Recent Advances in Therapeutics

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Medical Update Group

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Recent Advances in Therapeutics

Contents:

- Precision medicine
- Tirzepatide -New Dual GLP1/GIP agonist for management of diabetes
- New drugs in the management of obesity
- Miscellaneous drugs

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1.Precision Medicine

Definition:

"An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle of each person".

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Precision Medicine

Conventional Medicine: One size fits all approach – disease treatment/prevention strategies are developed for an average person with less consideration for the differences between individuals.

Precision Medicine: Tailor made approach to predict more accurately disease treatment/prevention strategies for individuals/group people.

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Precision Medicine

An example of an existing "precision medicine"

Blood transfusion – not from a randomly selected donor, instead there is blood matching.

Precision medicine is also known as "personalised medicine".

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Precision Medicine

Approach consists of strategies based on:

1) Genetics
2) Environmental factors
3) Lifestyle factors

The completion of the human genome project which provided the complete sequence information for the human genome in 2003, was a critical landmark in genetics.

Precision medicine initiative by President Obama gave a huge impetus to this field

Epigenetics-the idea that our environment/lifestyles can affect the way our genetic codes are expressed.

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Precision Medicine

"Can you expect a teenager to wear a shirt the same size and design as their grandparents?"

Obviously not.

But when individuals are sick, they receive the same medical treatment although they have many differences.

One size fits all approach is based on population strategies. In precision medicine, treatment in more targeted and individualized.

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Precision Medicine

Features

- Precision medicines brings together innovations in the field of genomics, metabolomics(study of small molecules(metabolites)within cells,biofluids,tissues or organisms), data sciences and environmental sciences.
- It utilizes technologies such as mobile health, gene sequencing, imaging, big data, artificial intelligence, social engagement and networking.
- Using Big Data tools, data sets are developed that can lead to preventive strategies for individuals/communities. These data sets can help predict risk to wellness, risk to disease progression (prognosis) and response/resistance to drug therapy.
- Bio-banks

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Precision Medicine

UC Davis precision medicine model

Person	- Factors including gender, age, demographic data
Markers	- Focus on scientific markers of health and illness, include genetics, genomics, metabolomics, pharmacogenomics and other omic platforms.
Exposeme	- Environmental influences (socio-economic, agriculture, food quality and diet)
Behavioural health	- Behavioural issues that can affect health (exercise, self-care, addiction, anxiety, life choices, etc).

UC Davis: University of California , Davis

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Precision Medicine

<u>Pharmacogenomics:</u>

- Part of precision medicine.
- It is the study of how genes affect a person's response to specific drugs.
- This field combines pharmacology (science of drugs) and genomics (study of genes and their functions) to develop effective, safe medications that are tailored to variations in a person's genes.

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Precision Medicine Research:

Benefits:

- Wider ability to use patients genetic and molecular information as part of routine medical care.
- Improved ability to predict which treatment will work best for specific patients.
- Better understanding of the underlying mechanisms by which various diseases occur.
- Improved approaches to preventing, diagnosing, and treating a wide a range of diseases.

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Benefits of Precision Medicine

- Shift the emphasis in medicine from reaction to prevention
- Predict susceptibility of disease (prevention)
- Improve disease detection
- Prevent disease progression
- Customise disease-prevention strategies
- Prescribe more effective drugs
- Avoid prescribing drugs with predictable negative seide effects (targeted treatment)
- Reduce the time, cost and failure rate of clinical trials.
- Eliminate trial and error inefficiencies that inflate healthcare costs and undermine patient care.

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Precision Medicine

Challenges:

1. Standardisation and collection of data storage of large amounts of patient data to create databases.
2. Limited availability and accessibility.
3. Ethical, social and legal issues: Data privacy and confidentiality, informed consent,discrimination, misuse of data by insurance companies/employers, etc
4. Complex regulatory landscape.
5. Cost – DNA sequencing, technology, tailormade drugs
6. Training for HCPs and other healthcare providers about molecular genetics/biochemistry.

