Pa grwpiau poblogaeth sydd wedi bod yn destun astudiaethau mewn treialon cyffuriau colli pwysau? A pha mor effeithiol yw'r cyffuriau yn y grwpiau hyn: Adolygiad cwmpasu ystwyth o'r llenyddiaeth

Lluniwyd gan: Hannah Shaw, Amy Hookway, Kate Shiells, Salina Khatoon, Golibe Ezenwugo, Iechyd Cyhoeddus Cymru

Dyddiad cyhoeddi: Medi 2025

Cynnwys

1. Cyflwyniad

Fel rhan o'r gwaith o gyflwyno cyffuriau colli pwysau newydd i'r llwybr rheoli pwysau yng Nghymru, mae angen nodi pa grwpiau o bobl fydd yn elwa fwyaf. Felly, mae'n bwysig nodi pa grwpiau poblogaeth sydd wedi cael eu harchwilio o fewn tystiolaeth y treial ar gyfer y gwahanol fathau o gyffuriau sydd ar gael ar hyn o bryd ar gyfer colli pwysau yng Nghymru.

Mae'r gwaith hwn yn adeiladu ar brosiect blaenorol a gynhaliwyd gan y Gwasanaeth Tystiolaeth (Hookway et al., 2024) a ymchwiliodd i effeithiolrwydd, diogelwch a chost-effeithiolrwydd cyffuriau colli pwysau fel ychwanegiad at ymyriadau ymddygiadol gyda ffocws penodol ar tirzepatide, semaglutide, liraglutide ac orlistat. Mae'r adolygiadau systematig a'r astudiaethau cynradd a gynhwyswyd o'r adroddiad blaenorol yn 2024 yn sail i'r darn hwn o waith, sy'n anelu at:

- Nodi pa grwpiau poblogaeth penodol a astudiwyd neu nad astudiwyd o fewn y treialon a gynhwyswyd yn adroddiad 2024,
- nodi pa grwpiau poblogaeth a archwiliwyd trwy ddadansoddi is-grwpiau ac archwilio'r canfyddiadau o'r rhain.

Gwnaethom hefyd archwilio adolygiadau systematig a oedd yn canolbwyntio ar grwpiau poblogaeth penodol i gynorthwyo llunwyr polisi i flaenoriaethu'r broses o ran cyffuriau colli pwysau yng Nghymru.

2. Amcanion

Amcan y gwaith hwn oedd nodi pa grwpiau poblogaeth penodol sydd wedi cael eu hastudio mewn treialon cyffuriau colli pwysau. Yn fwy penodol, roedden ni'n ceisio ateb y cwestiwn canlynol:

Pa grwpiau poblogaeth sydd wedi cael eu harchwilio mewn treialon cyffuriau colli pwysau?

Mae'n bwysig nodi nad oes unrhyw ymgais wedi'i gwneud i syntheseiddio'r dystiolaeth ar effeithiolrwydd y cyffuriau yn y grwpiau poblogaeth a nodwyd.

3. Negeseuon Allweddol

- Mae tystiolaeth gyfyngedig yn bodoli ynghylch defnyddio cyffuriau colli pwysau mewn is-boblogaethau clinigol penodol, ac nid yw'r gwaith sydd wedi'i wneud yn y poblogaethau mwyaf cyffredin a allai lywio gwaith blaenoriaethu.

- Mae nifer fach o adolygiadau systematig wedi archwilio effeithiolrwydd cyffuriau colli pwysau mewn is-boblogaethau clinigol sydd â'r cyflyrau canlynol:
    - Ennill pwysau a achosir gan gyffuriau gwrthseicotig
    - Clefyd Alzheimer
    - Trawsblannu arennau diabetig
    - Clefyd y galon
    - Clefyd hepatig
    - Gordewdra hypothalamig
    - Clefyd yr arennau
    - Apnoea cwsg rhwystrol
    - Osteoarthritis
    - Syndrom Ofarïau Polysystig
    - Cyn-ddiabetes
- Roedd cymhwysedd i dreialon cyffuriau colli pwysau yn amrywio, ond lle recriwtiwyd pobl dros bwysau a gordew, yn gyffredinol roedd gofyniad hefyd iddynt gael o leiaf un cyd-morbidrwydd sy'n gysylltiedig â phwysau.
- Mae nifer o gyflyrau meddygol wedi'u nodi'n benodol ym meini prawf gwahardd llawer o'r treialon cyffuriau colli pwysau yn y boblogaeth gyffredinol. Roedd y rhain yn cynnwys rhai cyflyrau penodol y gellir eu categoreiddio'n fras fel:
    - Arennol
    - Gastroberfeddol
    - Endocrinolegol
    - Iechyd Meddwl
    - Cardiofasgwlaidd
    - Clefyd hepatig
    - Canser
- Hyd yn oed lle mae tystiolaeth yn bodoli ar gyfer is-boblogaeth glinigol benodol, mae'n bwysig ystyried y nifer fawr o gyflyrau meddygol a nodwyd fel rhai sydd wedi'u gwrtharwyddo neu sydd â rhybuddion neu ragofalon arbennig i'w defnyddio gan y crynodeb meddyginiaethau electronig.
- Gan fod y rhan fwyaf o gyffuriau colli pwysau a ddefnyddir ar hyn o bryd yn y DU wedi'u trwyddedu fel ychwanegiad ochr yn ochr â diet calorïau isel a/neu ymarfer corff, wrth flaenoriaethu grwpiau poblogaeth, dylid ystyried eu gallu i ymgymryd â'r ymyriadau hyn yn ddiogel.

4. Ystyriaethau a chyfyngiadau methodolegol

Mae adolygiadau cwmpasu ystwyth yn defnyddio methodoleg gyflym i ddarparu trosolwg eang o'r sylfaen dystiolaeth ar bwnc o ddiddordeb. Eu bwriad yw arwain a llywio gwaith pellach yn hytrach na'u defnyddio ar gyfer polisi ac ymarfer. Canfyddiadau a chasgliadau'r awduron gwreiddiol sydd wedi'u cynnwys yma, nid

dehongliad gan y Gwasanaeth Tystiolaeth. Mae ffactorau sy'n berthnasol i ateb y cwestiwn a nodwyd o'r astudiaethau wedi'u tynnu allan a'u crynhoi'n fyr yn yr adroddiad hwn. Os yw ffactor penodol o ddiddordeb, fe'ch cynghorir i ddarllen y ffynonellau lle cawsant eu cymryd yn fwy manwl. Os ydych yn defnyddio unrhyw ymchwil sydd wedi'i chynnwys yn y cwmpas hwn i lywio polisi, mae'n bwysig ystyried ansawdd methodolegol a chyffredinolrwydd y canfyddiadau i'ch cyd-destun chi.

Mae'n annhebygol bod y chwiliad a gynhaliwyd ar gyfer yr adolygiad cwmpasu ystwyth hwn wedi nodi'r holl dystiolaeth sy'n ymwneud â'r pwnc hwn, gan nad oedd y chwiliadau'n gynhwysfawr.

5. Canfyddiadau

O gyfanswm o 29 o astudiaethau sylfaenol, nodwyd saith a oedd yn ymchwilio i is-boblogaethau clinigol penodol. Yn ogystal, nodwyd 30 o adolygiadau systematig a oedd yn edrych ar is-boblogaethau clinigol penodol. Gyda'i gilydd, archwiliodd y rhain effeithiolrwydd a diogelwch cyffuriau colli pwysau ymhlith pobl â'r cyflyrau meddygol canlynol:

- Antipsychotic drug induced weight gain (5) (Bak et al., 2024; Khaity et al., 2023; Hedge et al., 2024; Menon et al., 2024; Patoulias et al., 2023)
- Alzheimer's disease (1) (Bi et al., 2023)
- Diabetic kidney transplant (2) (Krisanapan et al., 2024; Bellos et al., 20214)
- Heart disease (5) (Beshr et al., 2025; Gupta et al., 2024; Peck et al., 2024; Kosiborod et al., 2023: Lincoff et al., 2023)
- Hepatic disease (6) (Malik et al., 2023; Mahmoud et al., 2024; Park et al., 2023; Ren et al., 2025; Wang et al., 2024; Zhu et al., 2023))
- Hypothalamic obesity (1) (Ng et al., 2024)
- Kidney disease (2) (Krisanapan et al., 2024b; Natale et al., 2025)
- Obstructive sleep apnoea (4) (Dutta et al., 2025; Li et al., 2024; Altobaishat et al., 2025; Blackman et al., 2016)
- Osteoarthritis (1) (Gudbergsen et al., 2021)
- Polycystic Ovary Syndrome (7) (Austregésilo et al., 2024; Bader et al., 2024; Bo et al., 2025; Goldberg et al., 2024; Machado et al., 2024; Tong et al., 2024; Jensterle, et al., 2021)
- Prediabetes (3) (Alsanea et al., 2024; Wilding et al., 2021; le Roux et al., 2017)

Mae manylion yr astudiaethau sylfaenol i'w gweld yn Atodiad A a cheir manylion yr adolygiadau systematig yn Atodiad B.

Asesodd y rhan fwyaf o'r adolygiadau systematig effeithiolrwydd cyfunol sawl GLP-1RA gwahanol, a dim ond rhai a gynhaliodd ddadansoddiadau ar wahân ar gyfer y gwahanol gyffuriau colli pwysau. Fodd bynnag, mae'r tabl isod yn amlinellu pa

gyffuriau a nodwyd fel rhai a astudiwyd ym mhob un o'r un ar ddeg o grwpiau is-boblogaeth glinigol a nodwyd. Mae'r rhain wedi'u nodi o'r adolygiadau systematig yn bennaf. Mae'r tabl yn dangos yn glir bod liraglutide wedi'i astudio'n helaeth ar draws y gwahanol is-grwpiau poblogaeth clinigol. Fodd bynnag, mae'n werth nodi, o ystyried bod tirzepatide yn gyffur newydd, ei bod yn annhebygol ei fod wedi cael ei astudio mor helaeth mewn poblogaethau penodol.

Lle archwiliodd adolygiadau GLP-1RAs ar y cyd, mae'n debygol bod y rhain wedi cynnwys cyffuriau colli pwysau perthnasol, ond nid oedd yr wybodaeth ar gael yn yr adolygiadau systematig, oni bai ei bod wedi'i hadrodd yn adran 5.1 isod. Mae hefyd yn werth nodi nad oedd pob treial a gynhaliwyd yn yr is-boblogaethau clinigol hyn wedi'i anelu at amcangyfrif effeithiolrwydd colli pwysau. Roedd rhai treialon yn archwilio effeithiau'r cyffuriau hyn ar symptomau neu'r risg o ddatblygu cymhlethdodau pellach, a allai fod wedi cynnwys ennill pwysau.

Yn ogystal, roedd y rhan fwyaf o dreialon ar gyfer cyffuriau colli pwysau yn eu gwerthuso fel ychwanegiad at ddeiet calorïau isel a/neu fwy o weithgarwch corfforol. Roedd rhai treialon yn cynnwys sawl breichiau, rhai a oedd yn cynnwys cyffur penodol ochr yn ochr â diet calorïau isel a/neu fwy o weithgarwch corfforol ac a gymharodd y rhain â changen reoli, a allai fod wedi cynnwys diet calorïau isel a/neu weithgarwch corfforol neu beidio. Efallai na fydd hyn yn addas ar gyfer rhai grwpiau poblogaeth clinigol a allai gael trafferth i wneud gweithgarwch corfforol.

Tabl 1: Pa gyffuriau colli pwysau sydd wedi cael eu hastudio mewn grwpiau poblogaeth penodol

	Liraglutide	Semaglutide	Orlistat	Tirzepatide	GLP-1RA
Ennill pwysau a achosir gan gyffuriau gwrthseicotig	X				X
Clefyd Alzheimer	X				X
Derbynwyr trawsblaniadau arennau diabetig	X	X			X
Clefyd y galon		X	X	X	
Clefyd hepatig	X	X	X		
Gordewdra hypothalamig	X				X
Clefyd Cronig yn yr Arennau	X	X			X
Apnoea cwsg rhwystrol	X			X	
Osteoarthritis	X				
Syndrom ofarïau polysystig	X	X	X		X
Cyn-ddiabetes	X	X			

5.1 Grwpiau is-boblogaethau clinigol

Mae'r adran hon yn amlinellu'r sail dystiolaeth ar gyfer pob un o'r un ar ddeg o is-boblogaethau clinigol a nodwyd uchod o'r llenyddiaeth sylfaenol ac eilaidd. Darperir gwybodaeth am faint y sail dystiolaeth, y cyffuriau penodol a astudiwyd, meintiau poblogaethau ac unrhyw wybodaeth berthnasol arall a nodwyd, lle roedd ar gael. Dylid nodi, lle nodwyd tystiolaeth eilaidd a chynradd, ei bod yn debygol iawn bod yr astudiaethau sylfaenol wedi'u cynnwys yn yr adolygiadau systematig. Yn ogystal, lle nodwyd nifer o adolygiadau systematig, mae'n debygol bod gorgyffwrdd rhwng yr astudiaethau a gynhwyswyd ar draws yr adolygiadau hyn.

5.1.1 Ennill pwysau a achosir gan gyffuriau gwrthseicotig

Gall rhai triniaethau gwrthseicotig achosi ennill pwysau, a all yn ei dro arwain at syndrom metabolig (Hedge et al., 2024). Asesodd pum adolygiad systematig (1 meta-dadansoddiad rhwydwaith, 3 meta-dadansoddiad ac 1 synthesis naratif) effeithiolrwydd GLP-1RAs ymhlith pobl a oedd wedi ennill pwysau o ganlyniad i ddefnyddio cyffuriau gwrthseicotig. Roedd y rhain yn cynnwys ystod eang o niferoedd astudiaethau, gyda meta-dadansoddiad y rhwydwaith yn cynnwys 68 o astudiaethau, tra bod y lleill yn cynnwys rhwng pedair a saith astudiaeth. Mae'n debygol iawn bod gorgyffwrdd rhwng yr astudiaethau sydd wedi'u cynnwys ar draws yr adolygiadau hyn.

Canolbwyntiodd tri o'r pum adolygiad (Hedge et al., 2024; Khaity et al., 2023; Patoulias et al., 2023) ar y paramedrau cardiometabolaidd sy'n risg adnabyddus ymhlith cleifion â sgitsoffrenia (Khaity et al., 2023). Canolbwyntiodd y ddau adolygiad sy'n weddill (Back et al., 2024 a Menon et al., 2024) ar golli pwysau, o ystyried bod cysylltiad rhwng llawer o gyffuriau seicotropig ac ennill pwysau cysylltiedig (Menon et al., 2024).

Roedd pob adolygiad yn cynnwys cyfranogwyr â diagnosis o sgitsoffrenia, ond roedd dau adolygiad hefyd yn cynnwys rhai treialon mewn pobl ag anhwylder deubegynol ac roedd un treial yn cynnwys y rhai a oedd wedi profi eu pwl gyntaf o seicosis.

Roedd y meta-dadansoddiad rhwydwaith (Hedge, et al., 2024) yn cynnwys 29 o astudiaethau a gynhaliwyd mewn cleifion â sgitsoffrenia y rhagnodwyd cyffuriau gwrthseicotig iddynt am y tro cyntaf, a oedd yn eu cymryd am lai na 4 wythnos, neu nad oeddent wedi ennill pwysau, a rhagnodwyd y lleihau pwysau fel strategaeth ataliol. Cynhaliwyd y 39 o astudiaethau sy'n weddill ar gleifion â sgitsoffrenia a oedd wedi ennill pwysau oherwydd meddyginiaethau gwrthseicotig, a rhagnodwyd y cyfryngau lleihau pwysau fel strategaeth driniaeth.

Roedd cyfanswm y cyfranogwyr a gynhwyswyd yn yr adolygiadau yn amrywio o 199 i 398. Ni wnaeth y metaddadansoddi rhwydweithiol adrodd ar gyfanswm nifer y cyfranogwyr. Fel arfer, roedd treialon yn archwilio'r defnydd o liraglutide 1.8mg neu 3.0mg bob dydd, ond roeddent hefyd yn cynnwys treialon yn edrych ar effeithiolrwydd GLP-1RAs eraill, ac nid oedd pob dadansoddiad yn gwahanu'r gwahanol gyffuriau.

5.1.2 Clefyd Alzheimer

Nodwyd un adolygiad systematig (Bi et al., 2023) a oedd yn gwerthuso effeithiau GLP-1RAs ar weithrediad gwybyddol pobl â chlefyd Alzheimer, yn hytrach na'r pwysau a gollwyd. Roedd y meta-dadansoddiad hwn yn cynnwys pum treial rheoledig ar hap gan ddefnyddio GLP-1RAs wrth drin clefyd Alzheimer i benderfynu a oes newidiadau yng ngweithrediad gwybyddol y cleifion hyn ar ôl y driniaeth. Cynhwyswyd cyfanswm o 177 o gyfranogwyr â diagnosis o glefyd Alzheimer. Roedd tair astudiaeth yn cynnwys trin cleifion â liraglutide 1.8mg ac yn eu cymharu â phlasebo. Ni chynhaliwyd unrhyw ddadansoddiad ar wahân mewn cyffuriau unigol. Er bod canlyniadau'n canolbwyntio ar weithrediad gwybyddol, cafodd cynnwys glwcos yn y gwaed a BMI, eu cynnwys fel canlyniad hefyd.

5.1.3 Derbynwyr trawsblaniad aren diabetig

Nodwyd dau adolygiad systematig, yr oedd un ohonynt yn cynnwys meta-dadansoddiad (Bellos et al., 20214; Krisanapan et al., 2024), a oedd yn archwilio diogelwch ac effeithiolrwydd GLP-1RAs ymhlith derbynwyr trawsblaniad aren diabetig. O ystyried y pryderon ynghylch digwyddiadau andwyol posibl yn y boblogaeth hon a'r sylfaen dystiolaeth gyfyngedig yn gyffredinol oherwydd eithriadau o dreialon rheoledig ar hap, teimlai'r awduron ei bod yn fuddiol gwerthuso diogelwch ac effeithiolrwydd GLP-1RAs yn yr is-grŵp poblogaeth clinigol hwn.

Roedd gan y mwyafrif helaeth o gleifion ddiabetes mellitus a oedd yn bodoli eisoes neu ar ôl trawsblaniad, ac nid oedd gan ychydig o gyfranogwyr hanes o ddiabetes. Roedd y meta-dadansoddiad (Krisanapan et al., 2024) yn cynnwys naw treial gyda chyfanswm o 338 o gyfranogwyr. O'r GLP-1RAs a gynhwyswyd, cynigiodd chwe astudiaeth rhwng 0.6mg ac 1.8mg/dydd o liraglutide i gyfranogwyr, a chynigiodd dwy astudiaeth wahanol semaglutide (dos heb ei adrodd). Roedd y synthesis naratif (Bellos et al., 2024) yn cynnwys 19 astudiaeth, gyda chyfanswm o 2,267 o gyfranogwyr a oedd yn cael naill ai GLP-1RAs, Atalyddion Protein Cludo Sodiwm-Glwcos 2 (SGLT2-i), neu blasebo. Roedd liraglutide (n=3 astudiaeth), a semaglutide (n=2 astudiaeth) ymhlith y GLP-1RAs a oedd dan ymchwiliad, ond ni adroddwyd ar unrhyw ddosau. Ni chynhaliwyd dadansoddiad ar wahân mewn cyffuriau unigol yn y naill adolygiad na'r llall.

5.1.4 Clefyd y galon

Nodwyd tri adolygiad systematig (Beshr et al., 2025; Gupta et al., 2024; Peck et al., 2024), un gyda meta-ddadansoddiad, a dau dreial (Kosiborod et al., 2023: Lincoff et al., 2023) wrth edrych ar effeithiolrwydd a diogelwch GLP-1RAs mewn pobl â chlefyd y galon. Canolbwyntiodd dau o'r tri adolygiad ar glefyd y galon a gordewdra, tra bod y trydydd yn cynnwys unrhyw un â chlefyd y galon (Gupta et al., 2024). Cynhwyswyd un treial (Kosiborod et al., 2023) ym mhob un o'r tri adolygiad. Roedd pob un o'r tri adolygiad yn cynnwys astudiaethau a oedd yn edrych ar effaith gwahanol ddosau o semaglutide. Roedd un adolygiad hefyd yn cynnwys astudiaeth a oedd yn edrych ar orlistat 120mg, ac roedd un adolygiad yn cynnwys un astudiaeth yn edrych ar tirzepatide 15mg. Roedd y meta-dadansoddiad (Beshr et al., 2025) yn cynnwys pedair astudiaeth yn cynnwys 2,194 o gyfranogwyr. Roedd Gupta et al. (2024) yn cynnwys pedair astudiaeth gyda 18,296 o gleifion diabetes math 2 a oedd mewn perygl o brofi pwl o fethiant y galon, neu a oedd wedi cael un. Edrychodd Peck et al. (2024) ar strategaethau colli pwysau bwriadol mewn cleifion dros bwysau a gordew â methiant y galon a gwnaeth gynnwys 22 astudiaeth. Ymchwiliodd tri o'r rhain i ffarmacotherapïau (Orlistat 120mg a semaglutide 0.25–2.4 mg) ymhlith cleifion gordew â gwahanol raddau o fethiant y galon, gyda neu heb ddiabetes.

Cafodd y dadansoddi ei grwpio yn Beshr et al. (2025) ond wedi'i wahanu yn ôl y cyffur yn Gupta et al. (2024) a Peck et al. (2024).

Nodwyd dau dreial (Kosiborod et al., 2023: Lincoff et al., 2023) gan ddefnyddio 2.4mg o semaglutide unwaith yr wythnos, a gynhaliwyd ymhlith cleifion â chlefyd cardiofasgwlaidd. Gwnaeth Kosiborod et al. (2023) recriwtio 529 o bobl â methiant y galon a ffracsiwn alldaflu cadwedig a gordewdra, a hynny'n benodol, i archwilio a allai semaglutide arwain at ostyngiad mewn symptomau a chyfyngiadau corfforol a gwell gweithrediad ymarfer corff. Gwnaeth Lincoff et al. (2023) recriwtio 17,604 o bobl a oedd wedi cnawdnychiant myocardiaidd, strôc, neu a oedd â chlefyd rhydwelïol ymylol symptomatig a gordewdra yn flaenorol i ganfod a oedd semaglutide ynghyd â gofal safonol yn lleihau'r risg o ddigwyddiadau cardiofasgwlaidd niweidiol mawr. Mae'n bwysig nodi bod y treialon hyn yn debygol o gael eu cynnwys yn yr adolygiadau systematig.

5.1.5 Clefyd hepatig

Nodwyd chwe adolygiad systematig, gan gynnwys tri meta-ddadansoddiad rhwydwaith (Park et al., 2023; Ren et al., 2025; Wang et al., 2024) a thri meta-ddadansoddiad (Malik et al., 2023; Mahmoud et al., 2024; Zhu et al., 2023) wrth ymchwilio i'r defnydd o liraglutide, semaglutide ac orlistat ymhlith cyfranogwyr â chlefyd hepatig. Diffinwyd y boblogaeth glinigol o ddiddordeb fel steatohepatitis di-alcohol mewn dau adolygiad, a chlefyd brasterog yr afu/iau di-alcohol mewn pedwar

adolygiad. Roedd mwyafrif y cleifion a oedd wedi'u cynnwys dros bwysau neu'n ordew, ac roedd rhai wedi cael diagnosis o ddiabetes math 2.

Roedd y metaddadansoddiadau rhwydweithiol yn cynnwys rhwng 25 a 174 o astudiaethau, a rhwng 2,237 a 10,183 o gyfranogwyr. Roedd y metaddadansoddiadau'n cynnwys rhwng tair a phum astudiaeth, gan gynnwys rhwng 180 a 458 o gyfranogwyr.

5.1.6 Gordewdra hypothalamig

Gall niwed i'r hypothalamws arwain at amhariadau yn homeostasis ynni, gan arwain at ordewdra hypothalamig, sef anhwylder cymhleth sy'n amlygu ei hun gyda hyperffagia, llai syrffed neu absenoldeb syrffed, llai o egni gwaelodol yn cael ei ddefnyddio, camweithrediad awtonomig a hyperinswlinemia, a phob un ohonynt yn arwain at ordewdra difrifol sy'n anodd ei drin. O ystyried nad yw gordewdra hypothalamig yn ymateb yn dda i ymyriadau colli pwysau confensiynol, ceisiodd un adolygiad systematig (Ng et al., 2024) archwilio effeithiolrwydd a diogelwch GLP-1RAs ar reoli gordewdra hypothalamig o ystyried bod gan y cyffuriau hyn fecanweithiau sy'n annibynnol ar yr hypothalamws.

Cynhwyswyd deg astudiaeth, adroddiadau achos neu astudiaethau achos yn bennaf, a fu'n cynnwys 54 o gleifion. Cranioffaryngioma oedd achos mwyaf cyffredin gordewdra hypothalamig, a fu'n effeithio ar 42 o gleifion (77.8%); roedd gan 8 ffurfiau eraill o diwmorau suprasellar gan gynnwys germinoma, roedd gan 2 astrosytoma, 1 anaf trawmatig i'r ymennydd ac 1 aneurysm ymenyddol gyda chysylltiad hypothalamig. Cafodd pump o'r cleifion hyn, o bedair astudiaeth, liraglutide. Roedd y dosau'n amrywio o 0.3mg i 3.0mg y dydd.

5.1.7 Clefyd Cronig yn yr Arennau

Asesodd dau adolygiad systematig gyda meta-dadansoddiad (Krisanapan et al., 2024b; Natale et al., 2025) ddiogelwch ac effeithiolrwydd GLP-1RAs mewn cleifion â diabetes math 2 â chlefyd cronig yr arennau. Roedd Krisanapan ac eraill (2024b) yn cynnwys cyfranogwyr â diabetes math 2 gyda chlefyd cronig datblygedig yn yr arennau neu glefyd yr arennau cam olaf, y rhan fwyaf ohonynt ar ddialysis, tra bod Natale et al. (2025) yn cynnwys cyfranogwyr â diabetes math 2 gydag ystod ehangach o glefyd yr arennau (camau 1-5) a allai fod wedi bod yn cael dialysis neu beidio. Roedd Natale ac eraill (2025) yn ceisio darganfod a allai GLP-1RAs wella rheolaeth ddiabetig a gweithrediad yr arennau, lleihau cymhlethdodau sy'n gysylltiedig â'r galon a lleihau'r risg o fethiant yr arennau. Er nad oedd y naill adolygiad na'r llall yn ceisio archwilio GLP-1RAs yn benodol mewn perthynas â cholli pwysau, cafodd y rhain eu cynnwys fel canlyniadau eilaidd.

Roedd Krisanapan ac eraill (2024b) yn cynnwys wyth astudiaeth a fu'n cynnwys 27,639 o gleifion yn y meta-dadansoddiad hwn. Liraglutide oedd y GLP-1RA a ddefnyddiwyd amlaf ar draws pum astudiaeth, gyda dosau'n amrywio o 0.3 i 1.8 mg y dydd. Gofal diabetes safonol oedd y cymharydd yn bennaf ,ond roedd hefyd yn cynnwys plasebo neu ddim rheolaeth. Roedd Natale ac eraill (2025) yn cynnwys pedwar deg dau o astudiaethau a fu'n cynnwys 48,148 o gyfranogwyr yn y synthesis naratif a 27 o astudiaethau yn cynnwys 37,820 o gyfranogwyr yn y meta-dadansoddiad. Archwiliwyd liraglutide mewn 7 astudiaeth, ynghyd â semaglutide. Gofal diabetes safonol oedd y cymharydd yn bennaf.

Ni chynhaliwyd dadansoddiad ar wahân mewn cyffuriau unigol yn y naill adolygiad na'r llall.

5.1.8 Apnoea cwsg rhwystrol

Mae gordewdra yn ffactor risg mawr ar gyfer apnoea rhwystrol cwsg, sef cyflwr cyffredin a nodweddir gan gwymp ffaryngeal rheolaidd yn ystod cwsg, a allai fod yn llwyr neu'n rhannol, gan arwain at apnoea neu hypopnoea. Mae torri ar lif yr aer yn arwain at lefelau ocsigen isel a lefelau uchel o garbon deuocsid yn y gwaed. Mae hyn yn aml yn cyfrannu at yr anhwylderau metabolaidd, cardiofasgwlaidd a niwrowybyddol sy'n gysylltiedig ag apnoea cwsg rhwystrol.

Nodwyd tri adolygiad systematig (Dutta et al., 2025; Li et al., 2024; Altobaishat et al., 2025), yr oedd pob un â meta-dadansoddiad ac un treial (Blackman et al., 2016) yn ymchwilio i effeithiolrwydd a diogelwch liraglutide a tirzepatide mewn poblogaeth o gyfranogwyr ag apnoea cwsg rhwystrol. Roedd y rhan fwyaf o'r cleifion, ond nid pob un, dros bwysau neu'n ordew gydag apnoea rhwystrol cwsg, ac roedd rhai ohonynt eisoes yn cael therapi CPAP i'w drin. Roedd Altobaishat ac eraill (2025) yn cynnwys dwy astudiaeth yn disgrifio tri threial yn cynnwys 828 o gyfranogwyr gordew nad oeddent yn ddiabetig, roedd Dutta et al. (2025) yn cynnwys pedair astudiaeth yn disgrifio pum treial a fu'n cynnwys 937 o gyfranogwyr, ac roedd Li et al. (2024) yn cynnwys chwe astudiaeth yn disgrifio saith treial a fu'n cynnwys cyfanswm o 1067 o gyfranogwyr ag apnoea cwsg rhwystrol cymedrol neu ddifrifol a naill ai gordewdra neu ddiabetes.

