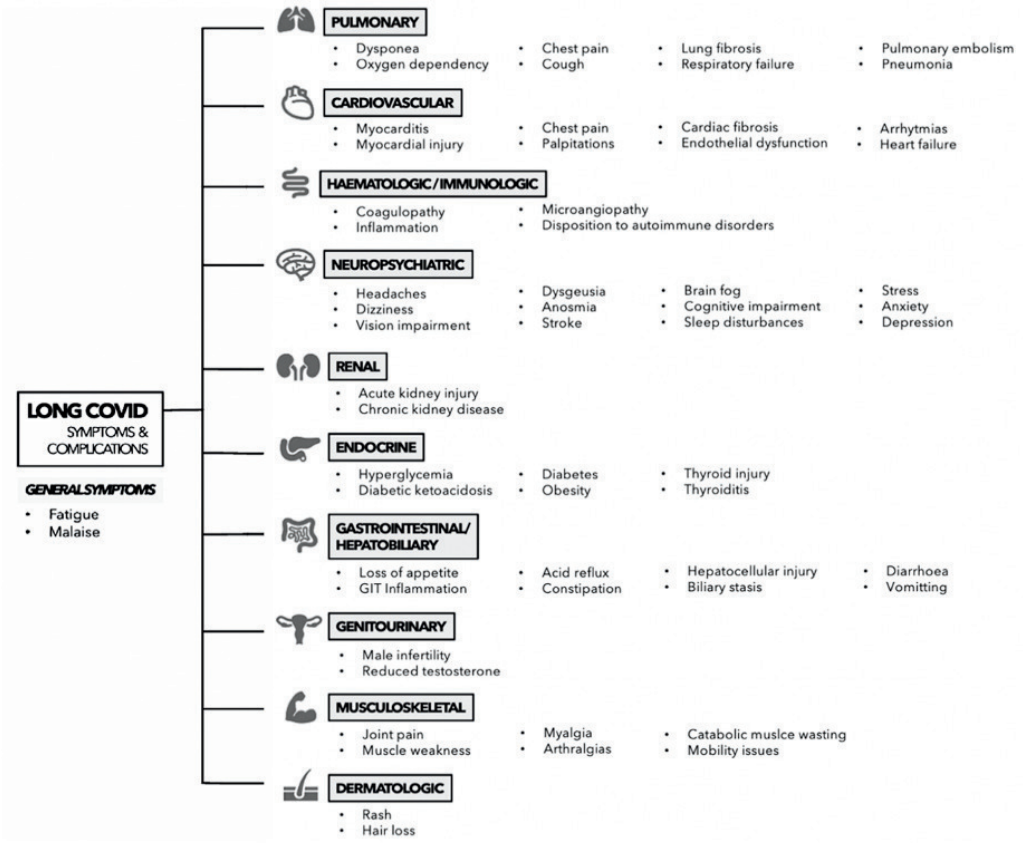

Figure 1. Multi-organ complications associated with long COVID
Adapted from Crook et al., (2021); Nalbandian et al., (2021)
Created with Microsoft PowerPoint – version 16.77, Microsoft Corporation, Washington, USA

It can be challenging to diagnose long COVID due to its varying recovery period and diverse complications that may arise (5). The symptoms can either persist or be relapsing and remitting in nature and may involve the persistence of acute COVID symptoms or the development of new ones (3). Most individuals with long COVID have negative PCR tests, indicating that they have recovered microbiologically, but not clinically (6).

that weakens the immune response and allows the virus to persist. The virus and its remnants can also provoke ongoing inflammation, which leads to a cycle that contributes to long COVID (7).

Entry of SARS-CoV-2 into host cell

The entry of the virus into host cells is facilitated by the ACE2 receptor, which is found on the surface of human cells. The coronavirus gains access to host

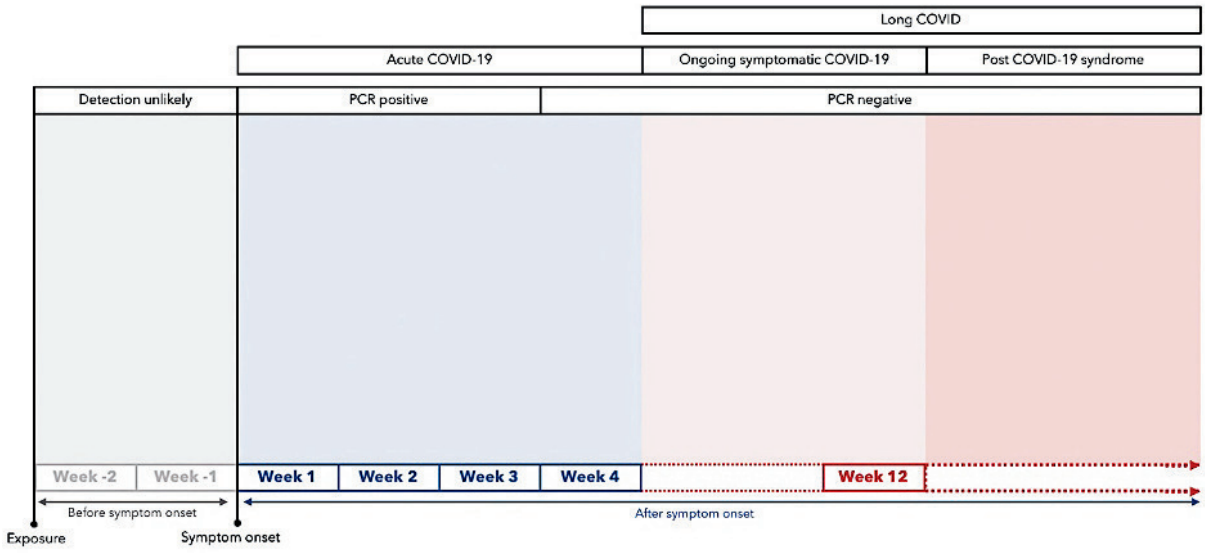

Figure 2. Timeline of long COVID
Reproduced from Nalbandian et al., (2021); Raveendran et al., (2021)
Created with Microsoft PowerPoint – version 16.77, Microsoft Corporation, Washington, USA

cells by attaching to the ACE2 receptor using its spike protein, which acts like a key to unlock the door to the cell, as shown in **Figure 3**.

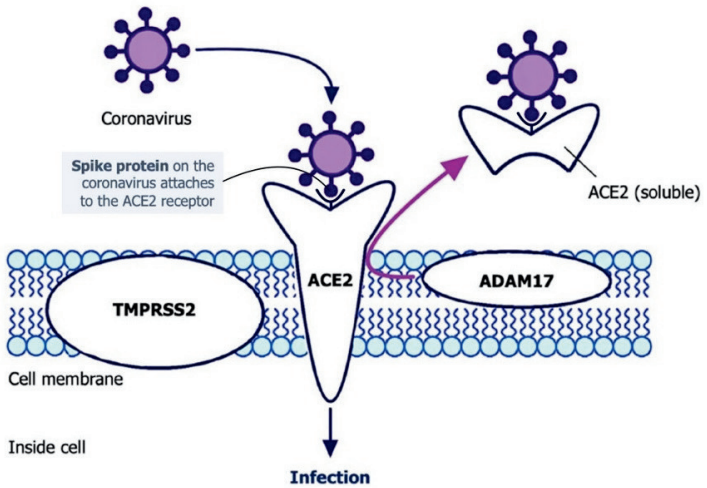

Figure 3. Entry of coronavirus into host cell
Reproduced from Pradhan & Olsson, (2020).
Created with Microsoft PowerPoint – version 16.77, Microsoft Corporation, Washington, USA

Transmembrane protease serine 2 (TMPRSS2) then cuts the spike protein, aiding the virus in fusing with and entering the targeted cell. Eventually, the virus is then internalized into the cell through a process called endocytosis, where the virus is enclosed in a membrane-bound vesicle called an endosome (8). Once the virus has entered the cell, it begins to replicate itself by hijacking the cellular machinery of the host cell. This process leads to the production of new virus particles, which can then go on to infect other cells and cause the spread of the infection throughout the body (9).

The binding of the coronavirus to the ACE2 receptor in these tissues can cause damage and inflammation, leading to the symptoms of COVID-19. This mechanism also explains why certain populations, such as older adults and those with underlying health comorbidities, may be more vulnerable to severe COVID-19 disease (9).

ADAM17 (a disintegrin and metalloproteinase 17), also known as TACE (tumour necrosis factor-α converting enzyme), is a protein that regulates several cellular processes, along with inflammation (10). In the context of COVID-19, ADAM17 can cleave the ACE2 receptor, which releases its ectodomain in a soluble form This soluble form can bind to the virus and potentially hinder its ability to infect cells (11).

The spike protein of the coronavirus can induce ADAM17 activation, leading to the shedding of ACE2 from the cell surface. When ACE2 is shed from the cell surface, the number of ACE2

receptors available for the virus to bind to is reduced. This reduction in the number of ACE2 receptors can reduce the immune system's ability to control the infection, as the virus has fewer targets to attack (10). This can ultimately result in increased susceptibility to the virus.

Furthermore, the shedding of ACE2 can also contribute to the development of acute respiratory distress syndrome (ARDS), which is a severe complication of COVID-19.

The physiological role of ACE2 receptors is to degrade angiotensin II, maintaining a delicate balance in the renin-angiotensin-aldosterone system (RAAS). However, the downregulation of these receptors by the virus results in an escalation of angiotensin II levels, contributing to systemic injury, pulmonary fibrosis, pulmonary inflammation, and other pathological manifestations, which ultimately lead to COVID-19 progression, especially in patients with comorbidities, such as hypertension, diabetes mellitus, and cardiovascular disease (12). However, it is notable that while some studies have suggested a potential role for ADAM17 in the pathogenesis of COVID-19, further insight is needed to fully understand its precise role and the mechanisms involved.

Genetic Factors Associated with Long COVID

The ACE2 gene codes for the ACE2 receptor, while the TMPRSS2 gene codes for the TMPRSS2, which is a serine protease that is expressed in many human tissues, such as the lungs, prostate, and colon (13). In the context of COVID-19, the expression of both ACE2 and TMPRSS2 in the respiratory tract is of particular importance, as this is where the virus primarily infects and replicates (9).

Genetic variation in the ACE and TMPRSS2 genes may be a contributing factor to the susceptibility, severity, and development of long COVID (14) but the findings are still inconclusive. A few notable studies have reported associations between certain ACE2 gene variants and COVID-19 severity. For example, the rs4646116 variant, which is situated in the ACE2 gene's promoter region, was linked to a higher likelihood of experiencing severe COVID-19. It was proposed that this variant might have an impact on the expression of ACE2 (15).

Cao et al., (2020) reported that individuals who carry the rs2285666 variant have been found to have an increased risk of experiencing severe COVID-19. This variant is thought to reduce the expression of ACE2, which may interfere with the immune system's ability to fight the virus.

The rs2106809 variant has been linked to an increased risk of contracting COVID-19 and developing severe disease. It is situated within an intron of the ACE2 gene and is believed to impact the splicing of ACE2 mRNA. Additionally, other studies found that this variant was more prevalent among men than women (17,18).

On the contrary, certain variants in the TMPRSS2 gene were correlated with a decreased risk for severe COVID-19. For example, the rs12329760 variant has been linked to reduced expression of TMPRSS2 and a lower risk of experiencing severe COVID-19 symptoms (19). Another example is the rs35074065 variant, which has also been associated with decreased expression of TMPRSS2 and a lower risk of severe COVID-19 (15).

Overall, these studies suggest that genetic factors, including genetic variations in the ACE gene, may contribute to the development of long COVID. It is important to note that these associations have been observed in different populations and may not be universal. The relationship between ACE gene variants and COVID-19 outcomes is an area of ongoing research, and further studies are needed to establish any definitive associations (14).

Numerous variants of the coronavirus have been identified and, while all of them have the potential to cause long COVID, certain variants have been more commonly linked to this condition. The Delta variant (B.1.617.2) has been found to be more strongly linked to long COVID compared to the

Alpha variant (B.1.1.7) and other variants (20). Moreover, being infected with the Delta variant is linked to an increased likelihood of being hospitalized and death compared to other variants (21). It is important to note, however, that long COVID can arise from infection with any variant of the coronavirus and the severity and duration of symptoms can vary greatly among individuals.

Dysregulation of the Immune System

The underlying mechanisms of long COVID are not yet well understood, but recent evidence suggests that dysregulation of the immune system might have a part to play. Initially, the body mounts a strong pro-inflammatory response to the virus, but this can eventually result in immunosuppression, which may help to balance the immune system and preserve immunological homeostasis but can also contribute to long COVID (22).

Furthermore, dysregulation of the macrophage cascade has been linked to the pathogenesis of long COVID. Macrophages are immune cells that respond to infection and tissue repair. During the acute phase of infection, macrophages are recruited to the site of infection, where they phagocytose viral particles and infected cells. This initial response is crucial for clearing the virus and preventing further spread (3). However, in some individuals, macrophages may become dysregulated, leading to chronic inflammation and tissue damage. This dysregulation may be attributed to many factors, including genetic predisposition, pre-existing conditions, and the severity of the initial infection (23).

Coperchini et al., (2020) revealed that individuals with long COVID had higher levels of a protein called CCL18, which is produced by macrophages, than recovered individuals or healthy controls, implicating dysregulated macrophage activity which may contribute to the persistent inflammation observed in long COVID. The role of CCL-18 in healthy macrophages is to recruit and activate other immune cells such as T cells and eosinophils to the site of infection or inflammation. CCL-18 also promotes the migration of dendritic cells which play an important part in initiating adaptive immune responses (25). While the exact mechanisms by which CCL-18 contributes to dysregulated macrophage activity in long COVID are not fully understood, it has been hypothesized that CCL-18 may contribute to the persistent inflammatory response observed in this condition. This may potentially lead to long-term tissue damage and dysfunction (24).

Recovered patients may be susceptible to reinfection or viral reactivation, and previous studies suggest that viral RNA can persist in various body fluids and tissues, including respiratory secretions, blood, stool, and urine, for several weeks or even months after infection (26). Therefore, acute COVID-19 infection can cause long-term activation of the immune system, which may contribute to the onset of long COVID.

However, the presence of viral RNA may not necessarily signify that the virus itself is still replicating in the body. It is possible that the viral RNA detected during post-infection periods is simply residual genetic material from the initial infection that has not yet been cleared by the immune system or eliminated from the body (26). The duration and extent of SARS-CoV-2 RNA shedding can vary among individuals and may be influenced by many factors, such as disease severity and immune status (27).

Risk Factors of Long COVID

Age, sex, severity of acute COVID-19 infection, pre-existing medical comorbidities such as obesity, heart disease and diabetes, socioeconomic status, and specific symptoms during acute infection are all significant risk factors for long COVID.

Age

Age difference plays a significant role in the incidence and severity of long COVID. Older people and those with pre-existing medical

conditions are more vulnerable to developing persistent symptoms and are at greater risk of experiencing serious complications from COVID-19 (28). The immune system of older adults is less efficient, and the presence of comorbidities such as heart disease, diabetes, and respiratory disease, which are more common in older age groups, can worsen the severity of COVID-19 symptoms and increase the risk for long COVID (29).

Collier et al., (2021) evaluated the vaccines' efficacy against variants of concern. Results revealed that after the first vaccine dose, the levels of binding IgG or IgA and serum neutralization were lower in older patients, especially those aged over eighty. The study concluded that the elderly population is a high-risk population which requires specific precautions to improve their vaccine responses, especially in situations where variants of concern are present.