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Precision Medicine(PM) in:

1. Oncology
2. Psychiatry/Neurology
3. Other diseases

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Precision Medicine in Oncology:

1. Identify people at high risk and lower their risk
2. Early detection
3. Diagnose a specific type of cancer correctly
4. Choose which cancer treatment options are best
5. Evaluate how well a treatment is working

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Precision Medicine in Oncology

- "Bio-markers" (molecular markers or "signature molecules") are now being used for pre-disposition, predictive, diagnostic, prognostic, toxicological,treatment or monitoring purposes and hence cancer patients are benefiting from more individualised treatment.
- Healthcare professionals need to have a sound knowledge of not just the precision medication but also of the biomarkers targeted and the pharmacogenomic tests available to detect them.

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Biomarkers

- A biomarker is a unique mutated nucleic acid sequence, protein, glycoprotein, group of proteins expressed by tumour cells but not normal healthy cells.
- 4 types
  - Predisposition – indicating likelihood to develop a disease
  - Diagnostic – to confirm if a patient has a particular type of cancer
  - Predictive – determine which cohort of patients can benefit from a particular drug therapy
  - Prognostic – suggesting how the cancer may develop in the individual

Each biomarker is relevant at different stages of the disease.

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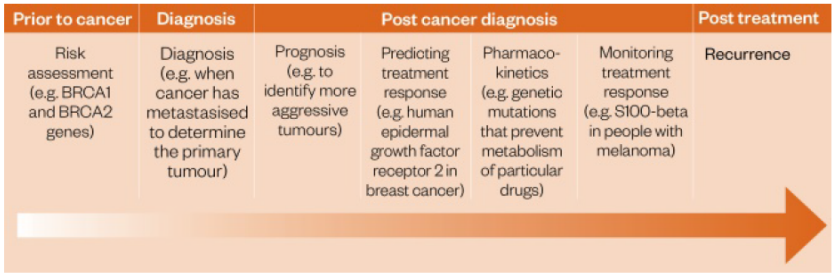
Role of biomarkers in Oncology



Source: Pharmaceutical Journal, 8 November 2019, Karim Awad et al

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Examples of biomarker tests in oncology

- Non-small cell lung cancer: Changes in genes such as KRAS, EGFR, ALK, ROS1, RET, MET, and BRAF
- Breast cancer: Estrogen receptor (ER) and progesterone receptor (PgR) proteins; HER2 gene or protein status; changes in genes such as BRCA1, BRCA2, and PIK3CA
- Colorectal cancer: Changes in genes such as KRAS, NRAS, ad BRAF
- Melanoma skin cancer: Changes in the BRAF gene
- Any cancer: Changes in NTRK genes; changes in mismatch repair (MMR) genes; levels of microsatellite instability (MSI); tumor mutational burden (TMB)

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Biomarker testing – How is it done?

- Solid tumour – biopsy
- Haematological cancer – blood sample or bone marrow sample
- For some cancers – body fluids (such as urine) might be tested.

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Limitations of biomarker testing

- Acceptability/Risk (biopsies) – Deep seated organs
- Access
- Measurement errors; laboratory errors, collection/transportation of samples, storage,etc
- Sampling bias
- Cost

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Pharmacogenomic Testing to guide Treatment Options

Pharmacogenomic Testing to Guide Treatment Options

American Cancer Society

American Cancer Society Cancer Action Network

Pharmacogenomic (PGx) testing can be helpful when deciding the best treatment for an individual. It is a part of precision medicine or personalized medicine.

Genes are pieces of DNA inside each cell. They tell the cell how to make the proteins it needs to function. Each gene contains the code (instructions) to make a certain protein, and each protein has a specific job in the cell. Genes tell cells when to grow and divide, and determine physical traits (eye color, hair color, and height) and other inherited information.

Pharmacogenomic testing checks a person's inherited genes (genes that you were born with) to find changes that may affect the way a medicine works in your body. This testing finds out how a patient's body breaks down, absorbs, and uses medicines.

For patients with cancer, **pharmacogenomic testing (PGx)** can guide decision-making by providing a more personalized treatment plan.

Talk to your cancer care team about treatment options for your cancer and if you would benefit from pharmacogenomic testing. You may want to reach out to your insurance company to see if insurance covers the testing.

By connecting people with cancer to the right treatment, and the right dose at the right time, pharmacogenomic (PGx) testing can guide cancer treatments for better outcomes.