Cynhaliwyd un treial (Blackman et al., 2016) mewn pobl ag apnoea cwsg rhwystrol cymedrol neu ddifrifol i ymchwilio i ganfod a oedd 3.0mg o liraglutide bob dydd yn lleihau difrifoldeb apnoea cwsg rhwystrol o gymharu â phlasebo mewn poblogaeth o 359 o bobl ordew.

Roedd pob adolygiad yn edrych ar liraglutide mewn gwahanol ddosau (1.2mg, 1.8mg neu 3.0mg bob dydd), a tirzepatide (10mg neu 15mg). Mae'n debygol y bydd gorgyffwrdd sylweddol rhwng yr astudiaethau sylfaenol a gynhwyswyd a'r adolygiadau hyn, ac yn wir, cafodd yr astudiaeth gyntaf a nodwyd gennym (Blackman et al., 2016) ei chynnwys ym mhob un o'r tri adolygiad.

5.1.9 Osteoarthritis

Cynhaliwyd un treial yn edrych ar effeithiolrwydd a diogelwch liraglutide 3.0mg y dydd o gymharu â phlasebo ar gyfer rheoli poen a phwysau mewn poblogaeth o 156 o bobl ordew sy'n dioddef o osteoarthritis y pen-glin (Gudbergsen et al., 2021).

5.1.10 Syndrom Ofarïau Polysystig

Ystyrir colli pwysau fel y driniaeth reng flaen ar gyfer syndrom ofarïau polysystig, gan y gall wella rhai paramedrau sy'n gysylltiedig â'r cyflwr.

Nodwyd chwe adolygiad systematig (Austregésilo et al., 2024; Bader et al., 2024; Bo et al., 2025; Goldberg et al., 2024; Machado et al., 2024; Tong et al., 2024), gan gynnwys un meta-ddadansoddiad rhwydwaith a thri meta-ddadansoddiad, ac un treial (Jensterle, et al., 2021). Roedd pob un yn anelu at nodi effeithiolrwydd a diogelwch GLP-1RAs mewn menywod â syndrom ofarïau polysystig o ran colli pwysau ac weithiau rheoleiddio hormonau. Lle adroddwyd, roedd mwyafrif y menywod hefyd dros bwysau neu'n ordew, ac roedd rhai cyfranogwyr yn gyn-diabetig neu ag ymwrthedd i inswlin. Roedd pum adolygiad yn cynnwys liraglutide (dosau amrywiol), roedd dau adolygiad yn cynnwys semaglutide, roedd dau yn cynnwys orlistat, ac archwiliodd un GLP-1RAs yn fwy cyffredinol. Roedd meintiau'r astudiaethau yn fach ar y cyfan.

Cynhaliodd un astudiaeth (Jensterle, et al., 2021) dreial peilot bach hefyd mewn 25 o fenywod gordew â syndrom ofarïau polysystig i archwilio effaith semaglutide 1.0mg dros 16 wythnos ar storio braster ar y tafod o gymharu â phlasebo.

5.1.11 Cyn-ddiabetes

Nodwyd un adolygiad systematig (Alsanea et al., 2024) a dau dreial (Wilding et al., 2021; le Roux et al., 2017) yn archwilio effaith cyffuriau colli pwysau ar bobl â chyn-ddiabetes. Roedd yr adolygiad systematig ac un o'r treialon yn edrych ar y defnydd o liraglutide, ac roedd un treial yn edrych ar y defnydd o semaglutide ymhlith y boblogaeth hon.

Roedd yr adolygiad systematig (Alsanea et al., 2024) yn cynnwys pum treial rheoledig ar hap yn archwilio effaith liraglutide (roedd y dos dyddiol rhwng 1.2mg a 3mg), gyda phoblogaeth o 2,463 o unigolion at ei gilydd. O'r ddau dreial, ymchwiliodd un (Wilding et al., 2021) i effeithiolrwydd semaglutide 2.4mg unwaith yr wythnos o gymharu â phlasebo fel ychwanegiad at ymyrraeth ffordd o fyw ymhlith poblogaeth o 1,961 o oedolion â gorbwysau neu ordewdra a heb ddiabetes. Roedd gan gyfanswm o 856 o gyfranogwyr gyn-ddiabetes a chynhaliodd yr awduron ddadansoddiad is-grŵp ar y boblogaeth hon. Roedd treial arall (le Roux, et al. 2017)

yn archwilio cyfran yr unigolion â chyn-ddiabetes a aeth ymlaen i ddatblygu diabetes math 2 ar ôl derbyn 3.0 mg o liraglutide. Recriwtiwyd cyfanswm o 1,505 o bobl i'r treial hwn.

5.2 Ystyriaethau pwysig

Mae'n werth nodi bod canllawiau gwerthuso technoleg perthnasol NICE ar gyfer y cyffuriau hyn yn cynnwys rhagor o wybodaeth am y rhai a allai fod mewn perygl, ac maent hefyd yn darparu dolen i'r dudalen berthnasol yn y crynodeb meddyginiaethau electronig (emc) sy'n tynnu sylw at y gwrtharwyddion, y rhybuddion arbennig a'r rhagofalon i'w defnyddio. Wrth ystyried pa is-boblogaethau clinigol y gellid rhoi blaenoriaeth iddynt, mae'n bwysig ystyried y rhain mewn unrhyw benderfyniadau a wneir. Felly mae'r tabl isod yn darparu dolenni i'r canllawiau gwerthuso technoleg perthnasol gan NICE a'r ddolen i'r emc.

Tabl 2 – Dolenni perthnasol NICE a'r emc

Cyffur	Gwerthusiad technoleg NICE	Dolen i'r crynodeb meddyginiaethau electronig
Liraglutide	NICE technology appraisal guidance on liraglutide for managing overweight and obesity TA664 (NICE, 2020)	https://www.medicines.org.uk/emc/product/2313/smpc
Semaglutide	NICE technology appraisal guidance Semaglutide for managing overweight and obesity TA875 (NICE, 2023)	https://www.medicines.org.uk/emc/product/13801/smpc
Tirzepatide	NICE technology appraisal guidance on tirzepatide for managing overweight and obesity TA1026 (NICE, 2024)	https://www.medicines.org.uk/emc/product/15486/smpc

5.3 Meini prawf cymhwysedd y treial

Wrth ystyried pa is-boblogaethau clinigol i'w blaenoriaethu, mae hefyd yn werth nodi meini prawf cynnwys ac eithrio'r treialon a nodwyd gennym. Roedd llawer o'r rhain yn eithrio cyflyrau meddygol penodol neu'n ei gwneud yn ofynnol i gyfranogwyr fod ag o leiaf un cydafiachedd sy'n gysylltiedig â phwysau. Fodd bynnag, roedd hyn yn amrywio ymhlith astudiaethau. Mae'n debyg bod y rhain yn gysylltiedig â'r arwyddion a'r gwrtharwyddion ar gyfer defnyddio'r cyffuriau hyn, fel y'u hamlygwyd gan yr emc a NICE.

Mae'r adran nesaf hon yn rhoi trosolwg byr o'r meini prawf cynnwys ac eithrio ar gyfer y tirzepatide, liraglutide a semaglutide a amlinellwyd yn y treialon astudiaeth sylfaenol. Mae amlinelliad mwy manwl o'r meini prawf cymhwysedd a ddarperir ym mhob treial i'w weld yn Atodiad A.

5.3.1 Tirzepatide

Roedd y meini prawf cymhwysedd ar gyfer yr holl dreialon tirzepatide (n=4, manylion yn atodiad A) yn cynnwys oedolion 18 oed a hŷn â BMI o 30 neu fwy, neu BMI o 27 neu fwy gydag o leiaf un cymhlethdod a fu'n gysylltiedig â phwysau. Roedd y rhain yn cynnwys gorbwysedd, dyslipidaemia, apnoea cwsg rhwystrol, neu glefyd cardiofasgwlaidd. Yn ogystal, roedd yn ofynnol i gyfranogwyr beidio â bod wedi cael diagnosis o ddiabetes math II ym mhob treial. Roedd tri threial hefyd yn ei gwneud yn ofynnol i gyfranogwyr fod wedi nodi un neu fwy o ymdrechion dietegol aflwyddiannus i golli pwysau. Yn ogystal, roedd dau dreial yn ei gwneud yn ofynnol i gyfranogwyr fod â chymhelliant da yn ôl barn yr ymchwilydd.

Tynnodd dau dreial sylw hefyd at baramedrau llym ynghylch gofynion benywaidd yn ymwneud â beichiogrwydd, menopos a defnyddio HRT yn eu meini prawf cymhwysedd.

Mae gwybodaeth fanwl am y meini prawf eithrio i'w gweld yn Atodiad A. Roedd y rhain yn llawer mwy manwl na'r meini prawf cynnwys yn gyffredinol, ac fe'u grwpiwyd yn gyflyrau meddygol sy'n gysylltiedig â diabetes (diabetes math I neu fath II), sy'n gysylltiedig â gordewdra (megis newid ym mhwysau'r corff >5 kg o fewn 3 mis cyn sgrinio) a chyflyrau meddygol eraill. Roedd y cyflyrau meddygol 'eraill' yn cynnwys:

- Arennol
- Gastroberfeddol
- Endocrinolegol

- Iechyd Meddwl
- Cardiofasgwlaidd
- Hepatig
- Canser
- Cyflyrau eraill (megis cyflyrau nad ydynt wedi'u rhestru o'r blaen ond sy'n wrtharwydd hysbys i agonistiau GLP-1R fel aros am drawsblaniad, rhai cyflyrau hematolegol a allai ymyrryd â mesur HbA1c ac ati.)

5.3.2 Liraglutide

Roedd y meini prawf cymhwysedd ar gyfer yr holl dreialon (n=14, ceir manylion yn atodiad A) yn cynnwys oedolion 18 oed neu hŷn â BMI o 27kg/^{m2} neu fwy. Fodd bynnag, roedd wyth treial yn cynnwys terfynau oedran llym, a oedd fel arfer yn cyfeirio at y terfyn oedran uchaf. Roedd hyn yn amrywio rhwng 55 a 74 mlwydd oed (Jensen et al., 2024; Astrup et al., 2009; Blackman et al., 2016; Gudbergsen et al., 2021; Halawi et al., 2017; Lean et al., Troni et al., 2014; Lean et al.; 2020; Wadden et al., 2019). Fodd bynnag, cyfyngodd un astudiaeth (Tronieri et al., 2020) gymhwysedd i'r rhai rhwng 21 a 70 oed. O ran BMI, roedd y rhan fwyaf o'r astudiaethau'n cynnwys y rhai â BMI o 30kg/^{m2} neu fwy, ond roedd rhai'n cynnwys y rhai â BMI o 27kg/ m2 os oedd cydafiachedd sy'n gysylltiedig â gordewdra yn bresennol. Gorbwysedd neu ddyslipidaemia oedd hyn fel arfer. Fodd bynnag, roedd pedair astudiaeth (Jensen et al., 2024; Astrup et al., 2009; Tronieri et al., 2020; Wadden et al., 2019) hefyd yn cynnwys ystod BMI, a oedd unwaith eto fel arfer yn cyfeirio at derfyn uchaf. Roedd yr ystod BMI ehangaf yn cynnwys 30 i 55kg/^{m²} (Tronieri et al., 2020 a Wadden et al., 2019), tra bod y terfynau BMI uchaf sy'n weddill yn 40kg/m² a 43kg/m² .

Gellir dod o hyd i feini prawf eithrio manwl yn Atodiad A. Yn gyffredinol, roedd y rhain yn llai cynhwysfawr na tirzepatide; fodd bynnag, cynhwyswyd cyflyrau iechyd meddwl a synio am hunanladdiad ym mhob treial. Roedd y rhan fwyaf o dreialon hefyd yn eithrio rhai neu bob un o'r cyflyrau canlynol:

- Arennol
- Endocrinolegol (fel arfer yn gysylltiedig â gordewdra)
- Cardiofasgwlaidd
- Hepatig
- Canser

Dim ond un astudiaeth a nododd gyflyrau gastroberfeddol yn ei meini prawf eithrio hefyd (Jenson et al., 2024).

5.3.3 Semaglutide

Roedd y meini prawf cymhwysedd ar gyfer yr holl dreialon (n=11, ceir manylion yn atodiad A) yn cynnwys oedolion 18 oed neu hŷn, ac eithrio un astudiaeth (Lincoff et al., 2023), a recriwtiodd bobl 45 oed neu hŷn. Nododd un astudiaeth (Friedrichsen et al., 2021) ystod oedran gymwys o rhwng 18 a 65 oed. Ni nododd astudiaeth arall (Jensterle et al., 2021) oedran yn eu meini prawf cymhwysedd.

Recriwtiodd saith treial (Wilding et al., 2022; Rubino et al., 2021; Garvey et al., 2022; Rubino et al., 2022; Wadden et al., 2021; Wilding et al., 2021; Lincoff et al., 2023) gyfranogwyr â BMI o 30 kg/^{m2} neu 27 kg/ m2 os oedd cyflwr meddygol sy'n gysylltiedig â phwysau hefyd yn bresennol. Diffiniwyd y rhain fel gorbwysedd, dyslipidaemia, apnoea cwsg rhwystrol, neu glefyd cardiofasgwlaidd mewn pump o'r treialon hyn. Nododd dau dreial (Blundell et al., 2017; Friedrichsen et al., 2021) ystod BMI o rhwng 30 a 45 kg/^{m2}. Dim ond 'gordewdra' oedd wedi'i nodi fel y meini prawf cymhwysedd mewn astudiaeth arall (Jensterle et al., 2021), ond nid oedd yn cynnwys diffiniad ar gyfer hyn. Fodd bynnag, efallai bod rhagor o wybodaeth ar gael mewn protocol, ond nid oedd modd i ni ddod o hyd i hon. Yn olaf, nododd Kosiborod et al. (2023) BMI o 30 kg/$^{m^2}$o leiaf.

Gellir dod o hyd i feini prawf eithrio manwl yn Atodiad A. Yn gyffredinol, roedd y rhain yn llai cynhwysfawr na tirzepatide a liraglutide; fodd bynnag, roedd pob treial yn eithrio'r rhai â diabetes, er nad oedd hyn wedi'i nodi'n eglur bob amser mewn perthynas â diabetes math 1 neu fath 2. Roedd y meini prawf eithrio'n cynnwys rhai neu bob un o'r cyflyrau canlynol. Mae niferoedd y treialon wedi'u cynnwys mewn cromfachau:

- Canser
- Pancreatitis
- Cardiofasgwlaidd
- Iechyd meddwl
- Arennol
- Gastroberfeddol
- Hepatig

Noder, oni nodir yn wahanol, nad oes unrhyw asesiad ansawdd wedi'i gynnal, felly ni all y Gwasanaeth Tystiolaeth wneud sylwadau ar ansawdd methodolegol y ffynonellau a amlinellir yn y tablau atodol. Os bwriedir defnyddio unrhyw bapur ar gyfer polisi a/neu ymarfer, byddwch cystal â chynnal asesiad ansawdd ac ystyriwch a yw'r canfyddiadau'n gallu cael eu cyffredinoli i'ch cyd-destun chi ai peidio.

6. Dulliau

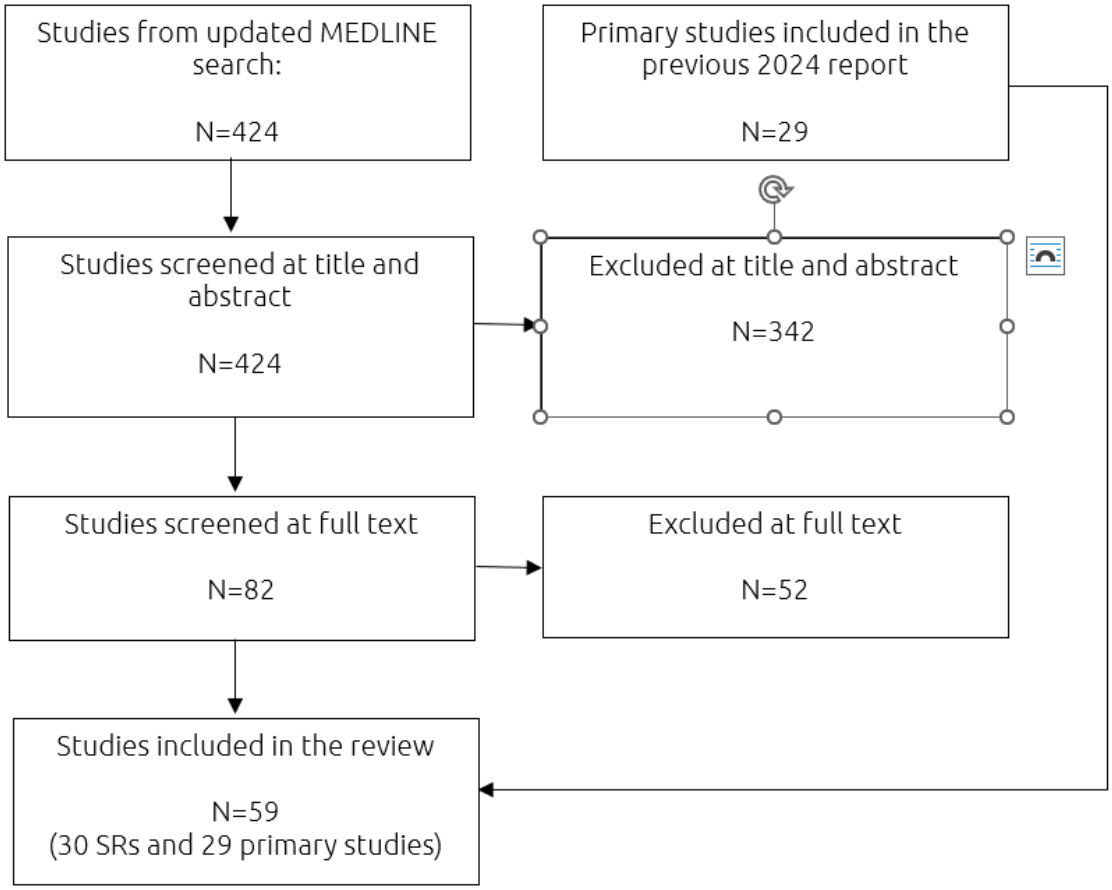
I ddechrau, archwiliwyd astudiaethau sylfaenol o dreialon clinigol a oedd wedi'u cynnwys yn yr adroddiad blaenorol a luniwyd yn 2024 i weld pa rai oedd wedi cynnal dadansoddiadau o is-grŵpiau mewn is-boblogaethau clinigol penodol (Atodiad A). Lle roedd y rhain yn adolygiadau systematig, cafodd yr astudiaethau sylfaenol a oedd wedi'u cynnwys ynddynt eu tynnu allan a'u harchwilio. Mae manylion y chwiliadau a'r fethodoleg a ddefnyddiwyd i'w gweld yn yr adroddiad hwnnw.

Gan fod y chwiliad gwreiddiol ar gyfer adolygiad 2024 yn eang, teimlwyd y gallai hefyd fod wedi cipio ymchwil eilaidd ar gyffuriau colli pwysau ar gyfer rheoli pwysau a allai fod wedi'i chynnal mewn grwpiau penodol. Byddai'r rhain wedi cael eu heithrio o adroddiad gwreiddiol 2024, ond efallai eu bod yn bodloni'r meini prawf cymhwysedd i'w cynnwys yn yr adolygiad hwn. Felly, ail-gynhaliodd y Gwasanaeth Tystiolaeth chwiliad MEDLINE yr adroddiadau gwreiddiol i gasglu ymchwil a gyhoeddwyd hyd at Ebrill 24 2025, a sgriniodd ganlyniadau'r chwiliad hwn a oedd wedi'i ddiweddaru yn erbyn y meini prawf cymhwysedd ar gyfer cynnwys adolygiadau systematig yn yr adolygiad cwmpasu hwn (Atodiad B).

Ffigur 1: Strategaeth Chwilio MEDLINE

Ovid MEDLINE(R) ALL <1946 to April 24, 2025>		
1	Liraglutide/ or Glucagon-Like Peptide-1 Receptor Agonists/ or Glucagon-Like Peptides/ or Orlistat/ or Anti-Obesity Agents/	14692
2	(orlistat or tirzepatide* or semaglutide* or liraglutide* or "glucagon-like peptide-1 receptor agonist*" or "GLP-1" or wegovy or Saxenda or Ozempic or rybelsus or Victoza or mounjaro or zepbound or Xenical or alli).ti,ab.	25555
3	1 or 2	32172
4	(overweight or obese or obesity or "body weight*" or "body mass*").ti,ab.	853459
5	Obesity/ or Overweight/ or Adipose Tissue/ or Body Weight/ or weight loss/ or Obesity, Abdominal/ or Obesity, Morbid/	543207
6	((manage adj3 weight) or (weight adj3 loss) or (weight adj3 reduc*) or (fat adj3 reduc*) or (fat adj3 loss)).ti,ab.	177794
7	4 or 5 or 6	1155443
8	("systematic review*" or meta-analys*).ti,ab.	518092
9	("systematic review" or meta analysis).pt.	377010
10	8 or 9	556235
11	3 and 7 and 10	997
12	limit 11 to yr="2023 -Current"	424

Ffigur 2: Diagram llif o'r astudiaethau a gynhwyswyd:



Dewiswyd astudiaethau ar sail y meini prawf cymhwysedd isod:

Tabl 3: Meini prawf cynnwys	
Cyfranogwyr	Pobl sydd dros bwysau ac yn ordew gyda neu heb gydafiachedd sy'n bodloni'r meini prawf ar gyfer mynediad i wasanaethau rheoli pwysau arbenigol yng Nghymru
Ymyriad / amlygiad	Orlistat, liraglutide (Saxenda®), semaglutide (Wegovy®) a tirzepatide fel ychwanegiad at ymyriadau ymddygiadol
Cymhariaeth	Gofal arferol neu ddim ymyrraeth, plasebo
Canlyniadau	Canlyniadau effeithiolrwydd (colli pwysau, BMI, nifer sydd angen ei drin, cylchedd y wast) Cost-effeithiolrwydd Digwyddiadau andwyol/niwed neu ganlyniadau anfwriadol
Ystyriaethau Eraill yr Astudiaethau	

Cymhwyswyd cyfyngiadau dyddiad i'n chwiliad am dystiolaeth ychwanegol yn ôl y dyddiad cyhoeddi neu ddiweddaru canllawiau perthnasol NICE. Y terfynau dyddiadau a gymhwyswyd oedd: Orlistat – o 2020 ymlaen Liraglutide (Saxenda®) – o 2020 ymlaen Semaglutide (Wegovy®) – o 2022 ymlaen Tirzepatide – o 2023 ymlaen

Ni chynhaliwyd unrhyw werthusiad beirniadol o'r llenyddiaeth sylfaenol na'r llenyddiaeth eilaidd

Cyfeiriadau

Alsanea S, et al. (2024) Liraglutide's Effect on Weight Management in Subjects With Pre-diabetes: A Systematic Review & Meta-Analysis. Endocrine Practice, 30(8), pp.737–745. DOI: 10.1016/j.eprac.2024.05.009

Altobaishat O, et al., (2025) Safety and efficacy of glucagon-like peptide-1 receptor agonists in patients with obstructive sleep apnea: a systematic review and meta-analysis of randomized controlled trials. European Clinical Respiratory Journal, [online] 12(1). DOI: 10.1080/20018525.2025.2484048.

Aronne L, et al. (2024). Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA, 331(1), 38–48. https://doi.org/10.1001/jama.2023.24945

Astrup A, et al. (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet (London, England), 374(9701), 1606–1616. DOI: 10.1016/S0140-6736(09)61375-1

Austregésilo B, et al., (2024) The efficacy and safety of GLP-1 agonists in PCOS women living with obesity in promoting weight loss and hormonal regulation: A meta-analysis of randomized controlled trials. Journal of Diabetes and its Complications, [online] 38(10), pp.108834–108834. DOI: 10.1016/j.jdiacomp.2024.108834

Bader S, et al. (2024) A systematic review of GLP-1 on anthropometrics, metabolic and endocrine parameters in patients with PCOS. Women's Health, [online] 20, p.17455057241234530. DOI: 10.1177/17455057241234530

Bak M, et al. (2024) Glucagon-like peptide agonists for weight management in antipsychotic-induced weight gain: A systematic review and meta-analysis. Acta Psychiatrica Scandinavica, 150(6). DOI: 10.1111/acps.13734

Bellos I, et al., (2024). Safety and Efficacy of Sodium-Glucose Transport Protein 2 Inhibitors and Glucagon-like Peptide-1 Receptor Agonists in Diabetic Kidney Transplant Recipients: Synthesis of Evidence. Journal of Clinical Medicine, 13(20), p.6181. DOI: 10.3390/jcm13206181.

Beshr M, et al. (2025). Efficacy of Semaglutide and Other GLP-1 Agonists in Patients with Heart Failure With Preserved Ejection Fraction and Obesity: A Systemic Review and Meta-Analysis. PubMed. DOI: 10.1097/crd.0000000000000915.

Bi Z, et al. (2023). Evaluating the effects of glucagon-like peptide-1 receptor agonists on cognitive function in Alzheimer's disease: A systematic review and meta-analysis. Advances in Clinical and Experimental Medicine, 32(11), pp.1223–1231. DOI: 10.17219/acem/161734.

Blackman A, et al. (2016) Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. International journal of obesity (2005), 40(8), 1310–1319. DOI: 10.1038/ijo.2016.52

Blundell J, et al. (2017) Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes, obesity & metabolism, 19(9), 1242–1251. DOI: 10.1111/dom.12932

Bo Y, et al. (2025) Comparative efficacy of pharmacological interventions on metabolic and hormonal outcomes in polycystic ovary syndrome: a Network Meta-Analysis of Randomized controlled trials. BMC Women's Health, 25(1). DOI: 10.1186/s12905-025-03594-6.

Dutta D, et al. (2025). Efficacy and Safety of Glucagon Like Peptide-1 Receptor Agonism Based Therapies in Obstructive Sleep Apnoea: A Systematic Review and Meta-Analysis. Indian journal of endocrinology and metabolism, [online] 29(1), pp.4–12. DOI: 10.4103/ijem.ijem_365_24

Electronic medicines compendium (2024) Mounjaro KwikPen 15mg solution for injection in pre-filled pen (updated: 14/03/25) Available from: https://www.medicines.org.uk/emc/product/15486/smpc [accessed: 12/05/25]

Electronic medicines compendium (2019) Saxenda 6 mg/mL solution for injection in pre-filled pen (updated: 14/10/24) Available from: https://www.medicines.org.uk/emc/product/2313/smpc [accessed: 12/05/25]

Electronic medicines compendium (2022) Wegovy 1 mg, FlexTouch solution for injection in pre-filled pen (updated: 02/05/25) Available from: https://www.medicines.org.uk/emc/product/13801/smpc [accessed: 12/05/25]

Friedrichsen M, et al. (2021) The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. Diabetes, obesity & metabolism, 23(3), 754–762. https://doi.org/10.1111/dom.14280

Garvey W, et al. (2022) Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nature medicine, 28(10), 2083–2091. DOI: 10.1038/s41591-022-02026-4

Goldberg A, et al. (2024). Anti-obesity pharmacological agents for polycystic ovary syndrome: A systematic review and meta-analysis to inform the 2023 international evidence-based guideline. Obesity reviews, 25(5). DOI: 10.1111/obr.13704

Gudbergsen H, et al. (2021) Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. The American journal of clinical nutrition, 113(2), 314–323. DOI: 10.1093/ajcn/nqaa328

Gupta N, et al. (2024). Semaglutide in Heart Failure: A Systematic Review of Outcomes of Semaglutide in Heart Failure Patients. Cureus, [online] 16(7). DOI: 10.7759/cureus.64668

Halawi H, et al. (2017) Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. The lancet. Gastroenterology & hepatology, 2(12), 890–899. DOI: 10.1016/S2468-1253(17)30285-6

Hegde N, et al. (2024). Pharmacological interventions for antipsychotic-induced weight gain in schizophrenia: A network meta-analysis. General hospital psychiatry, 90, pp.12–21. DOI: 10.1016/j.genhosppsych.2024.06.003

Hookway A, et al., (2024) What is the effectiveness, safety and cost effectiveness of weight loss drugs as an adjunct to behavioural interventions? An evidence briefing. (unpublished)

Li M, et al (2024). Glucagon-like Peptide 1 Receptor Agonists for the Treatment of Obstructive Sleep Apnea: a meta-analysis. SLEEP, [online] 48(4). DOI: 10.1093/sleep/zsae280

Jastreboff A, et al. (2022) Tirzepatide Once Weekly for the Treatment of Obesity. The New England journal of medicine, 387(3), 205–216. https://doi.org/10.1056/NEJMoa2206038

Jastreboff A, et al. (2025) Tirzepatide for Obesity Treatment and Diabetes Prevention. The New England journal of medicine, 392(10), 958–971. https://doi.org/10.1056/NEJMoa2410819

Jensen S, et al. (2024). Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial. EClinicalMedicine, 69, 102475. DOI: 10.1016/j.eclinm.2024.102475

Jensterle M, et al. (2021) Semaglutide reduces fat accumulation in the tongue: A randomized single-blind, pilot study. Diabetes research and clinical practice, 178, 108935. DOI: 10.1016/j.diabres.2021.108935

Khaity A, et al. (2023). Glucagon-like peptide-1 receptor-agonists treatment for cardio-metabolic parameters in schizophrenia patients: a systematic review and meta-analysis. Frontiers in Psychiatry, 14. DOI: 10.3389/fpsyt.2023.1153648

Kosiborod M, et al. (2023) Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. The New England journal of medicine, 389(12), 1069–1084. DOI: 10.1056/NEJMoa2306963

Krisanapan P, et al (2024). Safety and efficacy of glucagon-like peptide-1 receptor agonists among kidney transplant recipients: a systematic review and meta-analysis. Clinical Kidney Journal, [online] 17(2). DOI: 10.1093/ckj/sfae018

Krisanapan P, et al (2024b). Safety and Efficacy of GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus with Advanced and End-Stage Kidney Disease: A Systematic Review and Meta-Analysis. Diseases, 12(1), pp.14. DOI: 10.3390/diseases12010014

Lean M, et al. (2014) Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. International journal of obesity (2005), 38(5), 689–697. DOI: 10.1038/ijo.2013.149

le Roux C, et al. (2017) 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet (London, England), 389(10077), 1399–1409. DOI: 10.1016/S0140-6736(17)30069-7

Lincoff A, et al. (2023) Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. The New England journal of medicine, 389(24), 2221–2232. https://doi.org/10.1056/NEJMoa2307563

Machado M, et al. (2024). Clinical Effects of Glucagon-Like Peptide-1 Agonist Use for Weight Loss in Women With Polycystic Ovary Syndrome: A Scoping Review. Cureus, [online] 16(8). DOI: 10.7759/cureus.66691

Mahmoud A, et al (2024). Efficacy of orlistat in obese patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. Proceedings - Baylor University. Medical Center, 37(4), pp.1–10. DOI: 10.1080/08998280.2024.2335829

Malik A, et al. (2023). The effects of liraglutide on liver enzymes and metabolic factors in patients with nonalcoholic steatohepatitis: a meta-analysis of randomized controlled trials. Gastroenterology Review, 18(1), pp.100–109. DOI: 10.5114/pg.2022.112775

Menon T, et al. (2024). A systematic review on the efficacy of GLP-1 receptor agonists in mitigating psychotropic drug-related weight gain. CNS Spectrums, [online] 29(5), pp.347–353. DOI: 10.1017/S1092852924000531

Natale P, et al. (2025) Glucagon-like peptide 1 (GLP-1) receptor agonists for people with chronic kidney disease and diabetes. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD015849. DOI: 10.1002/14651858.CD015849.pub2.