On the other hand, Subramanian et al., (2022) demonstrated the opposite trend, revealing that advanced age was associated with a reduced risk of experiencing long COVID. Specifically, individuals aged 30 to 39 exhibited a 6% lower risk, while those aged 70 and above had a 25% lower risk, in comparison to those aged 18 to 30.

One possible explanation for this is that older adults may be less likely to mount an overly aggressive immune response to the infection, which is considered to be one of the underlying mechanisms contributing to the pathogenesis of long COVID. This is because the immune system tends to weaken as we age, which may result in a less robust response to the virus that is less likely to cause persistent symptoms.

Moreover, older adults might be at a higher risk of having pre-existing health conditions. While these conditions can intensify the severity of the acute infection, they may also provide a degree of protection against long COVID. The reasoning behind this is that individuals with pre-existing medical conditions may have already been dealing with chronic symptoms related to their underlying health issues before contracting COVID-19. In other words, their baseline health condition may have prepared their immune system or physiological responses in a way that influences the course and manifestation of symptoms during a COVID-19 infection. However, this is a speculative interpretation, since the field of long COVID is still being actively researched, and the interplay between pre-existing health conditions and the outcomes of long COVID is complex and not yet fully understood (32).

Children present with milder clinical manifestations than in adults. One study found that children exhibited heightened levels of Angiotensin II with diminished degradation, coupled with lower ACE2 protein expression. Additionally, TMPRSS2 showed no age-related changes. These findings may partially account for the lower susceptibility of children to COVID-19 (33). it is noteworthy that the interrelation between age and long COVID is not yet well understood, and further insight is needed to better understand the factors that contribute to long COVID in different age groups.

Sex

Studies have indicated a higher susceptibility to long COVID among women in comparison to men. In one study, electronic health records of COVID-19 patients were examined, and it was found that women had a greater risk of developing long COVID than men. Specifically, the study found that women were about 30% more likely than men to experience long COVID (20).

Carfì et al., (2020) analysed data from patients with confirmed or suspected COVID-19 and found that women reported more symptoms and had a longer duration of symptoms than men. The study also found that women were more likely to report fatigue, headache, and loss of smell and taste.

Although the specific causes of sex-based differences in long COVID are still unclear, they

could potentially be attributed to dissimilarities in immune response, hormone levels, and underlying medical conditions. Generally, women possess more robust immune responses compared to men, which could make them more vulnerable to autoimmune diseases and chronic inflammation (4). Hormone levels could also influence the immune response and inflammation in women. Besides, women have higher probabilities than men of suffering from underlying medical conditions such as thyroid disorders or autoimmune diseases, which could increase the risk of long COVID (22). Further insight is required to comprehend the fundamental mechanisms that give rise to these dissimilarities.

Comorbidities

Obesity

Obesity is linked to a state of chronic inflammation, which could increase the likelihood of experiencing long COVID. Moreover, obesity is recognized to impede immune functioning, rendering it more difficult for the body to combat infections, including COVID-19 (34).

A study revealed that there is a correlation between obesity and an increased risk of being hospitalized and dying from COVID-19, as well as an increased likelihood of experiencing long COVID symptoms, even in individuals with mild to moderate COVID-19 disease. The authors hypothesized that the systemic inflammation and immune dysregulation associated with obesity could increase the risk for long COVID (35).

Obesity increases the risk for long COVID due to the impact it has on the body's immune system and overall health. Obesity is a chronic condition that is associated with chronic inflammation, oxidative stress, and metabolic dysfunction, all of which can impair immune function and raise the incidence of severe COVID-19 and long COVID (36).Furthermore, obesity is correlated to several pre-existing medical conditions, which are also risk factors for severe COVID-19 and long COVID. Having these comorbidities can weaken the immune system and raise the risk of experiencing long COVID (37).

In addition, obesity is associated with respiratory dysfunction, such as reduced lung capacity and impaired gas exchange. This can make it more difficult to recover from pulmonary infections, including COVID-19, and increase the incidence of long-term respiratory complications (36). Moreover, obesity increases the risk of blood clotting disorders, such as stroke and thrombosis (38).

Given the growing evidence linking obesity to long COVID, it is essential to prioritize weight management and lifestyle interventions as part of the long-term care of recovered individuals, particularly those with obesity (34).

Diabetes

Diabetic individuals are at a greater risk for severe COVID-19 disease, being hospitalized, and dying from COVID-19 (39). Furthermore, people who have diabetes and contract COVID-19 with mild to moderate symptoms have a greater probability of experiencing long COVID symptoms compared to those without diabetes (20).

Diabetes impairs the immune system's ability to fight the virus and increases inflammation in the body (40). Diabetes is linked with chronic low-grade inflammation, which can result in an exaggerated immune response when the body encounters a novel pathogen like the SARS-CoV-2 virus. This exaggerated immune response can cause harm to the body's tissues and organs and contribute to long COVID symptoms.

Additionally, diabetic patients have a higher risk of developing other health conditions that are also risk factors for long COVID, such as heart disease and obesity (41). Generally, individuals with diabetes should take extra precautions to avoid COVID-19 infection, and if they do contract the virus, they should be closely monitored for long COVID symptoms.

Hypertension

Several mechanisms have been identified through which hypertension can increase the likelihood of long COVID. Firstly, hypertension is correlated to endothelial dysfunction, which is the impaired function of the cells that line the blood vessels. This results in inflammation and damage to the blood vessels, which might raise the incidence of blood clotting disorders and cardiovascular complications, both of which are risk factors for long COVID (42). Furthermore, hypertension is associated with comorbidities such as diabetes and heart disease, all of which are also risk factors for long COVID.

Heart Disease

Individuals with pre-existing cardiovascular disease (CVD) have a higher risk of experiencing long COVID. Patients with underlying CVD are more likely to require hospitalization, admission to the intensive care unit, and mechanical ventilation, and they have a higher incidence of dying from COVID-19 (43). The underlying mechanisms of how pre-existing CVD increases the risk of long COVID are not well understood, but it is thought to be related to the chronic inflammation and immune dysregulation that are present in CVD patients. COVID-19 infection can further exacerbate these underlying conditions, leading to increased damage to the cardiovascular system and increased risk of long COVID (44).

Chronic Lung Disease

Chronic lung disease, like chronic obstructive pulmonary disease (COPD) and interstitial lung disease, can increase the risk for long COVID in several ways. Firstly, these conditions can impair lung function and respiratory capacity, making it more difficult for individuals to recover from acute respiratory infections like COVID-19 (45). Secondly, chronic lung disease is associated with chronic inflammation and oxidative stress, which can weaken the immune system and make individuals more vulnerable to infections and complications (46).

Additionally, chronic lung disease can also increase the risk of comorbidities such as CVD and diabetes, which are also risk factors for long COVID. Finally, chronic lung disease is correlated to blood clotting disorders such as stroke and thrombosis, which can contribute to long-term complications of COVID-19 (28).

Many studies have explored the correlation between chronic lung disease and long COVID. For example, a study by Havervall et al., (2021) found that individuals with COPD were more likely to have persistent symptoms of COVID-19 six months after their initial infection compared to those without COPD. Similarly, a study by Carfì et al. 2020 found that individuals with interstitial lung disease had a greater risk of developing long COVID compared to those without pre-existing lung disease.

Cancer

There is limited information available on how cancer increases the risk for long COVID, as research on this topic is ongoing. However, cancer is considered a risk factor for severe COVID-19 and may contribute to the pathogenesis of long COVID through several mechanisms.

Cancer itself can weaken the immune system, making individuals more vulnerable to infections and complications. Medical procedures like chemotherapy or radiation therapy that are employed to treat cancer can debilitate the immune system and intensify the likelihood of developing infections. Moreover, cancer itself and the related treatments can lead to chronic inflammation and oxidative stress, which can lead to long-term harm to various organ systems in the body, including the lungs, brain, and heart (48). Nevertheless, more exploration is needed to better understand how cancer affects the risk of long COVID.

Demographic groups and Socioeconomic status

Recent studies have suggested that some

demographic groups are at greater risk of experiencing long COVID. For example, a study in the United States found that African American and Hispanic populations have a greater probability of experiencing long COVID compared to White populations (49). Additionally, Subramanian et al., (2022) demonstrated that when compared to white ethnic groups, a greater risk for long COVID was observed in Black Afro-Caribbean ethnic groups, mixed ethnicity, and other minority ethnic groups consisting of individuals with native American, Middle Eastern or Polynesian origins.

One possible factor is pre-existing health conditions that are more common among these groups, such as hypertension, obesity, and diabetes. These conditions have been identified as risk factors for severe COVID-19 and may also increase the likelihood of long COVID. Additionally, there may be genetic factors that contribute to the higher risk in these groups (50).

Another factor is structural racism and social determinants of health that may contribute to inequities in access to healthcare, among other factors. These inequities can lead to greater levels of stress and chronic health conditions, which all raise the risk for long COVID (51).

Subramanian et al., (2022) found that the risk of long COVID also rose as the level of socioeconomic deprivation increased. Individuals who were most socioeconomically deprived had an 11% higher risk compared to those who were least deprived. Socioeconomic deprivation is associated with a range of health disparities, including greater incidences of chronic health conditions, lower access to healthcare, and increased exposure to environmental hazards (52). All of these factors can collectively elevate the chances of experiencing severe COVID-19 symptoms and developing long COVID.

One possible factor is that individuals living in socioeconomic deprivation may be more likely to have jobs that require in-person work and have less flexibility for remote work (53). This may increase their exposure to the virus, leading to a greater risk of infection and subsequently, long COVID.

Additionally, individuals living in socioeconomic deprivation may have less access to healthcare and preventive services, making it more difficult to manage pre-existing health conditions that increase the risk for long COVID. They may also be less inclined to seek medical attention for symptoms related to long COVID, which could delay diagnosis and treatment (54).

Furthermore, individuals living in socioeconomic deprivation may have higher levels of stress and anxiety, which also increase the incidence of long COVID. Chronic stress has been shown to have a negative impact on the immune system, making it harder to fight off infections and recover from illness (53). Addressing these disparities through targeted interventions and policies could help reduce the incidence of long COVID in this population.

Smoking

Subramanian et al., (2022) revealed that individuals who smoke or previously smoked had a higher incidence of reporting long COVID symptoms compared to those who never smoked. Smoking is known to impair lung function and reduce the body's ability to fight off infections. This can make smokers more vulnerable to respiratory infections, including COVID-19, and may increase the disease's severity (55).

Additionally, smoking is correlated to a range of pre-existing medical conditions, including heart disease, COPD, and cancer, which increase the risk of long COVID. Having prior health conditions can compromise the immune system, which in turn elevates the chances of developing long COVID. (56). Furthermore, smoking is known to cause oxidative stress and inflammation, which can further damage the body's organs and tissues. This can contribute to long-term complications, such as chronic fatigue, neurological symptoms, and

respiratory problems (55). Lastly, smoking is also a known risk factor for blood clotting disorders such as stroke and thrombosis (56). Quitting smoking can help decrease the incidence of severe COVID-19 and long COVID, as well as improve overall health and well-being.

Severity of acute COVID-19 infection

A major contributing factor for developing long COVID is the severity of the acute infection. Individuals who experienced severe symptoms or required hospitalization are more likely to develop long COVID (57). It was pointed out that COVID-19 patients who are hospitalized in the ICU may also be at risk of developing post-intensive care syndrome. This suggests that there may be an interdependent correlation between the COVID-19 severity and post-intensive care syndrome (22).

Presence of specific symptoms

Another risk factor for long COVID is the presence of specific symptoms during the acute infection. For example, individuals who experienced shortness of breath, fatigue, or headaches during acute infection have a greater probability to develop long COVID symptoms (20).

With an increasing number of individuals experiencing long COVID, healthcare systems are anticipated to face a significant challenge in providing long-term care. To tackle this challenge, it is essential for researchers to scrutinize the current literature to determine the risk factors linked with long COVID. Establishing clear criteria to recognize susceptible individuals can facilitate healthcare authorities in the early identification and treatment of the condition (7). Identifying these major risk factors may help to recognise those who are most at risk of developing long COVID, allowing for earlier interventions and management of the condition.

Presence of specific symptoms

The development of long COVID has been linked with biomarkers that indicate the severity of COVID-19. For instance, individuals who experienced long COVID and had been hospitalized for COVID-19 had high levels of D-dimer and blood urea nitrogen, which increased their risk of pulmonary dysfunction three months after discharge (22).

High levels of D-dimer in COVID-19 patients are significant because it is a marker of blood clotting activation and the breakdown of blood clots in the body. COVID-19 can cause abnormal blood clotting, and high levels of D-dimer indicate that blood clotting is occurring in the body. This can lead to a greater risk of severe complications, such as stroke, heart attack, and pulmonary embolism (58). Therefore, monitoring D-dimer levels is important to identify those who may be at a greater risk for severe complications and may require more aggressive treatments such as anticoagulation therapy.

High levels of blood urea nitrogen (BUN) are significant because it is a marker of kidney dysfunction or injury (59).COVID-19 can affect the kidneys and lead to acute kidney injury, which can be a serious complication of the disease. Elevated BUN levels imply that the kidneys are not working efficiently enough to eliminate waste substances from the blood. This can lead to a build-up of toxins in the body, which can cause further damage to the kidneys and other organs (60). Monitoring BUN levels in COVID-19 patients is important to identify those who may be at a higher risk of kidney injury and may require more aggressive treatments such as dialysis.

COVID-19 survivors who showed elevated biomarkers of systemic inflammation and lymphopenia were also found to have radiological

lesions in different organs three months after they were discharged (61). To predict the advancement of long COVID, biomarkers of inflammation and lymphocyte counts should be considered alongside persisting symptoms in COVID-19 survivors (22).

Troponin is a protein biomarker that is commonly used to diagnose and monitor heart damage. High levels of troponin in long COVID patients may indicate that they have suffered some level of heart damage or injury, which could potentially lead to cardiovascular complications (62). However, it has been implied that elevated troponin levels may also be associated with chronic fatigue in long COVID patients.

Chronic fatigue is one of the most common and persistent symptoms reported by individuals with long COVID. It is characterized by profound and persistent exhaustion that is not relieved by rest. Although the exact cause of chronic fatigue in long COVID is not yet fully understood, experts have suggested that it may be related to inflammation and damage to various organs, including the heart (63).

It is important for healthcare providers to monitor troponin levels in long COVID patients to help identify those who may be vulnerable to developing cardiovascular complications and to identify long COVID patients who are at risk of developing chronic fatigue. More research is necessary to fully comprehend the relationship between troponin levels, heart damage, and chronic fatigue in long COVID patients, as well as to develop effective treatments for these symptoms.

To effectively manage the expected high number of long COVID patients, it is crucial to identify markers that can predict the onset of long COVID. Further research is needed to discover these predictors, which will aid long COVID clinics in prioritizing the most vulnerable individuals and providing care to those in need (7).

Long COVID symptom assessment and management

Assessment and management of long COVID requires a multidisciplinary approach and collaboration between different healthcare professionals – as depicted in **Figure 4**. Assessment of long COVID should begin with a thorough medical history and physical examination, including evaluation of vital signs, respiratory function, and cardiac function (64). Diagnostic testing may also be necessary to evaluate specific symptoms or comorbidities. Serologic testing for viral antibodies may be helpful in identifying patients who have been infected with the virus and are exhibiting symptoms consistent with long COVID. In addition, imaging studies such as chest X-rays or CT scans may be needed to evaluate respiratory symptoms or potential complications (65).