Prescribing Without Pharmacogenomic Testing

Same drug and dose + Same disease

Desired response | No response | Serious side effects

Prescribing With Pharmacogenomic Testing

Same disease + PGx testing

Responds to standard dose | A higher dose is needed for desired response | A lower dose is needed for desired response and to avoid serious side effects

Will not respond to this drug; a different drug is needed | Serious side effects cannot be avoided; a different drug is needed

To learn more, visit the American Cancer Society website at **cancer.org** or call us at **1-800-227-2345.** We're here when you need us.

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Pharmacogenomic testing

In Australia, it is done in community pharmacies. Once in a lifetime. Inside cheek swab, Results in 1 week.

Predicts safety and efficacy of drugs, improve chance of therapeutic success + decrease likelihood of adverse drug reactions. Done for drugs such as clopidogrel, esomeprazole, antidepressants, statins ,anticoagulants, etc.

For example, can determine risk of myopathy with statins, measure cytochrome P450 subtypes to predict metabolism, response to drugs, incidence to ADRs with clopidogrel, esomeprazole

Helps in dose titration- identify slow and fast metabolizers.

In US, Canada, Norway-GPs perform these tests.

Medicine optimization strategy

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Precision medicine in Oncology

- Multiple successes in the precision medicine approach in introducing improved treatments in the oncology area.

- Imatinib- first agent of this type

- Targets ATP binding pocket of mutant BCR-ABL protein in tumour cells of CML

- Patients are selected based on presence of genetic abnormality:

BCR – ABL1Ph+ (Philadelphia chromosome)

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Imatinib

Imatinib and its successors have made a noticeable difference to the lives of CML patients, with simple oral dosing, improved five-year survival, and lower level of side effects.

Move to 2nd generation agents in case of resistance to imatinib(dasatinib, nilotininb)

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Some examples of PM in oncology

Breast cancer: ER/PgR status, HER2 status

Target therapies (Tamoxifen, anastrozole)

Transtuzumab

Transtuzumab emtansine

CDK4 and CDK6 Kinases → inhibitors

(ribociclib, palbociclib)

Lung cancer – EGFR mutations → osermitinib

Colorectal cancer – EGFR, Ras mutation testing → cetuximab

Immunotherapy(Car T cell therapy, immune check point inhibitors, etc)

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PM in Oncology

PM in cancer therapy has progressed from concept phase to practical utility.

- More effective targeted therapies to patients with less side effects
- More expensive and require diagnostic rests to select patients
- It needs better trained health care professionals

Tissue agnostic agents:

e.g Pembrolizumab(Keytruda)- treat a wide variety of tumours with mutations

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PM in Psychiatry/Neurology

- Estimated that one in 10 people live with a mental disorder/neurological disease.
- Current treatment modalities can be remarkably effective, yet finding the right treatment for an individual can be a long, fraught process.
- Neurological/psychiatric diseases have high degrees of genetic/pathophysiological heterogeneity
- Precision psychiatry/neurology presents a new path
- The emerging model of precision psychiatry/neurology has the potential to mitigate the most pressing issues including improving disease classification, lengthy treatment duration, and sub-optimal treatment outcomes

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PM in Psychiatry/Neurology

- Neuroscience insights offer new ways to account for the heterogeneity within/across mental disorders and to consider treatment selections accordingly.
- These clinical insights link phenotypes to an individual biosignature (or biotypes)
- Maps genetic mutations to psychiatric/neurological disorders(schizophrenia, autism,mood disorders,etc)
- Tailoring treatment
- Four pillars: Biomarkers, Digital health technologies (eg neuroimaging), Datascience, AI.
- Alzheimer's disease

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PM in other diseases

- The same principle can be applied to other diseases.

e.g: Obesity/ diabetes/ NASH/ Hypertension/ Metabolic syndrome

  - Prediction
  - Tailormade options (personalisation)
  - Risk assessment/prognosis

- Cystic fibrosis(targeted therapy as gene defect has been identified(ivacaftor/lumacaftor oral tablet)
- Asthma
- Famililial Hypercholesterolaemia
- Rare disease detection

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PM – the future

The convergence of AI and precision medicine promises to revolutionize healthcare.

Precision medicine methods identify phenotypes of patients with less common responses to treatment or unique healthcare needs.

AI leverages sophisticated computation and interference to generale insights, enables the system to reason and learn and empowers clinician decision making through augmented intelligence.