Nexøe-Larsen C, et al. (2018) Effects of liraglutide on gallbladder emptying: A randomized, placebo-controlled trial in adults with overweight or obesity. Diabetes, obesity & metabolism, 20(11), 2557–2564. DOI: 10.1111/dom.13420

NG V, et al. (2024) The role of glucagon-like peptide 1 receptor agonists for weight control in individuals with acquired hypothalamic obesity—A systematic review. Clinical Obesity. 14:e12642. DOI: 10.1111/cob.12642

NICE (2024) Tirzepatide for managing overweight and obesity. TA1026. https://www.nice.org.uk/guidance/ta1026

NICE (2020) Liraglutide for managing overweight and obesity. TA664. https://www.nice.org.uk/guidance/ta664

NICE (2023) Semaglutide for managing overweight and obesity. TA875. https://www.nice.org.uk/guidance/ta875

O'Neil P, et al. (2018) Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet (London, England), 392(10148), 637–649. DOI: 10.1016/S0140-6736(18)31773-2

Park M, et al. (2023) Comparison of glucagon-like peptide-1 receptor agonists and thiazolidinediones on treating nonalcoholic fatty liver disease: A network meta-analysis. Clinical and Molecular Hepatology. 29:693-704. DOI: 10.3350/cmh.2022.0330

Patoulias D, et al., (2023) Effect of Glucagon-like Peptide-1 Receptor Agonists on Cardio-Metabolic Risk Factors among Obese/Overweight Individuals Treated with Antipsychotic Drug Classes: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biomedicines, [online] 11(3), pp.669–669. DOI: 10.3390/biomedicines11030669

Peck K, et al. (2024) Intentional weight loss in overweight and obese patients with heart failure: A systematic review. European Journal of Heart Failure. 26, 1907–1930. DOI:10.1002/ejhf.3270

Pi-Sunyer X, et al. (2015) A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. The New England journal of medicine, 373(1), 11–22. DOI: 10.1056/NEJMoa1411892

Ren Q, et al. (2025). Efficacy of Hypoglycemic Agents in Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD): A systematic review and network meta-analysis. Journal of Evidence-Based Medicine. DOI: 10.1111/jebm.70021

Rubino, D., et al. (2021) Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA, 325(14), 1414–1425. DOI: 10.1001/jama.2021.3224

Rubino D, et al. (2022) Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA, 327(2), 138–150. DOI: 10.1001/jama.2021.23619

Tong X, et al. (2024). Efficacy and safety of glucagon-like peptide-1 receptor agonists in the treatment of polycystic ovary syndrome- A systematic review and meta-analysis. The Journal of Metabolic Diseases, 130(6). DOI: 10.1080/13813455.2024.2380422

Tronieri J, et al. (2020) Effects of liraglutide on appetite, food preoccupation, and food liking: results of a randomized controlled trial. International journal of obesity (2005), 44(2), 353–361. DOI: 10.1038/s41366-019-0348-6

Wadden T, et al. (2013) Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. International journal of obesity (2005), 37(11), 1443–1451. DOI: 10.1038/ijo.2013.120

Wadden T, et al. (2019). Intensive Behavioral Therapy for Obesity Combined with Liraglutide 3.0 mg: A Randomized Controlled Trial. Obesity (Silver Spring, Md.), 27(1), 75–86. DOI: 10.1002/oby.22359

Wadden T, et al. (2020) Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT Randomized Controlled Trial. Obesity (Silver Spring, Md.), 28(3), 529–536. DOI: 10.1002/oby.22726

Wadden T, et al. (2021) Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA, 325(14), 1403–1413. DOI: 10.1001/jama.2021.1831

Wadden T, et al. (2023) Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med 29, 2909–2918 https://doi.org/10.1038/s41591-023-02597-w

Wang H, et al. (2024). Optimized strategy among diet, exercise, and pharmacological interventions for nonalcoholic fatty liver disease: A network meta-analysis of randomized controlled trials. Obesity Reviews. E13727. DOI: 10.1111/obr.13727

Wilding J, et al. (2021) Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England journal of medicine, 384(11), 989–1002. DOI: 10.1056/NEJMoa2032183

Wilding J, et al. (2022) Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes, obesity & metabolism, 24(8), 1553–1564. DOI: 10.1111/dom.14725

Zhu K, et al. (2023). Efficacy and safety of Semaglutide in non-alcoholic fatty liver disease. World Journal of Gastroenterology, 29(37): 5327-5338. DOI: 10.3748/wjg.v29.i37.5327

Atodiad A

Data extraction table for primary studies investigating the effectiveness of Liraglutide x 14			
Reference and trial details	Trial details	Outcomes	Sub-group analysis
Reference: Jensen, S., et al. (2024). Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial. EClinicalMedicine, 69, 102475. DOI: 10.1016/j.eclinm.2024.102475 **Study aim:** To investigate whether weight loss and improved body composition are sustained better at 1 year after termination of active treatment with glucagon-like peptide-1 (GLP-1) receptor agonist, supervised exercise program, or both combined for 1 year. **Study duration:** The study consisted of three phases: an eight-week weight loss phase (week −8 to 0), a 52-week randomised controlled weight maintenance phase (week 0–52), and a one-year post-treatment phase (week 52–104). The results of this paper are from the third phase (post-treatment year). **Population:** Liraglutide group= 49 (Female sex= 31, 63%; mean age=43; weight= 95.1 kg)	**Intervention:** Treatment group 1: Supervised exercise plus placebo. Treatment group 2: Liraglutide only. Treatment group 3: Combined exercise plus liraglutide. Liraglutide or volume-matched placebo was administered once daily. The starting dose was 0.6 mg per day with weekly increases of 0.6 mg until a tolerated dose of a maximum 3.0 mg per day was achieved. All participants who had undergone randomisation were invited to participate in the post-treatment study, which was composed of a set of outcome assessments one year after the planned completion of the 52-week weight maintenance intervention. **Comparison:** Volume-matched placebo **Inclusion criteria:** Participants who lost at least 5% of initial weight loss during the weight loss phase were then randomised. BMI of 32–43 kg/m^2; aged 18–65 years, safe contraceptive method or menopause for women.	**Outcomes: Primary outcome:** change in body weight from randomisation to one year after termination of the weight maintenance intervention (week 0–104). **Secondary outcome:** change in body-fat percentage from week 0 to 104 **Other outcomes:** changes from week 0 to 104 in fat mass, lean mass, waist and hip circumferences, HbA1c, fasting glucose, systolic and diastolic blood pressure, resting heart rate, and plasma levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Changes in quality-of-life outcomes.	**No relevant sub-group analysis was undertaken**

Liraglutide + exercise group= 49 (Female sex= 31, 63%; age=42; weight= 98.3 kg) Placebo + exercise group= 48 (Female sex= 3, 65%; age=43; weight= 96.8 kg) Placebo group= 49 (Female sex= 31, 63%; age= 43; weight= 96.7 kg)	**Exclusion criteria:** Patients diagnosed with any known serious chronic illness, including type 1 or 2 diabetes (or a randomly measured fasting plasma glucose >7mmol/L); Angina pectoris, coronary heart disease or congestive heart failure (NYHA Class III-IV); Severe renal impairment (creatinine clearance (GFR) <30mL/min); Severe hepatic impairment; Inflammatory bowel disease; Gastroparesis.; Cancer; Chronic obstructive lung disease; Psychiatric disease, a history of major depressive or other severe psychiatric disorders; The use of medications that cause clinically significant weight gain or loss; Previous bariatric surgery; A history of idiopathic acute pancreatitis; A family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma; Osteoarthritis, which is judged to be too severe to manage the exercise programme; Pregnancy, expecting pregnancy or breast feeding; Allergy to any of the ingredients of the study medication: liraglutide, disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid and sodium hydroxide; Regular exercise training at high intensity (eg, spinning)>2 hours per week).		
Reference: le Roux, C., et al. (2017) 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet (London, England), 389(10077), 1399–1409. DOI: 10.1016/S0140-6736(17)30069-7	**Intervention:** Liraglutide 3·0 mg daily. Starting at 0·6mg with weekly 0·6 mg incremental increases to 3·0 mg. All trial participants received standardised lifestyle intervention counselling from	**Outcomes: Primary outcome:** proportion of individuals with type 2 diabetes at 160 weeks, with time to onset of diabetes as the primary endpoint. Coprimary endpoints: mean weight loss, and the proportion of participants losing at least 5% of	**This trial was conducted in people with prediabetes**

Study aim: In the 3-year assessment of the SCALE Obesity and Prediabetes trial the aim was to evaluate the proportion of individuals with prediabetes who were diagnosed with type 2 diabetes. **Study duration:** 160 weeks **Population:** Liraglutide group= 1505 (Female sex= 1141 (76%), age=48; weight= 107.5 kg) Placebo group=749 (Female sex= 573 (77%); age= 47.3; weight= 107.9 kg)	randomisation to end of follow-up, about once a month. Participants were advised to achieve at least 150 minutes of physical activity per week and to reduce their daily energy intake to 500 kcal below their individualised energy requirement. **Comparison:** matched placebo **Inclusion criteria:** Adults aged 18 years or older with stable bodyweight and a body-mass index (BMI) of at least 30 kg/m², or at least 27 kg/m² with treated or untreated dyslipidaemia, or hypertension, or both. **Exclusion criteria:** Diagnosis of type 1 or type 2 diabetes, previous treatment with GLP-1 receptor agonists (including liraglutide or exenatide) within the last 3 months, untreated or uncontrolled hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone >6 mIU/L or <0·4 mIU/L Screening calcitonin ≥50 ng/L Family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC), Personal history of non-familial medullary thyroid carcinoma History of chronic pancreatitis or idiopathic acute pancreatitis Obesity induced by other endocrinologic disorders (e.g. Cushing's Syndrome) Current or history of treatment with medications that may cause significant weight gain, within 3 months prior to screening, including systemic corticosteroids (except for a short course of treatment, i.e.	their baseline bodyweight, and more than 10% of their baseline bodyweight assessed at week 56. **Secondary outcome:** changes from baseline to week 160 in glycaemic control parameters, mean and categorical bodyweight, BMI, waist circumference, cardiometabolic biomarkers, vital signs, and health-related quality of life.	

	7–10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (e.g. imipramine, amitriptiline, mirtazapin, paroxetine, phenelzine, clorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium) Diet attempts using herbal supplements or over-the-counter medications within 3 months before screening Current participation (or within the last 3 months) in an organised weight reduction programme or currently using or used within 3 months before screening: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phentermine, or metformin (either by prescription or as part of a clinical trial) Participation in a clinical trial within the last 3 months prior to screening Simultaneous participation in any other clinical trial of an investigational drug Previous surgical treatment for obesity (excluding liposuction if performed >1 year before trial entry) History of major depressive disorder within the last 2 years History of other severe psychiatric disorders, e.g. schizophrenia, bipolar disorder, a Patient Health Questionnaire-9 (PHQ-9) score of ≥15 Any lifetime history of a suicidal attempt A history of any suicidal behaviour in the last month prior to randomisation Any suicidal ideation of type 4 (active suicidal ideation with some intent to act without specific plan) or 5 (active suicidal ideation with specific plan and intent) on the Columbia Suicidality Severity Rating Scale (C-SSRS) in the last month prior to randomisation Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the		

	investigator Uncontrolled treated/untreated hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg). Cancer (past or present, except basal cell skin cancer or squamous cell skin cancer), which in the investigator's opinion could interfere with the results of the trial. Known or suspected hypersensitivity to trial product or related products. Previous participation in the randomised phase of this trial. Re-screening is allowed once within the limit of the recruitment period. Known or suspected abuse of alcohol or narcotics Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete the mental health questionnaire in the provided language Individuals from the same household participating in the trial Females of child-bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice). US: abstinence and the following methods: diaphragm with spermicide, condom with spermicide (by male partner), intrauterine device, sponge, spermicide, Norplant, Depo-Provera or oral contraceptives. Germany: adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal Intra-Uterine Device (IUD), sexual abstinence or vasectomised partner. UK: adequate contraceptive measures are defined as sterilisation, intra-uterine device, oral contraceptives, consistent use of 32 barrier methods, male sterilisation or true abstinence.		

	The receipt of any investigational drug within 4 weeks prior to screening for this trial (Brazil: The receipt of any investigational drug within 1 year prior to screening for this trial, unless there is direct benefit to the individual at the investigator discretion). France: Abnormality of the thyroid identified during the physical exam at screening.		
Reference: Pi-Sunyer, X., et al. (2015) A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. The New England journal of medicine, 373(1), 11–22. DOI: 10.1056/NEJMoa1411892 **Study aim:** To evaluate the efficacy and safety of 3.0 mg of liraglutide, injected subcutaneously once daily, as an adjunct to a reduced-calorie diet and increased physical activity, for weight management in overweight or obese adults who did not have diabetes at baseline. **Study duration:** 70 weeks. After 56 weeks, patients in the liraglutide group who did not have prediabetes at screening were randomly assigned in a 1:1 ratio to continue receiving liraglutide or to switch to placebo for a further 12 weeks to assess whether efficacy was maintained after discontinuation of liraglutide treatment and whether there were safety issues related to discontinuation. Patients in the placebo group continued to receive placebo. **Population:** Liraglutide group: 2437 (Female sex = 1957 (78.7%); Ag e= 45.2; Weight = 106.2 kg)	**Intervention:** Liraglutide - starting at a dose of 0.6 mg with weekly 0.6-mg increments to 3.0 mg daily. Both groups received counselling on lifestyle modification. **Comparison:** Matched placebo **Inclusion criteria:** Patients 18 years of age or older who had stable body weight and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, or 27 or higher if the patient had treated or untreated dyslipidemia or hypertension. **Exclusion criteria:** Diagnosis of type 1 or type 2 diabetes at screening, previous treatment with GLP-1 receptor agonists (including liraglutide or exenatide) within the last 3 months, untreated or uncontrolled hypothyroidism/hyperthyroidism, family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC), personal history of non-familial medullary thyroid carcinoma, history of chronic pancreatitis or idiopathic acute pancreatitis, obesity induced by other endocrinologic disorders (e.g. Cushing's Syndrome), current or history of treatment	**Outcomes: Primary outcome:** The change in body weight and the proportions of patients losing at least 5% and more than 10% of their initial body weight.	No relevant sub-group analysis was undertaken

Placebo group: 1225 (Female sex = 971 (78.1%); Age = 45.0; Weight = 106.2 kg)	with medications that may cause significant weight gain, within 3 months prior to screening, including systemic corticosteroids (except for a short course of treatment, i.e. 7–10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (e.g. imipramine, amitriptiline, mirtazapin, paroxetine, phenelzine, clorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium). Diet attempts using herbal supplements or over-the-counter medications within 3 months before screening. Current participation (or within the last 3 months) in an organized weight reduction program or currently using or used within 3 months before screening: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phenteremine, or metformin (either by prescription or as part of a clinical trial), participation in a clinical trial within the last 3 months prior to screening, simultaneous participation in any other clinical trial of an investigational drug. Previous surgical treatment for obesity (excluding liposuction if performed >1 year before trial entry). History of major depressive disorder within the last 2 years, history of other severe psychiatric disorders, e.g. schizophrenia, bipolar disorder. A patient health questionnaire (PHQ-9) score of ≥15 Any lifetime history of a suicidal attempt. A history of any suicidal behaviour in the last month		

	prior to randomization. Any suicidal ideation of type 4 or 5 on the Columbian Suicidality Severity Rating Scale (C-SSRS) in the last month prior to randomization 18 Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the investigator. Uncontrolled treated/untreated hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg). If white-coat hypertension is suspected at screening, a repeated measurement prior to other trial related activities is allowed. Cancer (past or present, except basal cell skin cancer or squamous cell skin cancer), which in the investigator's opinion could interfere with the results of the trial. Known or suspected hypersensitivity to trial product or related products. Previous participation in the randomized phase of this trial. Re-screening is allowed once within the limit of the recruitment period. Known or suspected abuse of alcohol or narcotics. Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete the mental health questionnaire in the provided language. Subjects from the same household participating in the trial.		

	Females of child-bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice). US: abstinence and the following methods: diaphragm with spermicide, condom with spermicide (by male partner), intrauterine device, sponge, spermicide, Norplant, Depo-Provera or oral contraceptives. Germany: adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal Intra-Uterine Device (IUD), sexual abstinence or vasectomized partner. UK: adequate contraceptive measures are defined as sterilization, intra-uterine device, oral contraceptives, consistent use of barrier methods, male sterilization or true abstinence. The receipt of any investigational drug within 4 weeks prior to screening for this trial. Brazil: The receipt of any investigational drug within 1 year prior to screening for this trial, unless there is direct benefit to the patient at the investigator discretion. France: Abnormality of the thyroid identified during the physical exam at screening.		
Reference: Astrup, A., et al. (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet (London, England), 374(9701), 1606–1616. DOI: 10.1016/S0140-6736(09)61375-1	Intervention: Four liraglutide dose groups (1·2 mg, 1·8 mg, 2·4 mg, or 3·0 mg), administered once daily. All individuals had a 500 kcal per day energy-deficit diet and increased their physical activity throughout the trial, including the 2-week run-in.	Outcomes Primary outcome: Percentage change in bodyweight during the 20 weeks of the study in the intention-to-treat population. The proportion of people losing more than 5% or 10% of baseline weight was also assessed.	No relevant sub-group analysis was undertaken

Study aim: To assess the effect of liraglutide on bodyweight and tolerability in obese individuals without type 2 diabetes. **Study duration:** 20 weeks **Population:** Liraglutide (1.2mg) group: 94 participants (Female sex: 77%; Age: 47; Weight: 96.2 kg) Liraglutide (1.8mg): 90 participants (Female sex: 76%; Age: 46; Weight: 98.0 kg) Liraglutide (2.4mg): 92 participants (Female sex: 76%; Age: 45; Weight: 98.4 kg) Liraglutide (3.0mg): 92 participants (Female sex: 75%; Age: 46; Weight: 97.6 kg) Orlistat group: 95 participants (Female sex: 77%; Age: 46; Weight: 96.0 kg) Placebo group: 98 participants (Female sex: 75%; Age: 46; Weight: 97.3 kg)	**Comparison:** Matched placebo or Orlistat (120 mg) three times a day orally **Inclusion criteria:** Men and women aged 18–65 years, with body-mass index (BMI) of 30–40 kg/m², stable bodyweight (<5% reported change during the previous 3 months), and fasting plasma glucose of less than 7 mmol/L at run-in. **Exclusion criteria:** (N.B) Full exclusion criteria not provided. Key exclusion criteria: Known type 1 or 2 diabetes mellitus, obesity induced by drug treatment, use of approved weight-lowering pharmacotherapy or participation in a clinical weight control study within the previous 3 months, previous surgical obesity treatment, and major medical conditions. There was no exclusion based on psychiatric illness.	**Secondary outcome:** Change in waist circumference, systolic and diastolic blood pressure, prevalence of metabolic syndrome, prediabetes status, fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and triglycerides), cardio vascular biomarkers (highly sensitive C-reactive protein, plasmino gen activator inhibitor-1, fi brino gen, and adiponectin), glucose metabolism parameters (fasting plasma glucose, fasting insulin, and glyco sylated haemoglobin [HbA1c]), and homoeostasis model assessment (HOMA) of β-cell function and insulin resistance. The change from 0 to 120 min in glucose, insulin, and C-peptide concentrations during oral glucose tolerance test (OGTT; 75-g glucose) measured at randomisation and week 20 was also a secondary endpoint. Patient-reported outcome scores of physical function, self-esteem, sexual life, public distress, and work were also secondary endpoints.	
Reference: Blackman, A., et al. (2016) Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive	**Intervention:** Eligible participants were randomly assigned 1:1 to once-daily subcutaneous liraglutide or placebo. To	**Outcomes:** **Primary outcome:** Change in apnea-hypopnea index.	**This trial was conducted in individuals**

sleep apnea: the SCALE Sleep Apnea randomized clinical trial. International journal of obesity (2005), 40(8), 1310–1319. DOI: 10.1038/ijo.2016.52 **Study aim:** To investigate whether liraglutide 3.0 mg reduces obstructive sleep apnea severity compared with placebo using the primary end point of change in apnea hypopnea index (AHI) after 32 weeks. Liraglutide's weight loss efficacy was also examined. **Study duration:** 32 weeks **Population:** Liraglutide group: 180 participants (Female sex: 51 (28.3%); Weight: 48.6 kg) Placebo group: 179 participants (Female sex: 50 (27.9%); Weight: 48.4 kg)	reduce the likelihood of gastrointestinal symptoms, liraglutide was started at the 0.6mg day − 1 dose and escalated in weekly 0.6mg increments to 3.0mg (week 4). The 3.0mg dose was maintained for another 28 weeks. All participants received counselling on diet and physical activity approximately every 4 weeks during treatment. Each participant was prescribed a daily energy intake 500 kcal below the aforementioned estimate. **Comparison:** Placebo dose-volume equivalent **Inclusion criteria:** Men and women aged 18–64 years with a stable body weight (o5% change during the previous 3 months) and body mass index (BMI) of ⩾ 30 kg m−2. Eligible individuals had to be diagnosed with moderate (apnea–hypopnea index (AHI) 15.0–29.9 events h − 1) or severe (AHI ⩾30.0 events h − 1) OSA and be unable or unwilling to use CPAP therapy **Exclusion criteria:** Treatment with glucagon-like peptide-1 (GLP-1) receptor agonists (including liraglutide or exenatide), dipeptidyl peptidase-4 (DPP-4) inhibitors or insulin within the last 3 months prior to screening.Diagnosis of type 1 or type 2 diabetes per judgement of the investigator Glycated hemoglobin (HbA1c) ≥6.5% (screening value). Significant craniofacial abnormalities that may be causing OSA. Respiratory and neuromuscular diseases that could interfere with the results of the trial in the opinion of the investigator	**Secondary outcome:** Changes from baseline to week 32 in OSA severity category, blood oxygen saturation parameters (lowest oxygen saturation, percentage of time with oxygen saturation o90% and oxygen desaturation ⩾4% index), sleep architecture parameters (total sleep time, wake time after sleep onset, proportion of sleep spent in supine position and sleep stage distribution), body weight-related parameters (fasting body weight, proportion of participants losing ⩾5% or 410% of baseline fasting body weight, BMI, waist and neck circumference), glycemic parameters (HbA1c and fasting plasma glucose), vital signs (systolic blood pressure (SBP) and diastolic blood pressure, pulse), fasting lipids (high-density lipoprotein, low-density lipoprotein, very-low-density lipoprotein, and total cholesterol and triglycerides), cardiovascular biomarkers (high-sensitivity C-reactive protein and urinary albumin:creatinine ratio), daytime sleepiness (Epworth Sleepiness Scale) and self- reported quality of life.	with moderate or severe obstructive sleep apnoea

	Known diagnosis prior to screening of periodic limb movement disorder Use of central stimulants, hypnotics, mirtazepine, opioids, trazodone within the previous 3 months prior to screening. Obesity induced by other endocrinologic disorders (eg, Cushing Syndrome). Treatment with medications within 3 months prior to screening that in the opinion of the investigator may cause significant weight gain. Weight loss attempts using herbal supplements or over-the-counter medications within 3 months prior to screening. Participation in an organized weight reduction program (current or within 3 months prior to screening). Treatment with pramlintide, sibutramine, orlistat, zonisamide, topiramate or phentermine within 3 months prior to screening. Previous surgical treatment for obesity; e.g., gastric banding procedure (excluding liposuction if performed more than one year before trial entry). Hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone (TSH) >6 mIU/L or <0.4 m IU/L; Calcitonin ≥50 ng/L at screening. Familial or personal history of Multiple Endocrine Neoplasia type 2 or familial Medullary Thyroid Carcinoma Personal history of non-familial Medullary Thyroid Carcinoma.		
Reference: Gudbergsen, H., et al. (2021) Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. The American journal of clinical nutrition, 113(2), 314–323. DOI: 10.1093/ajcn/nqaa328	**Intervention:** Patients were enrolled in a pre–random assignment dietary intervention period (week –8 to 0) consisting of a supervised dietary weight loss program including dietetic counselling and a low-calorie formula diet from the Cambridge Weight Plan (800–1000 kcal/d).	**Outcomes:** **Primary outcome:** Changes in body weight and the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale from week 0 to 52 (0–100 scale with 100 indicating no symptoms).	**This trial was conducted in people with knee osteoarthritis**

Study aim: To determine the efficacy and safety of liraglutide in a 30 mg/d dosing in patients with overweight/obesity and knee osteoarthritis. **Study duration:** 52 weeks **Population:** Liraglutide group: 80 participants (Female sex: 52 (65%); Age: 59.2; Weight: 96.3 kg) Placebo group: 76 participants (Female sex= 49 (64%); Age: 59.3; Weight: 90.8 kg)	Liraglutide starting with 0.6 mg/d and followed by incremental biweekly dose escalation steps of 0.6 mg/d to liraglutide 3 mg/d. The initial 8 weeks after random assignment included a dietician led partial reintroduction of regular meals in combination with formula diet products. In this period, all participants (irrespective of random assignment) were scheduled for group sessions led by a dietician every second week. No dietary consultancies were offered after week 8, but to prevent attrition patients were instructed to aim for an intake of 1200 kcal/d from week 0 to 8 and for an intake of 1500 kcal/d from week 8 to 52. In addition, patients were offered self-administration of 1 to 2 daily meal replacements with a formula diet from week 8 to 52. **Comparison:** Matched placebo **Inclusion criteria:** Adult patients between the ages of 18 and 74 y with overweight [BMI ≥27 (measured in kg/m2)], symptomatic KOA, early-to-moderate KOA changes in knee radiography, and stable body weight were eligible for enrolment. **Exclusion criteria:** Current or history of treatment with medications that may cause significant weight gain for at least 3 months before this trial. Current use or use within 3 months before this trial of GLP-1 receptor agonist, pramlintide, sibutramine, orlistat, zonisamide, topiramate, or phentermine.	**Secondary outcome:** The confirmatory secondary outcomes were changes in the KOOS symptoms, activity of daily living (ADL), sport and recreation, and health-related quality of life (QoL) subscales, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, stiffness, and function subscales, the total score and subscales in the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire, BMI, waist circumference, and the waist/hip ratio from baseline (week 0) to the last visit in the main study period (week 52). Moreover, the proportion of patients with ≥5% or ≥10% weight loss at the last visit in the main study period (week 52) also constituted confirmatory secondary outcomes.	