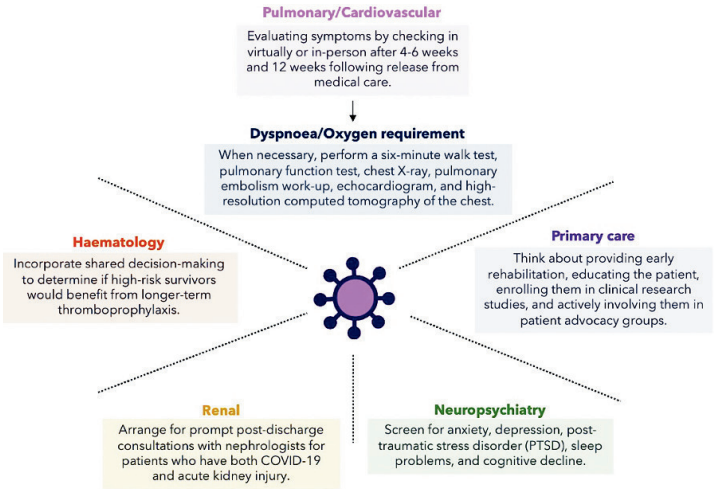

Figure 4. Interdisciplinary approach to managing long COVID patients
Reproduced from Nalbandian et al., (2021)
Created with Microsoft PowerPoint – version 16.77, Microsoft Corporation, Washington, USA

Priority may be given to those with a higher risk of experiencing long-term COVID-19 symptoms, including individuals who had severe acute COVID-19, required ICU care, are elderly, and have pre-existing health conditions, such as respiratory

disease, obesity, hypertension, CVD, diabetes, CKD, post-organ transplant, or active cancer (29). It remains unclear how long these symptoms last and if they are exclusive to COVID-19 or related to pre-existing health conditions.

Management of long COVID is focused on symptom relief and improving overall quality of life. Treatment may include medications to address specific symptoms, such as pain or shortness of breath. Rehabilitation programs, including physical and occupational therapy, may be helpful for patients experiencing weakness, fatigue, or cognitive impairment. Psychological support and counselling can also be important for addressing the emotional impact of long COVID, which can be significant for patients and their families (66).

It is noteworthy that there is limited information on the long-term outcomes of patients with long COVID, and research is ongoing to better understand the condition and develop effective treatments. In addition, COVID-19 vaccination has been shown to be effective in preventing severe illness and hospitalization from the virus and may also help prevent long COVID (67).

Concisely, long COVID is a complex condition that requires a comprehensive approach for assessment and management. A multidisciplinary team of healthcare professionals is essential for providing appropriate care and improving outcomes for patients. Ongoing research is required to gain a deeper comprehension of the condition and develop effective treatments.

Long COVID symptom assessment and management

In conclusion, long COVID is a serious and ongoing health concern for individuals who have experienced a COVID-19 infection. While the exact mechanisms underlying long COVID are still not fully understood, the condition can manifest in a variety of symptoms that can persist for months after the initial infection has resolved.

Moving forward, it is clear that more research is needed to better understand the causes and potential treatments for long COVID. This includes investigations into the underlying pathophysiology of the condition, as well as studies aimed at developing targeted interventions to improve outcomes for affected individuals. Additionally, efforts should be made to raise awareness of long COVID among healthcare providers, as well as the general public, in order to facilitate early diagnosis and appropriate management of the condition.

In terms of clinical management, there is currently no specific treatment or cure for long COVID. However, there are various interventions that may help to alleviate symptoms and improve the quality of life for affected individuals. These may include physical therapy, cognitive behavioural therapy, and pharmacologic interventions such as pain medications or antidepressants.

In summary, long COVID is a complex and multifaceted condition that requires further exploration and clinical attention. By continuing to study and address this issue, we can work towards improving outcomes for individuals affected by long COVID and better understanding the long-term impacts of COVID-19 on global health.

Author Contributions

KL contributed to the analysis and interpretation of the data and was responsible for drafting the manuscript. MZM provided critical revisions for the manuscript.

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Cardiac Syndrome X

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Abstract

Cardiovascular disease remains the leading global cause of death, most attributably due to a poor diet and lifestyle. However, there is still a large cohort of people who experience cardiovascular issues due to genetic reasons. This includes patients predominantly females, suffering from Cardiac Syndrome X. This condition is mostly genetic yet may be aggravated by an unhealthy diet and poor physical lifestyle. It is believed that a combination of vasospastic muscular arteries and endothelial dysfunction in the vessels supplying the heart may be the leading causes, yet its aetiology is still under-researched. Considering this, patients commonly present with severe retrosternal chest pain, discomfort, and shortness of breath, however following methodical testing, coronary angiography and electrocardiography, no cardiovascular lesions or abnormalities are revealed. This condition may still lead to fatal cardiogenic shock since myocardial infarction may supervene due to prolonged vasospastic closure of the arteries – which is why adequate knowledge and skilful management is required.

Introduction

Cardiac Syndrome X (CSX), also called 'Microvascular Angina' is a cardiovascular event characterised by typical or occasionally even atypical anginal chest pain. Distinctively, no coronary vascular abnormalities or lesions are evident during cardiac angiography (Mahtani et al. 2023). Nonetheless, it is still a type of ischemic heart disease which predominantly occurs predominantly in perimenopausal females and still carries a high morbidity rate if not diagnosed and managed early (Agrawal et al. 2014).

This condition has generally been linked to an increased risk of deadly cardiovascular events and poor quality of life. Treating and managing the condition remains empirical since each year 4000 new people are diagnosed with this illness in the United Kingdom (Bradley and Berry 2022).

It is believed to involve arterial-endothelial vasospastic dysfunction of the epicardial arteries supplying the myocardium, which results in myocardial ischemia (MI) followed by the sensation of anginal chest pain due to the release of adenosine and Tumour Necrosis Factor (TNF)-a from the endothelium that binds to nerve endings situated within the cardiac plexus responsible for the sensation of pain (Kaski 2006).

CSX may be pharmacologically managed and treated by a conventional triple combination therapy of anti-ischemic agents including nitrates, Beta (b)-blockers and calcium-channel blockers (Jarczewski et al. 2021). Supplementary agents may be used such as Angiotensin-converting enzyme (ACE) inhibitors, hydroxymethylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors along with other specific antianginal medications like ranolazine (Chou and Saw 2014).

Methodology

In identifying material relevant to this literature review, multiple databases that carried relevant

information were used. First, a wide and comprehensive search of peer reviewed journals and articles was conducted based on a wide range of keywords including Cardiac Syndrome X, microvascular angina, genetic predisposition and sequencing, coronary angiogram, and vasospasm. In total, five major sites were used including PubMed, Elsevier, ScienceDirect, the Cochrane Library and Google Scholar. Moreover, the reference section for each article found was searched to garner additional information with regards to the topic.

Pathophysiology

The pathophysiology of CSX remains poorly understood, which explains the absence of drugs explicitly used to treat this syndrome. The following points are believed to be the key aspects of the underlying cause of microvascular angina (Kanar and Sünbül 2018):

1. An inadequate oxygen supply to the myocardium due to vasospasm of the coronary arteries following microvascular dysfunction.
2. Endothelial dysfunction due to a reduced production of Nitric Oxide (NO) from the tunica intima following exercise, which promotes vasodilation of blood vessels. This can lead to vasoconstriction and consequently myocardial ischemia and infarction.
3. It is also suggested that patients suffering from CSX may have hyperalgesia or altered pain processing in the central nervous system (CNS). This may precipitate angina-like symptoms even in the absence of significantly reduced myocardial perfusion.
4. Chronic inflammation and oxidative stress may also contribute to impaired microvascular, smooth muscle and endothelial function. It has been shown that patients with CSX also have chronically higher levels of highly specific C-Reactive Protein (hs-CRP) in serum.
5. Hormonal factors, such as oestrogen deficiency in postmenopausal women have been proposed as one of the main contributors to the development of microvascular angina since oestrogen is known to be protective against cardiovascular events in females.

Clinical History and Presentation

Patients experiencing CSX typically present with an acute history of recurring and persistent substernal chest pain or discomfort that may radiate to the jaw, neck, left arm, back or epigastrium resembling symptoms of angina (Gulati et al. 2020). The nature of the retrosternal pain is usually sharp and compressing. Often, it is triggered by emotional or physical stress (Gulati et al. 2020). However, this pain is not caused by coronary lesions. Rarely, this anginal chest may also occur at rest. Other common symptoms patients may present with include tachycardia, tachypnoea, and malaise (Vancheri et al. 2020).

A thorough history and examination should be taken in patients presenting with such signs and symptoms, prior to any invasive testing or imaging modalities, along with careful evaluation of other potential pathogenic causes that may be of cause (Crea and Lanza 2004).

Seldom will patients ever be cyanotic, hypotensive, or unconscious as this would indicate severe progression of the disease and require urgent intensive therapy for stabilisation.

Clinical History and Presentation

Non-Invasive:

1. Electrocardiography (ECG):

on a standard 12-lead ECG, many patients with CSX present with only sinus tachycardia and otherwise completely normal ECG findings. However, during an ECG-based Exercise Stress Test (EST), these patients will demonstrate transient ST-segment depression during physical exertion and may also exhibit such findings on a 24-

hour Holter Monitoring (Ong et al. 2018). Anginal chest pain during stress testing in combination with ST-segment depression, and the lack of structural abnormalities on echocardiography demonstrate an increased likelihood of CSX (Acharya et al. 2020).

2. Technetium Sestamibi (99mTc) Scan:

this imaging modality will usually show in patients with CSX a heterogenous distribution of microscopic vascular defects distributed along all the coronary epicardial arteries rather than just one single major vessel (Del Buono et al. 2021).

Invasive

1. Coronary Angiography:

patients with CSX exhibit no significant focal coronary artery narrowing on angiography, but intracoronary administration of nitro-glycerine may increase coronary perfusion indicating global coronary vasoconstriction (Fig. 1.1).

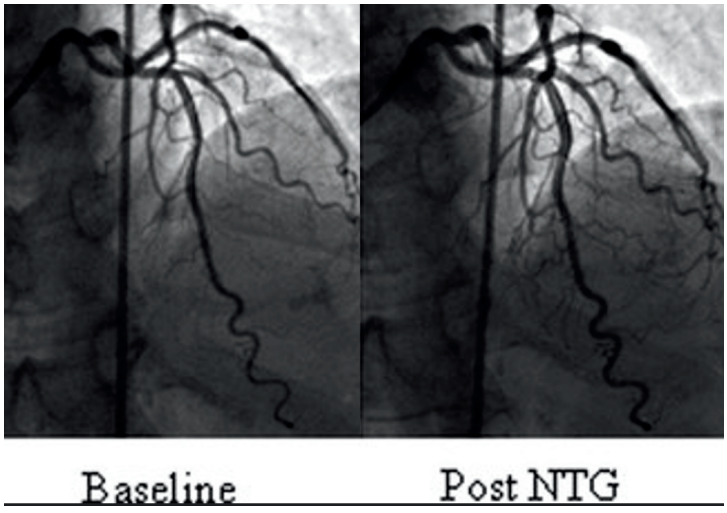

Fig. 1.1: depicting initial coronary angiography in patients with CSX followed by administration of nitro-glycerine indicating increased coronary perfusion.
Source: (Bairey Merz and Pepine 2011).

Treatment and Management

Since the aetiology of CSX is not fully understood, management of such patients may be challenging in nature. Its management ranges from controlling the modifiable risk factors to administering a triple combination therapy of ant-ischemic and antihypertensive agents.

1. Adopting a healthy heart lifestyle is of substantial benefit to these patients. This includes avoiding active and passive smoking, practising regular aerobic exercise, following a diet that is low in saturated fats and cholesterol, and even managing stress.

2. Beta-blockers (carvedilol, propranolol, and labetalol) have been demonstrated to be effective in improving exercise tolerance and symptoms in patients with CSX. More recently, third-generation beta-blockers such as nebivolol, have been shown to be potentially more effective since they enhance the vasodilatory activity of the endothelium (Soleymani et al. 2022).

Nifedipine, verapamil and diltiazem, which are calcium channel blockers, may be used as alternative therapy however are known to be less beneficial, even though they improve exercise tolerance and anginal attacks. It has also been noted that ranolazine, a new antianginal used in chronic anginal chest pain is also useful as an effective therapeutic option (Jarczewski et al. 2021).

Statins have an important role in the management of patients with CSX as they promote the vasodilatory function of the endothelium and prevent the further development and aggravation of atherosclerotic plaque in the coronary end arteries, hence, stabilising the plaque to prevent the possible rupture and consequential ischaemia of myocardium.

ACE inhibitors have shown to be advantageous, as they prevent the breakdown of bradykinin within the endothelium, which sustains vasodilatory function, further regulating microvascular tone within coronary arteries (Ford et al. 2018).

3. Analgesic medications may also be useful, based on the idea that patients with CSX have a heightened or impaired pain perception. Certain patients may benefit from the use of agents such as xanthine derivatives like aminophylline – that work by blocking the adenosine receptors within the cardiac plexus – and transcutaneous electrical nerve stimulation (TENS) (Johnson et al. 2022).

Complications

The risk for future adverse cardiovascular events, especially in females with uncontrolled anginal chest pain significantly increases, even though there are no signs of stenosis on imaging. MI, stroke, sudden cardiac death, and heart failure are subsequent examples of such events.

The quality of life in a patient with CSX significantly declines, and daily activities become more challenging. Since CSX is diagnosed in exclusion, a thorough workup is necessary which may be expensive and time-consuming. Due to the frequent failures of traditional medications for therapeutic management, the challenge of achieving therapeutic efficacy from pharmacotherapy presents additional obstacles. This frequently worsens the quality of life of CSX patients, increases and prolongs hospital stays, and furthermore limits daily activities.

Even though the prognosis of CSX remains guarded, recurrent episodes of anginal attacks necessitate periodic hospitalisation due to their high frequency of occurrence. Roughly 30% of patients experience a decline in clinical manifestations, whereas 10% endure a progressive worsening of symptoms. Individuals facing a declining course of their illness frequently encounter difficulties with diagnosis, investigations and treatment which may lead to disability (Asbury and Collins 2005).

Genetic Inheritance

An underlying genetic basis was uncovered for microvascular angina, which offers further mechanistic insight into its pathophysiology. In addition to genotyping 643 patients with this condition, researchers looked at 1536 single nucleotide polymorphisms (SNPs) in 76 genes that were linked to its pathology. SNPs in the VEGFA and CDKN2B-AS1 genes were extensively linked to microvascular dysfunction across the whole board of the researched population (Yoshino et al. 2014). Additionally, they discovered an SNP-sex interaction that could account for some of the pathophysiological variations between men and women who suffer from microvascular angina. Even though no potential SNPs were linked to the condition in females, SNPs in the MYH15, VEGFA and NT5E genes were also linked to microvascular dysfunction in males (Leopold 2014).

Conclusion

In conclusion, obstructive CAD and endothelial dysfunction show conspicuous connections to CSX, which is a difficult medical condition to diagnose, and primarily affects but is not exclusive to females. Improved knowledge of coronary vascular dysfunction will be of significant benefit to patients with CSX. Microvascular angina should remain a high research priority area due to its high prevalence, significant healthcare expenses, and dearth of information regarding effective treatment options.

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Reducing Cardiovascular Risk in Hypercholesterolemia

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Abstract

Hypercholesterolemia, characterised by elevated cholesterol levels, is a significant contributor to atherosclerosis and cardiovascular disease. This paper provides a comprehensive overview, exploring its genetic, lifestyle and metabolic intricacies. The cardiovascular risk factors associated with hypercholesterolemia, including age, family history, diabetes, smoking and low HDL-cholesterol levels, highlight the complexity of managing this condition.