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2. Tirzepatide

First GLP1/GIP agonist for diabetes(“twincretin”)

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- Incretin based analogues (GLP1 agonists) are already established in the treatment of type 2 diabetes. Incretin are gut enzymes that are released after eating
- The DPP4 inhibitors which act on the incretin system are also well established.
- The development of dual receptor agonists that bind to receptors not only for GLP-1 but also to receptors of GIP (Glucose dependent insulinotropic peptide) is intended to address different metabolic pathways for carbohydrate and lipid metabolism simultaneously.
- Seems an attractive option in the view of additive or synergistic effect in the treatment of T2D and obesity.

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Tirzepatide (Mounjaro)

- First dual GLP1/GIP agonist
- Approval by USA FDA in 2022 ad EMA in 2023 for treatment of T2D
- NICE recommendation
- Once weekly sub-cutaneous administration

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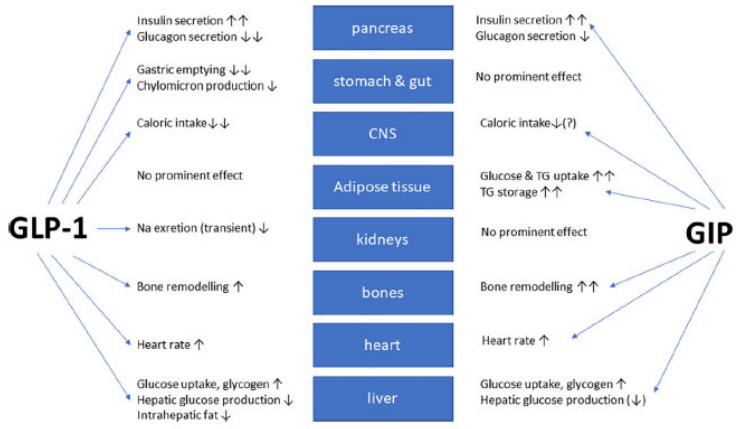

FIGURE 1
Overview of the biological glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) effects at the organ/tissue level (modified from (47)). The blue arrows depict relevant physiological effects.

Frontier in Endocrinology, Gallwitz, 13 October 2022

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Tirzepartide (Mounjaro)

- Dual GIP/GLP1 agonist

Pharmacodynamics:

- Binds with high affinity to both GLP1/GIP receptors
- Comparable potency in activation of GIP receptors to native GIP
- Less potent in binding to GLP1 receptors compared to GLP1 agonists
- Insulin secretion is increased, insulin sensitivity is increased, post prandial glucose concentration is decreased, glucagon secretion is decreased, gastric emptying delayed

Pharmacokinetics (after SC injection)

- Tmax (8 to 72h)
- Bioavailability (80%)
- Steady state concentration after four once weekly injections
- 99% of bioavailable Tirzepatide bound to plasma albumin
- Plasma half life 5 days
- Excretion via urine/ faeces
- Reduction in absorption of oral medication (due to delayed gastric emptying)

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Tirzepatide (Mounjaro)

Surpass trial

TABLE 2 Overview of the SURPASS clinical trial program with tirzepatide in the therapy of type 2 diabetes.