	Type 1 diabetes or type 2 diabetes treated with glucose-lowering drugs other than metformin. Alloplasty in target knee joint (most symptomatic knee at screening). End stage disease in target knee joint (Kellgren-Lawrence grade 4). Immuno-inflammatory disease. Chronic widespread pain. Pregnancy or insufficient anti-conception therapy for female fertile patients. Breastfeeding. Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x above upper normal range (UNR). Elective surgery scheduled during the trial duration period, except for minor surgical procedures. Surgical procedures such as arthroscopy or injections into a knee within 3 months prior to enrolment. Previous surgical treatment for obesity (excluding liposuction >1 year before trial entry). Obesity secondary to endocrinologic or eating disorders or to treatment with medicinal products that may cause weight gain. Family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.		

	Inflammatory bowel disease. Congestive heart failure, New York Heart Association (NYHA) class III-IV. Diabetic gastroparesis. History of or current diagnosis of pancreatitis (acute and/or chronic) or pancreatic cancer. History of cancer with the exception of in-situ malignancies of the skin or cervix uteri. History of major depressive disorder, a PHQ-9 (Patient Health Questionnaire-9) score of more than 15, or a history of other severe psychiatric disorders or diagnosis of an eating disorder. Subjects with a lifetime history of a suicide attempt or history of any suicidal behaviour within the past month before entry into the trial Inability to speak Danish fluently. A mental state impeding compliance with the program. Use of opioids or similar strong analgesics Allergic reactions to the active ingredients of Saxenda, such as hypotension, palpitations, dyspnea and edema		
Reference: Halawi, H., et al. (2017) Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. The lancet. Gastroenterology & hepatology, 2(12), 890–899. DOI: 10.1016/S2468-1253(17)30285-6 **Study** aim: To compare effects of liraglutide versus placebo on gastric motor functions,	**Intervention:** Liraglutide (3·0 mg). Liraglutide was escalated by 0·6 mg/day each week for 5 weeks and continued until week 16. Both groups received standardised nutritional and behavioural counselling **Comparison:** Matched placebo	**Outcomes:** **Primary outcome:** change in gastric emptying (delay relative to baseline) of solids T1/2 (time taken for half the radiolabelled meal to empty from the stomach), measured at 5 weeks and 16 weeks in all patients who received at least one dose of study drug, with missing data imputed.	No relevant sub-group analysis was undertaken

satiation, satiety, and weight in obese individuals over 16 weeks. **Study duration:** 26 weeks **Population:** Liraglutide group: 19 participants (Age: 42; Weight: 103.7 kg) Placebo group: 21 participants (Age: 37; Weight: 99.1 kg) Information on sex of participants not described.	**Inclusion criteria:** Overweight adults (BMI ≥27 kg/m²) with an obesity related comorbidity and adults with obesity (BMI >30 kg/m²), aged 18 to 65 years residing within 125 miles of the Mayo Clinic, Rochester, MN, USA, were recruited. Permitted concomitant medications during the study were the birth control pill, oestrogen and thyroxin replacement therapy, and any medication administered for comorbidities as long as they did not alter gastric emptying or accommodation or satiation. Specifically, statins for hyperlipidaemia, diuretics, β-adrenergic blockers, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin antagonists for hypertension, and metformin for type 2 diabetes or prediabetes were permissible **Exclusion criteria:** No unstable psychiatric or medical disease or treatment that could interfere with the study conduct or interpretation. Participants were excluded if they were taking resin sequestrants for hyperlipidaemia (which may reduce gastric emptying and appetite), α2-adrenergic agonists for hypertension, other GLP-1 receptor agonists (eg, exenatide) or amylin analogues (eg, pramlintide), which delay gastric emptying, were not permissible. Individuals with delayed gastric emptying of solids (>90th percentile according to sex) were excluded, since it was considered potentially dangerous to significantly increase	**Secondary outcome:** Weight loss at weeks 5 and 16, satiation (volume to fullness and maximum tolerated volume), satiety, and fasting and postprandial gastric volumes at 16 weeks	

	the delay in gastric emptying with a GLP-1 receptor agonist.		
Reference: Lean, M., et al. (2014) Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. International journal of obesity (2005), 38(5), 689–697. DOI: 10.1038/ijo.2013.149 **Study aim:** To evaluate routinely collected data on nausea and vomiting among individuals on liraglutide and their influence on tolerability and body weight. **Study duration:** 52 weeks **Population:** Liraglutide (1.2mg) group: 95 participants (Female sex: 77%; Age: 47.2; Weight: 96.2 kg) Liraglutide (1.8mg) group: 90 participants (Female sex: 76%; Age: 45.5; Weight: 98.0 kg) Liraglutide (2.4mg) group: 93 participants (Female sex: 76%; Age: 45.0; Weight: 98.4 kg) Liraglutide (3.0mg) group: 93 participants (Female sex: 75%; Age: 45.9; Weight: 97.6 kg) Orilstat group: 95 participants (Female sex: 77%; Age: 45.9; Weight: 96.0 kg) Placebo group= 98 participants (Female sex= 75%; Age: 45.9; Weight: 97.3 kg)	**Intervention:** Liraglutide doses of either 1.2, 1.8, 2.4 or 3.0 mg were administered once, starting with doses of 0.6 mg per day and increasing by weekly increments of 0.6 mg. During the run-in period (2 weeks) and throughout treatment, all participants received dietary counselling for a nutritionally balanced low-calorie diet (with about 30% of total caloric intake from fat, 20% from protein and 50% from carbohydrates), providing an energy deficit of approximately 500 kcal per day below the estimated 24-h energy requirements (calculated as basal metabolic rate physical activity level 1.3). Participants were also advised to maintain or increase physical activity. **Comparison:** Placebo or Orlistat capsules (3 x 120 mg per day) **Inclusion criteria:** Eligible participants were aged 18–65 years and were of stable weight, with body mass index (BMI) of 30–40 kg m 2 and fasting plasma glucose of o7 mmol l 1 (126 mg dl 1) at the start of the run-in period. **Exclusion criteria:** Type 1 or 2 diabetes mellitus or major medical conditions, had used approved weight-loss drugs within the previous 3 months, had received drug treatment known to induce weight gain or had received surgical obesity treatment	**Outcomes: Primary outcome:** The following information was recorded on the form: adverse-event diagnosis (if known, otherwise symptoms were listed), whether the event was serious or of special interest (requiring completion of a separate form), the date of onset, severity (mild, moderate or severe), outcome (recovered, recovering, recovered with sequelae, not recovered, fatal or unknown), causality in relation to the trial product (in the investigator's opinion) and whether any action regarding trial products was taken. **Other outcomes:** health-related QoL, body weight.	**No relevant sub-group analysis was undertaken**

Reference: Nexøe-Larsen, C., et al. (2018) Effects of liraglutide on gallbladder emptying: A randomized, placebo-controlled trial in adults with overweight or obesity. Diabetes, obesity & metabolism, 20(11), 2557–2564. DOI: 10.1111/dom.13420 **Study aim:** To conduct a single-centre, double-blind, 12-week trial comparing the effect of 0.6 mg liraglutide and steady-state liraglutide 3.0 mg with placebo on gallbladder emptying in adults with body mass index (BMI) ≥27 kg/m2 and without diabetes. **Study duration:** 12 weeks **Population:** Liraglutide group: 26 participants (Female sex: 13 (50%); Age: 47.6; Weight: 98.2 kg) Placebo group: 25 participants (Female sex: 13 (50%); Age: 47.5; Weight: 99.8 kg)	**Intervention:** Liraglutide once daily, starting at 0.6 mg and with 0.6-mg weekly increments to 3.0 mg Both groups received nutritional and physical activity counselling **Comparison:** Matched placebo **Inclusion criteria:** Men or women aged between 18 and 64 years (inclusive), with a body mass index (BMI) ≥27.0 kg/m2 , stable body weight (<3 kg self-reported change during the previous 90 days), and an ultrasound assessment of gallbladder volume of acceptable quality (investigator judgment) at screening were included in the trial. **Exclusion criteria:** Known or suspected hypersensitivity to trial product or related products Previous participation in this trial (defined as having signed informed consent) Participation in another clinical trial within 90 days before screening Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (intrauterine devices or hormonal contraception (oral contraceptive pills, implants, transdermal patches, vaginal rings or long-acting injections)	**Outcomes:** **Primary outcome:** The primary endpoint was GBEFmax after 12 weeks. **Secondary outcome:** Secondary endpoints related to gallbladder motility comprised: GBEFmax after the first 0.6-mg dose; fasting gallbladder volume; area under the GBEF–time curve 0 to 60 minutes after the start of the meal (GBEF AUC0-60 min); time to GBEFmax (tmax); and time from tmax to when the gallbladder had reverted to the fasting volume after the 0.6-mg dose and at steady-state after 12 weeks of treatment. **Other outcomes:** Other endpoints included change from week 0 to week 12 in body weight and secondary safety endpoints, comprising adverse events and changes from screening to week 12 in haematology, biochemistry, including fasting lipase and amylase, calcitonin, vital signs and physical examination.	**No relevant sub-group analysis was undertaken**

	History of gastrointestinal surgery or other medical procedure precluding gallbladder emptying assessment (appendectomy is allowed) or any significant digestive disease as per the judgement of the investigator Prior treatment with GLP-1RAs or participation in an organised weight reduction programme within 3 months before screening Any disorder which in the investigator's opinion might jeopardise participant safety or protocol compliance Diagnosis of type 1 or 2 diabetes mellitus Anticipated change in lifestyle (e.g. eating or exercise pattern other than the lifestyle intervention required by the protocol) during the trial Any laboratory safety parameter at screening outside the below extended laboratory ranges: • Albumin outside LNL -5% and UNL +5% • ALT outside LNL -100% and UNL +50% • Creatinine outside UNL +10% • Haemoglobin outside LNL -5% and UNL +10% • Leukocytes outside LNL -20% and UNL +20% • Thrombocytes outside LNL -15% and UNL +15% • Bilirubin (total) outside UNL +15%		

	• Amylase ≥ UNL +100% • Lipase ≥ UNL +100% • Calcitonin ≥50 ng/L Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as TSH <0.4 mIU/L or > 6 mIU/L Obesity induced by endocrinologic disorders (e.g. Cushing Syndrome) Blood draw >25 mL in the past month, or donation of blood or plasma >400 mL in 90 days before screening Use of any prescription or non-prescription medication, which could interfere with trial PK or PD results within 2 weeks prior to screening except for oral contraceptives, routine vitamins, occasional use of paracetamol, acetylsalicylic acid, or ibuprofen, as judged by the investigator or specifically: • Use of cholinergic antagonists such as atropine, including ophthalmic preparations • Use of herbal products and non-routine vitamins • Within 3 months prior to screening use of any pharmacotherapy that may cause weight gain, including systemic corticosteroids (except for a short course of treatment, i.e. 7-10 days), tricyclic antidepressants, atypical antipsychotic and mood stabilisers		

	• Within 3 months prior to screening use of statins, antihyperlipidaemics including fibrates or nicotinic acid and its derivates, and bile acid sequestrants • Within 3 months prior to screening use of pramlintide, orlistat, zonisamide, topiramate, phenteremine, lorcaserin, bupropion, naltrexone or other weight loss drugs • Co-treatment with antihypertensive drugs, unless treatment has been stable for ≥1 month prior to screening, in which case treatment should preferably remain unchanged during the trial Personal or family history of MTC or MEN type 2 History of pancreatitis (acute or chronic) or any gallbladder disease (including gallstones, gallbladder sludge, or polyps) History of major depressive disorder or other severe psychiatric disorders, e.g. schizophrenia or bipolar disorder within the last 2 years or lifetime history of suicide attempt Surgery scheduled for the trial duration period, except for minor, non-gastrointestinal surgical procedures at the discretion of the investigator Sitting systolic BP ≥160 mmHg or diastolic BP ≥ 100 mmHg or heart rate ≥ 90 beats/min		

	after resting for at least 5 minutes (if white-coat hypertension is suspected, one repeat measurement is allowed; last measure being conclusive and to be recorded in the case report form) Cancer (past or present, except basal cell skin cancer or squamous cell skin cancer), which in the investigator's opinion could interfere with the results of the trial Known or suspected alcohol abuse within 1 year from screening (defined as regular intake of more than 14 units weekly for men and 7 units weekly for women - one unit of alcohol equals about 300 mL of beer or lager, one glass (100 mL) of wine, or 25 mL spirits) or a positive result of an alcohol test Known or suspected drug/chemical substance abuse within 1 year from screening or a positive drug test result Smoking or use of nicotine products within the last three months prior to screening or a positive nicotine test Inability or unwillingness to perform self-injection at the screening visit (with a placebo test pen)		

	Mental incapacity, language barriers or unwillingness to comply with the requirements of the protocol, which may preclude adequate understanding or co-operation during the trial, as judged by the investigator Investigator, any sub-investigator, research assistant, pharmacist, trial coordinator, other staff, sponsor staff or relatives directly or indirectly involved in the conduct of the trial cannot participate in the trial Being from the same household as another participant		
Reference: O'Neil, P., et al. (2018) Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet (London, England), 392(10148), 637–649. DOI: 10.1016/S0140-6736(18)31773-2 **Study aim:** To evaluate the efficacy and safety of the glucagon-like peptide-1 (GLP-1) analogue semaglutide in comparison with liraglutide and a placebo in promoting weight loss. **Study duration:** 52 weeks	**Intervention:** Participants received semaglutide at one of five doses (0·05 mg, 0·1 mg, 0·2 mg, 0·3 mg, or 0·4 mg) or liraglutide (3·0 mg) as once-daily subcutaneous injections. Semaglutide was initiated at 0·05 mg per day and incrementally escalated to the next dosing level every 4 weeks until reaching the final dose. Two additional fast-escalation groups of semaglutide (0·3 mg and 0·4 mg) were escalated every 2 weeks, which was exploratory. Liraglutide was initiated at 0·6 mg per day and escalated by 0·6 mg per week to 3·0 mg. **Comparison: Matched placebo**	**Outcomes: Primary outcome:** The primary endpoint was the relative percentage change in bodyweight from baseline to week 52. Prespecified secondary endpoints were categorical weight loss of 5% or more or 10% or more of baseline, absolute change in weight, waist circumference, waist-to-hip ratio, and BMI; change in glucose metabolism (glycated haemoglobin A1c, fasting glucose), cardiovascular risk factors (blood pressure, lipids, C-reactive protein); changes in SF-36 scores; compliance with nutritional counselling; proportions of participants with changes in antihypertensive or lipid-lowering	**No relevant sub-group analysis was undertaken**

Population: Semaglutide groups: 718 participants (Female sex: 66-67 (64-65%); Age: 44-48; Weight: 108.1-114.5 kg) Liraglutide group: 103 participants (Female sex: 67 (65%); Age: 49; Weight: 108.7kg) Placebo pooled: 136 participants (Female sex: 88 (65%); Age: 46; Weight: 114.2 kg)	**Inclusion criteria:** Male or female, age ≥ 18 years at the time of signing informed consent. Body Mass Index (BMI) ≥ 30.0 kg/m2 at the screening visit. Stable body weight i.e. less than 5 kg self-reported change within 90 days before screening. At least one unsuccessful weight loss attempt per investigator judgement. **Exclusion criteria:** A HbA1c ≥ 6.5% at screening or diagnosed with type 1 or type 2 diabetes mellitus Hypothyroidism/hyperthyroidism defined as TSH > 6 mIU/L or < 0.4 mIU/L Treatment with glucose lowering agent(s) within 90 days before screening Screening calcitonin ≥ 50 ng/L (pg/mL) Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 History of pancreatitis (acute or chronic) Obesity induced by an endocrinologic disorder (e.g. Cushing Syndrome) Treatment with any medication within 90 days before screening that based on investigator's opinion may cause significant weight change Diet attempts using herbal supplements or over-the-counter medications within 90 days before screening	medications; and the number of adverse events. Categorical weight loss of 15% or more or 20% or more of baseline was assessed post hoc.	

	Participation in an organised weight reduction program (e.g. WeightWatchers®) within 90 days before screening Treatment with orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion, naltrexone, GLP-1 RAs alone or in combination prescribed for weight loss or any other medication that could promote weight loss in the opinion of the investigator within 90 days before screening Previous surgical treatment for obesity (liposuction and/or abdominoplasty is allowed if performed > 1 year before screening) History of major depressive disorder within 2 years before randomisation History of other severe psychiatric disorders (e.g. schizophrenia, bipolar disorder) A Patient Health Questionaire-9 (PHQ-9) score of ≥ 15 at screening or randomisation Any lifetime history of a suicidal attempt Any suicidal behaviour within 30 days before randomisation Any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or randomisation		

	Surgery scheduled for the trial duration period, except for minor surgical procedures, in the opinion of the investigator Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening History or presence of malignant neoplasms within the last 5 years before screening (except basal and squamous cell skin cancer, polyps and in-situ carcinomas) Known or suspected abuse of alcohol or narcotics Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures Known or suspected hypersensitivity to trial product(s) or related products Previous participation in this trial. Participation is defined as signed informed consent Subjects from the same household participating in the trial Participation in another clinical trial within 90 days before screening Any condition which, in the investigator's opinion might jeopardise subject's safety or compliance with the protocol		

	Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice)		
Reference: Tronieri, J., et al. (2020) Effects of liraglutide on appetite, food preoccupation, and food liking: results of a randomized controlled trial. International journal of obesity (2005), 44(2), 353–361. DOI: 10.1038/s41366-019-0348-6 **Study aim:** To evaluate the long-term appetitive effects of liraglutide 3.0 mg. **Study duration:** 52 weeks **Population:** IBT-alone group: 36 participants (Female sex: 27 (75.0%); Age: 47.4) IBT-liraglutide group: 37 participants (Female sex: 31 (83.8%); Age: 44.3) Multicomponent group: 40 participants (Female sex: 28 (70.0%); Age: 48.4) Information on mean bodyweight not described	**Intervention:** Intensive behavioural Therapy (IBT) with liraglutide 3.0 mg/day IBT-liraglutide combined with a 12-week meal replacement diet **Comparison:** IBT-alone **Inclusion criteria:** Participants were aged 21–70 years, had a body mass index (BMI) ≥30 and ≤55 kg/m², and had no serious medical or psychological conditions (e.g., diabetes mellitus, recent cardiovascular disease, current major depressive disorder) or contraindications to the use of liraglutide (e.g., personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome). **Exclusion criteria:** personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome; types 1 or 2 diabetes; renal, hepatic, or recent cardiovascular disease; blood pressure ≥160/100 mm Hg; medications that substantially affect body weight (e.g., corticosteroids); substance abuse; current major depression, suicidal ideation, or history of suicide attempts; bariatric surgery; use of weight loss medications or products, as well as	**Outcomes:** **Primary outcome:** Participants rated their hunger, fullness after meals, liking of meals, and food preoccupation (all as experienced over the past week).	**No relevant sub-group analysis was undertaken**

	weight loss ≥ 4.5 kg in past 3 months; and pregnancy/lactation. Anti-depressant medications were permitted, except for those associated with marked weight gain (e.g., paroxetine) or loss (e.g., bupropion		
Reference: Wadden, T., et al. (2013) Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. International journal of obesity (2005), 37(11), 1443–1451. DOI: 10.1038/ijo.2013.120 **Study aim:** The study assessed the efficacy of liraglutide in maintaining weight loss achieved with a low-calorie diet (LCD). **Study duration:** 56 weeks **Population:** Liraglutide group: 207 participants (Female sex: 84%; Age: 45.9; Weight= 100.4kg) Placebo group: 206 participants (Female sex: 79%; Age: 46.5; Weight: 98.7 kg)	**Intervention:** To qualify for randomization, participants had to lose ⩾ 5% of initial body weight during a variable-length (4–12 weeks) LCD run-in period. During this period, participants were prescribed 1200–1400 kcal per day, which included the daily use of up to three liquid meal replacements (for example, Boost, Ensure and Glucerna). To facilitate dietary adherence, participants met face-to-face, every other week with a nutritionist and had telephone calls on alternate weeks. They were encouraged to exercise regularly (recommended 150 min per week of brisk walking) As soon as individuals lost ⩾ 5% of screening body weight, they were randomly assigned 1:1 to receive once-daily liraglutide 3.0 mg. Dosing was initiated at 0.6 mg per day, increasing weekly by 0.6 mg per day throughout a 4-week dose escalation (maximum 5 weeks) to the 3.0 mg dose. At randomization, participants were prescribed a 500 kcal per day deficit diet, based on estimated 24-h energy expenditure. Participants were instructed to continue the recommended physical activity. Face-to-face	**Outcomes:** **Primary outcome:** (1) mean percentage change in fasting body weight from randomization; (2) the proportion of individuals that maintained the X5% reduction in fasting body weight achieved during LCD run-in; and (3) the proportion that lost X5% of fasting body weight after randomization. **Secondary outcome:** weight change (kg) from randomization to week 56; the proportion of participants that lost 410% of fasting randomization weight; the proportion that maintained 450 and 475% of fasting weight loss during run-in; and fasting weight change (kg) from randomization to week 68. Additional end points included CVD risk factors and glycemic control parameters. (After the study began, two modifications to the trial0 s end points were made to comply with requests for changes to the investigational new drug application	**No relevant sub-group analysis was undertaken**

	lifestyle counseling visits (15–20 min) were provided at weeks 0, 1, 2, 3 and 4 (during drug escalation) and weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46 and 52, for a total of 17 visits over 56 weeks. **Comparison:** Matched placebo **Inclusion criteria:** Eligible participants included men and women aged ⩾ 18 years, with stable body weight and body mass index (BMI) ⩾ 30 kg m 2 or ⩾ 27 kg m^2 with comorbidities of treated or untreated dyslipidemia and/or treated or untreated hypertension **Exclusion criteria:** Any clinically significant disease which in the Investigators' opinion could interfere with the safety of trial participants or with the results of the trial Diagnosis of type 1 or type 2 diabetes per the judgment of the Investigator FPG ³ 126 mgdl-1 (7 mmoll-1) at start of run-in period Previous treatment with GLP-1 receptor agonists (including liraglutide or exenatide) within the last 3 months Visit 1 thyroid-stimulatory hormone outside of the range of 0.4-6.0 mIUl-1. History of chronic pancreatitis or idiopathic acute pancreatitis Obesity induced by other endocrinological disorders (e.g., Cushing syndrome)	made by the United States Food and Drug Administration. The end point 'proportion of participants who lost ⩾ 5% of randomization weight' was added and the treatment phase was increased to 56 weeks. In addition, the secondary end point 'the proportion of participants that lost 410% of randomization weight' had originally been 'the proportion that lost ⩾ 10% of randomization weight' but was changed to comply with the European Medicines Agency guidance	

	Current or history of treatment with medications that may cause significant weight gain within 3 months prior to screening visit, including systemic corticosteroids (except for a short course of treatment, i.e., 7-10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilisers (e.g., imipramine, amitriptyline, mirtazapin, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium) Current participation in an organized diet reduction program (or within the last 3 months) Currently using or have used within the last 3 months before screening for this trial: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phentermine, or metformin (either by prescription or as part of a clinical trial) Diet attempts using herbal supplements or over-the-counter medications within 3 months before screening for this trial Participation in a clinical trial of weight control within the last 3 months prior to screening for this trial Previous surgical treatment for obesity (excluding liposuction if performed >1 year before study entry) History of major depressive disorder or a PHQ-9 >15 within the last 2 years (completed at		

	visit 1) or history of other severe psychiatric disorders (e.g., schizophrenia or bipolar disorder) or diagnosis of an eating disorder such as restrained eating, binge eating, or bulimia (based on Questionnaire for Diagnosing Binge Eating Disorder and Bulimia Nervosa completed at visit 1) Participants with a lifetime history of a suicide attempt or history of any suicidal behavior within the past month before entry into the trial Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the Investigator Impaired liver function, defined as screening aspartate aminotransferase or alanine aminotransferase ³ 2.5 times upper normal range (one re-test analyzed at the central laboratory within 1 week is permitted with the last sample being conclusive) Impaired renal function defined as serum creatinine ³152 mmoll-1 (³ 1.72 mgdl-1) (one retest within one week through the central laboratory is permitted with the result of the last sample conclusive) Known clinically significant active cardiovascular disease, including history of unstable angina, acute coronary event, other significant cardiac events (including history of arrhythmias, myocardial infarction (MI), or conduction delays on electrocardiogram [ECG]), or cerebral stroke within the past 6 months and/or heart failure (New York Heart		

	Association [NYHA] Class III or IV) at the discretion of the Investigator Uncontrolled treated/untreated hypertension (systolic blood pressure ³160 mmHg and/or diastolic blood pressure ³100 mmHg). If white-coat hypertension is suspected at the screening visit a repeated measurement at run-in prior to other trial-related activities is allowed Cancer (past or present, except basal cell skin cancer or squamous cell skin cancer), which in the Investigator's opinion could interfere with the results of the trial Known or suspected allergy to trial product(s) or related products Previous participation in the run-in or randomized phase of this trial. Re-screening is allowed once within the limit of the recruitment period Known or suspected abuse of alcohol or narcotics Language barrier, mental incapacity, unwillingness or ability to understand and being able to complete the mental health questionnaire in the provided language Participants from the same household participating in the trial Women of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate		

	contraceptive methods (abstinence and/or the following methods: diaphragm with spermicide, condom with spermicide (by male partner), intrauterine device, sponge, spermicide, Norplant, Depo-Provera or oral contraceptives) Positive screening for hepatitis B antigen, hepatitis C antibodies, positive human immunodeficiency virus (HIV) antibodies The receipt of any investigational drug within four weeks prior to screening for this trial.		
Reference: Wadden, T., et al. (2019). Intensive Behavioral Therapy for Obesity Combined with Liraglutide 3.0 mg: A Randomized Controlled Trial. Obesity (Silver Spring, Md.), 27(1), 75–86. DOI: 10.1002/oby.22359 **Study aim:** This study assessed whether the provision of a portion-controlled diet would increase weight loss further when added to Intensive Behavioural Therapy plus liraglutide. **Study duration:** 52 weeks **Population:** IBT-alone group: 50 participants (Female sex: 39 (78%); Age: 49.5; Weight: 105.8 kg) IBT-liraglutide group: 50 participants (Female sex: 42 (84%); Age: 45.2; Weight: 107.8 kg)	**Intervention:** IBT-Liraglutide: the medication was initiated at 0.6 mg/day for 1 week and increased by 0.6 mg/day in weekly intervals until 3.0 mg/day was achieved. Multi-component: These participants received the same treatment as those in IBTliraglutide, with one exception. At week 4, they were prescribed, for 12 weeks, a 1000–1200 kcal/day diet that provided four servings daily of a liquid shake and an evening meal of a frozen food entrée (250–300 kcal), with a serving of fruit and salad **Comparison:** IBT-alone **Inclusion criteria:** Eligibility criteria included: ages 21–70 years; body mass index (BMI) of 30–55 kg/m2; prior lifetime weight-loss effort with diet and exercise (before considering anti-obesity medication); and agreement to participate for 1 year	Outcomes **Primary outcome:** Mean percentage reduction in baseline body weight at week 52. **Other outcomes:** Waist circumference and blood pressure, as well as fasting glucose, insulin, triglycerides, C-reactive protein, and lipids. Quality of life and symptoms of depression.	**No relevant sub-group analysis was undertaken**

IBT-liraglutide combined with a 12-week meal replacement diet: 50 participants (Female sex: 38 (76%); Age: 48.0; Weight: 117.7 kg)	**Exclusion criteria:** Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome; types 1 or 2 diabetes; renal, hepatic, or recent cardiovascular disease; blood pressure ≥160/100 mm Hg; medications that substantially affect body weight (e.g., corticosteroids); substance abuse; current major depression, suicidal ideation, or history of suicide attempts; bariatric surgery; use of weight loss medications or products, as well as weight loss ≥ 4.5 kg in past 3 months; and pregnancy/lactation. Anti-depressant medications were permitted, except for those associated with marked weight gain (e.g., paroxetine) or loss (e.g., bupropion.		
Reference: Wadden, T., et al. (2020) Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT Randomized Controlled Trial. Obesity (Silver Spring, Md.), 28(3), 529–536. DOI: 10.1002/oby.22726 **Study aim:** The primary objective of the trial was to compare the effect of liraglutide 3.0 mg versus placebo, as an adjunct to CMS-based IBT, on weight loss in individuals with obesity. Secondary objectives were to investigate the effects of these interventions on cardiometabolic and other efficacy end points, as well as to evaluate the safety and tolerability of liraglutide 3.0 mg versus placebo as an adjunct to CMS-based IBT. **Study duration:** 56 weeks	**Intervention:** Liraglutide-IBT **Comparison:** Placebo-IBT **Inclusion criteria:** Eligible participants were aged ≥18 years, with stable body weight (maximum 5-kg self-reported weight change within 90 days before screening) and BMI≥30 kg/m2. **Exclusion criteria:** glycated hemoglobin (HbA1c)≥6.5%, type 1 or 2 diabetes, use of medications (in the past 90 days) known to induce significant weight loss or gain, inadequately treated hypertension, pregnancy or breastfeeding, history of cardiovascular disease, severe congestive heart failure, second-degree or greater heart block, medullary thyroid carcinoma, multiple endocrine neoplasia type 2, pancreatitis, major depressive disorder within the past 2 years,	**Outcomes:** **Primary outcome:** change in body weight (percent) from baseline to week 56 and the proportion of participants who lost ≥5% of baseline body weight. **Secondary outcome:** the proportion of participants who lost >10% or >15% of baseline body weight at week 56 and the proportion who lost ≥4% of baseline body weight at week 16. Changes from baseline to week 56 in waist circumference and in self-reported quality of life related to physical function, physical functioning score. Change in objective physical capacity was	**No relevant sub-group analysis was undertaken**

Population: Liraglutide-IBT: 142 participants (Female sex: 119 (83.8%); Age: 45.4; Weight: 108.5 kg) Placebo-IBT: 140 participants (Female sex: 116 (82.9%); Age: 49.0; Weight: 106.7 kg)	history of suicide attempt, or malignancy within the past 5 years.	measured by a 6-minute walk test (6MWT). Supportive secondary end points included change from baseline to week 56 in cardiometabolic parameters (HbA1c, fasting plasma glucose, systolic and diastolic blood pressure, and lipids). Changes from baseline to week 56 were also evaluated for other domains of health-related quality of life. Safety was assessed by adverse events, physical examination, resting pulse, electrocardiogram, and laboratory measurements.	