Current treatments, particularly statins demonstrate effectiveness in lowering LDL cholesterol and reducing cardiovascular events. However, challenges bring up the need for alternative therapies, such as PCSK9 inhibitors and gene therapy, revealing the evolving landscape of hypercholesterolemia management. In summary, this review urges ongoing efforts and comprehending, managing and advancing hypercholesterolemia treatments. By combining existing knowledge with ongoing research and prioritising patient-centred approaches, we aim to improve outcomes and better address the challenges posed by hypercholesterolemia.

Keywords: Hypercholesterolemia, cardiovascular disease, atherosclerosis, risk factors, PCSK9 inhibitors, gene therapy, personalised medicine, patient adherence, integrated cardiovascular risk management

Introduction

Hypercholesterolemia is a prevalent and multifaceted medical condition, emerging as a focal point in discussions surrounding cardiovascular health. Characterised by elevated levels of cholesterol in the bloodstream, hypercholesterolemia significantly contributes to the development of atherosclerosis (1), a leading cause of cardiovascular disease, as well as the primary cause of death in the United States, with about 50% of Americans between the ages of 45 and 84 unknowingly having atherosclerosis (2). As a complex interplay of genetic predisposition, lifestyle factors and metabolic intricacies, this condition demands a comprehensive understanding to address its implications on public health. The significance of cardiovascular risk reduction lies in its pivotal role in mitigating the potential for life-threatening events, such as myocardial infarction and strokes (3), thereby fostering enhanced longevity, improved quality of life and a substantial reduction in healthcare burdens.

Methodology

A literature review was conducted across academic databases including PubMed and Science Direct, utilising keywords such as “hypercholesterolemia”, “LDL cholesterol”, “atherosclerosis”, “cardiovascular risk”, “treatment” and “patient adherence.

Articles were screened based on their titles and abstracts to identify potentially relevant studies. Full-text review was then performed for articles meeting the following criteria:

1. Relevance to preventing cardiovascular risk in hypercholesterolemia
2. Availability in the English language
3. Original research articles, reviews and clinical trials.

Key data points were extracted from selected studies, including study objectives, methodology employed, participant demographics and numbers, key findings and the conclusion drawn by the authors.

The extracted data was then synthesized according to theme to identify the common patterns, trends and gaps in the literature pertaining to reducing the cardiovascular risk in individuals suffering from hypercholesterolemia. This involved categorising the studies based on the focus areas mentioned above. Through this process, a comprehensive understanding of the current landscape of hypercholesterolemia research was achieved in this review, allowing for insights and implications for clinical practice and public health initiatives.

Hypercholesterolemia: A Brief Overview

Hypercholesterolemia is a hyperlipidaemia: a condition that describes a high level of lipids in the human body (4), primarily high serum level of Low Density Lipoprotein (1), also known as LDLs. Lipids are a group of naturally occurring molecules with a low water solubility and a high solubility in organic solvents. Circulating lipids, namely cholesterol, triglycerides and phospholipids are transported as plasma lipoproteins (3). These lipoproteins are divided into five distinct classes, according to their size. These are the following, from largest to smallest (5):

1. Chylomicrons
2. Very Low Density Lipoproteins (VLDL)
3. Intermediate Low Density Lipoproteins (IDL)
4. Low Density Lipoproteins (LDL)
5. High Density Lipoproteins (HDL

HDL is the only class that is anti-atherogenic (5) meaning that it prevents atherogenesis, which is the progression and development of a build-up of fatty deposits, cellular debris, cholesterol and other substances on the inner arterial walls. This accumulation then leads to plaque formation, restricting blood flow and contributing to the onset of cardiovascular disease (6). LDL is rich in cholesterol, with some derived from the liver by VLDLs or from circulating HDL. LDL formation rate is observed to be markedly higher in obesity and with a diet containing high amounts of saturated fat, such as the Western diet (7, 8).

There are two types of hypercholesterolemia: genetic (familial) and acquired, with familial hypercholesterolemia (FH) being the classical type. This results from a genetic mutation in the LDL-receptor gene, which accounts for over 85% of FH, causing high LDL-C levels – 3.7mmol/L (>145 mg/dl) in heterozygotes and even higher levels in homozygotes – 11.6mmol/L (>450 mg/dl) (1). Other genetic mutations in FH are defects in apolipoprotein B (apo-B) and proprotein convertase subtilisin / Kexin type 9 (PCSK9) (9).

Cholesterol, vital for cellular functions, undergoes meticulous control, with the endoplasmic reticulum (ER) serving to sense and regulate cholesterol levels (11). The ER houses inactive transcription factors that respond to cellular cholesterol levels. Cholesterol homeostasis is also regulated through sterol regulatory element-binding proteins (SREBPs) (11). SREBPs activate the expression of over 30 genes dedicated to synthesising and uptake of lipids including cholesterol, phospholipids, triglycerides and fatty acids, as well as the NADPH cofactor for the synthesis of these molecules (12). When cellular cholesterol rises, SREBPs do not reach the Golgi apparatus, and transcription of target genes declines (12). Furthermore, the ER-bound translation factor Nuclear Respiratory Factor 1 (NRF-1) plays a role in sensing heightened

cholesterol levels, leading to the activation of liver X receptor (LXR) and subsequent cholesterol excretion (11).

Cardiovascular Risk Factors Associated with Hypercholesterolemia

As previously discussed, elevated levels of cholesterol is a thoroughly documented risk factor for cardiovascular disease.

In Malta, hypercholesterolemia has been increasing since the 1980s (10), posing a growing challenge to public health initiatives and necessitating a comprehensive examination of contributing factors, lifestyle trends, and potential interventions to address and mitigate this concerning upward trajectory. The primary risk factors for hypercholesterolemia and cardiovascular disease include (13):

- Age

Males over the age of 45 and females over the age of 55 are at increased risk of hypercholesterolemia.

- A family history of premature atherosclerotic cardiovascular disease

Premature refers to <55 years in males and <65 years in females.

- Diabetes

According to the Heart UK website, diabetes damages the arterial wall. This makes it more likely that cholesterol binds to them, causing narrowing and blockage. Diabetes is also associated with a lower level of HDL cholesterol and a higher level of LDL cholesterol, further increasing the risk of atherosclerotic plaque (14).

- Smoking

Nicotine, an addictive compound found in tobacco, causes a decrease in HDL cholesterol levels and an increase in LDL cholesterol levels, also causing lipid adhesion and accumulation in the arterial wall (15).

- Low HDL-Cholesterol Levels

This is defined as <1mmol/L (40 mg/dl) in males and <1.4mmol/L (55 mg/dl) in females.

Other risk factors include lifestyle factors such as a diet rich in saturated (16) and trans fats (17), as well as an excessive intake of cholesterol-containing foods. A lack of regular physical activity can also lead to an impaired lipid metabolism and weight gain, ultimately leading to overall poor cardiovascular health (18). Hypertension also contributes to these risk factors by damaging arteries and accelerating the development of atherosclerosis, especially in individuals with hypercholesterolemia (19).

Atherosclerotic Plaque Formation

The formation of an atherosclerotic plaque is a multifaceted process involving (20):

1. Lipoprotein retention:

The central concept in atherogenesis is the sub-endothelial retention of apo-B-containing lipoproteins, serving as the key initiating event. This retention triggers a local chronic and maladaptive inflammatory reaction, leading to the development of atherosclerotic lesions. (21)

2. Inflammatory leukocyte recruitment

Pro-inflammatory leukocytes drive the progression of atherosclerosis by using soluble mediators and tissue-specific molecules. These act to influence the adhesion and transmigration of leukocytes. Multiple adhesion receptor-ligand pairs, such as selectins and integrins, guide the recruitment cascade. The plaque begins with a deposition of oxidised low-density lipoproteins (oxLDL) in the sub-endothelial space. The interactions between oxLDL and tissue-resident macrophages act to trigger a pro-inflammatory immune response, dominated by myeloid cells. The infiltrated leukocytes interact with stromal cells, secreting pro- or anti-inflammatory cytokines, influencing inflammation and tissue remodelling. The continuous accumulation of leukocytes in the plaque leads to its progression. (22)

3. Formation of Foam Cells

Foam cell development arises from elevated

oxLDLs internalisation and the increased lipid droplet accumulation within macrophages. This progression triggers fatty streak formation, evolving into primary atherosclerotic lesions. The integral role of foam cells in atherosclerosis pathogenesis becomes apparent, particularly in the sub-endothelial space of compromised arteries. This early sequence of events involving the creation and build-up of foam cells significantly contributes to atherosclerotic plaque formation (23)

4. Apoptosis of endothelial smooth muscle

Apoptosis is also known as programmed cell death (PCD) (24). It is a detrimental process when it comes to plaque stability, while when it comes to macrophages, it can be beneficial for plaque stability (25).

5. Necrosis

In contrast to apoptosis, necrosis is a more passive and unintentional cell death triggered by external disturbances, leading to the uncontrolled release of inflammatory cell contents (26). Necrotic cell death is marked by cell swelling, membrane rupture and the formation of a large necrotic core that characterises unstable plaques (27). In advanced plaques, increased necrosis results in the release of proinflammatory cytokines and Damage-Associated Molecular Patterns (DAMPs), intensifying inflammation and plaque destabilisation. (27)

6. Smooth muscle cell (SMC) proliferation

Triggered by endothelial cell damage, LDL accumulation prompts monocyte recruitment, transforming them into foam cell macrophages. SMCs then migrate to the tunica intima, proliferating and secreting extracellular matrix proteins. This process predisposes to plaque development. In advanced stages, SMCs play a role in stabilising lesions by forming a fibrous cap around the necrotic core. However, cap thinning increases rupture risk, leading to thrombus formation and potential complications. (28)

7. Matrix synthesis

SMCs migrate, proliferate and secrete extracellular matrix proteins, such as collagen, elastin, fibronectin and proteoglycans, forming the fibrous cap. (29)

8. Calcification

Micro-calcifications indicate and active stage linked to inflammation, while spotty calcifications associate with extensive atherosclerosis and increased disease progression. Large calcifications may contribute to stable plaques (30).

9. Angiogenesis

The formation of new blood vessels plays a dual role in atherosclerosis. In early stages, oxidative stress in the hyperplastic intima promotes neo-angiogenesis. In advanced plaques, chronic inflammation and oxidised lipids contribute to angiogenesis, resulting in leaky capillaries prone to injury. This leads to intra-plaque haemorrhages, cholesterol accumulation and plaque instability, increasing the risk of rupture (31).

10. Arterial remodelling

Arterial remodelling involves changes in vessel size in response the various triggers such as atherosclerosis and restenosis. Expansive remodelling prevents luminal narrowing, while constrictive remodelling accelerates it. (32)

11. Rupture of fibrous cap

A self-explanatory process, cap rupture is the leading cause of coronary thrombosis, leading to an infarction. In severe cases, this can lead to sudden cardiac death. (33)

12. Thrombosis

Described as the formation of blood clots in veins, thrombosis disrupts normal blood flow. Its complex diagnosis and management involves factors like location, acuity and underlying conditions, impacting treatment decisions (34).

Some plaques are asymptomatic, some are obstructive – leading to stable angina, and some can even lead to acute thrombosis, which can lead to an acute coronary syndrome (20).

Elevated LDL levels contribute to arterial injury, promoting endothelial dysfunction. Infiltration of LDL-containing lipoproteins triggers an inflammatory response, formation of foam cells and atherosclerotic development (35). On the other hand, HDL cholesterol efflux is consistently

associated with a reduced risk of cardiovascular disease (35).

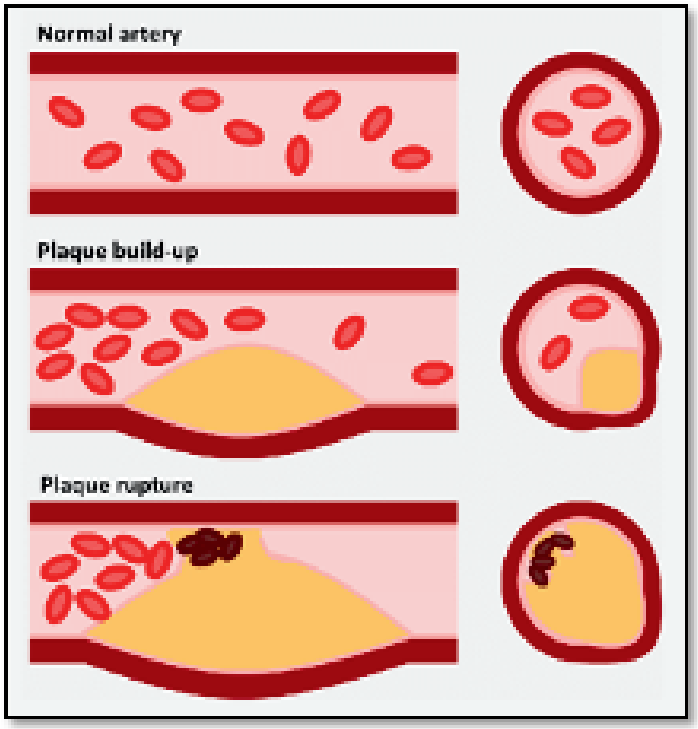

Figure showing the development of an atherosclerotic plaque. Retrieved from Ward, Liam. (2019). Sex differences in atherosclerosis and exercise effects.

Current Hypercholesterolemia Treatments and Efficacy of Statins

The primary approach for managing hypercholesterolemia involves lifestyle modifications such as maintaining a healthy weight and regular exercise (~150 minutes a week) (1). Furthermore, a diet high in vegetables, fruit, whole-grains, low-fat dairy, fish and omega-3 fatty acids is encouraged over one containing high levels of saturated and trans fats and refined carbohydrates (36).

Statins

Statins are the preferred drug class for treating hypercholesterolemia, able to lower LDL cholesterol by 22-50%, and reduce cardiovascular events (1). This is due to their inhibition of hydroxymethylglutaryl-CoA reductase enzyme (HMG-CoA), which is the enzyme that converts HMG-CoA to mevalonate in cholesterol synthesis (38). It also reduces apoB100 containing lipoproteins from the liver, which leads to a lower level in cholesterol concentrations (38). According to studies, statins have demonstrated effectiveness in preventing both mortality and cardiovascular morbidity among individuals with a low risk of cardiovascular events (39). The observed reductions in relative risk parallel those observed in patients with a known history of coronary arterial disease (CAD) (40). As such, existing recommendations for statin use rely on the anticipated risk of experiencing an atherosclerotic event rather than solely on the presence or absence of established CAD (39). Additional studies suggest that statin treatment for the primary prevention of cardiovascular disease in individuals with low or medium risk may have a beneficial effect if there is optimal treatment adherence (40).

However, they have side effects such as elevated transaminases, an indicator of liver dysfunction (37), myalgia and myopathy may occur. When monotherapy via statins proves insufficient, cholesterol absorption inhibitors such as ezetimibe, and bile acid sequestrants can be used (1).

PCSK9 inhibitors and other Novel Therapies including Gene Therapies

For patients with FH or those unable to achieve target LDL levels using the above approaches, new options like PCSK9 inhibitors have become available (1,37). PCSK9 regulates plasma LDL levels by influencing expression of LDL receptors (41). When cholesterol biosynthesis inhibitors like statins are administered, they can initially deplete hepatic cholesterol levels, therefore activating PCSK9. This leads to increased degradation of LDL receptors, attenuating effects of statins on LDL receptor expression. . Inactivating PCSK9 in mice has been shown to heighten sensitivity to statin treatment (42). Therefore, by blocking PCSK9 activity, these inhibitors help maintain higher levels of functional LDL receptors on the cell surface,

facilitating increased LDL clearance from the bloodstream. (41).