Study	Subjects (*n*)	Baseline therapy	Diabetes treatment in the comparator arm	Study duration (weeks)	HbA1c lowering *vs.* comparator (%)	Body weight change (kg)	Publication/anticipated end of the trial
SURPASS-1	478	None	Placebo	40	BL: 7.9 5 mg: −1.91 10 mg: −1.93 15 mg: −2.11	−7.0 to −9.5	Rosenstock et al. Lancet 2021;398:143–155 (70)
SURPASS-2	1,879	Metformin	Semaglutide 1 mg	40	BL: 8.28 5 mg: −2.01 10 mg: −2.24 15 mg: −2.30 Semaglutide: −1.87	5 mg: −1.9 10 mg: −3.6 15 mg: −5.5	Frias et al. NEJM 2021;385:503–515 (71)
SURPASS-3	1,437	Metformin or metformin + SGLT-2i	Insulin degludec	52	BL: 8.17 5 mg: −1.93 10 mg: −2.20 15 mg: −2.37 Insulin degludec: 1.34	−7,5 to −12.9 Insulin degludec: +2.3	Ludvik et al. Lancet 2021;398:583–598 (72)
SURPASS-4	1,995	1-3 OAD with metformin, SGLT-2i, or SU	Insulin glargine	52	BL: 8.52 5 mg: −2.24 10 mg: 2.43 15 mg: 2.58 Insulin glargine: 1.44		Del Prato et al. Lancet 2021; 398:1811–1824 (73)
SURPASS-5	475	Insulin glargine ± metformin	Placebo	40	BL: 8.31 5 mg: 2.11 10 mg: 2.40 15 mg: 2.34		Dahl et al. JAMA 2022;327:534–545 (75)
SURPASS-6	1,182	Insulin glargine ± metformin	Insulin lispro	52			Estimated study end Q2 2022
SURPASS-J mono	636	Therapy naive or 1 OAD	Dulaglutide 0,75 mg	52			Study finished, results not yet published
SURPASS-J combo	441	1 OAD	No comparator arm (safety study, endpoint >1 SAE)	52			Study finished, results not yet published
SURPASS AP combo	956	Metformin ± SU	Insulin glargine	40			Study recruitment completed, study still ongoing
SURPASS CVOT	12,500	OAD or injectable antidiabetic medication	Dulaglutide 1.5 mg	Event driven regarding MACE-3			Estimated study end 2024/25

SGLT-2i, SGLT-2 inhibitor; OAD, oral antidiabetic drug; SU, sulfonylurea; SAE, serious adverse event; MACE-3, major cardiovascular event (cardiovascular death, nonfatal myocardial infarct, or nonfatal stroke); BL, baseline.

Frontier in Endocrinology, Gallwitz, 13 October 2022

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Tirzepatide (Mounjaro)

Indications:

- Once weekly administration as an adjunct to diet and exercise for patients with type 2 diabetes:
  - As monotherapy when metformin is inappropriate due to contraindication or intolerance.
  - In combination with metformin, sulfonylureas , SGLT2 inhibitors or basal insulin
- Has not been studied in combination with short acting, medium acting or dual formulation insulins.

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Dose: 2.5mg SC for treatment initiation, after 4 weeks increase to 5mg.

If additional glycaemic control is needed, increase the dosage in 2.5 mg increment after no less than 4 weeks.

Maximum dosage: 15mg once weekly

- If added, dose reduction of 20% of basal insulin → ↓ risk of hypoglycaemia. Different sites of injection
- No dose adjustment in renal impairment, hepatic insufficiency, geriatrics
- Can be injected in abdomen, thigh or upper arm.

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- Adverse effects like GLP1 agonists
- Increase in heart rate
- Gastrointestinal side effects

Symptom	Tirzepatide 5 mg (total *n* = 237; % of subjects)	Tirzepatide 10 mg (total *n* = 240; % of subjects)	Tirzepatide 15 mg (total *n* = 241; % of subjects)	Placebo/comparator (total *n* = 235; % of subjects)
Nausea	12	15	18	4
Diarrhea	12	13	17	9
Decreased appetite	5	10	11	1
Vomiting	5	5	9	2
Constipation	6	6	7	1
Abdominal pain	6	5	5	4

Frontier in Endocrinology, Gallwitz, 13 October 2022

- Contraindicated in individuals with personal or family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia type 2 Syndromes
- Look out for pancreatitis/diabetes retinopathy complications
- Risk of hypoglycaemia with sulfonylureas/insulin
- Oral contraceptive pill failure.

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Tirzepatide (Zepbound)

In Obesity

- In clinical trials (SURMOUNT study), Tirzepatide resulted in significant body weight reductions.
- Approved by FDA/EMA for management of obesity. Nice recommendation

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Tirzepatide (Mounjaro/Zepbound)

- Has demonstrated dose dependant reductions in glycaemic parameters in patients with T2D
- Cardiovascular end points are awaited
- Early analysis demonstrated cardiovascular safety
- Demonstrated weight loss effects
- Present data suggests that Tirzepatide has exceeded the glucose lowering effects to established GLP1 agonist
- May find a prominent place in the treatment algorithm for therapy T2D and obesity
- Extended indications: MASH, CKD, Obstructive Sleep apnoea?
- Expected to be next major blockbuster drug ?