Data extraction table for studies investigating the effectiveness of semaglutide x 11			
Reference and trial details	Trial details	Outcomes	Sub-group analysis
Reference: Wilding, J., et al. (2022) Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes, obesity & metabolism, 24(8), 1553–1564. DOI: 10.1111/dom.14725 **Study aim:** To explore changes in body weight and cardiometabolic risk factors after	**Intervention:** Once weekly semaglutide 2.4 mg (n = 1306), plus lifestyle intervention. The lifestyle intervention consisted of counselling every 4 weeks on diet (500 kcal deficit per day relative to total estimated energy expenditure at randomization) and physical activity (150 minutes per week). Semaglutide was initiated at 0.25 mg, with escalation every 4 weeks until the 2.4 mg target dose was reached.	**Outcomes:** **Primary outcome:** The extension addressed two exploratory objectives: (1) to examine the change in body weight and cardiometabolic risk factors in participants who completed treatment in the main phase	**No relevant sub-group analysis was undertaken**

treatment withdrawal in the STEP 1 trial extension. **Study duration:** 68 weeks treatment period, followed by 52 week off-treatment follow-up period. **Population:** Extension analyses set included 327 participants: Semaglutide group • Female sex: 152 (66.7) • Age: 48 • Weight: 105.6 kg Placebo group Female sex= 67 (67.7%) Age= 50 Weight= 105.4 kg Full analysis set included 1961 participants. Semaglutide group • Female sex: 955 (73.1%) • Age: 46 • Weight: 105.4kg Placebo group Female sex= 498 (76.0%) Age=47 Weight= 105.2 kg	**Comparison:** Placebo plus lifestyle intervention **Inclusion criteria:** Participants were adults (aged ≥ 18 years) with a body mass index (BMI) of 30 kg/m2 or higher, or of 27 kg/m2 or higher with at least one weight-related co-morbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease), and a history of at least one self-reported unsuccessful dietary effort to lose weight. **Exclusion criteria:** Diabetes, a glycated hemoglobin level of 48 mmol per mole (6.5%) or greater, a history of chronic pancreatitis, acute pancreatitis within 180 days before enrollment, previous surgical obesity treatment, and use of antiobesity medication within 90 days before enrollment	and were followed during the off-treatment period; and (2) to evaluate the consistency of the 68-week treatment effect of semaglutide (relative to placebo) in participants in the main phase and extension phase. Endpoints included changes (from week 68 to week 120 for the first objective; from week 0 to week 68 for the second objective) in body weight (% and kg), BMI, systolic and diastolic blood pressure (SBP and DBP), CRP, HbA1c and lipids, including triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol and free fatty acids (the latter for the second exploratory objective only, because of different fasting conditions in the main and extension phases). HbA1c was also used to determine glycaemic category (normoglycaemia, prediabetes or diabetes, as per American Diabetes Association HbA1c criteria21) and changes in the proportion of participants in each category were assessed.	

		Post hoc analyses explored changes in body weight from baseline to week 120 and in a variety of participant subgroups (from baseline to week 68 and week 120, and from week 68 to week 120), and the proportion of participants with 5% or higher weight loss from baseline at week 120.	
Reference: Rubino, D., et al. (2021) Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA, 325(14), 1414–1425. DOI: 10.1001/jama.2021.3224 **Study aim:** To compare continued once-weekly treatment with subcutaneous semaglutide, 2.4mg, with switch to placebo for weight maintenance (both with lifestyle intervention) in adults with overweight or obesity after a 20-week run-in with subcutaneous semaglutide titrated to 2.4mg weekly. **Study duration:** Weeks 0-20: run-in period where all participants were given semaglutide dose escalated. Weeks 20-68: participants randomised to either continue semaglutide or switch to placebo **Population:** Semaglutide arm: 535 participants (Female sex: 429 (80.2%); Age: 47; Weight= 96.5 kg)	**Intervention:** All participants initially received open-label once-weekly subcutaneous semaglutide, 0.25mg, increased every 4 weeks to the maintenance dose of 2.4mg once weekly by week 16, and continued to week 20 (run-in period). Participants receiving semaglutide, 2.4 mg, at week 20 were randomized in a 2:1 ratio using a blocking schema (block size of 6) in a double-blind manner, via an interactive web-based response system, to continue this treatment or switch to matching placebo for 48 weeks (weeks 20-68; randomized period), with a 7-week follow-up. Participants unable to tolerate semaglutide, 2.4mg/wk, during the randomized period were permitted to receive 1.7mg/wkat the treating investigator's discretion and were recommended to make at least 1 attempt to re-escalate. All participants received a lifestyle intervention from week 0 to week 68, including monthly counseling by qualified healthcare professionals, in-person or by telephone.	**Outcomes:** **Primary outcome:** The primary end point was percentage change from baseline in body weight at week 68. **Secondary outcome:** Confirmatory secondary end points (in hierarchical testing order)were change fromweek 20 to week 68 in waist circumference, systolic blood pressure, and physical functioning score on the Short Form 36 Version 2 Health Survey, Acute Version. Supportive secondary end points were changes from week 20 to week 68 in absolute body weight (in kilograms), haemoglobin A1c, fasting plasma glucose, fasting serum insulin, diastolic blood pressure, lipid levels, and the SF 36	**No relevant sub-group analysis was undertaken**

Placebo arm: 268 participants (Female sex: 205 (76.5%); Age: 46; Weight: 95.4 kg)	Participants were prescribed a reduced-calorie diet (500-kcal/d deficit relative to estimated energy expenditure calculated atweek0) and increased physical activity (150 min/wk), recorded daily by participants (using paper diaries, apps, or other tools) and reviewed during counseling visits. Comparison: Matched placebo given between weeks 20-68. Inclusion criteria: Adults (≥18 years old) with at least 1 self-reported unsuccessful dietary effort to lose weight and with a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or higher or a BMI of 27 or higher with at least 1 treated or untreated weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease; type 2 diabetes was excluded) were enrolled) Exclusion criteria: Participants were excluded from the trial if any of the following criteria applied: Glycemia-Related: - Hemoglobin A1c (HbA1c) ≥6.5% (48 mmol/mol) as measured by the central laboratory at screening. - History of type 1 or type 2 diabetes (T1/2D). - Treatment with glucose-lowering agent(s) within 90 days before screening. Obesity-Related: - A self-reported change in body weight >5 kg (11 lb) within 90 days before	physical and mental component summary scores (other than physical functioning, changes in domain scores are not reported); whether participants achieved the SF-36 physical functioning responder threshold (data not reported) and gained weight from week 20 to week 68; and total overall and categorical weight loss from week 0 to week 68. Other outcomes: Exploratory end points included changes in antihypertensive and lipid-lowering medication use.	

	screening irrespective of medical records. - Treatment with any medication for the indication of obesity within the past 90 days before screening. - Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening; (2) lap banding, if the band has been removed >1 year before screening; (3) intragastric balloon, if the balloon has been removed >1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening. - Uncontrolled thyroid disease, defined as thyroid stimulating hormone >6.0 mIU/L or <0.35 mIU/L as measured by the central laboratory at screening. Mental Health - History of major depressive disorder within 2 years before screening. - Diagnosis of other severe psychiatric disorder (eg, schizophrenia, bipolar disorder). - A Patient Health Questionnaire-9 score ≥15 at screening. - A lifetime history of suicidal attempt. - Suicidal behavior within 30 days before screening. - Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale within the past 30 days before screening.		

	General Safety - Presence of acute pancreatitis within the past 180 days prior to the day of screening. - History or presence of chronic pancreatitis. - Calcitonin ≥100 ng/L as measured by the central laboratory at screening. - Personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma - Renal impairment measured as estimated glomerular filtration rate value of <15 ml/min/1.73 m2 as defined by Kidney Disease: Improving Global Outcomes 20121 by the central laboratory at screening. - History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed. - Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischemic attack within the past 60 days prior to screening. - Participant classified as being in New York Heart Association Class IV. - Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator. - Known or suspected abuse of alcohol or recreational drugs. - Known or suspected hypersensitivity to trial product(s) or related products.		

	- Previous participation in this trial. Participation is defined as signed informed consent. - Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening. - Other individuals from the same household participating in any semaglutide or liraglutide trial. - Female who is pregnant, breast-feeding, or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method. - Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the participant's safety or compliance with the protocol. The criteria were assessed at the investigator's discretion unless otherwise stated		
Reference: Garvey, W., et al. (2022) Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nature medicine, 28(10), 2083–2091. DOI: 10.1038/s41591-022-02026-4 **Study aim:** To assess the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo (both plus behavioral intervention) for long-term treatment of adults with obesity, or overweight with at least one weight-related comorbidity, without diabetes. **Study duration:** 104 weeks	**Intervention:** Participants received subcutaneous semaglutide 2.4 mg or placebo once-weekly for 104 weeks, in addition to standard behavioral intervention, followed by 7 weeks without treatment. Semaglutide was initiated at 0.25 mg per week for the first 4 weeks via a pre-filled pen injector, escalating in a fixed-dose regimen every 4 weeks to reach the maintenance dose of 2.4 mg by week 16 (lower maintenance doses were permitted if participants were unable to tolerate 2.4 mg).	**Outcomes:** **Primary outcome:** Co-primary endpoints were percentage change in body weight from baseline to week 104 and achievement of weight loss of at least 5% of baseline weight at week 104. These were tested first in the statistical testing hierarchy, followed by the confirmatory secondary endpoints, which were tested in the following order: achievement of weight loss of at	**No relevant sub-group analysis was undertaken**

Population: Semaglutide group: 148 participants (Female sex: 123 (80.9%); Age: 47.3; Weight: 105.6 kg) Placebo group: 134 participants (Female sex: 113 (74.3%); Age: 47.4; Weight: 106.5 kg)	Behavioral intervention consisted of counseling by a dietitian or similarly qualified healthcare professional every 4 weeks via in-person visits or telephone on adherence to a reduced-calorie diet (500 kcal deficit a day relative to the energy expenditure estimated at **Comparison:** placebo **Inclusion criteria:** Male or female, aged ≥18 years at the time of signing informed consent. BMI ≥ 30.0 kg m–2 or ≥27.0 kg m–2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease. History of at least one self-reported unsuccessful dietary effort to lose body weight. **Exclusion criteria:** Glycemia-related: - HbA1c ≥ 48 mmol mol–1 (6.5%) as measured by the central laboratory at screening. - History of type 1 or type 2 diabetes. - Treatment with glucose-lowering agent(s) within 90 days before screening. Obesity-related - A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records.	least 10% or 15% at week 104; and change from baseline to week 104 in waist circumference and systolic blood pressure. **Secondary outcome:** Supportive secondary endpoints were not included in the statistical testing hierarchy and were: achievement of weight loss of ≥20% at week 104; change from baseline to week 104 in body weight (in kg), BMI, HbA1c, fasting plasma glucose, fasting serum insulin, diastolic blood pressure, lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, free fatty acids and triglycerides) and C-reactive protein; change from baseline to week 52 in body weight (percentage change and kg change), BMI and waist circumference; and achievement of weight loss of ≥5%, ≥10%, ≥15% and ≥20% at week 52. **Other outcomes:** Exploratory endpoints reported herein include change from baseline to week 104 in glycemic category, antihypertensive medication use and lipid-lowering medication use. Glycemic category	

	- Treatment with any medication for the indication of obesity within the past 90 days before screening. - Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening; (2) lap banding, if the band had been removed >1 year before screening; (3) intragastric balloon, if the balloon had been removed >1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve had been removed >1 year before screening. - Uncontrolled thyroid disease, defined as thyroid-stimulating hormone >6.0 mIU l–1 or <0.4 mIU l–1 as measured by the central laboratory at screening. Mental health - History of major depressive disorder within 2 years before screening. - Diagnosis of other severe psychiatric disorder (for example, schizophrenia, bipolar disorder). - A Patient Health Questionnaire-9 score of ≥15 at screening. - A lifetime history of a suicidal attempt. - Suicidal behavior within 30 days before screening. - Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale within the past 30 days before screening. General safety	(normoglycemia, prediabetes or type 2 diabetes) was determined by investigators on the basis of available information (for example, medical records, concomitant medication, and blood glucose variables) and in accordance with American Diabetes Association criteria, which for prediabetes includes fasting plasma glucose levels of 100 mg dl–1 (5.6 mmol l–1) to 125 mg dl–1 (6.9 mmol l–1) or HbA1c levels of 5.7–6.4% (39–47 mmol l–1), and for type 2 diabetes includes fasting plasma glucose levels of ≥126 mg dl–1 (7.0 mmol l–1) or HbA1c levels ≥6.5% (48 mmol l–1). The allowance for investigators to use all available information (for example, concomitant medication) to assess glycemic category was primarily included to account for scenarios in which glucose-lowering medications were initiated during the trial that would confound glycemic category assessment if based purely on fasting plasma glucose or HbA1c levels (for example, if a patient developed diabetes during the study and received a glucose-lowering drug that resulted in their glucose level being below	

	- Presence of acute pancreatitis within the past 180 days before the day of screening. - History or presence of chronic pancreatitis. - Calcitonin ≥100 ng l–1 as measured by the central laboratory at screening. - Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. - Renal impairment measured as estimated glomerular filtration rate value of <15 ml min 1.73 m–2 as defined by KDIGO 2012 (ref. 30) by the central laboratory at screening. - History of malignant neoplasms within the past 5 years before screening. Basal and squamous cell skin cancer and any carcinoma in situ were allowed. - Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischemic attack within the past 60 days before screening. - Participant classified as being in New York Heart Association Class IV. - Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator. - Known or suspected abuse of alcohol or recreational drugs. - Known or suspected hypersensitivity to trial product(s) or related products. - Previous participation in the trial. Participation was defined as signed informed consent.	the American Diabetes Association threshold for type 2 diabetes diagnosis). Additional exploratory endpoints for which data are not reported were: permanent discontinuation of trial product between baseline and week 104; time to permanent discontinuation of trial product; and Control of Eating Questionnaire scores from the four domains and 19 individual items (applicable for United States and Canada only). Safety endpoints included the number of treatment-emergent adverse events and serious adverse events, assessed between baseline and week 111; and change from baseline to week 104 in pulse, amylase, lipase and calcitonin. An independent external event adjudication committee reviewed cardiovascular events, acute pancreatitis and deaths.	

	- Participation in another clinical trial within 90 days before screening. - Other person(s) from the same household participating in any semaglutide trial. - Female who was pregnant, breast-feeding, or intended to become pregnant, or was of child-bearing potential and not using a highly effective contraceptive method. - Any disorder, unwillingness or inability not covered by any of the other exclusion criteria which, in the investigator's opinion, might have jeopardized the participant's safety or compliance with the protocol.		
Reference: Rubino, D. et al. (2022) Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA, 327(2), 138–150. DOI: 10.1001/jama.2021.23619 **Study aim:** To compare the efficacy and adverse event profiles of once-weekly subcutaneous semaglutide, 2.4 mg, vs once-daily subcutaneous liraglutide, 3.0 mg (both with diet and physical activity), in people with overweight or obesity. **Study duration:** 68 weeks **Population:** Semaglutide group: 126 participants (Female sex: 102 (81.0%); Age: 48; Weight: 102.5 kg)	**Intervention:** Once-weekly subcutaneous semaglutide, 2.4mg, or once-daily subcutaneous liraglutide, 3.0 mg **Comparison:** Matched placebo **Inclusion criteria:** Adults (≥18 years old) with 1 or more self-reported unsuccessful dietary weight loss efforts and a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 30 or greater or 27 or greater with 1 or more weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). **Exclusion criteria:** Subjects are excluded from the trial if any of the following criteria apply: Glyceamia related:	**Outcomes: Primary outcome:** The primary end point was percentage change from baseline in body weight at week 68. **Secondary outcome:** Confirmatory secondary end points (hierarchical testing order) were achievement of weight loss of 10% or more, 15% or more, and 20% or more by week 68. Primary and confirmatory secondary end points were assessed for semaglutide vs liraglutide; comparisons vs pooled placebo were supportive secondary end points.	**No relevant sub-group analysis was undertaken**

Liraglutide group: 127 participants (Female sex: 97 (76.4%); Age: 49; Weight: 103.7 kg) Placebo group: 85 participants (Female sex: 66 (77.6%); Age: 51; Weight: 108.8 kg)	- HbA1c ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening - History of type 1 or type 2 diabetes mellitus - Treatment with glucose-lowering agent(s) within 90 days before screening Obesity related: - A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records - Treatment with any medication for the indication of obesity within the past 90 days before screening - Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening, (2) lap banding, if the band has been removed > 1 year before screening, (3) intragastric balloon, if the balloon has been removed > 1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year before screening - Uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) > 6.0 mIU/L or < 0.35 mIU/L as measured by the central laboratory at screening Mental health: - History of major depressive disorder within 2 years before screening - Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)	Other supportive secondary end points were changes from baseline in absolute bodyweight waist circumference, blood pressure, fasting lipid concentrations, C-reactive protein, HbA1c, fasting plasma glucose, fasting serum insulin, and glycemic status, and permanent trial product discontinuations, all assessed to week 68 for semaglutide vs liraglutide. Change in glycemic status data will be reported separately. Achievement of 5% ormore weight loss was a prespecified exploratory end point. Separate placebo group body weight changes and changes in pulse were assessed post hoc. Adverse events were assessed at week 75.	

	- A Patient Health Questionnaire-9 (PHQ-9) score ≥ 15 at screening - A lifetime history of suicidal attempt - Suicidal behaviour within 30 days before screening - Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening General Safety: - Presence of acute pancreatitis within the past 180 days prior to the day of screening - History or presence of chronic pancreatitis - Calcitonin ≥ 100 ng/L as measured by the central laboratory at screening - Personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma - Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <15 ml/min/1.73 m2 as defined by KDIGO 201245 by the central laboratory at screening - History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed - Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening.		

	- Subject presently classified as being in New York Heart Association (NYHA) Class IV - Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator - Known or suspected abuse of alcohol or recreational drugs - Known or suspected hypersensitivity to trial product(s) or related products. - Previous participation in this trial. Participation is defined as signed informed consent. - Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening. - Other subject(s) from the same household participating in any semaglutide or liraglutide trial - Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method - Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol		
Reference: Wadden, T., et al. (2021) Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial.	**Intervention:** Once weekly subcutaneous semaglutide, 2.4 mg, or visually identical placebo for 68 weeks.	Outcomes **Primary outcome:** The co–primary end points, in the order planned for sequential hierarchic testing, were the	No relevant sub-group analysis was undertaken

JAMA, 325(14), 1403–1413. DOI: 10.1001/jama.2021.1831 **Study aim:** To compare the effects of once-weekly subcutaneous semaglutide, 2.4 mg vs placebo for weight management as an adjunct to intensive behavioral therapy with initial low-calorie diet in adults with overweight or obesity. **Study duration:** 68 weeks **Population:** Semaglutide group: 407 participants (Female sex: 315 (77.4%); Age: 46; Weight: 106.9 kg) Placebo group: 204 participants (Female sex: 180 (88.2%); Age: 46; Weight: 103.7 kg)	Semaglutide was initiated at 0.25 mg, with dose escalation every 4 weeks until the target dose of 2.4 mg/wk was reached at week 16. For the first 8 weeks after randomization, participants received a low-calorie diet (1000-1200 kcal/d) provided as meal replacements (eg, liquid shakes, meal bars, portion controlled meals [provided by Nutrisystem, supplied by the sponsor]). Participants subsequently transitioned to a hypocaloric diet (1200-1800 kcal/d) of conventional food for the remainder of the 68 weeks, with prescribed calorie intake based on randomization body weight. At randomization, participants were prescribed 100 minutes of physical activity per week (spread across 4-5 days), which increased by 25 minutes every 4 weeks, to reach 200min/wk. During the 68 weeks, participants were provided with 30 individual intensive behavioral therapy visits with a registered dietitian, who instructed them in diet, physical activity and behavioural strategies. **Comparison:** matched placebo **Inclusion criteria:** Eligible participants were aged 18 years or older, reported 1 or more unsuccessful dietary efforts to lose weight, and had either body mass index (BMI) of 27 or higher with at least 1 weight related comorbidity (cardiovascular disease, dyslipidemia, hypertension, or obstructive sleep apnea) or BMI of 30 or high	percentage change in body weight and the proportion of participants who lost at least 5% of baseline weight by week 68. **Secondary outcome:** Confirmatory secondary end points (in hierarchic testing order) included the proportions of participants achieving weight reductions of at least 10% or 15%, and the change from baseline to week 68 in waist circumference, systolic blood pressure, and physical functioning score assessed by the 36-Item Short Form Health Survey (SF-36), Acute Version	

	Exclusion criteria: Participants were excluded if they had diabetes, glycated haemoglobin levels of 6.5% or more (≥48 mmol/mol), self-reported body weight change greater than 5 kg within 90 days before screening, or prior or planned obesity treatment with surgery or a weight loss device.		
Reference: Wilding, J., et al. (2021) Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England journal of medicine, 384(11), 989–1002. DOI: 10.1056/NEJMoa2032183 **Study aim:** To evaluate the efficacy and safety of semaglutide as compared with placebo as an adjunct to lifestyle intervention for reducing body weight and meeting other related end points in adults with overweight or obesity and without diabetes. **Study duration:** 68 weeks **Population:** Semaglutide group: 1212 participants (Female sex: 955 (73.1%); Age: 46; Weight: 105.4 kg) Placebo group: 577 participants (Female sex= Female: 498 (76.0%); Age: 47; Weight: 105.2 kg)	**Intervention:** Semaglutide at a dose of 2.4 mg administered subcutaneously once a week for 68 weeks or matching placebo, in addition to lifestyle intervention; this 68-week period was followed by a 7-week period without receipt of semaglutide or placebo or lifestyle intervention. Semaglutide, administered with a prefilled pen injector, was initiated at a dose of 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to reach the maintenance dose of 2.4 mg weekly by week 16 (lower maintenance doses were permitted if participants had unacceptable side effects with the 2.4-mg dose). Participants received individual counseling sessions every 4 weeks to help them adhere to a reduced-calorie diet (500-kcal deficit per day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (with 150 minutes per week of physical activity, such as walking, encouraged) **Comparison:** Matched placebo **Inclusion criteria:** Adults (18 years of age or older) with one or more self-reported unsuccessful dietary efforts to lose weight and	**Outcomes:** **Primary outcome:** The coprimary end points were the percentage change in body weight from baseline to week 68 and achievement of a reduction in body weight of 5% or more from baseline to week 68. **Secondary outcome:** Confirmatory secondary end points (in hierarchical testing order) were achievement of a reduction in body weight of 10% or more and 15% or more by week 68 and the change from baseline to week 68 in waist circumference, systolic blood pressure, physical functioning score on the 36-item Short Form Health Survey (SF-36), version 2, and physical function score on the Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT) questionnaire. Body composition (total fat, total lean body mass, and regional [abdominal] visceral fat mass)	**A separate analysis was conducted for participants with pre-diabetes.**

	either a BMI of 30 or greater or a BMI of 27 or greater with one or more treated or untreated weight-related coexisting conditions (i.e., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). **Exclusion criteria:** Key exclusion criteria were diabetes, a glycated hemoglobin level of 48 mmol per mole (6.5%) or greater, a history of chronic pancreatitis, acute pancreatitis within 180 days before enrollment, previous surgical obesity treatment, and use of antiobesity medication within 90 days before enrollment	was measured in the DXA subpopulation as a supportive secondary end point.	
Reference: Blundell, J., et al. (2017) Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes, obesity & metabolism, 19(9), 1242–1251. DOI: 10.1111/dom.12932 **Study aim:** The aim of this trial was to investigate the mechanism of action for body weight loss with semaglutide **Study duration:** 12 weeks **Population:** Semaglutide group: 30 participants Placebo group: 28 participants (Participant characteristics by group not described) Mean age, body weight and BMI were 42 years, 101.3 kg and 33.8 kg/m2, respectively. Two-thirds of subjects were male	**Intervention:** Semaglutide (1.34 mg/mL). The starting dose was 0.25 mg (4 weeks), escalating to 0.5 mg (4 weeks) and then 1.0 mg (4 weeks). Subjects received a fifth dose (administered at the clinic) of 1.0 mg at the last visit of each treatment period and assessments were conducted. **Comparison:** Matched placebo **Inclusion criteria:** Eligible subjects were ≥18 years of age, with a body mass index (BMI) of 30 to 45 kg/m2, HbA1c < 6.5% and stable body weight (< 3 kg change during the 3 months prior to screening). **Exclusion criteria:** Diagnosis of type 1 or 2 diabetes; history of chronic/idiopathic acute pancreatitis; personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; previous surgical treatment for obesity; smoking or use of any nicotine products; use of any medication that could interfere with trial results; or anticipated	**Outcomes:** **Primary outcome:** the primary endpoint was ad libitum energy intake during a lunch meal (5 hours after a standardised breakfast meal) after 12 weeks of treatment. **Secondary outcome:** Secondary endpoints included: ad libitum energy intake during a subsequent evening meal and from an evening snack box; total daytime ad libitum energy intake until midnight; duration of ad libitum lunch; ratings of appetite parameters, thirst, nausea and well-being before and after a standardised breakfast meal; palatability of ad libitum meals; energy expenditure (resting metabolic rate [RMR] and respiratory quotient [RQ]); control of eating	**No relevant sub-group analysis was undertaken**

	change in lifestyle (e.g., eating, exercise or sleeping pattern) during the trial	and food cravings over the past week; food preference; body weight; and body composition (fat and fat-free mass).	
Reference: Jensterle, M., et al. (2021) Semaglutide reduces fat accumulation in the tongue: A randomized single-blind, pilot study. Diabetes research and clinical practice, 178, 108935. DOI: 10.1016/j.diabres.2021.108935 **Study aim:** To evaluate the effect of the latest GLP-1 RA semaglutide on tongue fat storage in obese women **Study duration:** 16 weeks **Population:** 25 patients completed the study. Thirty women (aged 33.7 ± 5.3 years, mean ± SD) with PCOS and obesity (BMI 36.1 ± 3.9 kg/m2, mean ± SD)	**Intervention:** Semaglutide was initiated at a dose of 0.5 mg once weekly for the first 4 weeks, and increased to 1.0 mg once weekly for the remaining treatment period **Comparison:** Placebo **Inclusion criteria:** Women with polycystic ovary syndrome and obesity. **Exclusion criteria:** Any known serious chronic illness, including diabetes, angina pectoris, coronary heart disease, congestive heart failure, severe renal and hepatic impairment, inflammatory bowel disease, gastroparesis, cancer, chronic obstructive lung disease, psychiatric and neurological disease. The use of medications that cause clinically significant weight gain or loss, previous bariatric surgery, a history of idiopathic acute pancreatitis, a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma, current smoking, pregnancy, expecting pregnancy or breast feeding, allergy to any of the ingredients of the study medication and anticipated change in lifestyle (e.g. eating, exercise or sleeping pattern) during the trial.	**Outcomes:** **Primary outcome:** All participants underwent standard anthropometric measurements: height, weight, waist and neck circumference. Visceral fat was assessed by a Dual Energy X-ray Absorptiometry (Discovery A; Hologic, Waltham, MA) with the software provided by the manufacturer (QDR for Windows Version 12.5). The instrument generated values for whole-body fat mass, lean body mass and bone mineral content and all these parameters separately for different body parts. Glucose metabolism parameters and plasma lipids were assessed by routine laboratory procedures. Oral glucose tolerance test was performed as recommended. Blood samples for glucose were drawn at 0, and 120 min of OGTT. To assess insulin resistance, homeostasis model assessment (HOMA-IR) was calculation. Glucose levels	**This trial was conducted in women with polycystic ovary syndrome**