Additionally, combinations of medications may be necessary, and in extreme cases, LDL apheresis or liver transplantation could be considered (1). While lipoprotein apheresis effectively prevents atherosclerosis progression, using plasma exchange, double-membrane filtration and selective LDL adsorption – the latter of which is adopted globally, early initiation in crucial, especially in homozygous patients (42). Those starting apheresis in adulthood exhibited a poorer prognosis than those starting in childhood (42). Meanwhile, other studies state that liver transplantation is the only way to correct abnormal hepatic cholesterol metabolism in FH until now (43).

There have also been explorations in the applications of gene therapy in the FH field. Gene therapy involves inserting a functional gene into a human cell to correct genetic errors or introduce new functions (44). Current gene therapies that have undergone clinical trials for FH include:

1. Virus Vector-Mediated Gene Therapy

Adeno-associated virus (AAV) serves as a safe and effective gene-delivery system for treating hypercholesterolemia (45). Studies, including a clinical trial (NCT02651675, 2019), have highlighted the efficacy of AAV vectors in delivering the human LDLR gene, demonstrating a reduction in cholesterol levels. AAV8 has particularly shown superior hepatocyte transduction (46) and an improved lipid profile (47) when compared to AAV2. A phase 1 clinical trial reported successful reductions in serum cholesterol levels with AAV8-mediated LDLR gene therapy for Homozygous FH. The trial displayed safety and significant cholesterol reduction, setting the stage for further exploration of AAV-mediated gene therapy in hypercholesterolemia treatment.

2. Antisense Oligonucleotides (ASOs)

ASOs are short DNA strands designed to bind to specific mRNA sequences. Mipomersen, an ASO targeting apoB-100 mRNA reduces LDL-c levels in FH patients (45), with studies showing a 24.7% LDL-c reduction in a phase three trial (48). Another ASO, SISIS-APO(a)Rx, lowers Lipoprotein a levels by up to 89% (50). These ASOs offer potential in managing lipid disorders with promising efficacy and acceptable safety profiles (45).

3. Small Interfering RNAs (siRNAs) Targeting PCSK9 Synthesis

siRNAs like Inclisiran inhibit PCSK9 synthesis by subcutaneous administration. In the ORION-1 trial, 501 high-risk patients received single or two doses of Inclisiran, showing LDL-c reductions of 27.9% to 52.6% at 180-day follow-up. LDL-c and PCSK9 levels remained significantly lower at the 240-day follow-up. These promising results suggest siRNAs targeting PCSK9 may be beneficial for high-risk patients in lowering cardiovascular risk (50).

Potential Prospects in Novel Approaches in Pre-Clinical Development

Novel approaches in pre-clinical development for treating FH show promise. Mini-circle DNA vectors, which are compact non-viral plasmids, express therapeutic genes such as LDLR (51). In mouse studies, they controlled LDL-c levels effectively, but delivery challenges need addressing (51).

MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression, and according to results from animal studies, several of them influence the LDL-c pathway and delay atherosclerotic progression in mice (52). Numerous miRNAs regulate FH-associated genes, suggesting a potential novel therapy (45).

Long non-coding RSNs (lncRNAs), over 200nt RNA molecules, also regulate gene expression. In an AAV8 vector study, lncRNA targeting a specific sequence reduced cholesterol biosynthesis genes and atherosclerosis in mice (53).

The CRISPR/Cas9 system, a precise gene-editing tool, holds therapeutic potential. Using CRISPR/Cas9, researches knocked down PCSK9 expression, reducing plasma cholesterol levels (54).

The newer CRISPR/Cpf1 system shows promise for multiplex gene editing in vivo, and can repair mutations, providing potential treatment for monogenic inherited disease (35). Studies demonstrate its success in correcting genetic deficiencies related to FH, making it a promising therapeutic tool for the future (35, 46).

Challenges of Novel Approaches

While these approaches offer exciting prospects, some face challenges. Mini-circle DNA vectors, though effective, encounter delivery issues that need further exploration (35). miRNA-based therapies show potential but require additional research for clinical validation. lncRNA-based therapeutics show potential in mouse studies, but need more investigations for clinical validation (53). The CRISPR/Cas9 system, although powerful, necessitates ongoing research to address potential off-target effects and ensure its safety and efficacy for FH treatment (35).

Personalised Medicine

The aforementioned pre-clinical developments highlight diverse strategies for addressing FH, with each approach presenting unique advantages and challenges, emphasizing the need for continued research to refine and validate these novel therapeutic avenues for potential clinical use in the future. It is necessary to have multifaceted treatment approaches for personalised medicine as individuals exhibit unique genetic, environmental and lifestyle factors influencing their health. Certain medications diminish statin effectiveness by either reducing bioavailability or increasing metabolism, exemplified by rifampicin (56). Conditions affecting cholesterol metabolism, such as hypothyroidism, also impact statin efficacy (57, 58). Genetic variations within lipid metabolism-related genes also influence statin response (59). Moreover, a substantial proportion of treated patients (over 40%), fail to achieve target LDL-C levels (60). Barriers to reaching LDL-C goals encompass failure to start therapy, non-adherence, side effects, inappropriate drug/dose selection, and insufficient dose titration (55). Tailoring interventions to specific patient characteristics will allow for more precise and effective healthcare strategies.

Patient Adherence and Challenges in Treatment

Maintaining adherence to chronic disease treatment is crucial for its effectiveness and holds significant implications for public health and healthcare economics (61). Various factors contribute to low adherence, stemming from patients, physicians and healthcare systems. Widespread non-adherence to dietary recommendations and lipid-lowering drug therapies, especially for hypercholesterolemia, poses a significant challenge, limiting the potential benefits of serum lipid reduction in cardiovascular prevention. Many patients discontinue treatment, and adherence diminishes over time, highlighting the need for strategies to improve adherence (61).

The success of primary and secondary prevention strategies achieved through reducing LDL cholesterol, represents a milestone in medicine (62, 63). Notably, real-world adherence to lipid-lowering therapy, particularly with statins, falls below levels reported in controlled trials, contributing to reduced cardiovascular prevention efficacy. Therefore, translating the positive outcomes observed in clinical trials into real-world scenarios requires consistent adherence to prescribed therapies (64). Recognised as a major public health concern, poor adherence to chronic disease treatment compromises its effectiveness, influencing mortality, morbidity and healthcare costs (64).

Understanding the causes of poor adherence is crucial, with estimates suggesting that approximately half of patients not correctly follow long-term therapy prescriptions, saying that they were “no longer necessary”, “ineffective”, posing an “adverse reaction”, “too expensive” and even “inadequately covered by insurance” (65). Recognising physical-related barriers is imperative, emphasizing the need for efforts by scientific

societies to enhance physician awareness of their role in adherence improvement. Systematic strategies to reduce non-adherence should be advocated within healthcare systems.

Emphasizing the importance of dietary and lifestyle changes for cardiovascular risk reduction, guidelines recommend optimal dietary options and strategies in order to enhance patient adherence (61). Strengthening the cultural understanding of good adherence among patients and physicians is essential. Despite the recognised impact of good adherence on health outcomes, there remains a lack of knowledge on how modern technology could support both drug and dietary adherence. Further research in this area is deemed necessary to address this crucial aspect (61).

Impact of Cardiovascular Risk Reduction on Patient Outcomes

In a study by Smits et al (2023), the long-term outcomes of an integrated cardiovascular risk management program organised by a care group in the Netherlands was examined with the aim to understand changes in LDL cholesterol, systolic blood pressure (SBP) and smoking status among high-risk patients participating in the program from 2011 to 2018 (66).

The care group implemented a protocol for delegated practice nurse activities and utilised a multidisciplinary data registry for uniform registration. Annual education sessions were organised for general practitioners (GPs) and practice nurses on cardiovascular topics, along with regular meetings for practice nurses to discuss complex cases and implementation issues (66). Practice visitations were initiated in 2015 to support practices in organising integrated care. The study analyses data from 145 general practices affiliated with the Primary care group PoZoB (Praktijkondersteuning Zuidoost Brabant).

Results indicate positive trends for both primary and secondary prevention. Cholesterol-lowering and blood pressure-lowering medication prescriptions increased, accompanied by decreases in mean LDL cholesterol and mean SBP. The proportion of patients on target for LDL cholesterol and SBP also increased. The prevalence of smoking decreased and the percentage of non-smokers with both SBP and LDL cholesterol on target saw significant improvement (66).

The study emphasizes the importance of improved registration practices between 2011 and 2013, contributing to a sharp increase in patients meeting LDL cholesterol and SBP targets. The integrated care approach involved a comprehensive support system, including protocolled practice nurse involvement, a multidisciplinary registry, education, practice visitations and quarterly benchmark reports (66).

Strengths of this study include a large study population from routine clinical practice, standardized protocols and a real-life monitoring over an 8-year long period. Limitations include the lack of a reference group for comparison and some missing data between 2010 and 2013 (66). Comparisons with existing literature highlight the challenges of implemented structured care in randomised controlled trials, with carrying results (66). This study, focusing on real-world, long-term outcomes, contributes valuable insights into the effectiveness of integrated cardiovascular risk management in primary care.

Conclusion

In conclusion, this comprehensive exploration of hypercholesterolemia has provided valuable insights into its multifaceted nature, cardiovascular risk factors, current treatments and novel therapeutic approaches. The key findings of this review underscore the interplay between genetics, lifestyle and metabolic intricacies in the development of hypercholesterolemia, emphasizing the need for a holistic understanding to address its implications on public health.

The cardiovascular risk factors associated with

hypercholesterolemia shed light on the increasing challenge to public health initiatives. Factors such as age, family history, diabetes, smoking and low HLD-cholesterol levels contribute to the complexity of managing this condition. The detailed exploration of atherosclerotic plaque formation elucidates the intricate process involved, providing a foundation for the understanding of the progression of cardiovascular disease.

Current treatments, with a focus on statins, highlight the effectiveness of these drugs in lowering LDL cholesterol and reduce cardiovascular events. However, challenges such as side effects that lower quality of life, and the need for alternative therapies, including PCSK9 inhibitors and gene therapies, demonstrate the evolving landscape of hypercholesterolemia management.

The discussion on personalised medicine underscores the importance of tailoring interventions to individual characteristics, considering factors that may affect statin effectiveness. The exploration of patient adherence and challenges in treatment emphasizes the critical role of consistent adherence in achieving optimal outcomes, with a need for strategies to improve adherence in real word scenarios.

The impact of cardiovascular risk reduction on patient outcomes as evidenced by the study conducted in the Netherlands highlights the positive trends resulting from an integrated cardiovascular risk management program. This real-world evidence reinforces the importance of comprehensive support systems, education, and multidisciplinary approaches in primary care.

In conclusion, this review sets the stage for a continued and concerted effort in understanding, managing and advancing the treatment landscape for hypercholesterolemia. The synthesis of current knowledge, coupled with ongoing research and a focus on patient-centred approaches, will contribute to better outcomes and a more effective response to the challenges posed by this prevalent medical condition.

Declarations

Conflict of interest: N.A.
Ethical statement: N.A.

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List of Abbreviations

Abbreviation	Definition
AAV	Adeno-Associated Virus
ASO	Anti-Sense Oligonucleotides
CAD	Coronary Artery Disease
CAMPs	Damage Associated Molecular Patterns
ER	Endoplasmic Reticulum
FH	Familial Hypercholesterolemia
HDL	High Density Lipoproteins
HMG-CoA	Hydroxymethylglutaryl-CoA Reductase Enzyme
IDL	Intermediate Density Lipoproteins
LDL	Low Density Lipoproteins
lncRNA	Long non-coding RNA
LXR	Liver X Receptor
miRNA	Micro RNA
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NRF-1	Nucleotide Respiratory Factor-1
oxLDL	Oxidised Low-Density Lipoproteins
SBP	Systolic Blood Pressure
siRNAs	Small Interfering RNAs
SMC	Smooth Mucle Cell
SREBP	Sterol Regulatory Element Binding Proteins
PSCK9	Proprotein Convertase Subtilisin / Kexin type 9
VLDL	Very Low Density Lipoproteins

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Latest insights into the role of astrocytes in Alzheimer's Disease and Parkinson's Disease: a Literature Review

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Abstract

Astrocytes are key players when it comes to maintaining healthy neuronal tissue. Their multitude of functions make them truly indispensable, however they have also been implicated in the pathophysiology of several neurological disorders. This review discusses the current literature and introduces the latest advancements in the role of astrocytes in (1) Alzheimer's Disease and (2) Parkinson's Disease, from a pathophysiological standpoint, as well as a therapeutic point of view. A PubMed literature search (2018-2024) using the following search strings: (astrocytes) AND (Parkinson's disease) as well as (astrocytes) AND (Alzheimer's disease) was performed. Astrocytes have been implicated in the contribution of neuroinflammation, leading to neuronal death in Alzheimer's Disease. Similarly, astrocytes may contribute to progression of Parkinson's Disease alpha-synuclein-induced neuroinflammation. Promising therapeutic interventions in this field make use of astrocytes, converting them into neurones to counteract the neurodegeneration that occurs in diseases like Parkinson's Disease.

Keywords: Alzheimer's Disease, Parkinson's Disease, Astroglia, Alzheimer's, Neuroinflammation, Neurodegeneration

Introduction

Astrocytes constitute the majority of cells in the central nervous system (CNS) and have a multitude of crucial roles in maintaining healthy neuronal tissue. From developmental to structural, as well as homeostatic functions, amongst others, these glial cells prove to be essential in the overall health and functioning of the nervous system (1–3). Indeed, astrocytes play a role in pH and ion regulation, maintenance of blood brain barrier, cerebral blood flow regulation and they also express receptors for a wide range of neurotransmitters (1,3). This makes them key players in the uptake and metabolism of neurotransmitters like noradrenaline and glutamate (2). Astroglia have also been implicated in glial scar formation, a mechanism for neuronal protection in traumatic brain injury (TBI), in order to preserve and limit the extent of damage (4). However, astrocytes have also been implicated in the pathophysiology of several neurological disorders, including Alzheimer's Disease (AD) and Parkinson's Disease (PD), just to mention a few (3,5,6). Changes in number, size and appearance of astrocytes have all been linked to pathological conditions (7,8). Astrocytic scar formation as a response to TBI can also have pathologic long-term effects (9). This review aims to discuss the latest advancements in relation to astrocytes and their relationship with (1) Alzheimer's disease and (2) Parkinson's disease.

Methods

A PubMed literature search using the following search strings: (astrocytes) AND (Parkinson's disease) as well as (astrocytes) AND (Alzheimer's disease) was performed. Case reports, clinical studies, trials as well as meta-analysis and randomised controlled trials published between 2018 and 2023 were analysed. The articles were chosen according to a relevant title and abstract, although conclusions were also taken into consideration for the selection process. Articles written in English and open access articles were analysed. The exclusion criteria included articles older than 2018, articles which were not open access as well as any articles that tackled different subject matters. Additional relevant literature was also obtained via reference snowballing.

Results/Discussion

Alzheimer's Disease

Alzheimer's Disease prevalence is on the rise worldwide, and it is the leading cause of dementia. It is an irreversible, neuropsychiatric disorder with characteristic progressive, global cognitive impairment (including memory loss, anosognosia, executive function loss) with additional non-cognitive symptoms including irritability, appetite disturbances and mood disturbances.

There is conflicting data about AD incidence and prevalence rates. On one hand, it is widely reported that AD incidence rates are decreasing in Europe (10–12) and North America (10,11). The Alzheimer Europe 2019 analysis (13) reports a decline in AD prevalence. One possible hypothesis for these observations revolves around the fact that education and health interventions are reducing risk factors predisposing to AD (10). Additionally, angiotensin-converting enzyme inhibition also slows the neurodegeneration that leads to dementia, as it indirectly influences said risk factors (eg hypertension, diabetes) (9).