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3. New Drugs In The Management Of Obesity

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Obesity

- Major public health threat.
- Associated with an increased risk for various metabolic, cardiovascular, skeletal co-morbidities and cancer.
- Obesity treatment guidelines should be multidisciplinary, including lifestyle modifications, behavioural therapy, pharmacotherapy and/or bariatric surgery.
- Obesity is determined by the balance of energy intake and expenditure. Rate has increased because calories have become more readily available.

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As per WHO,

BMI 25-30 is considered overweight.

BMI >30 is considered obese.

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Obesity Statistics

Worldwide

- 13% of adults in the world are obese.
- 39% of adults in the world are overweight.
- Linked to around 5 millions death globally.
- One in five children and adolescents, globally, are overweight.
- Prevalence has doubled since 1980.

Mauritius

- Obesity prevalence stood at 36.2%,

29.9% among men and 41.6% among women

- Overweight prevalence stood at 36%,

with 38.7% among men and 33.8% among women

- Worldwide situation has worsened during the Covid pandemic

NCD survey, Ministry of Health and Wellness, Mauritius.

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Obesity

Co-morbidities

1. Insulin resistance/Type 2 diabetes
2. Atherosclerosis and Cardiovascular diseases
3. Hypertension
4. Lipid Profile
5. Others: Polycystic Ovary Syndrome, Obstructive Sleep Apnoea, Infertility, Mental Health Issues, Cancers, etc

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Pharmacotherapy

Drug therapy → suitable option for people unsuccessful in losing weight with lifestyle changes.

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Current Therapy

1. Orlistat
2. Buproprion/Naltrexone Combination (Contrave)
3. Phentermine/Topiramate (Qsymia)
4. Liraglutide (Saxenda) – GLP1 agonist

Monogenic obesity(excess weight caused by mutation in a single gene)

- Metreleptin, setmelanotide(<5% of cases)-SC injection.

Bariatric surgery

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Drug (trade name)	Approval FDA/EMA (year)	Mechanism of action	Adverse events[a]	Contraindications[b]
Orlistat (Xenical, Alli)	FDA 1999 EMA 1998	Gastric and pancreatic lipase inhibitor	Oily rectal leakage, abdominal distress, abdominal pain, flatulence with discharge, fecal urgency, steatorrhea, fecal incontinence, increased defecation	Patients with chronic malabsorption syndrome or cholestasis, pregnancy
Phentermine/ Topiramate (Qsymia)	FDA 2012	NE agonist/GABA agonist, glutamate antagonist	Elevation in heart rate, mood and sleep disorders, cognitive impairment, metabolic acidosis, paresthesia, dry mouth	Glaucoma, hyperthyroidism, during or within 14 days following the administration of monoamine oxidase inhibitors, hypersensitivity to sympathomimetic amines, pregnancy
Naltrexone/ Bupropion (Contrave/ Mysimba)	FDA 2014 EMA 2015	Opioid receptor antagonist/DA and NE reuptake inhibitor	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea, sleep disorder	Chronic opioid use, acute opioid withdrawal, uncontrolled hypertension, seizure disorder, bulimia or anorexia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiseizure drugs; concomitant use of MAOIs, patient receiving linezolid or IV methylene blue, pregnancy
Liraglutide (Saxenda)	FDA 2014 EMA 2015	GLP-1 analogue	Increased heart rate, hypoglycemia, constipation, diarrhea, nausea, vomiting, headache	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy
Semaglutide (Wegovy)	FDA 2021 EMA 2021	GLP-1 analogue	Nausea, vomiting, diarrhea, abdominal pain, constipation, headache	Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2, pregnancy
Setmelanotide (Imcivree)	FDA 2020 EMA 2021	MC4R agonist	Injection site reactions, hyperpigmentation, nausea, headache, diarrhea, vomiting, abdominal pain	None
Tirzepatide[c]	Under consideration by FDA	GIP/GLP-1 dual agonist	Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, known serious hypersensitivity to tirzepatide or any of the excipients

Abbreviations: DA, dopamine; EMA, European Medicines Agency; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; IV, intravenous; MAOIs, monoamine oxidase inhibitors; MC4R: melanocortin-4 receptor; NE, norepinephrine. [a]Adverse events presented here are those that are present in more than 10% of the population, based on the FDA approval leaflet. [b]Contraindications are based on the FDA approval leaflet. [c]Under expedited consideration for FDA approval.