	Subjects with contraindications for magnetic resonance imaging (MRI) scanning (implants, claustrophobia ect) were also excluded.	were determined using a standard glucose oxidase method (Beckman Coulter Glucose Analyzer, Beckman Coulter Inc CA, USA). Insulin was determined by immunoradiometric assay (Biosource Europe S.A., Nivelles, Belgium). Lipids were determined using Adiva 1800, Siemens analysis. Tongue volume and its fat tissue and fat proportion by magnetic resonance imaging.	
Reference: Kosiborod, M., et al. (2023) Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. The New England journal of medicine, 389(12), 1069–1084. DOI: 10.1056/NEJMoa2306963 **Study aim:** To explore whether once weekly semaglutide at a dose of 2.4 mg might lead to reductions in symptoms and physical limitations and to improved exercise function, in addition to weight loss, in patients with heart failure with preserved ejection fraction and obesity. **Study duration:** 52 weeks **Population:** Semgalutide group: 263 participants (Female sex= 149 (56.7%); Age: 70 (62–75); Weight: 104.7 kg) Placebo group: 266 participants (Female sex= 148 (55.6%); Age: 69 (62–75); Weight: 105.3 kg)	**Intervention:** once weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 52 weeks. Semaglutide treatment was initiated at a dose of 0.25 mg once weekly for the first 4 weeks, and the dose was escalated every 4 weeks with the aim of reaching the maintenance dose of 2.4 mg by week 16 **Comparison:** Placebo **Inclusion criteria:** Persons 18 years of age or older were eligible to participate if they had a left ventricular ejection fraction of at least 45%; a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of at least 30; New York Heart Association functional class II, III, or IV symptoms; a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) of less than 90 points	**Outcomes: Primary outcome:** The dual primary end points were the change in the KCCQ-CSS and the percentage change in body weight from baseline to week 52. The KCCQ is a standardized, 23-item, participant-administered instrument that quantifies heart failure– related symptoms (frequency, severity, and recent changes), physical function, quality of life, and social function. **Secondary outcome:** The confirmatory secondary end points were the change in the 6-minute walk distance from baseline to week 52, a hierarchical composite end	**This trial was conducted in people with heart failure**

	(scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations); a 6-minute walk distance of at least 100 m; and at least one of the following findings: elevated left ventricular filling pressures (on the basis of direct invasive measurements), elevated natriuretic peptide levels (with thresholds stratified according to the BMI at baseline) plus echocardiographic abnormalities, or hospitalisation for heart failure in the 12 months before screening plus ongoing treatment with diuretics or echocardiographic abnormalities **Exclusion criteria:** Key exclusion criteria were a patient-reported change in body weight of more than 5 kg within 90 days before screening and a history of diabetes (glycated hemoglobin level of ≥6.5% based on medical record data within 3 months before screening or on a local laboratory value at the time of screening; patients were also excluded if they had a known medical history of diabetes).	point (described in detail below) for which the number of wins was compared between the semaglutide and placebo groups, and the change in the log-transformed C-reactive protein (CRP) level from screening (week −2) to week 52. The hierarchical composite end point included death from any cause from baseline to week 57; the number and timing of heart failure events (defined as adjudicated events of hospitalization for heart failure or urgent visits in which intravenous therapy was administered, baseline to week 57); differences of at least 15, at least 10, and at least 5 points in the change in the KCCQ-CSS from baseline to week 52; and a difference of at least 30 m in the change in the 6-minute walk distance from baseline to week 52.	
Reference: Friedrichsen, M., et al. (2021) The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. Diabetes, obesity & metabolism, 23(3), 754–762. https://doi.org/10.1111/dom.14280 **Study aim:** To investigate the effects of once-weekly subcutaneous (s.c.) semaglutide 2.4 mg	**Intervention:** Participants were randomized equally to once-weekly s.c. semaglutide 2.4 mg (initially undergoing a 16-week dose-escalation consisting of 0.25, 0.5, 1.0 and 1.7 mg once weekly for 4 weeks each, followed by 2.4 mg for five doses; 21 doses in total over 20 weeks) **Comparison:** Matched placebo	**Outcomes: Primary outcome:** The primary endpoint compared the effect of once-weekly s.c. semaglutide 2.4 mg and placebo on gastric emptying assessed by the paracetamol absorption method at week 20, using the area under the concentration–time curve (AUC) for	**No relevant sub-group analysis was undertaken**

on gastric emptying, appetite, and energy intake in adults with obesity. **Study duration:** 20 weeks **Population:** Semaglutide group: 35 participants (Female sex: 12 (33.3%); Age: 40.7; Weight: 106.2 kg) **Placebo group:** 35 participants (Female sex: 16; (44.4%); Age: 45.0; Weight: 104.9 kg)	**Inclusion criteria:** Participants were men and women, aged 18 to 65 years, with body mass index (BMI) of 30.0 to 45.0 kg/m2. **Exclusion criteria:** clinically significant body weight change (≥5%) or dieting attempts in the prior 90 days; use of medications in the prior 14 days (other than contraceptives, occasional paracetamol or acetylsalicylic acid, or stable doses of antihypertensives or lipid-lowering drugs); use of weight lowering drugs or drugs that may cause weight gain within the prior 12 months; presence of gastrointestinal disorders or symptoms of such disorders that may affect absorption of drugs or nutrients; prior obesity surgery or presence of gastrointestinal implant; and glycated haemoglobin (HbA1c) ≥48 mmol/mol or fasting glucose ≥7.0 mmol/L	paracetamol 0 to 5 hours after a standardized meal (AUC0–5h,para). **Secondary outcome:** Secondary endpoints related to gastric emptying included paracetamol AUC from 0 to 1 hour after a standardized meal (AUC0–1h,para), maximum observed paracetamol concentration (Cmax,para) and time to maximum observed paracetamol concentration (tmax,para). Energy intake during the ad libitum lunch was compared between semaglutide and placebo at week 20 as a secondary endpoint. The effect of semaglutide compared with placebo on appetite was assessed using mean postprandial participant-reported visual analogue scale (VAS) appetite ratings following a standardized breakfast meal at week 20, focusing on hunger, fullness, satiety, prospective food consumption and overall appetite suppression score (secondary endpoints). **Other outcomes:** Additional exploratory endpints included assessment of fasting and mean postprandial change from fasting ratings for VAS items	

		measuring thirst, nausea and wellbeing following a standardized breakfast. Participant-reported control of eating was evaluated as an exploratory endpoint using Control of Eating Questionnaire (CoEQ) completed at week 2	
Reference: Lincoff, A. et al. (2023) Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. The New England journal of medicine, 389(24), 2221–2232. DOI: 10.1056/NEJMoa2307563 **Study aim:** To test the hypothesis that the addition of semaglutide to standard care would be superior to placebo in reducing the risk of major adverse cardiovascular events among patients with overweight or obesity and preexisting cardiovascular disease who did not have diabetes. **Study duration:** The mean duration of exposure to semaglutide or placebo in the overall trial population was 34.2±13.7 months (33.3±14.4 months for semaglutide and 35.1±13.0 months for placebo) **Population:** Semaglutide group: 8803 participants (Male sex: 6355 (72.2%); Age: 61.6; Weight: 96.5 kg) Placebo group: 8801 participants (Male sex: 6377 (72.5%); Age: 61.6; Weight: 96.8 kg)	**Intervention:** Once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The starting dose of semaglutide was 0.24 mg once weekly, and the dose was increased every 4 weeks (to onceweekly doses of 0.5, 1.0, 1.7, and 2.4 mg) until the target dose of 2.4 mg was reached after 16 weeks. If dose escalation led to unacceptable adverse effects, the dose-escalation intervals could be extended, treatment could be paused, or maintenance doses below the 2.4 mg per week target dose could be used. **Comparison:** Placebo **Inclusion criteria:** Patients were eligible for enrollment if they were 45 years of age or older, had a BMI (the weight in kilograms divided by the square of the height in meters) of 27 or greater, and had established cardiovascular disease. Cardiovascular disease was defined as previous myocardial infarction, previous stroke, or symptomatic peripheral arterial disease **Exclusion criteria:** Key exclusion criteria were a previous diagnosis of diabetes, a glycated hemoglobin level of 6.5% (48 mmol per mole) or higher measured at screening, treatment with	**Outcomes:** **Primary outcome:** The primary cardiovascular efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, assessed in a time-to-first-event analysis. **Secondary outcome:** Confirmatory secondary end points, assessed in time-to-first-event analyses and tested in hierarchical order, were death from cardiovascular causes, a composite heart failure end point (death from cardiovascular causes or hospitalization or an urgent medical visit for heart failure), and death from any cause.	**This trial was undertaken in people with cardiovascular disease**

	any glucose lowering medication or GLP-1 receptor agonist within the previous 90 days, New York Heart Association class IV heart failure, or end-stage kidney disease or dialysis. Patients could not be enrolled within 60 days after a cardiovascular or neurologic event or if they planned to undergo coronary, carotid, or peripheral revascularization		

Data extraction table for studies investigating the effectiveness of tirzepatide x 4			
Reference and trial details	Trial details	Outcomes	Sub-group analysis
Reference: Aronne, L. et al. (2024). Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA, 331(1), 38–48. DOI: 10.1001/jama.2023.24945 **Study aim:** To assess the effect of tirzepatide, with diet and physical activity, on the maintenance of weight reduction. **Study duration:** 36-week, lead-in period followed by a 52-week, double-blind, placebo-controlled period. **Population:** Tirzepatide=335 (Age=49 years;	**Intervention:** Tirzepatide was administered once weekly as a subcutaneous injection. During the 36-week, open-label lead-in period, the starting dose of tirzepatide was 2.5 mg and was increased by 2.5 mg every 4 weeks until a maximum tolerated dose of 10 or 15 mg was achieved. At the end of the lead-in period, participants who attained the maximum tolerated dose of tirzepatide (10 or 15 mg) were randomized in a 1:1 ratio by a computer-generated random sequence using an interactive web-response system to either continue receiving the maximum tolerated dose of tirzepatide or switch to matching placebo for an additional 52 weeks. All participants received lifestyle counselling by a qualified health care professional throughout the	**Outcomes: Primary outcome:** The percent change in bodyweight from randomization (week 36) to week 88. **Secondary outcome:** end points capturing weight maintenance and regain, respectively, were the proportion of participants at week 88 maintaining at least 80% of the body weight loss during the 36-week open-label period and time during the 52-week double-blind treatment period to first occurrence of participants returning to greater than 95% baseline body weight for those	**No relevant sub-group analysis was undertaken**

Female sex= 236 (70.4%); Body weight= 84.6kg) Placebo=335 (Age=48 years; Female sex= 237 (70.7%); Body weight= 85.8kg)	study to encourage adherence to a healthy 500 kcal/d deficit diet and at least 150 minutes of physical activity per week. **Comparison:** Matched placebo **Inclusion criteria:** Eligible participants (18 years or older) had a body mass index (BMI) greater than or equal to 30 or greater than or equal to 27 and at least 1 weight-related complication (ie, hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). **Exclusion criteria:** Medical conditions Diabetes-related • Have type 1 or type 2 diabetes, history of ketoacidosis, or hyperosmolar state/coma • Have at least 1 laboratory value suggestive of diabetes during screening, including 1 or more of: HbA1c ≥6.5% (≥48 mmol/mol), fasting glucose ≥126 mg/dL (≥7.0 mmol/L), and random glucose ≥200 mg/dL (≥11.1 mmol/L) Obesity-related • Have a self-reported change in body weight >5 kg within 3 months prior to screening • Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to screening) • Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening (for example, mucosal ablation, gastric artery embolization, intragastric balloon, or duodenal-jejunal endoluminal liner) Other medical • Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 , calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening • Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction) or	who lost at least 5% during the open-label lead-in period. Key secondary end points also included change in absolute body weight and waist circumference during the double-blind period (week 36 to 88) and the proportion of participants achieving weight reduction thresholds of at least 5%, at least 10%, at least 15%, and at least 20% since enrolment (week 0 to 88); the proportion of participants achieving at least 25% weight reduction from week 0 to 88 was a prespecified exploratory end point. Additional secondary end points included change from randomization (week 36) to week 88 and from enrolment (week 0) to week 88 in cardiometabolic risk factors including glycemic parameters, fasting insulin, lipids, blood pressure, and patient-reported outcomes measured by the Short Form-36 Version 2 Health Survey (SF-36 v2) acute form and Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT).	

	chronically take drugs that directly affect gastrointestinal motility • Have a history of chronic or acute pancreatitis • Have thyroid-stimulating hormone (TSH) outside of the range of 0.4 to 6.0 mIU/L at the screening visit Note: Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 3 months and their TSH at screening falls within the range indicated above. Note: Participants with a history of subclinical hypothyroidism but a TSH at screening within the range indicated above, may be included if, in the investigator's opinion, the patient is unlikely to require initiation of thyroid hormone replacement during the course of the study. • Have obesity induced by other endocrinologic disorders (for example, Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome) • Have a history of significant active or unstable major depressive disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years Note: Participants with MDD or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications. • Have a lifetime history of suicide attempt • Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more on or before Visit 2 • On the Columbia-Suicide Severity Rating Scale (C-SSRS) on or before Visit 2: o a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS © 2023 American Medical Association. All rights reserved. or o a "yes" answer to		

	Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the “Suicidal Ideation” portion of the C-SSRS or o a “yes” answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the “Suicidal Behavior” portion of the C-SSRS and o the ideation or behavior occurred within the past month • Have uncontrolled hypertension (systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg) • Have any of the following cardiovascular conditions within 3 months prior to Visit 2: acute myocardial infarction, cerebrovascular accident (stroke), unstable angina, or hospitalization due to congestive heart failure (CHF) • Have NYHA Functional Classification Class IV CHF • Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or any of the following, as determined by the central laboratory during screening: o alanine aminotransferase (ALT) level >3.0X upper limit of normal (ULN) for the reference range o alkaline phosphatase (ALP) level >1.5X ULN for the reference range, or o total bilirubin (TBL) level >1.2X ULN for the reference range (except for cases of known Gilbert’s Syndrome) Note: Participants with NAFLD are eligible to participate in this trial if their ALT level is ≤3.0X ULN for the reference range. • Have a serum calcitonin level (at Visit 1) of: o ≥20 ng/L, if eGFR ≥60 mL/min/1.73 m2 o ≥35 ng/L, if eGFR <60 mL/min/1.73 m2 • Have a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN) syndrome type 2 • Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years • Have any other condition not listed in this section (for		

	example, hypersensitivity or intolerance) that is a contraindication to glucagon-like peptide-1 (GLP-1) receptor agonists • Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol • Have history of use of marijuana or tetrahydrocannabinol (THC)-containing products within 3 months of enrolment or unwillingness to abstain from marijuana or THC-containing products use during the trial Note: If a participant has used cannabidiol oil during the past 3 months but agrees to refrain from use for the duration of the study, the participant can be enrolled. • Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant • Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease) Prior/concomitant therapy • Are receiving or have received within 3 months prior to screening chronic (>2 weeks or >14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) during the course of the study • Have current or history of (within 3 months prior to Visit 2) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotics, and mood stabilizers Note: Selective serotonin reuptake inhibitors other than paroxetine are		

	permitted. © 2023 American Medical Association. All rights reserved. • Have taken, within 3 months prior to Visit 2, medications (prescribed or over-the-counter) or alternative remedies that promote weight loss Note: Use of metformin or any other glucose-lowering medication, whether prescribed for polycystic ovary syndrome (PCOS) or diabetes prevention, is not permitted. • Have started implantable or injectable contraceptives (such as Depo Provera®) within 18 months prior to screening Prior/concurrent clinical study experience • Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study • Within the last 30 days, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an IP, 5 half-lives or 30 days, whichever is longer, should have passed • Have previously completed or withdrawn from this study or any other study investigating tirzepatide after receiving at least 1 dose of IP Other exclusions • Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted • Are Eli Lilly and Company employees.		
Reference: Jastreboff, A., et al. (2025) Tirzepatide for Obesity Treatment and Diabetes Prevention. The New England journal of medicine, 392(10), 958–971. DOI: 10.1056/NEJMoa2410819 **Study aim:** To report the 3-year safety and efficacy outcomes with tirzepatide, including its effect on achieving and sustaining longer-term weight reduction	**Intervention:** Participants were randomly assigned in a 1:1:1:1 ratio to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or placebo, administered subcutaneously once weekly for 176 weeks, followed by a 17-week off-treatment period (safety follow-up), for a total trial duration of 193 weeks. All groups received lifestyle intervention, including regular lifestyle counselling sessions with a dietitian or a qualified health care professional with a focus on	**Outcomes: Primary outcome:** The results for the coprimary end points (percent change in body weight and percentage of participants with ≥5% weight reduction) and key secondary end points (controlled for type I error) for 72-week outcomes have been published.	**No relevant sub-group analysis was undertaken**

and preventing type 2 diabetes in participants with prediabetes at baseline. Study duration: 193 weeks (Participants with obesity and without prediabetes at baseline were offered treatment for 72 weeks, whereas participants with obesity and prediabetes at baseline were offered treatment for 176 weeks.) Population: Tirzeptaide 5mg- 172 (Age= 49.3; Female sex= 160 (64.8%); Body weight= 104.6 kg) Tirzepatide 10mg- 185 (Age= 47.4; Female sex= 168 (64.1%); Body weight= 108.9 kg) Tirzepatide 15mg-184 (Age= 48.4; Female sex= 161 (63.6%); Bodyweight= 108.6kg) Placebo- 136 (Age= 47.7; Female sex= 170 (63.0%); Bodyweight= 107.3kg)	healthful, balanced meals, with a 500-kcal deficit per day, and at least 150 minutes of physical activity per week. Comparison: Placebo Inclusion criteria: Participants were eligible to be included in the study only if all of the following criteria applied: Type of Participant and Disease Characteristics • Had a BMI ≥30 kg/m2 or ≥27 kg/m2 and previously diagnosed with at least one of the following weight related comorbidities: - hypertension: treated or with systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure ≥80 mmHg - dyslipidemia: treated or with low-density lipoprotein (LDL) ≥160 mg/dL (4.1 mmol/L) or triglycerides ≥150 mg/dL (1.7 mmol/L), or high-density lipoprotein (HDL) <40 mg/dL (1.0 mmol/L) for men or HDL<50 mg/dL (1.3 mmol/L) for women - obstructive sleep apnea - cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association (NYHA) Functional Class I-III heart failure) • Had a history of at least one self-reported unsuccessful dietary effort to lose body weight • In the investigator's opinion, were well-motivated, capable, and willing to • learn how to self-inject study drug, as required for this protocol (visually impaired persons who were not able to perform the injections must have had the assistance of a sighted individual trained to inject study drug; persons with physical limitations who were not able to perform the injections must have had the assistance of an individual trained to inject study drug)	Secondary outcome: Key secondary end points that were assessed in the current analysis, with control for type I error, were the percent change in body weight from baseline to week 176 (assessed in the 10-mg and 15-mg tirzepatide groups and the placebo group) and onset of type 2 diabetes during the 176-week and 193-week periods (assessed in the pooled tirzepatide groups and the placebo group). Safety assessments included adverse events and serious adverse events that occurred through week 193.	

	• inject study drug (or receive an injection from a trained individual if visually impaired or with physical limitations) • follow study procedures for the duration of the study, including, but not limited to: follow lifestyle advice (for example, dietary restrictions and exercise plan), maintain a study diary, and complete required questionnaires Participant Characteristics Were 18 years or older • male participants: - Male participants with partners of childbearing potential should have been willing to use reliable contraceptive methods throughout the study and for 5 half-lives of study drug plus 90 days, corresponding to 4 months after the last injection • female participants: - Female participants not of childbearing potential may have participated and included those who were: - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy or tubal ligation), congenital anomaly such as Mullerian agenesis - postmenopausal, defined as either 1. a woman at least 40 years of age with an intact uterus, not on hormone therapy, who had cessation of menses for at least 1 year without an alternative medical cause, AND a folliclestimulating hormone ≥40 mIU/mL; women in this category must have tested negative in pregnancy test prior to study entry or 2. a woman 55 or older not on hormone therapy, who had at least 12 months of spontaneous amenorrhea or 3. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy - Female participants of child-bearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must have: - tested negative for pregnancy at Visit 1 based on a serum pregnancy test and		

	- if sexually active, agreed to use 2 forms of effective contraception, where at least 1 form was highly effective, for the duration of the trial and for 30 days thereafter - not been breastfeeding. Exclusion criteria: Participants were excluded from the study if any of the following criteria applied: Medical Conditions, Diabetes-related • Had type 1 diabetes mellitus (T1DM) or T2DM, history of ketoacidosis, or hyperosmolar state/coma • Had laboratory evidence diagnostic of diabetes mellitus during screening, including 1 or more of: HbA1c ≥6.5% (≥48 mmol/mol), FG ≥126 mg/dL (≥7.0 mmol/L), random glucose or 2-hour glucose measurement from a 2-hour OGTT ≥200 mg/dL (≥11.1 mmol/L) Obesity-related: • Had a self-reported change in body weight >5 kg within 3 months prior to screening • Had a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to screening) • Had or planned to have endoscopic and/or device-based therapy for obesity or had device removal within the last 6 months (for example, mucosal ablation, gastric artery embolization, intragastric balloon and duodenal-jejunal bypass sleeve) Other medical: • Had renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening • Had a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction) or had		

	been chronically taking drugs that directly affect GI motility • Had a history of chronic or acute pancreatitis • Had thyroid-stimulating hormone (TSH) outside of the range of 0.4 to 6.0 mIU/L at screening visit Note: Patients receiving treatment for hypothyroidism may have been included, provided their thyroid hormone replacement dose had been stable for at least 3 months Note: TSH values above the normal range can, in some patients, suggest subclinical hypothyroidism. If, in the investigator's opinion, the participant had subclinical hypothyroidism and may have required initiation of thyroid hormone replacement during the course of the study, the patient should have been excluded from the study • Had obesity induced by other endocrinologic disorders (for example, Cushing Syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome) • Had a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years Note: Patients with MDD or generalized anxiety disorder whose disease state was considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may have been considered for inclusion if they were not on excluded medications • Had any lifetime history of a suicide attempt Had a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 1 or 3, prior to randomization • Had on the C-SSRS at Visits 1, 2, or 3, prior to randomization:		

	- a “yes” answer to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or - a “yes” answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the “Suicidal Ideation” portion of the C-SSRS, or - a “yes” answer to any of the suicide-related behaviours (Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Act or Behaviour) on the “Suicidal Behaviour” portion of the C-SSRS And - the ideation or behaviour occurred within the past month • Had uncontrolled hypertension (SBP above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg) • Had any of the following cardiovascular conditions within 3 months prior to randomization: acute myocardial infarction (MI), cerebrovascular accident (stroke), unstable angina, or hospitalization due to congestive heart failure (CHF) • Have NYHA Functional Classification IV CHF • Had acute or chronic hepatitis, signs, and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory during screening: - alanine aminotransferase (ALT) level >3.0X the upper limit of normal (ULN) for the reference range, or - alkaline phosphatase (ALP) level >1.5X the ULN for the reference range, or - total bilirubin (TBL) level >1.2X the ULN for the reference range (except for cases of known Gilbert’s Syndrome) Note: Participants with nonalcoholic fatty liver disease were eligible to participate in this trial if their ALT level was ≤3.0X the ULN for the reference range • Had a calcitonin level (at Visit 1) of: - ≥20 ng/L at Visit 1, if eGFR ≥60 mL/min/1.73 m2		

	- ≥35 ng/L at Visit 1, if eGFR <60 mL/min/1.73 m2 • Had a family or personal history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia (MEN) Syndrome type 2 • Had a history of an active or untreated malignancy or were in remission from a clinically significant malignancy (other than basal- or squamous-cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years • Had any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1R agonists • Had a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the investigator, may have precluded the participant from following and completing the protocol • Had history of use of marijuana within 3 months of enrolment and unwillingness to abstain from marijuana use during the trial. Participants should also have refrained from use of cannabidiol oil for the duration of the study • Had a transplanted organ (corneal transplants [keratoplasty] allowed) or were awaiting an organ transplant • Had any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease) Prior/Concomitant Therapy • Were receiving or had received within 3 months prior to screening chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) or had evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that had required (within the last 3 months)		

	or was likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular or inhaled preparations) in the next 12 months • Had current or history of (within 3 months prior to randomization) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotic and mood stabilizers Note: Selective serotonin reuptake inhibitors other than paroxetine were permitted • Had taken within 3 months prior to randomization, medications (prescribed or over-the counter) or alternative remedies intended to promote weight loss • Had started implantable or injectable contraceptives (such as Depo-Provera®) within 18 months prior to screening		
Reference: Jastreboff, A. et al. (2022) Tirzepatide Once Weekly for the Treatment of Obesity. The New England journal of medicine, 387(3), 205–216. DOI: 10.1056/NEJMoa2206038 **Study aim:** The SURMOUNT-1 trial evaluated the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes. **Study duration:** 72 weeks **Population:** Tirzepatide 5 mg (N = 630; Age- 45.6; female sex- 426 (67.6%), Body weight- 102.9kg) Tirzepatide 10 mg (N = 636; 10 mg Age- 44.7;	**Intervention:** Participants were randomly assigned in a 1:1:1:1 ratio to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or placebo, administered subcutaneously once weekly for 72 weeks as an adjunct to lifestyle intervention. Lifestyle intervention included regular lifestyle counselling sessions, delivered by a dietitian or a qualified health care professional, to help the participants adhere to healthful, balanced meals, with a deficit of 500 calories per day, and at least 150 minutes of physical activity per week. **Comparison:** placebo **Inclusion criteria:** Adults who were 18 years of age or older, with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or more, or a BMI of 27 or more and at least one weight-related complication (e.g., hypertension, dyslipidemia, obstructive sleep apnea, or	**Outcomes: Primary outcome:** The percentage change in body weight from baseline to week 72 and a weight reduction of 5% or more at week 72. **Secondary outcome:** Weight reduction of 10% or more, 15% or more, and 20% or more at week 72; the change in weight from baseline to week 20; and the change from baseline to week 72 in waist circumference, systolic blood pressure, fasting insulin and lipid levels, and the physical function score on the 36-Item Short Form Health Survey (SF-36), version 2, acute form. The percentage change in total body-fat mass from baseline to week	**No relevant sub-group analysis was undertaken**

Female sex- 427 (67.1%); Body weight- 105.8kg) Tirzepatide 15 mg (N = 630; Age-44.9; Female sex- 425 (67.5%); Body weight- 105.6kg) Placebo (N = 643; Age- 44.4; Female sex- 436 (67.8%); Body weight- 104.8kg)	cardiovascular disease), and who reported one or more unsuccessful dietary effort to lose weight were eligible to participate. Exclusion criteria: type 1 diabetes mellitus or T2DM, history of ketoacidosis, or hyperosmolar State/coma Have laboratory evidence diagnostic of diabetes mellitus during screening, including 1 or more of: HbA1c ≥6.5% (≥48 mmol/mol), FG ≥126 mg/dL (≥7.0 mmol/L), random glucose or 2-hour glucose measurement from a 2-hour OGTT ≥200 mg/dL (≥11.1 mmol/L) • Have a self-reported change in body weight >5 kg within 3 months prior to screening • Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to screening) • Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months (for example, mucosal ablation, gastric artery embolization, intragastric balloon and duodenal-jejunal bypass sleeve) • Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening • Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility • Have had a history of chronic or acute pancreatitis • Have thyroid-stimulating hormone (TSH) outside of the range of 0.4 to 6.0 mIU/L at screening visit Note: Patients receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 3 months. Note: TSH values above the normal range can,	72 was assessed in a subgroup of 255 participants who underwent dual-energy x-ray absorptiometry.	

	in some patients, suggest subclinical hypothyroidism. If, in the investigator's opinion, the participant has subclinical hypothyroidism and may require initiation of thyroid hormone replacement during the course of the study, the patient should be excluded from the study. • Have obesity induced by other endocrinologic disorders (for example, Cushing Syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome) • Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years. Note: Patients with MDD or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications • Have any lifetime history of a suicide attempt • Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 1 or 3, prior to randomization • On the C-SSRS at Visits 1, 2, or 3, prior to randomization: - a "yes" answer to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or - a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS or - a "yes" answer to any of the suicide-related behaviors (Actual Attempt, Interrupted 12 Attempt, Aborted Attempt, Preparatory Act or Behavior) on the "Suicidal Behavior" portion of the C-SSRS and		

	- the ideation or behavior occurred within the past month • Have uncontrolled hypertension (SBP above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg) • Have any of the following cardiovascular conditions within 3 months prior to randomization: acute myocardial infarction (MI), cerebrovascular accident (stroke), unstable angina, or hospitalization due to congestive heart failure (CHF) • Have NYHA Functional Classification IV CHF • Have acute or chronic hepatitis, signs, and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory during screening: - alanine aminotransferase (ALT) level >3.0X the upper limit of normal (ULN) for the reference range or - alkaline phosphatase (ALP) level >1.5X the ULN for the reference range or - total bilirubin (TBL) level >1.2X the ULN for the reference range (except for cases of known Gilbert's Syndrome) Note: Participants with nonalcoholic fatty liver disease are eligible to participate in this trial if their ALT level is ≤3.0X the ULN for the reference range • Have a calcitonin level (at Visit 1) of: - ≥20 ng/L at Visit 1, if eGFR ≥60 mL/min/1.73 m2 - ≥35 ng/L at Visit 1, if eGFR <60 mL/min/1.73 m2 • Have a family or personal history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia (MEN) Syndrome type 2 • Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal- or squamous-cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years		

	• Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1R agonists • Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol • Have history of use of marijuana within 3 months of enrollment and unwillingness to abstain from marijuana use during the trial. Participants should also refrain from use of cannabidiol oil for the duration of the study • Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant • Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease) Prior/Concomitant Therapy • Are receiving or have received within 3 months prior to screening chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) or have evidence of a significant, active autoimmune 13 abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular or inhaled preparations) in the next 12 months • Have current or history of (within 3 months prior to randomization) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotic and mood stabilizers		

	Note: Selective serotonin reuptake inhibitors other than paroxetine are permitted. • Have taken within 3 months prior to randomization, medications (prescribed or over-the counter) or alternative remedies intended to promote weight loss.		
Reference: Wadden, T. et al. (2023) Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med 29, 2909–2918 DOI: 10.1038/s41591-023-02597-w **Study aim:** To evaluate the efficacy of tirzepatide at 72 weeks post randomization in adults with obesity or overweight (but not diabetes) who successfully lost ≥5% of baseline weight during a 12-week lead-in period that provided intensive lifestyle intervention. **Study duration:** 72 weeks **Population:** Tirzepatide MTD= 287 (Age=45.4; Female sex= 181 (63.1%) Placebo= 292 (Age=45.7 Female sex= 183 (62.7%)	**Intervention:** Eligible participants were enrolled in a 12-week intensive lifestyle intervention lead-in period. The lead-in lifestyle intervention included frequent in-person lifestyle counselling sessions (that is, eight sessions over 12 weeks), delivered by a dietitian or similarly qualified healthcare professional. Women were instructed to consume approximately 1,200 kcal per day and men 1,500 kcal per day. The dietary intervention could include up to two meal replacements (liquid meal replacements or prepackaged, portion-controlled meals) per day. Participants were encouraged to engage in at least 150 min of moderate-intensity physical activity per week (for example, brisk walking). They were counselled on behaviour modification strategies to help implement and adhere to the diet and exercise recommendations and were encouraged to complete 3-day diet and exercise logs before each counselling visit. Tirzepatide and matched placebo were administered once weekly as a subcutaneous injection using a single-dose pen. The starting dose of tirzepatide was 2.5 mg, increasing by 2.5 mg every 4 weeks until an MTD dose of 10 or 15 mg was reached. **Comparison:** Placebo **Inclusion criteria:** BMI of ≥30 kg/m2 or ≥27 kg/m2 and previously diagnosed with at least one of the following weight-related comorbidities:	**Outcomes: Primary outcome:** Per cent change in body weight and the proportion of study participants who achieved ≥5% weight reduction from randomization to week 72. **Secondary outcome:** Key secondary endpoints, controlled for type 1 error rate, included: the proportion of study participants who achieved ≥10, ≥15 or ≥20% weight reduction from randomization to week 72. The proportion of study participants who achieved ≥25% reduction in body weight was a prespecified exploratory endpoint. Key secondary endpoints also included the proportion of participants who, at week 72, maintained ≥80% of the body weight loss achieved during the 12-week lead-in period, as well as change in waist circumference (cm) from randomization to week 72.	**No relevant sub-group analysis was undertaken**

	• hypertension: treated or with systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg • dyslipidemia: treated or with LDL ≥ 160 mg dl−1 (4.1 mmol l−1) or triglycerides ≥150 mg dl−1 (1.7 mmol l−1) or HDL < 40 mg dl−1 (1.0 mmol l−1) for men, or HDL < 50 mg dl−1 (1.3 mmol l−1) for women • obstructive sleep apnea • cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association Functional Classification Class I–III heart failure) 2. had a history of at least one self-reported unsuccessful dietary effort to lose body weight 3. in the investigator's opinion, were well motivated, capable and willing to: • learn how to self-inject study drug, as required for this protocol (visually impaired persons who were not able to perform the injections must have had the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who were not able to perform the injections must have had the assistance of an individual trained to inject the study drug) • inject study drug (or receive an injection from a trained individual if visually impaired or with physical limitations) • follow study procedures for the duration of the study, including—but not limited to—following lifestyle advice (for example, dietary restrictions, exercise plan), maintaining a study diary and completing required questionnaires Participant characteristics. 4. were at least 18 years of age and age of majority according to local laws and regulations a. male participants:	Additional secondary endpoints included change in anthropometrics (absolute body weight and BMI), cardiometabolic risk factors (blood pressure, lipids, fasting glucose, HbA1c and fasting insulin) and patient-reported outcomes (the Physical Functioning domain score on the SF-36v2 acute form, and the IWQOL-Lite-CT Physical Function composite score). These additional secondary endpoints were evaluated both from randomization (week 0) and from the start of the lead-in period (week –12) to week 72. In addition, changes in the intensity of antihypertensive and lipid-lowering therapies in the double-blind period, as reported by the investigator, were assessed as prespecified exploratory endpoints. Safety endpoints included treatment-emergent adverse events and serious adverse events that occurred during the reporting period. Major adverse cardiovascular events, acute pancreatitis and deaths were reviewed by an independent external adjudication committee.	