On the other hand, several studies (14–16) report an increased global AD prevalence, which increases with age in view of ageing populations. In general, whilst the AD incidence may be possibly decreasing, it is still unlikely to have a significantly altered AD prevalence in the near future (17,18).

It is understood that AD causation involves both environmental and genetic factors (19,20). The pathophysiology includes extracellular toxic Beta-amyloid peptide accumulation and plaque formation, which damage neuronal cells, causing synapse loss and chronic neuroinflammation. There is also intracellular hyperphosphorylated tau neurofibrillary bundles, which are hallmark of AD (21–23). These abnormal proteins contribute the aforementioned cognitive symptoms. In addition to this, studies suggest that Beta-amyloid plaques activate astrocytes, as part of the brain's immune response, in order to clear said plaques (24,25).

In neuropathology, whether acute or chronic neurological disease, reactive astrocytes undergo prominent remodelling in a process known as 'reactive astrogliosis' (26). This astrocyte reaction is a way of responding to central nervous system (CNS) insults and disease, in order to restore homeostasis, in a process fully regulated through signalling pathways (7). The mechanism of reactive astrogliosis varies depending on the disease context and its severity.

Generally, following astrocyte activation, they undergo changes in molecular expression, hypertrophy and, at times, proliferation with scar formation. This scar physically contains any areas of tissue damage and inflammation (27). It has been proven that one cytoskeletal protein called glial fibrillary acid protein (GFAP) is essential for reactive astrogliosis, and in fact, there is GFAP upregulation during this process. GFAP is specific to astrocytes (28). The reactive astrogliosis process is hallmark of AD and it potentially contributes to the disease progression as well as severity.

In fact, the intensity of GFAP levels, and therefore of astrogliosis, were reported to increase with increasing progression of AD Braak stages, which classify the disease into different phases, from pre-clinical AD to advanced stage AD (29). Additionally, the inflammatory signals secondary to reactive astrogliosis may also have neurotoxic effects (30). However, recent evidence shows that reactive astrocytes can also be beneficial, and can be used to regenerate neuronal tissue (31,32,33).

The role of Astrocytes in Alzheimer's Disease

Neuroinflammation is hypothesized to play a role in the development and/or the progression of AD. Regarding the contribution of astrocyte-mediated inflammation to neuronal loss by Beta-amyloid plaques, Garwood et al. (34) conclude that reactive astrocytes are triggers for the production of Aβ-induced tau phosphorylation. This is because there is an association between the neurotoxicity caused by the plaques and the increased activity of caspase-3, a key player in the apoptotic pathway. Interestingly, astrocytes further exacerbated this increased caspase-3 activity, which leads to neuronal death in vitro. Lian et al. (35) conclude that there is increased astrocytic activation of NF-KB pathway by Aβ plaques, resulting in upregulation of C3 complement protein by astrocytes, which ultimately results in altered intraneuronal electrolyte balance and the consequent impaired synaptic transmission seen in AD. Contrasting evidence has also shown that one astrocyte phenotype also plays an active role in plaque clearance, in response to chemokines released by the Aβ plaques in AD mice models (36). These highlight the multiple roles of astrocytes in AD albeit having both detrimental and neuroprotective functions; understandably making them potential therapeutic targets in future studies.

Past human post-mortem studies have investigated the role of astrocytes in the entorhinal cortex of AD patients, responsible for memory function.

One might hypothesise that this conflicting evidence is possibly due to the age of the post-mortem patients from whom the samples were taken. The cohort contained more elderly patients in the study by Porchet et al. (37), compared to Rodríguez et al. (41), with a discrepancy of about 10 years. The studies have different sample sizes, with that of Rodríguez et al. (41) and Hsu et al. (42) being larger than that of Porchet et al. (37) and therefore more representative of the population. Additionally, the study by Rodríguez et al. (41) was performed 20 years following that of Porchet et al. (37), and therefore discrepancies due to technological advancements cannot be excluded. Therefore, enhancing our understanding of the precise functioning of astroglia in the context of neurodegenerative disease is evidently the way forward, allowing the introduction of astrocyte-targeted therapy for AD patients. Being able to perform such studies on living patients would also be revolutionary in this aspect (42).

A number of genes have also been identified as possible risk factors for AD, including amyloid precursor protein (APP) gene, presenilin-1 (PSEN1) and presenilin-2 (PSEN2) genes as well as apolipoprotein E (APOE) (43). APOE originates from astrocytes, and allelic variation in this gene is the most prevalent of all genetic risk factors identified to date. One of the functions of APOE is lipid transport throughout the body. Having investigated the effects of the different APOE isoforms with reference to AD, Simonovitch et al. (44) demonstrate that the ApoE4 allele in mice astrocytes renders them less able to clear Aβ plaques, possibly driven by impaired endocytosis, autophagy and lysosomal degradation. Interestingly, the contrary applies for the ApoE2 isoform, which is protective against AD (45). Using this information, mice models were developed in order to further understand the mechanisms underlying this neurodegenerative disorder (34,46).

The Role of Astrocyte-induced cytokines in Alzheimer's Disease Progression

Neuroinflammation involves the release of 'TIC' cytokines, ie. tumour necrosis factor (TNF), Interleukin-1α (IL-1α) together with complement protein 1q (C1q) (47). Neuroinflammation has been closely linked to AD, and it has been recently speculated to contribute majorly to the early phase of AD pathogenesis (48,49). Astrocytes play a crucial role in this neuroinflammatory process, by increasing astrocyte-derived cytokines (including Interleukin-6 [IL-6]) (5,50). This is sphingomyelinase-mediated in astrocytes (34). This neuroinflammatory response might precede Aβ plaques in AD, but it is evident that neuroinflammation becomes more severe as plaques accumulate and the disease develops. In human neurodegenerative diseases, including AD, the TIC cytokines were also found to induce A1 neurotoxic reactive astrocytes, which drive neuronal and oligodendrocyte death through unidentified neurotoxin release (51), reactive oxygen species, nitric oxide and proteolytic enzymes, amongst others (52). At present, the scope behind the production of a neurotoxic astrocyte remains unclear. However, it is evident that these processes influence later stages of the disease, driving its progression with ever-evolving complications (48).

A high level of astrocytic IL-6 secretion was observed in mild and moderate AD patients (53). A 2022 study (54) investigated the effects of astrocytic IL-6 overexpression in transgenic mice from ages 3 months to 1 year of age, in relation to neuronal degeneration. Although IL-6 is typically considered to be "neuroprotective" (5,52), it was concluded that with increased astrocytic IL-6 expression, there was a significantly decreased cerebellar volume with possible cerebellar neuronal loss for mice aged 1 year (54). This is in keeping with (47), where TIC cytokines were found to contribute to the maintenance of neuroinflammation, and in fact, this decreased when TIC cytokines were removed, in the context of a stroke, in 8-week-old mice.

On the other hand, Interleukin-4 (IL-4) plays the role of an "anti-inflammatory" cytokine in vitro, contributing to the enzymatic clearance of Aβ plaques (53). Interleukin-10, for instance, also plays an important neuroprotective role in AD (55). Therefore, one can conclude that whilst astrocytes produce a multitude of cytokines which are crucial and necessary for the host defence, it is the imbalance between the pro- and anti-inflammatory mediators that is evidently pathologic. Although the cytokines benefit the CNS to a great extent, being non-specific, the surrounding neurones confer some inevitable damage in this way.

Neuronal regeneration from astrocytes in the treatment of Alzheimer's disease

Much of the existing literature has revolved around the generation of new neurones from neuroprogenitor cell transplants (56–58). However, novel reprogramming tools using viral vectors to target astrocytes are being introduced to establish neurogenesis in vivo. The latest advancements include the work of Zhang et al. (31), who demonstrated the in vivo reactive astrocyte conversion into neurones at the injury site, in the context of TBI. This not only generates neuronal tissue, but also simultaneously decreases the amount of reactive glial cells. TBI mice models induced reactive astrogliosis at the injury site, with astrocyte proliferation and accumulation. An AAV Cre-FLEX vector system was developed, which targets astrocyte DNA, specifically at the loxP site. The aim was to integrate NeuroD1 transcription factor, which induces the change to neuronal cells. In order to monitor the expression of NeuroD1, a separate vector including a dye (mCherry) was developed, FLEX-CAG::NeuroD1-P2A-mCherry together with a control AAV mCherry, without NeuroD1. The reactive astrocytes were exposed to the virus 10 days post-injury, as well as 21 days post-injury, in separate experiments. The results show that in both cases, ie. both before and after the formation of the glial scar, reactive

astrocytes were successfully converted into functional neurones, expressing NeuroD1 and NeuN, with large sodium and potassium currents as well as repetitive action potentials. Such therapy can potentially be used for neuronal repair in the days and months following neurotrauma.

Similarly, Liu et al. (32) make use of the glial scar formed during reactive astrogliosis post-TBI and reprogram it, to form neural tissue. The aim was to target astrocytes, not neurones, using modified adenoviral (AAV9P1) vectors, having an astrocyte-targeting P1 peptide on their surface. TBI was induced in mice using controlled cortical impact and immunostaining confirmed reactive astrocyte formation. AAV9P1-shPTBP1 vector was injected intra-venously, which reduced expression of polypyrimidine tract-binding protein 1 (PTBP1) and consequently astrocyte reprogramming was observed, forming neuronal cells.

This was confirmed by comparing the uptake of enhanced green fluorescent protein in mice treated with AAV9P1-shPTBP1 compared to control mice given AAV9P1-shCtrl. Although this proves that astrocyte-to-neurone conversion is possible in vivo using modified adenoviral vectors, no motor function improvement was observed in the mice, when tested on a beam walk.

The evidence reviewed here suggests a pertinent role for the therapeutic targeting of astrocytes in neural regeneration post-injury. Such approaches, however, have failed to address reactive astrogliosis secondary to neurodegenerative pathologies, including AD. There was no significant motor function amelioration seen in mice models either, indicating the need for more definitive evidence. Additionally, one must keep in mind the multitude of limitations when it comes to mouse models of human disease. The most important of which is the varying similarity to human pathology, especially when it comes to reproducing neuronal loss (59,60) as well as gene inconsistencies between mouse vs human reactive astrocytes (61).

These, together with other limiting factors, contributes to the low predictability of animal research in human clinical trials.

BACE-1 Targeted Therapy for Alzheimer's Disease Prevention

Toxic Beta-amyloid peptide accumulation and plaque formation is one of the features of AD. It is the Beta-site amyloid precursor protein cleaving enzyme-1 (BACE-1) that contributes to the formation of Beta-amyloid peptide, and there is BACE-1 overexpression during periods of chronic stress (52,62). Animal and human studies revolving around BACE-1 targeted therapy have been ongoing for around 20 years. The advancements that have been made in the past few years have been promising. In terms of pharmaceutical developments, Neumann et al. (63) investigated the effects of BACE-1 inhibitor CNP520 for the long-term prevention of AD.

At present, approved AD medications control the symptoms, but do not prevent AD. In the previously mentioned study (63), APP-23 transgenic mice were exposed to CNP520 for over 6 months. Its effects were monitored using a Beta-amyloid specific antibody. Compared to controls, the treated mice were found to have reduced insoluble Beta-amyloid Aβ40 and Aβ42 levels. This study also concludes that CNP520 also shifts metabolism away from the amyloidogenic pathway. Additionally, plaque-associated neuroinflammation, mediated by activated astrocytes, was reduced by the BACE-1 inhibitor in the brains of mice amyloidosis models. This therefore targets the prevention of impaired neurologic function and cognitive deficits in AD.

Parkinson's Disease

PD is one of the leading progressive, neurodegenerative disorders worldwide with both physical and neuropsychiatric symptoms (64,65). There is a global rise in PD prevalence, with WHO reporting a double in PD prevalence since 1997 (66). Interestingly however, a steep rise in PD cases was reported in China (65,67,68) as well as in high-income European countries (65,69). The 2017 Global Burden of Disease Study (70) attributes the latter to their increasingly ageing population, when compared to the global population.

The pathophysiology of this movement disorder involves neuroinflammation in the substantia nigra pars compacta as well as early death of the dopaminergic nigrostriatal pathway neurones, in the midbrain (71–73). The cause of this is still not entirely clear, however, like AD, environmental factors as well as genetics seem to play a role (9,74,75). To date, several genetic mutations were found to have an association with PD. Initially, 26 years ago, it was the association of SNCA gene mutations with early-onset PD (76) that hinted to a hereditary component of PD. Indeed throughout the years to follow, the emergence of mutations in Parkin (PARK2 gene) (77), PTEN induced putative kinase 1 (PINK1 gene) (78), Daisuke-Junko-1 (DJ-1 [PARK-7 gene]) (79), Leucine-rich repeat kinase 2 (LRRK2 [PARK8 gene]) (80) and vacuolar protein sorting 35 (VPS35) (81) have further confirmed this.

Do Mutated Genes in Astrocytes Play a Role in Parkinson's Disease Pathophysiology?

In an effort to understand how mutations in these genes cause PD, several theories have emerged. Interestingly, certain PD-associated genes were found to be expressed in high levels within astrocytes of PD patients. For instance, DJ-1, which is involved in the regulation of astrocyte signal transduction (82); LRRK2 missense mutations were linked to lysosomal dysfunction and protein degradation (83); parkin mutations are hypothesized to lead to astrocytic dysfunction and therefore, neuronal death (5). This raises the question of whether having mutated genes contributes to the pathophysiology of PD, and if so, to what extent.

In 2021, Bartyl et al. (84) found no variants of glucocerebrosidase (GBA), LRRK2 and SNCA, which are risk genes for PD, within their study cohort, which included cerebrospinal fluid immunoassay analysis of 252 PD patients and 115 healthy control patients, over a timespan of 4 years. On the other hand, Di Maio et al. (85) investigated the possibility of the contribution of LRRK2 kinase gene mutation to PD. In fact, they used rodent models to show that there is an increased wildtype LRRK2 kinase activity in neurones, as well as in the nigral microglia, in idiopathic PD cases. This was causative of lysosomal dysfunction and phosphorylated alpha-synuclein protein accumulation, which are hallmarks of PD. One might attribute these conflicting results possibly due to a small sample size, patients at varied PD stages and animal model discrepancies.

The role of astrocytes in Parkinson's Disease

Idiopathic PD is characterised by cytoplasmic alpha-synuclein in brainstem neurones (86). These proteins are main components of Lewy bodies, when aggregated (87) and these aggregates negatively affect astrocytes in terms of function (5,88). Research has shown that astrocytes take up alpha-synuclein released from neurones, primarily via endocytosis (87,89–92), and subsequently this causes the production of pro-inflammatory cytokines and chemokines leading to neuroinflammation in PD patients (93,94). PD development (91). Of all brain cells, it is microglia that are the most efficient in the uptake of alpha-synuclein, and not astrocytes (95). However, recently the focus has shifted towards the potential spread of toxic molecules during aggregate

clearance by astrocytes (92,94,96) in a prion-like propagation, following their internalization (88). It is the release of aggregated alpha-synuclein that exerts toxic effects, compared to the monomeric form (96). The spread has recently been hypothesized to be due to the astrocytes' inability to completely eliminate alpha-synuclein (97,98). It is therefore possible that astrocyte-mediated spread of alpha-synuclein plays a role in the pathophysiology or progression of PD (99,100). Further in-depth research about the molecular mechanisms by which astrocytes interact with alpha-synuclein in the context of PD is vital for the development of potential therapies, including vaccines to clear extracellular alpha-synuclein, alpha-synuclein gene silencing (92), reduction (101) and immunotherapy (102,103).