Table 1: **Anti-obesity medications: approval, mechanism of action, adverse events, and contraindications.**

wwww.thelancet.com Vol 58 April, 2023

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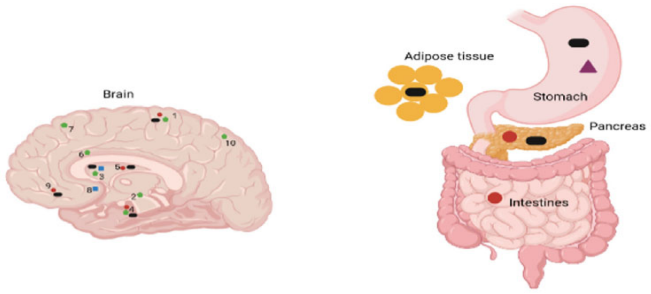

Medication	Central site of action	Peripheral site of action
GLP-1 Receptor Agonists	1,3,4,5,9	Gastrointestinal tract
Naltrexone/Bupropion	1,2,3,4,6,7,10	None
Phentermine/Topiramate	2,3,8	None
Orlistat	None	Gastrointestinal tract
GIP/GLP-1 dual agonists	1,3,4,5,9	Adipose tissue, gastrointestinal tract

Fig. 1: **Site of action of FDA approved anti-obesity medications.** (1): parietal cortex, (2) hippocampus, (3) hypothalamus, (4) insula, (5) putamen, (6) dorsal anterior cingulate, (7) superior frontal cortex, (8) nucleus accumbens, (9) orbitofrontal cortex, (10) superior parietal cortex. For GLP-1 receptor agonists and naltrexone/bupropion, the central sites of action are derived from animal studies and brain functional MRI studies in humans; For phentermine/topiramate, the central sites of action are derived from animal studies. Animal studies showed that GLP-1 agonists act on the hypothalamus and the nucleus of the solitary tract.[35] GLP-1 agonists act also on the parietal cortex, insula, putamen, and orbitofrontal cortex in response of food images, as demonstrated in functional MRI studies.[37,38] Naltrexone/bupropion acts on the hypothalamus, superior parietal cortex, posterior insula, dorsal anterior cingulate, hippocampus. There are inconsistent data on its role in the superior frontal cortex, the amygdala and nucleus accumbens.[36,41–43] Phentermine acts on the hypothalamus. Topiramate acts on the hypothalamus and the hippocampus, as shown in animal models[39] and the nucleus accumbens, in a proof-of-concept study for the treatment of alcohol dependence, not for weight management.[40] GLP-1, glucagon-like peptide-1; HCl, hydrochloric acid. This figure was created using BioRender (https://biorender.com/).

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Obesity

Anti-obesity medications were marked by the failure of several ones, secondary to serious adverse effects: Rimonabant, Dexfenfluramine Sibutramine, Lorcaserin .

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Obesity

New drug in the management of obesity:

Semaglutide (Wegovy)

- Injectable prescription medication for adults with obesity (BMI ≥ 30), or overweight (≥ 27) who have also weight related medical problems, to help lose weight and keep it off.
- Should be used with a reduced calorie meal plan and increased physical activity.
- Once weekly GLP-1 analogue for chronic weight management (pen form SC)
- Extension of indication to children ≥ 12 years.
- Available also as an oral formulation (Rybelsus) and injectable formulation (Ozempic) for type 2 diabetes. Lower doses in diabetes

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Wegovy – Step Trial

Primary End Points:

14.9% mean weight loss v/s 2.4% weight loss with placebo at 68 weeks.

Mean base line BMI : 37.9

83.5% on Wegovy vs 31.1% of patients on Plaebo achieved ≥ 5% of weight loss at 68 weeks.

Secondary End Points:

1 out of 3 patients taking Wegovy (30.2 %) vs 1.7% of patients with Placebo achieved ≥ 20% (≥ 46 lb) weight loss at 68 weeks.

Improvements in blood sugar, cholesterol and blood pressure parameters

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Semaglutide(Wegovy) – Mode of action

- Incretin analogue (GLP1) – Natural gut hormone (Wegovy 94% similar to the naturally occurring GLP1)
- Affects gut, brain, and other organs to give a sense of satiety, reduced cravings and appetite.