	• Male participants with partners of childbearing potential should have been willing to use reliable contraceptive methods throughout the study and for five half-lives of study drug plus 90 days, corresponding to 4 months after the last injection. b. female participants: • Female participants not of childbearing potential may have participated and included those who were: ∘∘ infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy or tubal ligation) or congenital anomaly (such as Mullerian agenesis) or ∘∘ postmenopausal (defined as either: a woman at least 40 years of age with an intact uterus, not on hormone therapy and who had cessation of menses for at least 1 year without an alternative medical cause, and follicle-stimulating hormone ≥40 mIU ml−1; women in this category must have tested negative in pregnancy test before study entry or a woman 55 years or older not on hormone therapy and who had at least 12 months of spontaneous amenorrhea or a woman at least 55 years of age with a diagnosis of menopause before starting hormone replacement therapy • Female participants of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopausal) must have: ∘∘ tested negative for pregnancy at visit 1 based on a serum pregnancy test ∘∘ if sexually active, agreed to use two forms of effective contraception where at least one form was highly effective for the duration of the trial plus 30 days, corresponding to 2 months after the last injection; and ∘∘ not have been breastfeeding Note: contraceptive use by men or women should have been consistent with local regulations regarding the methods of contraception for those participating in clinical studies.		

	Exclusion criteria: Medical conditions: 6. had type 1 or type 2 diabetes mellitus, history of ketoacidosis or hyperosmolar state/coma 7. had at least one laboratory value suggestive of diabetes mellitus during screening, including one or more of: HbA1c ≥6.5% (≥48 mmol mol−1), fasting glucose ≥126 mg dl−1 (≥7.0 mmol l−1) or random glucose ≥200 mg dl−1 (≥11.1 mmol l−1) Obesity related. 8. had a self-reported change in body weight >5 kg within 3 months before screening 9. had a previous planned surgical treatment for obesity (excluding liposuction or abdominoplasty, if performed >1 year before screening) had or planned to have endoscopic and/or device-based therapy for obesity or had device removal within the past 6 months before screening: • mucosal ablation • gastric artery embolization • intragastric balloon • duodenal–jejunal endoluminal liner Other medical. 11. had renal impairment measured as eGFR < 30 ml min−1 1.73 m−2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening 12. had a known clinically important gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction) or chronically took drugs that directly affect GI motility 13. had a history of chronic or acute pancreatitis 14. had thyroid-stimulating hormone (TSH) outside of the range 0.4–6.0 mIU l−1 at the screening visit Note: participants receiving treatment for hypothyroidism may have been included, provided their thyroid		

	hormone replacement dose had been stable for at least 3 months and their TSH at screening fell within the range indicated above. Note: participants with a history of subclinical hypothyroidism but a TSH at screening within the range indicated above may have been included if, in the investigator's opinion, the patient was unlikely to require initiation of thyroid hormone replacement during the course of the study. 15. had obesity induced by other endocrinologic disorders (for example, Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, melanocortin 4 receptor deficiency or Prader–Willi syndrome) 16. had a history of substantial active or unstable major depressive disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder or other serious mood or anxiety disorder) within the past 2 years Note: participants with MDD or generalized anxiety disorder and whose disease state was considered stable for the past 2 years and was expected to remain stable throughout the course of the study, in the opinion of the investigator, may have been considered for inclusion if they were not on excluded medications 17. had a lifetime history of suicide attempt 18. had a PHQ-9 score of 15 or more at visit 1 19. on the Columbia Suicide Severity Rating Scale (C-SSRS) at any time from visit 1 to visit 2: a 'yes' answer to Question 4 (active suicidal ideation with some intent to act, without specific plan) on the 'Suicidal Ideation' portion of the C-SSRS or a 'yes' answer to Question 5 (active suicidal ideation with specific plan and intent) on the 'Suicidal Ideation' portion of the C-SSRS or a 'yes' answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the 'Suicidal Behavior' portion of the C-		

	SSRS and the ideation or behavior occurred within the past month 20. had uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg) 21. had any of the following cardiovascular conditions within 3 months before visit 2: • acute myocardial infarction • cerebrovascular accident (stroke) • unstable angina • hospitalization due to congestive heart failure 22. had New York Heart Association Functional Classification Class IV congestive heart failure 23. had acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD) or any of the following, as determined by the central laboratory during screening: • alanine aminotransferase level >3.0 times upper limit of normal (ULN) for the reference range • alkaline phosphatase level >1.5 times ULN for the reference range • total bilirubin level >1.2 times ULN for the reference range (except for cases of known Gilbert syndrome) Note: participants with NAFLD were eligible to participate in this trial if their alanine aminotransferase level was ≤3.0 times ULN for the reference range. 24. had a serum calcitonin level (at visit 1) of ≥20 ng l−1, if eGFR ≥60 ml min−1 1.73 m−2; ≥35 ng l−1, if eGFR <60 ml min−1 1.73 m−2 25. had a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 26. had a history of an active or untreated malignancy or were in remission from a clinically important malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix or in situ prostate cancer) for <5 years		

	27. had any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1 R agonists 28. had a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder or other psychiatric disorder) that, in the opinion of the investigator, may have precluded the participant from following and completing the protocol 29. had a history of use of marijuana or tetrahydrocannabinol containing products within 3 months of enrollment, or unwillingness to abstain from marijuana or tetrahydrocannabinol containing products use during the trial Note: if a participant had used cannabidiol oil during the past 3 months but agreed to refrain from use for the duration of the study, the participant could be enrolled. 30. had had a transplanted organ (corneal transplants (keratoplasty) were allowed) or were awaiting an organ transplant 31. had any hematological condition that may have interfered with HbA1c measurement (for example, hemolytic anemias, sickle cell disease) Previous and/or concomitant therapy. 32. were receiving or had received within 3 months before screening chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular or inhaled preparations) or had evidence of a substantial, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that had required (within the past 3 months) or was likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular or inhaled preparations) during the course of the study 33. had current treatment with or history of (within 3 months before visit 2) treatment with medications		

	that may cause substantial weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotics and mood stabilizers (Examples: imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid (and its derivatives) or lithium Note: selective serotonin reuptake inhibitors other than paroxetine were permitted. 34. had taken, within 3 months before visit 2, medications (prescribed or over-the-counter) or alternative remedies that promote weight loss (Examples included, but were not limited to: Saxenda (liraglutide 3.0 mg), Xenical/Alli (orlistat), Meridia (sibutramine), Acutrim (phenylpropanolamine), Sanorex (mazindol), Apidex (phentermine), BELVIQ (lorcaserin), Bontril (phendimetrazine), Qsymia (phentermine/topiramate combination), Contrave (naltrexone/bupropion), Note: use of metformin, or any other glucose-lowering medication, whether prescribed for polycystic ovarian syndrome or diabetes prevention, was not permitted. 35. had started implantable or injectable contraceptivees (such as Depo Provera) within 18 months before screening Previous and/or concurrent clinical study experience. 36. were currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study 37. within the past 30 days had participated in a clinical study and received treatment, whether active or placebo. If the study involved an investigational product, five half-lives or 30 days, whichever was longer, should have passed. 38. had previously completed or withdrawn from this study or any other study investigating tirzepatide after		

	receiving at least one dose of investigational product Other exclusions. 39. were investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family was defined as a spouse, parent, child or sibling, whether biological or legally adopted. 40. were Lilly employees		

Atodiad B

Data extraction table for systematic reviews investigating weight loss drugs in specific populations		
Antipsychotic induced weight gain		
Reference:	**Description of included studies:**	**Author's conclusions:**

Bak M, et al. (2024) Glucagon-like peptide agonists for weight management in antipsychotic-induced weight gain: A systematic review and meta-analysis. Acta Psychiatrica Scandinavica, 150(6). DOI: 10.1111/acps.13734 **Study population:** Populations aged 18 years or older using an antipsychotic drug in an inpatient or outpatient setting without diagnostic restrictions except for eating disorders. **Intervention:** GLP-1 agonist – exenatide and liraglutide **Comparison:** Placebo **Outcomes:** Body weight change in kilogrammes (kg) and change in BMI (in kg/square metre) after the initiation of the GLP-1 agonist, severity of psychopathology, proportions of patients experiencing adverse effects (nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain, and headache), systolic and diastolic blood pressure, fasting glucose and H1Abc, levels of total cholesterol, HDL (high-density lipoprotein cholesterol), LDL (low-density lipoprotein cholesterol), and triglycerides. **Primary:** Body weight change in kilogrammes (kg) and change in BMI (in kg/square metre) after the initiation of the GLP-1 agonist.	Six papers were included in the data meeting inclusion and exclusion criteria. These six studies included a total of 269 patients. Of the included articles, three RCTs (Patino et al., 2015; Ishoy et al., 2023; Siskind et al., 2018) reported on weight loss after treatment with exenatide and two RCTs (Larsen et al., 2017; Whicher et al., 2021) and one cohort study (Lee et al., 2021) reported on weight loss after treatment with liraglutide. The study by Svensson et al., (2019) was a long-term follow-up of Larssen et al., (2017) and not included in the meta-analysis to avoid doubling inclusion of same subjects. **Quality of included studies:** Cochrane risk of bias tool (RoB 2) was used to for quality assessment. **Synthesis:** Meta-analysis and narrative **Findings:** The study by Svensson et al., (2019) was a long-term follow-up of Larssen et al., (2017) and not included in the meta-analysis to avoid doubling inclusion of same subjects. Only data for exenatide and liraglutide could be included, that is, five RCTs and one cohort study. **Weight loss in exenatide-treated group** For exenatide the mean weight loss was -2.48 kg (95% Confidence Interval (CI) -5.12 to +0.64; p = 0.07). **Weight loss in liraglutide-treated group** For liraglutide, the mean weight loss was -4.70 kg (95% CI -4.85 to -4.56; p < 0.001).	In the search for effective interventions in patients with antipsychotic-induced weight gain, the addition of liraglutide and exenatide may result in weight loss. These GLP-1 agonists are associated with an acceptable level of adverse effects (mainly nausea) without affecting psychiatric symptoms. GLP-1 agonists may offer patients and clinicians additional options in the management of antipsychotic-induced weight gain. **Limitations:** A methodological problem with this systematic review is that it included a follow-up study by Svensson et al. (2019). The authors excluded this study because it included the same patients as the Larsen study. Of the five available GLP-1 agonists, only two compounds (exenatide and liraglutide) have been studied in patients with antipsychotic-induced weight gain. The duration of follow-up was rather short with a maximum of 24 weeks, which means that little is known about the longer-term effects. Only the study by Svensson et al. (2019) had a longer follow-up (68 weeks) after stopping liraglutide and found that the weight loss was partially maintained.

Secondary: The severity of psychopathology, proportions of patients experiencing adverse effects (nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain, and headache), systolic and diastolic blood pressure, fasting glucose and H1Abc, levels of total cholesterol, HDL (high-density lipoprotein cholesterol), LDL (low-density lipoprotein cholesterol), and triglycerides. **Search dates:** Databases were searched from date of inception till 25 August 2023. **Included study types:** Randomised controlled trials, cohort retrospective chart review.	Meta-regression analysis showed no difference in weight change between GLP-1 agonists exenatide and liraglutide (B = -2.58; p = 0.27). **BMI change in liraglutide-treated groups** For liraglutide, the mean change in BMI was -1.52 (95% CI -1.83 to -1.22; p< 0.001) in the liraglutide groups. **BMI change in exenatide-treated groups** For exenatide, the mean change in BMI was -0.82 (95% CI -1.56 to -0.09; p = 0.03). Meta-regression analysis showed no difference in BMI change between GLP-1 agonists exenatide and liraglutide (B = -0.67; p = 0.23) Subgroup analysis by study design for liraglutide, showed a mean change in BMI of -1.61 (95% CI -1.94 to -1.27; p < 0.001) for RCTs and a mean change in BMI of -1.15 (95% CI -1.87 to -0.43; p = 0.002) for the cohort study. The difference between the GLP-1-agonists remained nonsignificant (B = -0.81; p = 0.27) when we analysed RCTs only. When we excluded studies for which we calculated SDs (Ishoy et al., 2017; Lee et al., 2021) the results for liraglutide remained unchanged. For exenatide, the change in BMI remained essentially the same, but was no longer statistically significant.	Second, no data could be included that looked at GLP-1 withdrawal strategies and their effect on body weight. Does it remain stable or do patients regain weight? Therefore, the question whether patients regain weight after stopping the GLP-1 antagonist, could not be answered here. Third, the selected studies did not include lifestyle interventions in combination with the GLP-1 agonist interventions. Therefore, it is not known whether the combination of lifestyle changes and GLP-1 addition in the treatment of antipsychotic-induced weight gain leads to more weight loss than lifestyle changes or GLP-1 agonists alone. **Comments:** There were other outcomes reported by the paper which have not been extracted here.
Reference: Menon, T et al. (2024). A systematic review on the efficacy of GLP-1 receptor agonists in mitigating psychotropic drug-related weight gain. *CNS Spectrums*, [online] 29(5), pp.347–353. DOI: 10.1017/S1092852924000531 **Study population:** Adults aged 18 or older who had previously or currently been prescribed a psychotropic drug and	**Description of included studies:** Six RCTS were included in this review. Three of these studies were conducted in Denmark, and one in the UK, USA and Australia respectively. Four studies used liraglutide in their intervention group, and two studies used exenatide. **Quality of included studies:** Quality assessment was conducted using Cochrane's revised risk-of-bias tool for randomised trials. All six included studies each received a low risk of bias rating.	**Author's conclusions:** The results indicate that substantial and clinically meaningful effects of GLP-1RAs on weight and associated metabolic parameters is observed in persons with mental disorders receiving these agents either specifically to mitigate PDWG and/or contemporaneous therapeutic targeting of obesity as well as

experienced drug-related weight gain, clinically diagnosed as obese or overweight. **Intervention:** GLP-1RA – liraglutide, exenatide **Comparison:** Placebos **Outcomes:** Weight change **Primary:** **Secondary:** **Search dates:** Databases were searched from inception until January 1, 2024 **Included study types:** Randomised controlled trials	**Synthesis:** Narrative **Findings:** **Weight change** There were convergent results across six studies reporting significant weight reduction with GLP-1RA treatment in persons with psychotropic drug-related weight gain. Patients administered GLP-1RAs experienced average weight losses ranging from 3.0 to 5.3 kg, highlighting the potential of these agents to counteract the weight gain typically induced by antipsychotic medications. Wang et al. (2023) reported that participants administered subcutaneous exenatide reported an overall mean change in body weight of -5.29 kg. In addition, the mean weight loss of participants taking subcutaneous liraglutide was found to be 5.3 kg more than those in the placebo group. Similarly, McElroy et al. (2024) reported that persons administered subcutaneous liraglutide demonstrated a -3.7 kg mean change in body weight. Moreover, in a separate study by Whicher et al. (2021), it was observed that 53% of participants administered liraglutide experienced an overall weight change of ≥ 5% ($p = 0.015$). In addition, notable improvements in metabolic parameters, such as fasting plasma glucose levels dropping by up to 1.2 mmol/L and HbA1c decreasing by approximately 0.6% was reported in studies focused on prediabetic persons. More specifically, these metabolic benefits are especially critical for patients at an increased risk of diabetes and cardiovascular diseases. Only one study reported a post-intervention follow-up period of the weight effect over a 12-month period upon completion of the trial. The other studies did not include the post-intervention follow-up periods, so the review is unable to conclude on the sustained effects of GLP-1 use on weight on psychotropic drug-related weight gain.	metabolic parameters. In addition to their benefit across weight and metabolic parameters, these agents are well-tolerated and safe with no identified serious safety concerns. Future research vistas include adequate well-controlled studies with GLP-1RAs in psychiatric populations evaluating obesity, metabolic and safety outcomes (e.g., suicidality). **Limitations:** First, it is important to note that although the data generally suggest that the use of GLP 1RAs is beneficial in mitigating psychotropic drug-related weight gain, the current data are mixed, and a portion of the studies are not placebo-controlled. Overall, three of the reviewed studies where patients were blinded to their treatment and one study without blinding showed a benefit of using GLP-1RAs to mitigate psychotropic drug-related weight gain. Conversely, two studies reported no significant benefit of using GLP-1RAs for body weight reduction. Additionally, significant heterogeneity across the studies concerning patient demographics, illness characteristics, comorbidities, and treatment regimens presents a challenge. For instance, variations

	Comparison of exenatide and liraglutide in treating psychotropic drug-related weight gain All studies reported on the effects of exenatide or liraglutide on psychotropic drug-related weight gain, and both have demonstrated significant efficacy in promoting weight loss. However, their effectiveness and application vary across different populations, presenting distinct clinical implications. The specific evaluation of the use of exenatide in obese adults with schizophrenia treated with olanzapine and/or clozapine found an average weight loss of 5.29 kg, significantly more than the 1.12 kg loss in the usual care group. This is a substantial reduction in BMI by 1.78 kg/m² and improvements in fasting glucose levels and HbA1c. These findings underscore exenatide's specific utility in mitigating the challenging metabolic side effects of antipsychotic medications in patients with schizophrenia who are treated with olanzapine and/or clozapine. In contrast, investigations of daily liraglutide 3.0 mg in a broader population of overweight and obese individuals demonstrated a higher average weight loss of around 8–10% of initial body weight. Liraglutide demonstrated sustained efficacy over 6 months, with significant reductions in BMI and improvements in lipid profiles, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, while increasing high-density lipoprotein (HDL) cholesterol levels. This broader applicability suggests liraglutide may offer more pronounced weight reduction benefits compared to exenatide, particularly in patients with generalized obesity and associated cardiovascular risks. For instance, an obese patient without psychiatric comorbidities but with a high cardiovascular risk profile might find liraglutide's comprehensive metabolic benefits more advantageous.	in baseline anthropometric and metabolic status and the presence of other health conditions could have influenced the outcomes, affecting the generalisability of the findings. The psychotropic medications prescribed in the extant studies included were also not uniform and the results reported may not apply to other psychotropic regimens. Moreover, within class (e.g., antipsychotics), there is a gradient of liability for weight change; hence, no statements regarding specific mitigating capability can be made with GLP-1RAs for any particular agent. Additionally, the duration of the studies varied considerably, with some extending several months in duration, limiting the observation of long-term effects and potential side effects of GLP-1RAs. Only one study had a post-intervention follow-up, which allows the observation of the sustained effect of GLP-1. Another critical limitation is the diversity in the types of GLP-1RAs used and the dosages administered, which may affect both efficacy and safety findings with GLP-1RAs in the psychiatric population. Comments:
Reference:	Description of included studies:	Author's conclusions:

Patoulias, D et al., (2023) Effect of Glucagon-like Peptide-1 Receptor Agonists on Cardio-Metabolic Risk Factors among Obese/Overweight Individuals Treated with Antipsychotic Drug Classes: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Biomedicines*, [online] 11(3), pp.669–669. DOI: 10.3390/biomedicines11030669 **Study population:** obese or overweight adult subjects with an underlying psychotic disorder treated with antipsychotic drugs **Intervention:** GLP-1RAs **Comparison:** a control **Outcomes:** **Primary:** change in body weight **Secondary:** change in body mass index (BMI) and in waist circumference, along with indices of glycemia, lipid profile, and blood pressure **Search dates:** from inception to 1 December 2022 **Included study types:** RCTs	Data was pooled from 4 trials (2 with liraglutide and 2 with exenatide) in a total of 199 enrolled subjects. Two trials utilized liraglutide versus SOC, while the remaining two trials compared exenatide with SOC. Trials were conducted in Denmark, the United Kingdom, and Australia. Enrolled subjects were mainly diagnosed with schizophrenia or schizoaffective disorder. Mean BMI ranged from 33.7 to 39.5 kg/m^2 in the GLP-1RA arms and from 33.9 to 41 kg/m^2 in the control arms. Two trials excluded subjects with co-morbid diabetes mellitus, while the relative numbers of subjects with underlying T2DM were relatively low in the two remaining trials. **Quality of included studies:** Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) was used for the primary efficacy outcome. Overall, the risk of bias across the selected RCTs included in the present systematic review with meta-analysis is considered low. **Synthesis:** meta-analysis **Findings:** GLP-1RA treatment, compared to control, resulted in a significant decrease in body weight by 3.8 kg [mean difference (MD) = −3.80, 95% CI; −6.35 to −1.24, I^2 = 64%]. In addition, GLP-1RA treatment led to a significant decrease in BMI, compared to control, of 1.04 kg/m2 (MD = −1.04, 95% CI; −1.92 to −0.17, I^2 = 35%). However, no significant effect on waist circumference was shown (MD = −3.2, 95% CI; −6.47 to 0.08, I^2 = 88%). A significant improvement in glycemia and lipid profiles was also demonstrated with GLP-1RAs. No subgroup difference between liraglutide and exenatide was shown, and the use of GLP-1RAs did not increase the risk for treatment discontinuation compared to the control group.	GLP-1RAs appear to be an efficacious treatment option for weight management in individuals with obesity related to antipsychotic drugs, also improving glycemia and lipid profile parameters. Future trials with semaglutide are awaited in order to provide definitive answers for this interesting and challenging treatment issue. **Limitations:** Regarding the primary efficacy outcome, visual inspection of the corresponding funnel plot revealed the presence of asymmetry, possibly indicative of publication bias, although Cochrane suggests tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis. **Comments:** please note, paper does report findings for additional outcomes not extracted here.