Targeting Astrocytes Therapeutically

In order to counteract the neuronal loss that occurs in neurodegenerative disorders, including PD, therapeutic neuronal replenishment has been attempted. A 2013 in vitro study (104) demonstrated the trans-differentiation of fibroblasts to functional neurones through repression of a single RNA binding protein (Polypyrimidine tract-binding protein). Less than a decade later, Zhou et al. (105) have demonstrated the in vivo neuronal induction, from glial cells, in PD model mice. Initially, the researchers were able to virally deliver a novel RNA-targeting CRISPR system CasRx to mice retinas, causing a Ptbp 1 knockdown. This, in turn, resulted in the conversion of Müller glia into retinal ganglion cells (RGCs) as well as amacrine cells. This led to resolution of disease symptoms associated with RGC loss, although 2022 studies (106,107) argue that this was unlikely due to Ptbp1 knockdown in Müller glial cells. This paved the way for the similar conversion of astrocytes into neuronal tissue, for the therapeutic use in neurodegenerative diseases including PD.

In a similar manner, the conversion of astrocytes to dopaminergic neurones was subsequently attempted by (105), also in vivo, in order to induce neurons in the striatum of PD model mice. The aim was to resolve disease symptoms associated with dopaminergic neuronal loss in PD, by targeting astrocytes. PD was induced in the mouse model using 6-hydroxydopamine and striatal injection with AAV-GFAP-CasRx-Ptbp1 (or AAV-GFAP-CasRx as a control) was performed 3 weeks later. The latter causes the Ptbp1 knockdown in astrocytes, and consequently, their conversion into neurones. Astrocytes were fluorescently labelled, in order to check for expression of the mature dopaminergic marker glutaminase, which, interestingly, most induced neurones expressed. The PD mice showed an improved motor function and therefore, significantly reduced motor dysfunction.

Another example of successful direct conversion of astrocytes to dopaminergic neurones is the work of Qian et al. (108). Following chemical PD-induction using 6-hydroxydopamine, astrocytes which contributed to the reactive astrocytic response were treated with AAV-shPTB (or AAV-empty as a control). The aim was to decrease PTBP1 levels, and therefore reverse the inhibition on the neural induction loop. Indeed, the percentage of cells expressing NeuN protein, ie. that were transformed neurones, was found to increase with increasing time post-infection, reaching 80% of AAV-shPTB infected cells after 10 weeks. These converted neurones were also found to express mature neurone markers, including glutamatergic or GABAergic neuronal markers. These neurones expressed DA neurone markers including DAT, and upon testing their electrical activity, it resulted in repeated action potential firing and characteristics of mature DA neurones. Mice treated with AAV-empty did not show a significant increase in nerve fibres in the striatum, on the contrary to AAV-shPTB mice, which demonstrated a 33% restoration of damaged neurones.

Activity-induced dopamine levels were also restored in 75% of mice, which also demonstrated correction of motor phenotypes post-PD induction. Similar successful results are seen in (109–111).

Although this provides a therapeutic potential for degenerative diseases including PD, additional investigations are warranted in order to comprehensively understand the therapeutic reprograming of astrocytes and the implications associated with it. In fact, many have challenged these studies, and have not observed such results (106,107,112). For instance, Wang et al. (113) hypothesise that previous studies that reported a supposed increase in astrocyte-converted neurones, were actually detecting endogenous neurones. In their experiment, brain injury was induced in adult mice and bromodeoxyuridine (BrdU) was given, which was used as a dye to label reactive astrocytes, as well as other proliferating cells. After 1 week, AAV5 viral vectors were used to induce the co-expression of NEUROD1, a transcription factor which induces neuronal development. Whilst 74% of labelled cells did express NeuN protein, only 2% of them were positive for BrdU and NeuN proteins, ie. originating from reactive astrocytes. There were no significant changes in the density of either astrocytes or neurones, in the cortex exposed to the virus. This research also challenges the shRNA-based approach seen in (108). Apart from the low percentage of converted neurones, they were also found to be non-astrocytic in origin, using astrocyte lineage reporter yellow fluorescent protein, and PTBP1 knockdown resulted in no astrocyte-neuron conversion in vivo. This highlights the importance of lineage-tracing in order to confirm the cell origin, apart from detection of immature neurones and pre-labelling of reactive cells.

Therapeutic Potential of LRRK2 Inhibition in Parkinson's Disease

Missense LRRK2 mutations are the leading cause of autosomal dominant PD (80) and LRRK2 activation is a common finding in vulnerable dopaminergic neurons in human idiopathic PD (85). This has led to investigations regarding the therapeutic targeting of LRRK2. Jennings et al. (114) have established LRRK2 inhibition using DNL201, an LRRK2 kinase inhibitor. Astrocytes from mice that were treated with DNL201 showed reduced lysosomal protein degradation, and therefore improved function, in contrast to untreated mice. Jennings et al. have subsequently performed a clinical study where this inhibitor was evaluated in both healthy and PD patients, however further clinical studies with larger sample sizes are still needed (115). Similarly, Sanyal et al. (116) investigated the lysosomal and autophagic pathways, mainly mutations in GBA1 gene (encoding for glucocerebrosidase enzyme) as well as LRRK2 gene (encoding for the leucine-rick repeat kinase 2 enzyme). Autosomal recessive mutations in the GBA1 gene cause Gaucher's disease, a lysosomal storage disorder and the heterozygous phenotype is a risk factor for PD. This study shows that inhibition of LRRK2 reversed lysosomal deficits caused by GBA1 mutations in mice astrocytes, making it a promising strategy for PD treatment.

Conclusion

Astrocytes are truly indispensable cells when it comes to neuronal health and functioning, exhibiting diverse roles and contributions. This literature review discusses the complex interplay between astrocytes and the two main neurodegenerative disorders; AD and PD. In AD, Beta-amyloid peptide accumulation and plaque formation is the main pathophysiological mechanism of the disease.

As part of the brain's innate response to CNS insult, astrocytes attempt to respond through 'reactive astrogliosis' in order to restore homeostasis. However, although being inherently beneficial, this process has been linked to the neurotoxicity and impaired synaptic transmission seen in AD. Additionally, astrocyte-derived cytokines were found to contribute to the progression of AD. Similarly, in PD, astrocytes indirectly contribute to neuroinflammation and subsequent neuronal death through endocytosis of neuronal alpha-synuclein aggregates, in an effort of astrocytes to clear these aggregates. In light of this, astroglia have been largely targeted therapeutically for AD and PD, with the latest advancements revolving around the conversion of reactive astrocytes and glial scars into potential neuronal tissue. However, challenges and limitations still persist, highlighting the need for more definitive evidence surrounding astrocytic involvement in order to ultimately have improved, effective clinical strategies.

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List of Abbreviations

Abbreviation	Definition
AD	Alzheimer's Disease
PD	Parkinson's Disease
TBI	Traumatic Brain Injury
GFAP	Glial Fibrillary Acid Protein
APP	Amyloid Precursor protein
PSEN1	Presenilin-1
PSEN2	Presenilin-2
APOE	Apolipoprotein E
TNF	Tumour Necrosis Factor
IL-1α	Interleukin-1α
IL-6	Interleukin-6
IL-4	Interleukin-4
C1q	Complement Protein 1q
CNS	Central Nervous System
PTBP1	Polypyrimidine Tract-Binding Protein 1
BACE-1	Beta-site Amyloid Precursor Protein Cleaving Enzyme-1
RGCs	Retinal Ganglion Cells
BrdU	Bromodeoxyuridine

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Emotionally Unstable Personality Disorder: An In-Depth Analysis in Clinical Practice

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Abstract

Emotionally Unstable Personality Disorder (EUPD), formerly known as Borderline Personality Disorder (BPD) is a multifaceted mental health condition affecting approximately 1.6% of the general population and 20% of psychiatric inpatients. This disorder manifests in intense and unstable relationships, emotional dysregulation, impulsivity and an inconsistent sense of self. Individuals with EUPD often face challenges in daily life, including conflicts, fear of abandonment and difficulties in occupational and educational pursuits. This paper presents a comprehensive literature review on EUPD, focusing on its clinical presentation, diagnosis and treatment approaches. The DSM-V and IDC-11 criteria are discussed, highlighting common features and differences. Various psychotherapeutic approaches, such as Dialectical Behavioural Therapy (DBT), Mentalisation-Based Treatment (MBT), Schema-Focused Therapy (SFT) and Transference-Focused Psychotherapy (TFP) are explored. Pharmacotherapy, including antidepressants, anticonvulsants, antipsychotics, mood stabilisers, Cannabis-Based Medicinal Products (CBMP) and Omega-3 Fatty Acids are examined. Challenges in clinical practice, such as diagnosis disclosure, referral to specialist therapy and involuntary hospitalisation are addressed. The paper concludes by emphasizing the importance of understanding recovery and quality of life for individuals with EUPD. It acknowledges the promising prospects of CBMPs and Omega-3 Fatty Acids in treatment, urging further research. Furthermore, the study contributes to the broader understanding of EUPD, guiding future research and clinical efforts.

Key words: EUPD, BPD, diagnosis, Dialectical Behavioural Therapy, pharmacotherapy, quality of life

An Overview on Emotionally Unstable Personality Disorder

Emotionally Unstable Personality Disorder (EUPD) is a complex mental health condition characterised by a significant negative impact to one's personality, leading to at least one pathological personality trait. Some surveys estimated the prevalence of 1.6% of the total general population to have this disorder, as well as 20% of the psychiatric inpatient population (1). People who have this disorder demonstrate 'intense and unstable interpersonal relationships, dysregulation of emotions and impulses and an inconsistent sense of self' (2). This can lead to noticeable consequences in a person's daily life and social functioning, such as high levels of conflict, a fear of abandonment and dependency and a general sense of instability (3). Some symptoms may manifest as self-destructive impulsive behaviours such as self-harming, often pronounced with co-morbidities like feeding and eating disorders (FEDs) (4), alcohol use disorder (AUD) (5) and substance misuse (6). Individuals with EUPD generally have a poorer level of occupational and educational outcomes than others do (6). They may also encounter 'difficulties with the healthcare system due to stigma', unfortunately barring access to necessary treatments (7, 8). In fact, there is ample documentation which states that patients with personality disorders consult psychiatric

services less, compared to individuals with 'other conditions such as depression or schizophrenia' (9). From a study based on the Netherlands Mental Health Survey and Incidence Study-2, an attempt was made Disorder Examination. From the total population studied, 25.2% had 1-2 EUPD symptoms and 4.9% had over three symptoms (10). It was also discovered that the number of symptoms had a positive relationship vis-à-vis living with partner, unemployment and/or having the aforementioned comorbidities of substance use, mood or anxiety disorders (10). This particularly highlights the importance of being well-informed and aware of the presence of this disorder in the community. Despite its clinical utility, the term "Borderline Personality Disorder" has often been associated with stigma surrounding this disorder. The word "borderline" can imply a sense of ambiguity or 'being on the edge', which can perpetuate misconceptions and negative stereotypes, while "emotionally unstable" personality disorder places more emphasis on the core features of the condition. By centering the term around these key characteristics, individuals diagnosed with the condition are more accurately represented and it is a crucial step forward in promoting greater empathy towards them.

EUPD patients have been found to be at an increased morbidity and mortality, when compared to the rest of the population, underlining the importance of studying and monitoring this disorder's presence in the community (11).

Methodology

A literature review was conducted across academic databases including PubMed and Science Direct, utilising keywords such as "EUPD", "BPD", "aetiology", "pharmacotherapy", "treatment" and "challenges". The search encompassed articles mainly published within the past decade, written in English and focused on the various aspects of EUPD, its definition, diagnosis and treatment modalities.

Articles were screened based on their titles and abstracts to identify potentially relevant studies. Full-text review was then performed for articles meeting the following criteria:

1. Relevance to Emotionally Unstable Personality Disorder and its ties to Clinical Practice
2. Availability in the English language
3. Original research articles, reviews and clinical trials.

Key data points were extracted from selected studies, including study objectives, methodology employed, participant demographics and numbers, key findings and the conclusion drawn by the authors.

The extracted data was then synthesized according to theme to identify the common patterns, trends and gaps in the literature pertaining to EUPD. This involved categorising the studies based on the focus areas mentioned above. Through this process, a comprehensive understanding of the current landscape of EUPD research was achieved in this review, allowing for insights and implications for clinical practice and public health initiatives.

Clinical Presentation and Diagnosis

Both the Diagnostic and Statistical Manual 5th edition Text Revision (DSM-V-TR) and the International Classification of Diseases 11th revision (ICD-11) attempt to create a set of criteria for EUPD (referred to as BPD at the time of publication). The DSM-V-TR refers to it as BPD, while the ICD-11 refers to it as EUPD.

Common Features of the description of EUPD in DSM-V-TR AND ICD-11

- An impairment in inter-personal functioning, causing a struggle with forming and maintaining healthy relationships.

- Identity disturbance, such as an unstable self-image, a general sense of uncertainty a general feeling of emptiness.

- Affective instability: Emotional dysregulation and intense mood swings are pivotal features for the diagnosis. This can also be the cause for the co-morbidities seen in EUPD such as anxiety and depression – with patients suffering from EUPD having a range of 71-83% rate of lifetime depression comorbidity, and a rate as high as 88% for anxiety disorder (12).

- Impulsive behaviours: Potentially harmful impulsive behaviours such as substance abuse, gambling and sexual promiscuity (13).

Differences of the Description of EUPD in DSM-V AND ICD-11

- Terminology: While the DSM-V-TR uses the term "Borderline Personality Disorder", the ICD-11 uses the term "Emotionally Unstable Personality Disorder".

- Criteria: The DSM-V states nine criteria for diagnosis of EUPD as follows (14):

    1. Frantic efforts to avoid real or imagined abandonment
    2. A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation
    3. Identity disturbance: markedly and persistently unstable self-image or sense of self
    4. Impulsivity in at least two areas that are potentially self-damaging
    5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour
    6. Affective instability due to a marked reactivity of mood
    7. Chronic feelings of emptiness
    8. Inappropriate, intense anger or difficulty controlling anger
    9. Transient, stress-related paranoid ideation or severe dissociative symptoms

The DSM-V requires meeting five out of nine criteria for a diagnosis of BPD (14). After recognising and characterising a number of these trait domains, one can also further differentiate the personality disorder by adding a "Borderline Pattern Specifier", which is based on the nine DSM-V-TR BPD diagnostic criteria, as stated above (19).
In contrast, the ICD-11, first diagnoses the impairments to personal functioning, both to the self and to other people, and classifies them according to their severity: Mild, Moderate or Severe Personality Disorder (15). Additionally, the patient can be assigned a 'sub-threshold' Personality Difficulty Code. Trait domains are used to further sub-specify the individual features that contribute to the disorder, these being:

- Negative Affectivity - A personality trait encompassing experiences of negative emotions and a diminished self-concept including anger, disgust, fear and anxiety (16).

- Detachment: The disengagement or disconnect from other people, which manifests both physically and emotionally (17).

- Dissociality: This includes negative variability in emotional states such as trust, compassion and respectfulness (18). Disturbances can be marked by transient symptoms or episodes such as paranoia in situations of elevated emotional arousal (19).

- Disinhibition: The inability of self-regulation or control over one's own behaviour. High disinhibition is displayed as spontaneity and a lack of consideration to long-term consequences that may potentially arise from their actions (20).

- Anankastia: Anankastia is etymologically derived from anankatikos – a Greek word meaning "compulsion". This trait encompasses perfectionism, stubbornness and preservation (18).