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Semaglutide (Wegovy)

- Dose escalation
- Warnings (Risk of thyroid C-Cell tumours, acute pancreatitis, hypoglycaemia, acute kidney injury)
- Approved by both EMA/FDA.
- NICE recommendation

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Tirzepatide (Zepbound)

New drug approval in obesity management end of 2023 (already approved by EMA/FDA in type 2 diabetes)

Surmount trials

Tirzepatide (Zepbound) – Dual GLP1/GIP analogue

Data analytics (around 18000 patients in the US) show that it is more effective than GLP1 agonist in weight loss(5.9% vs 3.6% after 3 months and 15.3% vs 8.9% after one year). Head-to-Head randomized clinical trial is needed to confirm these results.

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Tirzepatide(Zepbound)

Indications:

For chronic weight management as an adjunct to calorie-controlled diet/increased physical activity for patients with an initial BMI of:

- 30kg/m2 or greater(obesity)
- 27kg/m2 or greater(overweight) in at least one weight related conditions(e.g hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease or OSA)
- One weekly injection. Dose escalation every 4 weeks

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New weight loss drugs:

Future extended indications(Trials awaited)?;

- NASH
- CKD/Kidney health
- Cardiovascular diseases(Lowering of risk)
- OSA

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New weight loss drugs- Challenges

- Shortages
- Online sales/Abuse
- Counterfeit drugs
- New side effects: Suicide, Vision loss?

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In summary

Accumulating evidence indicates that the next few years will be a period of innovative drugs for obesity. This will revolutionise obesity management and through loss in body weight ,the way cardio-renal/metabolic complications of obesity is treated including diabetes, cardiac and liver co-morbidities.

In trials: CagriSema(combination of semaglutide and cagrilintide-an amylin analogue in injectable form for weekly administration) and Orforglipron (non-peptide oral GLP-1 agonist)

The future – Gene therapy coding for GLP1 expression/ triple agonist therapy(Retatrutide)

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4. Miscellaneous drugs:

- New drugs for Migraine
- Inclisiran- LDL reduction/ Hypercholesterolemia/Mixed hyperlipidaemia
- Rhokinase inhibitors-glaucoma
- Zuranolone- post-partum depression
- Lenacapavir-HIV
- Ritlecitinib-alopecia areata
- Resmetirom-NASH

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Miscellaneous drugs

- **Migraine**:

New drugs (CGRP blockers):

1. Monoclonal antibodies-e.g Erenumab (SC injection once monthly – preventive treatment)
2. Gepants(oral tablet)- e.g Rimegepant. Acute Migraine treatment(fast action)

- **Inclisiran:**

LDL reduction/ Hypercholesterolemia/Mixed hyperlipidaemia. Adjunct to statin and diet. SC injection every 6 months,

Interferes with PCSK9 messenger RNA- Limits production of PCSK 9- Upregulation of LDL Receptors in liver, increasing uptake of LDL cholesterol from blood and reducing its level.

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Miscellaneous drugs

- **Rhokinase inhibitors**:

Glaucoma treatment

Netarsudil eye drops- increase aqueous outflow by acting on the trabecular meshwork

- **Zuranolone**

First oral treatment for post-partum depression. Given for 14 days.

Acts on GABA system

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Miscellaneous drugs

- **Lenacapavir:**

HIV- treatment of multi-resistant HIV-1 infection in patients for whom it is otherwise not possible to construct a suppressive anti-viral regimen(in combination with other antivirals)

Six-monthly SC injection-long acting. First-in-class Capsid inhibitor

- **Ritlecitinib**

First and only approved oral once daily treatment for alopecia areata(autoimmune disorder)- JAK/Tyrosine Kinase inhibitor

Affects teens, 20's or 30's with patchy or complete hair loss

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Miscellaneous drugs

- **Resmetirom**

First NASH therapy in patients with moderate to advanced liver fibrosis-Unmet clinical need

Oral treatment

Thyroid hormone receptor beta agonist that works directly on the liver(association between thyroid dysregulation and NASH)

NAFLD- most chronic liver disease affecting 1/3 of world population. Risk factors include overnutrition, metabolic syndrome, T2D, obesity.

Improves NASH by increasing fat metabolism and reducing lipotoxicity.

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Thank you

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