Aetiology in EUPD

EUPD has been found to have a significant genetic component, with twin studies indicated a heritability rate of over 50%, surpassing that of major depressive disorder (21). Environmental factors also play a crucial role, notably childhood maltreatment such as physical, sexual or neglectful experiences, found in up to 70% of individuals with EUPD. Theories suggest that a lack of resilience to stressors, invalidating environemtns and disturbances in early maternal relationships contribute to its development. Neuroimaging studies indicate differences in brain regions and misattribution of emotions in EUPD patients, alongside impared serotonin function (22).

Treatment Approaches to EUPD

Psychotherapy

Once thought untreatable, advancements in treating EUPD involve outlining generalist care models versus specialist treatments, and recognising crucial elements of psychotherapy such as Dialectical Behavioural Therapy (DBT). DBT is an evidence-based treatment for EUPD that originated from the efforts to address suicidal behaviour in multi-problematic women.

It incorporates cognitive-behavioural interventions, emphasizing acceptance and change-oriented strategies within a dialectical philosophy. The functions DBT aims to challenge are (23):

1. Enhancing and generalising capabilities
2. Improving motivation
3. Maintaining therapist capabilities
4. Structuring the environment

DBT conceptualises the challenges associated with EUPD as arising from the interplay between individuals inherently sensitive to emotions and "invalidating environments". These environments, represented by people or systems such as families and the workplace, are characterised by an inability to comprehend, perceive and effectively respond to the vulnerabilities of individuals with such a high emotional sensitivity.

DBT uses mindfulness and acceptance interventions to help the patient manage their emotions, showing promise in cases involving substance abuse disorders, binge-eating disorders and even depressed elderly patients (23).

While research on pharmacological interventions is limited, no specific medications have been proven to offer standalone treatment (24).
Some of the other treatments for EUPD include:

1. Mentalisation-Based Treatment (MBT)

Focuses on enhancing the individual's ability to mentalise, which involves understanding thoughts and feelings in one's own and others' minds to navigate interpersonal interactions. For those with EUPD, MBT addresses symptoms stemming from a breakdown in mentalisation, leading to distorted perceptions, a disconnection from reality and heightened attachment distress. MBT aims to stabilize EUPD issues by reinforcing patients' capacity during stress, using a therapeutic approach that prioritises curiosity, uncertainty and patient-driven exploration (24).

2. Schema-focused therapy (SFT)

An integrative form of psychotherapy developed for treating personality disorders, particularly EUPD. It incorporates concepts from cognitive behavioural therapy, attachment theory, gestalt therapy and psychodynamic perspectives, focusing on Early Maladaptive Schemas (ESM) and schema modes to understand and address dysfunctional patterns of thoughts, behaviours and emotions developed during childhood. This is done with the goal of improving self-understanding and emotional regulation in individuals with EUPD (25).

3. Transference-focused psychotherapy (TFP)

A psychanalytically informed treatment primarily designed for patients with EUPD. It works by exploring and understanding the patterns of emotions, thoughts and behaviours that individuals with EUPD may experience in their relationships, as a result of internal conflict in the working models of relationships (24) The therapy focuses on the concept of "transference" where feelings and attitudes from past relationships are unconsciously transferred onto the therapist. By addressing these patterns and emotions into the therapeutic relationship, indivudals gain insight into their interpersonal difficulties and learn healthier ways to relate to others. Overall, the goal is to improve self-awareness, emotional regulation and interpersonal functioning (26).

4. Systems Training for emotional predictability and problems solving (STEPPS)

A psychotherapeutic model applied to severely affected patients with EUPD or personality disorders with significant borderline features with a mood disorder. STEPPS focuses on emotional predictability and problem-solving, emphasizing stable settings, defined therapeutic goals and an active role for the therapist in addressing emotional and behavioural dysregulation in these individuals. (27)

It is important to note that STEPPS, although not designed as a stand-alone treatment, some research indicates that STEPPS' group sessions can enhance concurrent EUPD treatments (26).

Pharmacotherapy

There has been about three decades of research on treating EUPD with pharmacotherapy, and yet, there has not been a single medication that has been approved as a 'stand-alone' treatment by the national drug authority (24, 28). However, despite the lack of evidence, the use of pharmacotherapy remains commonly used to help EUPD patients for symptom control, with up to 90-95% of patients with EUPD receiving pharmacotherapy (29).
Classes of drugs used in EUPD:

1. Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) have been found to have a minimal effect on the impulsive aggression in EUPD. However they may have modest effects in decreasing symptoms such as depression, anxiety and mood swings – such as with Paroxetine, which showed a possible decrease in suicidal tendencies, or fluvoxamine, which showed a mild improvement in affective impulsivity (31)

2. Anticonvulsants
Anticonvulsants are used in EUPD due to their therapeutic benefits in managing mood swings, impulsivity and aggression. These medications stabilise excitatory neurotransmission by modulating the activity of neurotransmitters, such as glutamate, and affecting the balance of signalling pathways in the brain. While there were earlier indications of lithium's efficacy, its limitations and associated risks have reduced its clinical utility. Affective instability in EUPD shares some similarities with rapid-cycling bipolar disorder, leading to the exploration of alternative mood stabilisers. Valproate, lamotrigine and topiramate are considered more beneficial for treating affective instability and impulsivity,

with anticonvulsant medications showing moderate or better effects on impulsive aggression and overall functioning. The specific mechanisms of therapeutic response in EUPD for these medications remain unclear, and long-term risk-benefit analysis needs to be determined on a case-by-case basis, considering the potential teratogenicity risks for women of childbearing age. (31)

3. Antipsychotics

Antipsychotics are used in EUPD to help manage emotional stability, agitation, aggression and psychotic symptoms, such as brief episodes of psychosis and paranoia. There are two types of antipsychotics:

1. The first-generation antipsychotics (Dopamine Receptor Antagonists)
2. The second-generation antipsychotics (Dopamine and Serotonin Blockers) (30)

While antipsychotics have shown efficacy in managing cognitive-perceptual symptoms, the prevalence of adverse side effects often leads to their preference for exclusively use in acute relapse treatment. Olanzapine, a frequently studied antipsychotic, has demonstrated effectiveness in reducing impulsivity, hostility, psychotic symptoms and affective instability in EUPD. However, its use is associated with metabolic side effects, impacting tolerability. Limited research also suggests the potential benefits of aripiprazole and haloperidol in treating EUPD, particularly in managing symptoms of anger (31). Other antipsychotics such as quetiapine, respiradone and olanzapine are also regularly used to treat EUPD (32, 33).

4. Mood stabilisers

Mood stabilisers including lamotrigine, topiramate, lithium and valproate are identified as effective for managing impulsivity, aggression and behaviour control in EUPD.

Lithium, in particular, demonstrates effectiveness in preventing suicide in EUPD patients, although its usage is limited due to significant side effects such as cognitive dulling, nausea, diarrhoea, polyuria, tremor, weight gain and sexual dysfunction (34). Preliminary evidence suggests omega-3 fatty acids as a potential adjunct to primary medication treatment, especially when combined with mood stabilisers to prevent recurrent self-harm. Meta-analyses also highlight that mood stabilisers and low-dose antipsychotics are more effective than antidepressants for addressing affective dysregulations in individuals with EUPD (11).

5. Cannabis-Based Medicinal Products (CBMP)

In a case study of seven EUPD-diagnosed participants treated with CBMPs by Sultan et al (2022), the participants underwent an initial assessment and were followed up one month after CBMP prescription. The findings indicate that CBMPs were both effective and well tolerated, with six participants reporting noticeable improvements in symptoms and functioning. No adverse side effects were reported, contributing to potential medication adherence, a significant factor in EUPD treatment. The study acknowledges the need for further research to determine the long-term tolerability, efficacy, and dosing strategy for CBMPs in EUPD. While promising, the study emphasizes the preliminary nature of the results due to the inherent limitations of the case series design and the small number of participants. The potential benefits of CBMPs are suggested to complement psychological therapies rather than replace them, acting as an initial catalyst for symptom control and fostering hope for clinical improvement. Despite encouraging findings, rigorous research in controlled clinical settings is advocated to further explore the use of CBMPs as a potential treatment alternative for EUPD (35), since there is not enough research available to warrant CBMP an affirmed position as treatment for EUPD.

6. Omega-3 Fatty Acids

Omega-3 fatty acids are essential polyunsaturated fats found in certain fish and algae. In a study by Bellino et al (2014), 43 patients with a DSM-IV diagnosis of BPD were recruited. Two treatment groups were established one receiving a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two omega-3 fatty acids, and the other undergoing monotherapy with valproic acid, a medication used in the treatment of various medical and psychiatric conditions, such as manic episodes associated with bipolar disorder, epilepsy, agitation, impulsivity and aggression (36). Valproic acid doses ranged from 800mg/day to 1300mg/day. After 12 weeks, 79.07% of the patients completed the trial, with both treatment modalities showing similar efficacy in addressing global symptoms, EUPD-related symptoms, anxiety, depressive symptoms and social functioning. The combined therapy, however, demonstrated superiority in reducing impulsivity, anger and self-mutilating behaviours. Adverse effects were mild, with gastrointestinal disturbances more prevalent in the combined therapy group. While encouraging, the study has limitations, including a small sample size and a lack of a placebo group (37).

Challenges in Clinical Practice

Managing individuals with EUPD poses unique challenges in clinical practice, particularly in secondary care mental health services where the prevalence of EUPD is estimated at 20% (38). The wide spectrum of symptoms presented by EUPD patients can significantly influence the therapeutic process. Addressing these challenges requires a comprehensive understanding of the disorder, tailored treatment approaches, and a recognition of the complex interplay between psychological and pharmacological interventions.

In navigating the intricacies of EUPD care, clinicians encounter hurdles related to treatment adherence, comorbidities and the balance between symptom relief and long-term therapeutic goals. The potential for self-harm, particularly with lithium prescriptions, demands cautious prescribing. Additionally, medical comorbidities, such as chronic pain and unexplainable symptoms, further complicate diagnosis and management (10).

One of the first challenges faced by clinicians is the disclosure of an EUPD diagnosis, as well as the associated risk, such as the increased risk of suicide. It is a historically debated issue in psychiatry, rooted in the belief that the disorder carried a negative prognosis. However, contemporary understanding suggests that sharing the diagnosis and all relevant information can be beneficial for patients (39). It serves as a guiding label for treatment, helping patients comprehend their suffering. Transparency about the genetic and neurobiological factors contributing to interpersonal problems in EUPD is a sign of respect to the patient and fosters trust in the psychiatrist. Some psychiatrists involve patients in reviewing the diagnostic criteria, allowing self-identification and promoting engagement in the treatment process. Sharing this information instils hope, a crucial factor, particularly for suicidal patients. Overall, the shift towards openness about diagnoses aligns with improved treatment outcomes and patient well-being (39).

Another conflicting challenge faced in clinical practice is the question on whether or not the patient needs to be referred to specialist psychological therapy. A significant number of patients are not deemed ‘ready’ for specialist treatments, leading to missed opportunities for improving functioning and reducing suffereing (41). Clinicians face the difficulty of managing patients in community mental health teams (CMHTs) that may exhibit chaotic and risky behaviour, posing obstacles to treatment. Patient perspectives

6highlight feelings of being passed around services, emphasising the need for effective strategies to enhance readiness for therapy. The lack of specific guidelines on increasing readiness adds to the complexity, necessitating a nuanced approach that considers the trans-theoretical model of change and incorporates various interventions to support patients at different stages (41). The trans-theoretical model of change is a theory that health behaviour change involves six stages through which one must progress. These six stages are:

1. Pre-contemplation
2. Contemplation
3. Preparation
4. Action
5. Maintenance
6. Termination (41)

Being able to assess the stage the patient is in could ultimately aid healthcare workers in their referral (41)

Coordination with personality disorder services, addressing external factors, and promoting continuity of care are crucial aspects of managing these challenges in clinical practice.

Furthermore, when managing patients with EUPD, psychiatrists must address the complex issue of involuntary hospitalisation when the patient's well-being is at risk. Recognising factors that elevate imminent risks, such as specific subtypes of EUPD with higher suicidal tendencies, is crucial. Psychiatrists may initiate a dialogue with patients, emphasizing their expertise and the possibility that, during stressful periods, patients may struggle to assess their needs accurately. Establishing early agreement on the potential for the psychiatrist to "know best" in certain hospitalisation decisions can facilitate future interventions.

Despite concerns about legal liability, psychiatrists are cautioned against acting solely for self-protection.

Collaborative decision-making with colleagues, along with thorough documentation, provides a more defensible position. Ethically, it is acknowledged that chronic suicidal patients diagnosed with EUPD may experience better outcomes without hospitalisation, despite remaining with a level of risk (39).

Recovery and Quality of Life

In examining the complex landscape of EUPD, a critical focal point emerges – the interplay between recovery and the quality of life experienced by individuals contending this disorder.
A comprehensive PRISMA (2016) guided systematic search dedicated to researching the recovery from EUPD had a number of interesting findings (42). The review considers perspectives from consumers, clinicians, family and carers. Qualitative studies reveal three key themes in consumer perceptions of recovery.

1. The active willingness to engage in the journey of recovery
2. Improvement in clinical characteristics of EUPD
3. The conceptualisation of recovery

A multitude of factors such as vocation and motivational drive activate willingness to recovery, while an enhanced emotional regulation, identity development and interpersonal skills are essential for clinical improvement. The review also highlights gaps in literature, urging further exploration of family, carer and clinician perspectives on recovery.
On remission, recurrence and diagnosis retainment, it was discovered that varied definitions and methodologies contributed to differences. Factors like diagnostic tools, patient drop-out rates and the follow-up duration influence outcomes. The stability of EUPD over time is noted, with higher remission rates in the longer follow up periods.

In another study by Katsakou, C. et al (2012) (43), the perspectives on recovery of individuals with EUPD. Out of the 54 invited participants, 48 were interviewed. The findings revealed key themes related to recovery:

1. Personal Goals and Achievements

Accepting oneself and building self-confidence were primary goals, with participants expressing a desire to understand their problems and develop a positive self-image. Moreover, taking control of emotions, moods and negative thinking was crucial, emphasizing the importance of managing emotions without the use of harmful behaviours. Practical achievements and employment were seen as essential for boosting confidence and a sense of normalcy.

2. Balancing Personal Goals and Service Targets

Some participants felt a tension between their personal recovery goals and the focus of therapeutic interventions, which often concentrated on specific issues, potentially neglecting other important aspects. One participant believed that they had made no progress following treatment, stating "I'm just fat… I look at myself and I go, what … have I become?" (43)

3. Stages of recovery

Participants described varied states of recovery, ranging from feeling no progress to experiencing fluctuations in recovery. Many reported progress but not full recovery. This was only emphasised by the fact that some participants found the term 'recovery' to be problematic, perceiving it as implying a binary distinction between having problems and being fully recovered. They expressed concern about unrealistic expectations and the potential for relapse.

Conclusion and implications for clinical practice

This review article underscores the importance of diagnosis disclosure, referring patients to specialist therapy and managing involuntary hospitalisation while navigating the complexities of comorbidities. Emphasising recovery, this study highlighted the active willingness and clinical improvement crucial for individuals contending with EUPD. As research progresses, avenues such as CBMPs and Omega-3-Fatty Acid use in treating EUPD offer promising prospects, urging further investigation. The Netherlands Mental Health Survey's additional insights into the positive correlation between EUPD symptoms and various life factors contribute to the broader understanding of this challenging disorder, ultimately guiding future research and clinical endeavours in addressing EUPD. In closing, one can only hope for an increased focus on EUPD, particularly within the Maltese Healthcare System, with more research papers delving into the specific nuances and challenges faced by individuals in Malta grappling with this complex mental health condition, since there is dearth of literature available on the Maltese context regarding EUPD. This warrants attention to give policy makers sufficient perspective to improve on the healthcare provided to people with EUPD.

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