Reference: Hegde NC, et al. (2024). Pharmacological interventions for antipsychotic-induced weight gain in schizophrenia: A network meta-analysis. *General hospital psychiatry*, 90, pp.12–21. DOI: 10.1016/j.genhosppsych.2024.06.003 **Study population:** Patients diagnosed with schizophrenia by the Diagnostic Statistical Manual (DSM-III/IV/5) or International Classification of Disease (ICD10) criteria and who were being treated with antipsychotic agents and weight-reducing agents **Intervention:** 30 different pharmacological interventions at all doses used in clinical trials were evaluated. These treatments included alpha-lipoic acid, amantadine, Atomoxetine, berberine, betahistine, bezafibrate, bupropion, d-fenfluramine, dehydroepiandrosterone (DHEA), dietary fibre, exenatide, famotidine, fluoxetine, fluvoxamine, **liraglutide**, metformin, melatonin, minocycline, naltrexone, nizatidine, orlistat, phenylpropanolamine, probiotics, ranitidine, reboxetine, rosiglitazone, samidorphan, sibutramine, topiramate and zonisamide. **Comparison:** Placebo **Outcomes:** change in body weight from baseline **Primary:** **Secondary:** **Search dates:** up to May 2024.	**Description of included studies:** The network plot was constructed from the data from 68 studies, with 4132 participants were included in the final NMA (Fig. 1). [15–82] Among 68 studies, 29 were conducted in patients who were prescribed antipsychotic drugs for the first time, were consuming for <4 weeks duration, or had not experienced weight gain, and the weight-reducing agents were prescribed as a preventive strategy. The remaining 39 studies were conducted on patients who had experienced weight gain due to antipsychotic medications, and the weight-reducing agents were prescribed as a treatment strategy. **Quality of included studies:** The risk of bias in individual studies was assessed using the standardized risk-of-bias assessment tool 2 (RoB2) of the Cochrane Collaboration. Findings of the risk of bias were presented in supplementary data, but don't appear to have been discussed in detail in the review. **Synthesis:** Network meta-analysis **Findings:** **Orlistat** From one study Orlistat 120mg, compared to placebo, no significant weight difference was found in patients with antipsychotic-induced weight gain (MD −1.7; 95% CI: −6.8 to 3.5). **Liraglutide** From one study liraglutide 1.8 mg was found to significantly reduce weight in patients with antipsychotic-induced weight gain (MD 5.2 kg; 95% CI: -10.00 to -0.080). This intervention had a moderate level of certainty.	**Author's conclusions:** In this NMA, the highest weight loss with high certainty of the evidence was seen with metformin 750 mg with lifestyle modification, topiramate 200 mg, metformin 750 mg and moderate certainty of evidence with topiramate 100 mg, and sibutramine 15 mg. From the result of the present NMA, authors conclude that metformin and topiramate are the best choices among all pharmacological agents for AIWG. Considering the limited number of studies and the small sample size in each of the currently available published literature, future multicentric active-controlled clinical trials may be conducted to validate the findings of the present NMA. **Limitations:** Authors noted the following limitations; the number of included studies and sample size for some treatment agents were limited. Hence, we should treat the result of those agents with caution, and more future RCTs are required for translation into clinical practice. The lifestyle intervention, which showed a significant impact, could not be objectively described in this NMA as the lifestyle intervention administered included psychoeducation, which is highly

Included study types: RCTs	From a different study liraglutide 3mg did not show any significant difference compared to placebo (MD: −6.0; 95% CI: −12.00 to 0.23). However, liraglutide 3 mg showed a significant difference of 12 kg, i.e., the highest weight reduction among the pharmacological interventions when adjusted for a centering body weight value of 77.40 kg. This may be representative of the fact that these interventions may act better if co-prescribed with antipsychotics rather than prescribed after weight gain due to antipsychotics.	subjective, and heart rate reserve calculated exercise, which requires expertise and is impractical to administer in day-to-day clinical practice. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Reference: Khaity A, et al. (2023). Glucagon-like peptide-1 receptor-agonists treatment for cardio-metabolic parameters in schizophrenia patients: a systematic review and meta-analysis. *Frontiers in Psychiatry*, 14. DOI: 10.3389/fpsyt.2023.1153648 **Study population:** schizophrenia or schizoaffective disorder patients who were administrated antipsychotic treatments and were overweight or obese or prediabetes. **Intervention:** subcutaneously injection of GLP1-RA whether once-weekly exenatide or once-daily liraglutide. **Comparison:** placebo **Outcomes:** body weight, metabolic syndrome parameters [blood pressure (BP), waist circumference, and fasting plasma glucose (FPG)], and adverse drug reaction, Body mass index (BMI), HbA1c, insulin, and bone turnover markers, including Procollagen type I N-terminal	**Description of included studies:** Seven RCTs (398 patients) were included in this systematic review and meta-analysis; four used liraglutide and three studies rely on exenatide. The basic characteristics of the included studies revealed that participant age ranged from 18 to 75 years old (mean age = 42.3 years, SD = 10.7). Most of the participants were male 63.3%. Additionally, the mean BMI of the included population was 36.1 kg/m^2 (SD 6.3). **Quality of included studies:** The quality of included articles ranged from fair to poor quality by the Cochrane Risk of Bias assessment tool for RCTs. **Synthesis:** meta-analysis **Findings:** **Body Weight** Five studies reported the efficacy of GLP-1RA on body weight compared to placebo. The findings presented a significant difference between the two groups [MD = −4.7 (-4.91,−4.48), p value < 0.00001]. The pooled studies were heterogeneous (P-value < 0.00001, I^2 = 96%). After performing the sensitivity analysis and excluding a single study, the heterogeneity was resolved (p value 0.8, I^2 = 0%). The results were still significant	**Author's conclusions:** Ultimately, GLP-1RA appears to be a promising therapeutic candidate, along with their additional neuroprotective effects, through improving insulin signalling, neurotransmission, neuroinflammation, and synaptic plasticity. Nonetheless, the present evidence is not enough to verify the efficacy of GLP-1RA on bone formation status. Accordingly, more trials with an increased sample size are recommended. **Limitations:** The major limitations noted by authors in this review included: (1) a limited number of included trials that assessed the role of GLP-1RA on bone turnover markers in schizophrenia patients, and (2) they observed a marked heterogeneity in some outcomes, which can be accredited to the discrepancy in the

propeptide (PINP) level and C-terminal cross-linking telopeptide of type I collagen (CTX) level. **Primary:** **Secondary:** **Search dates:** from inception until 1 August 2022 **Included study types:** RCTs	and prefer the experimental group [MD = −5.19 (-5.43, −4.95), p value < 0.00001]. **Waist circumference** Waist circumference was investigated by five studies. There was a significant difference among both groups [MD = −3.67 (-3.9, −3.45), p value < 0.00001], but there was a heterogeneity between the studies (p value < 0.00001, I^2 = 97%). However, sensitivity analysis resolved the heterogeneity. **BMI** Five studies reported the effect of GLP-1RA on the BMI compared to placebo. The consequences revealed that there was a significant difference among both groups [MD = −1.09 (-1.25, −0.93), p value < 0.00001]. The pooled studies were heterogeneous (p value = 0.003, I^2 = 75%). After performing the sensitivity analysis and excluding a single study, the heterogeneity was resolved (p value = 0.87, I^2 = 0%). The results were still significant and prefer the experimental group [MD = −1.65 (-1.97 to −1.33), p value < 0.00001.	period of intervention. Therefore, we recommend further well-designed and high-quality studies with an increased sample size to enhance the possibility of providing level 1 evidence using meta-analysis investigating the efficacy of GLP-1RA on cardiometabolic parameters and bone turnover markers in schizophrenic patients who underwent antipsychotic therapy. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Alzheimer’s disease		
Reference: Bi Z, et al. (2023). Evaluating the effects of glucagon-like peptide-1 receptor agonists on cognitive function in Alzheimer’s disease: A systematic review and meta-analysis. Advances in Clinical and Experimental Medicine, 32(11), pp.1223–1231. DOI: 10.17219/acem/161734. **Study population:** Participants were aged ≥18 years with a diagnosis of Alzheimer’s disease or with cognitive impairment without a diagnosis of Alzheimer’s disease **Intervention:**	**Description of included studies:** Five randomised controlled trials were included, consisting of 27 studies. In all trials, the treated groups had similar baseline demographics, including age and gender. The total enrolment was 177. The mean patient age was 68 years. All patients were diagnosed with AD before the trial. In 3 of the studies, patients were treated with liraglutide, whereas exenatide was used in the other 2 studies. All cognitive function tests were conducted using a scale. The scales used were the Mini-Mental State Examination (MMSE) and the Wechsler Memory Scale–Fourth Edition (WMS-IV). **Quality of included studies:**	**Author’s conclusions:** Our study summarised current clinical studies and found that GLP-1 receptor agonists can effectively improve cognitive function, BMI and blood glucose levels in Alzheimer's disease patients. There have been several previous animal studies demonstrating the effectiveness of GLP-1 receptor agonists on Alzheimer's disease, based on neural or metabolic pathways. Therefore, we would suggest that GLP-1 receptor agonists may help slow the progression of Alzheimer's disease.

GLP-1 receptor agonist – liraglutide and exenatide **Comparison:** None mentioned **Outcomes:** Cognitive function, insulin levels, blood glucose level and body mass index **Primary:** Cognitive function **Secondary:** Insulin level, blood glucose level and body mass index **Search dates:** Search date not reported however, search limits were from 1990 and 2022 **Included study types:** Randomised controlled trials	The Cochrane Risk of Bias Assessment Tool RoB2 was used for quality assessment. All five included studies displayed a low risk of bias. **Synthesis:** Meta-analysis **Findings:** Cognitive function Cognitive function was assessed using a random-effects model that included 177 patients. In the test of heterogeneity, I2 = 0% and p = 0.62, indicating low heterogeneity. After combining effect size, the meta-analysis showed that mean difference (MD) = 2.16, 95% confidence interval (95% CI): 1.45–2.88 and p < 0.05, and no publication bias was found (Begg's Test = 0.806, Egger's test = 0.153) BMI: The BMI changes were studied using a random effects model, and the results showed that heterogeneity was low (I2 = 0%, p = 0.72), with MD = −1.16, 95% CI −1.71–−0.61 and p < 0.05. The results of the sensitivity analysis showed that all the studies had little influence on the total combined effect size, and the results were reliable and acceptable.	These findings provide a relevant basis for the prevention of Alzheimer's disease. However, more clinical trials will need to be included to overcome the limited sample size and complement these findings. **Limitations:** First, because of the small number of studies meeting the inclusion criteria, only 5 reports were extracted and merged, which increased the uncertainty of the results. Second, the sample size of the study was small; therefore, verification of the results may be weak. More recent research reports should be included to supplement this meta-analysis. However, this study is the first to report the effect of GLP-1 receptor agonists during the treatment of Alzheimer's disease, which is undoubtedly significant, and more research in similar direction should be conducted in the future. **Comments:** Small sample of studies were used in this meta-analysis. Also, the paper does report findings for additional outcomes not extracted here.
Diabetic kidney transplant recipients		
Reference: Bellos, I et al., (2024). Safety and Efficacy of Sodium-Glucose Transport Protein 2 Inhibitors and	**Description of included studies:** A total of 19 studies were included. Glucagon-like Peptide-1 Receptor Agonists (GLP1-RA) were administered to 270	**Author's conclusions:** the present systematic review and meta-analysis suggests that GLP1-RA

Glucagon-like Peptide-1 Receptor Agonists in Diabetic Kidney Transplant Recipients: Synthesis of Evidence. Journal of Clinical Medicine, 13(20), p.6181. DOI: 10.3390/jcm13206181. **Study population:** Kidney transplant recipients, with or without diabetes mellitus. **Intervention:** Any SGLT2-i or GLP1-RA: semaglutide, dulaglutide, empagliflozin, dapagliflozin, canagliflozin, canagliflozin, liraglutide, ertugliflozin, exenatide, ipragliflozin **Comparison:** Placebo, standard care **Outcomes:** All-cause mortality, allograft failure, cardiovascular events (including nonfatal myocardial infarction, stroke, and hospitalisation for heart failure), glycated haemoglobin (HbA1c), body weight, eGFR, proteinuria, and systolic blood pressure **Primary:** Not specified **Secondary:** Not specified **Search dates:** From the inception of each database to 25 August 2024 **Included study types:**	recipients and Sodium-Glucose Transport Protein 2 Inhibitors (SGLT2-i) to 1003 kidney transplant recipients. A control group was included in eight studies (994 participants). The follow-up period ranged from 4 to 72 months. The median percentage of male patients was 66%. The median age of patients ranged from 51.3 to 66 years. The vast majority of patients had pre-existing or post-transplant diabetes mellitus, and only four participants had no history of diabetes. Out of the 19 studies, twelve interventions were SGLT2-i, and seven interventions were GLP1-R agonists. For the purposes of our review, the findings will only highlight GLP1-RA interventions and studies. The seven studies are Mahzari M, et al. (2024), Mallik R, et al. (2023), Vigara L, et al. (2022), Kim H, et al. (2021), Kukla A, et al. (2020), Mahmoud T, et al. (2023), and Sato T, et al. (2023). Four studies were conducted in Asia (Saudi Arabia, South Korea, Japan, and Kuwait), two in Europe (UK and Spain) and one in the USA. Body weight outcomes were only assessed in five of the seven studies. **Quality of included studies:** The methodological quality of RCTs was appraised using the RoB-2 tool and the ROBINS-I tool [15] was applied to evaluate the quality of observational studies. All seven GLP1-RA interventions were retrospective cohort studies. Three of these studies had a 'serious' risk of bias rating, and four had a 'moderate' risk of bias rating. **Synthesis:** Meta-analysis	and SGLT2-i administration in diabetic kidney transplant recipients is associated with better glycemic control and reduced body weight, presenting an acceptable safety profile. As current evidence is mainly observational, well-designed large-scale studies are warranted to elucidate the effects of GLP1-RA and SGLT2-i on hard outcomes after kidney transplantation. **Limitations:** The current evidence is mainly based on small-scale observational studies at moderate to serious risk of bias, with confounding and various forms of selection bias complicating the safe interpretation of outcomes. More specifically, the reliability of the reported results may be limited by the inadequate adjustment for important covariates in combination with the potential risk of bias in the selection of participants and the lack of a comparator group in single-arm studies. The number of existing studies was small, especially concerning cardiovascular endpoints; thus, further research is needed before safe conclusions can be reached. It should be also noted that the existing evidence concerns almost exclusively kidney transplant recipients with diabetes mellitus; thus, the generalization of outcomes

Retrospective cohort design, prospective cohort, randomised controlled trial	**Findings:** Body Weight The body weight change before and after GLP1-RA treatment was assessed in five studies [29,30,31,32,34]. The meta-analysis indicated that body weight was significantly lower after GLP1-RA therapy (MD: −3.32 kg; 95% CI: −5.04 to −1.59). Statistical heterogeneity was low (I2: 10.0%), and the 95% prediction intervals ranged from −5.51 to −1.12. The trim–fill method imputed two missing studies (new MD: −3.03; 95% CI: −4.45 to −1.61). The meta-regression analysis suggested no significant effects of study location, follow-up duration, or risk of bias. The certainty of evidence was appraised as moderate because of concerns about study limitations. The pooling of observational studies indicated that the use of GLP1-RA was associated with benefits in terms of glycemic control and body weight reduction, without significant effects on kidney function and blood pressure control.	in the non-diabetic population is not feasible. **Comments:** For the purposes of our review, the findings section of the extracted data only reported on GLP1-RA interventions and body weight outcomes. There were other outcomes in this study which have not been highlighted in this table.
Reference: Krisanapan, P, et al (2024). Safety and efficacy of glucagon-like peptide-1 receptor agonists among kidney transplant recipients: a systematic review and meta-analysis. *Clinical Kidney Journal*, [online] 17(2). DOI: 10.1093/ckj/sfae018 **Study population:** adults ≥18 years of age who have received kidney transplantation. **Intervention:** GLP-1RA **Comparison:** not noted	**Description of included studies:** This systematic review included nine studies with a sample size of 338 participants, including seven retrospective cohort studies without control groups and two retrospective cohort studies with control groups. The median follow-up time was 12 months [interquartile range (IQR) 6–23] with a range from 1 to 49.4 months. 240 individuals received GLP-1RAs and 98 individuals from two studies received non-GLP-1RAs. Almost all KTRs (98.5%) had DM, with 80% having pre-existing T2DM and 18.7% experiencing PTDM. Notably, only 5 of 338 participants from one study had no DM. Overall, 65% of participants were male with a mean age of 57.0 ± 10.5 years (from 331 participants across eight). The mean body weight was 89.1 ±	**Author's conclusions:** While GLP-1RAs may lead to an elevated risk of GI side effects in KTRs, they demonstrate significant benefits in reducing proteinuria, improving blood glucose control and promoting weight loss while avoiding changes in tacrolimus levels. **Limitations:** Authors acknowledge that only two of the nine included studies had comparator groups, meaning all

Outcomes: **Primary:** mortality and CV diseases (e.g. myocardial infarction, stroke and heart failure), on kidney graft function [e.g. changes in creatinine, estimated glomerular filtration rate (eGFR), urine protein:creatinine ratio (UPCR) or 24-hour urine protein excretion], on glycaemic and metabolic outcomes (e.g. change in blood glucose or haemoglobin A1c (HbA1c), blood pressure (BP) and lipid profile] and on weight reduction. **Secondary:** tacrolimus levels, allograft rejection and any adverse events. **Search dates:** from inception through May 2023 **Included study types:** Clinical trials and observational studies	18.8 kg (from 169 participants across seven studies and the mean BMI was 28.9 ± 6.0 kg/m2 (from 265 participants across seven studies). Dulaglutide was the most commonly prescribed GLP-1RA (46.5%), with a weekly dosage of 0.75–1.5 mg. Liraglutide (34.5%) was the second most frequently prescribed GLP-1RA, with doses ranging from 0.6 to 1.8 mg/day in six studies, followed by semaglutide (18.3%) in two studies and exenatide (0.7%). The timing for initiation of GLP-1RAs after kidney transplantation was reported in only two studies as a mean of 7.7 ± 5.3 months [49] and a median of 24 months (IQR 15–61) **Quality of included studies:** For randomized controlled trials, the Cochrane Risk of Bias Tool was used. For non-randomized studies, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool and Newcastle–Ottawa Scale were used. No comment was made in the findings or discussion about the quality of the included studies. **Synthesis:** meta-analysis **Findings:** **Weight reduction** Of eight studies with a total of 167 participants receiving GLP1RAs, the overall impact on weight reduction was statistically significant with an MD of −4.03 kg (95% CI: −5.30 to −2.77, $p < 0.001$, I^2 0%). Subgroup analysis, stratified by treatment duration, revealed that GLP-1RAs significantly reduced weight in both short-term treatment [MD −4.08 kg; 95% CI: −5.36 to −2.81; $p < 0.001$, I^2 0%; seven studies] and long-term treatment [MD −4.38 kg; 95% CI: −7.27 to −1.50; p 0.003, I^2 = 0%; two studies].	meta-analyses were performed by comparing outcomes with the baseline rather than the control group. Second, there was significant heterogeneity among the included studies, particularly in eGFR, UPCR and HbA1c outcomes. This may be due to follow-up duration, as one of the included studies had the shortest follow-up time of 1 month. In an effort to mitigate this heterogeneity, subgroup analyses were conducted based on treatment duration. However, even stratified within these subgroups, a notable degree of heterogeneity persisted. Third, due to limited available data in included studies, subgroup analyses for the type and dosage of GLP-1RAs, relationship between GLP-1RAs and other oral hypoglycaemic drugs and types of DM (T2DM versus PTDM) were precluded. Fourth, despite an Egger's test showing no significant publication bias, the forest and funnel plots for eGFR and HbA1c changes suggest the presence of a potential publication bias and small-study effect. This finding implies that smaller studies might have disproportionately influenced the pooled SMD/MD and heterogeneity values. This recognition necessitates a cautious interpretation of our findings. Lastly, this systematic review could not assess long-term CV outcomes or death due to the short-

	Sensitivity analyses excluded two studies based on the premise they were cohort studies, the impact of GLP-1RAs on weight reduction remained statistically significant, with an MD of −4.09 kg (95% CI: −5.37 to −2.81; $p < 0.001$, $I^2 = 0\%$). **BMI** Meta-analysis included six studies involving 198 participants receiving GLP-1RAs. GLP1RAs exhibited a significant reduction in BMI compared with baseline, with an MD of −1.34 kg/m^2 (95% CI: −1.80 to −0.89; $p < 0.001$, $I^2 = 0\%$). Subgroup analysis stratified by treatment duration also demonstrated a significant reduction in BMI with GLP-1RAs treatment for both short-term [MD −1.30 kg/m^2; 95% CI: −1.76 to −0.83; $p < 0.001$, $I^2 = 0\%$; five studies] and long-term use [MD −0.95 kg/m^2; 95% CI: −1.82 to −0.07, $p = 0.034$, $I^2 = 0\%$; three studies].	term follow-up period of the majority of included studies. Findings from the quality assessment were not noted in the review. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Heart disease		
Reference: Peck, KH et al. (2024) Intentional weight loss in overweight and obese patients with heart failure: A systematic review. European Journal of Heart Failure. **26**, 1907–1930. DOI:10.1002/ejhf.3270 **Study population:** adults aged ≥18 years, with a BMI >25 kg/m2, and a diagnosis of heart failure. **Intervention:** lifestyle or pharmacotherapy, or bariatric surgery. **Comparison:** **Outcomes:** mortality, hospitalization, symptoms, quality of life (QOL), exercise capacity by 6-min walking distance (6MWD), peak oxygen consumption (VO2), New York Heart Association (NYHA) class	**Description of included studies:** A total of 22 article were included. Nine studies evaluated the effects of lifestyle intervention (e.g. diet control, exercise training), **three articles studied the effects of pharmacotherapy (PCT) (weekly subcutaneous 0.25–2.4 mg semaglutide for 52weeks and oral 120 mg orlistat three times a day),** and 10 articles studied the effects of bariatric surgery (BS) (e.g. sleeve gastrectomy, Roux-en-Y gastric bypass, gastric banding). Sample sizes across the studies ranged from 7 to 33,720. The Orlistat study involved 21 individuals, and the Semaglutide studies involved 136 and 529 individuals. **Quality of included studies:** An assessment of the risk of bias for RCTs was made using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Non-randomized studies were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I).	**Author's conclusions:** This review found that there remains a clinical equipoise for intentional weight loss in HFpwO for survival and hospitalization. However, weight loss interventions are likely to improve QOL, symptoms and NYHA class. There is some evidence for bariatric surgery in improving LVEF in patients with HFrEF and obesity. These potential benefits need to be weighed against potential general harmful effects such as hypotension, hypoglycaemia, renal impairment, and more specific harmful effects related to the type of intervention such as MSK injury following exercise, GI side-effects from orlistat or

status, effects on echocardiographic parameters, biomarkers, metabolic and haemodynamic variables, and adverse events. **Primary:** **Secondary:** **Search dates:** not provided **Included study types:** clinical trials, RCTs, and prospective and retrospective observational studies.	There were a total of nine RCTs, of which four had high concerns for risk of bias, four had some concerns and one had low concern. Of the 13 non-RCTs, six were considered to have serious risk of bias and seven were considered to have moderate risk of bias. **Synthesis:** Narrative **Findings:** Findings for lifestyle and bariatric surgery are not reported here. **Semaglutide** Two studies in HFrEF and HFpEF patients, with type 2 diabetes mellitus and BMI >30 kg/m2.20,21 suggested that semaglutide was associated with significant reduction in body weight (−12.7 to −13.9 kg) over a year. There were no significant differences in all-cause mortality, or cardiovascular death. Semaglutide was also associated with improvements in QOL, NYHA class and 6MWD. After 1 year of treatment with semaglutide, there was a significant reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in one study, and a non-significant reduction in another study. Semaglutide was associated with a high incidence of gastrointestinal (GI)-related adverse events. **Orlistat** Orlistat 120 mg thrice daily for 3months led to 8.6 kg weight loss and improvements in 6MWD (45.8 [5.2–86.4] m, p=0.031) and NYHA functional class (−0.6±0.5, p=0.014), in patients with HFrEF and BMI >30 kg/m2.22. Orlistat 120 mg thrice daily did not lead to an improvement in LVEF or BNP after 3months of treatment.	semaglutide, or surgical complications from bariatric surgery. **Limitations:** Review authors found a moderate to high risk of bias in most of the studies included in our review. Causes of bias included small retrospective studies prone to confounding effects, absence of reporting of baseline medications, and analysis of outcomes which are not pre-specified endpoints. Excluded studies not reported in English language. **Comments:** please note, paper does report findings for additional outcomes not extracted here.

	Orlistat was associated with dose reduction in one of 11 patients due to diarrhoea.	
Reference: Beshr M, et al. (2025). Efficacy of Semaglutide and Other GLP-1 Agonists in Patients with Heart Failure With Preserved Ejection Fraction and Obesity: A Systemic Review and Meta-Analysis. PubMed. DOI: 10.1097/crd.0000000000000915. **Study population:** Patients with Heart Failure with Preserved Ejection Fraction (HFpEF) and obesity **Intervention:** Semaglutide and Tirzepatide **Comparison:** **Outcomes:** Changes in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), percentage change in body weight, and changes in 6-minute walk distance, changes in CRP levels from baseline, hospitalization or urgent medical visits for HF, and death from any cause. **Primary:** Changes in the KCCQ-CSS, percentage change in body weight, and changes in 6-minute walk distance **Secondary:** Changes in CRP levels from baseline, hospitalization or urgent medical visits for HF, and death from any cause.	**Description of included studies:** Four articles were included. Three of these papers were randomised control trials (Kosiborod M, et al. 2023; Kosiborod M, et al. 2024; Packer M, et al. 2025) and one (Rehman A, et al. 2024) was a retrospective cohort study. Three studies investigated the use of semaglutide and one study investigated the use of tirzepatide. **Quality of included studies:** For randomised controlled trials the Cochrane risk-of-bias tool, Risk of Bias version 2 was used, and the studies showed a low risk of bias. The observational cohort study was assessed using the Newcastle-Ottawa Scale (NOS) and scored 8, indicating high quality. **Synthesis:** Meta-analysis **Findings:** Walking distance The 6-minute walking distance change was reported in all of the included studies. The MD was 17.14 m, with a 95% CI of 11.92–22.35 and a P-value of <0.001, indicating that GLP-1 agonists significantly increased the number of meters in the 6-minute walking distance test compared with placebo. KCCQ-CSS The KCCQ-CSS change was reported in 3 studies. The MD was 7.3 points, with a 95% CI of 5.09–9.51 and a P-value <0.001, indicating that GLP-1 agonists significantly increased the KCCQ-CSS points, which correlates with improvement in HF symptoms and physical activity status compared with placebo.	**Author's conclusions:** In patients with HFpEF and obesity, GLP-1 agonists significantly improved physical function, symptoms, and quality of life in our paper. These findings were supported by the significant changes in the 6-minute walking distance and KCCQ-CSS scores. In addition, GLP-1 agonists were associated with significant weight loss, decreased inflammatory markers, and reduced hospitalisations or urgent care visits related to heart failure. These findings further support their superiority and benefit in patients with HFpEF and obesity, regardless of whether they have diabetes or not. Long-term data beyond 1 year are needed to examine whether these benefits can be sustained. **Limitations:** The mixed design of the included studies in our review is affected by the lack of randomized controlled trials. This may introduce potential variability in the data due to differences in study protocols and patient selection criteria. Most of the included trials examined the effect of GLP-1 agonists for a duration of 52 weeks, so long-term studies would be beneficial. The included trials had

Search dates: Initial search was conducted on 18 October 2024, and the update search was performed on 6 March 2025 **Included study types:** Randomised controlled trials, retrospective cohort study	Body weight percentage The change in body weight percentage was reported in all studies. The MD was −7.19, with a 95% CI of −11.28 to −3.09 and a P-value of 0.001, indicating that GLP-1 agonists resulted in greater weight loss in the treatment group compared with the placebo.	a low non-white population; therefore, including different ethnicities in future trials would further support the generalizability of these findings. **Comments:** This paper has a small sample size so generalisability should be approached with caution. Also, please note, paper does report findings for additional outcomes not extracted here.
Reference: Gupta N, et al. (2024). Semaglutide in Heart Failure: A Systematic Review of Outcomes of Semaglutide in Heart Failure Patients. *Cureus*, [online] 16(7). DOI: 10.7759/cureus.64668 **Study population:** Patients who were either at risk of or already had experienced an episode of heart failure. **Intervention:** Semaglutide **Comparison:** Placebo **Outcomes:** change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and the change in body weight. **Primary:** **Secondary:** **Search dates:** from their inception until May 10, 2024.	**Description of included studies:** Four studies were included (three RCTs and one observational study). Eighteen thousand two hundred and ninety-six T2DM patients were included in our study out of which 10,904 patients took semaglutide. These studies in general had around the same age and gender in their cohort. Two studies were from the USA while one each was from Spain and Canada. The mean age was 65.07 years with 41.7% females in the studies. Two studies used only the subcutaneous route while the other two studies used both oral and subcutaneous routes. **Quality of included studies:** The quality and bias of the studies were assessed using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Collaboration Tool for clinical trials. All studies were found to have a low risk of bias. **Synthesis:** narrative. **Findings:**	**Author's conclusions:** In conclusion, this systematic review underscores the promising efficacy of semaglutide in decreasing the incidence of HF, though it does not significantly affect the hospitalization burden associated with the condition. Objective improvements in HF management were observed through notable enhancements in the KCCQ-CSS, reductions in body weight, and increased six-minute walk distances. Furthermore, a comprehensive evaluation of clinical trials revealed significant improvements in cardiovascular events, including reductions in both fatal and non-fatal myocardial infarctions and strokes, alongside decreased CRP levels. Despite the occurrence of some adverse effects, semaglutide stands

Included study types: Observational studies and RCTs	Two of the four studies reported change in body weight outcomes. Of these, both found semaglutide produced a significant reduction in body weight (MD -13.3%, in contrast to -2.6% with placebo; estimated difference - 10.7 percentage points; 95% CI -11.9 to -9.4; P<0.001) and (12.7 kg) and body mass index (BMI) (7.1 kg/m²).	out as a potential therapeutic option for patients with HF. These findings highlight the importance of semaglutide in improving various cardiovascular parameters, suggesting its potential to contribute significantly to HF management. However, it is crucial to acknowledge the need for further research and long-term monitoring to better understand the full scope of semaglutide and other GLP1 agonists' impact in this context. **Limitations:** Limitations were not discussed in this review. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Hepatic diseases (inc. Non-alcoholic fatty liver disease & MASLD)		
Reference: Zhu K, et al. (2023). Efficacy and safety of Semaglutide in non-alcoholic fatty liver disease. *World Journal of Gastroenterology*, 29(37): 5327-5338. DOI: 10.3748/wjg.v29.i37.5327 **Study population:** Adults age 18+ with Non-alcoholic fatty liver diagnosis (NAFLD). Diagnosed via imaging (US, CT, MRI) or liver biopsy. Includes the spectrum of NAFLD (fatty liver, non-alcoholic steatohepatitis, cirrhosis). **Intervention:** Semaglutide, regardless of route or dose.	**Description of included studies:** Three RCTs included in the review. One study took place in Germany (2 sites), one across 5 countries (38 sites) and one across 16 countries (143 sites). Sample sizes ranged from 67 – 320 Mean age ranged from 55 to 60 yrs. % male ranged from 31% to 70%. % who also had Type 2 diabetes ranged from 62-75%. All three studies examined the effect of **subcutaneous Semaglutide**, however doses ranged from 0.1mg once daily to 2.4mg once weekly.	**Author's conclusions:** In conclusion, our meta-analysis of RCTs demonstrates that semaglutide has beneficial histologic, radiologic, liver enzyme, and cardiometabolic effects in patients with NAFLD, with a well-tolerated safety profile. Semaglutide is particularly beneficial for patients with NAFLD and features of metabolic syndrome, given its notable effects on lowering HbA1c and promoting weight loss. However, the results are limited by the small number of included studies and

Semaglutide in addition to standard of care (e.g. patient already on other anti-diabetic medications for diabetes) **Comparison:** Placebo. **Outcomes:** SR included any outcomes. Those assessed by the three included studies were: **Primary:** - Resolution of NASH - Liver stiffness MRE at week 48. - Liver fibrosis stage **Secondary:** - Liver fibrosis stage, total and component of NAS, ALT, AST, liver stiffness, liver steatosis, cardiometabolic parameters, adverse events. - Liver stiffness at weeks 24 and 72, liver steatosis, ALT, AST, cardiometabolic parameters, adverse events. - Liver stiffness, liver steatosis, NASH resolution, total and component of NAS, ALT, AST, cardiometabolic parameters, adverse events. **Search dates:** 1ST May 2023 **Included study types:** RCTs, non-RCTs, Prospective controlled trials.	**Quality of included studies:** ROB assessed using Cochrane ROB2 tool, and quality of evidence evaluated using GRADE framework. **Synthesis:** Meta-analysis **Findings:** Effect of semaglutide on histological parameters: - Semaglutide associated with significantly higher likelihood of NASH resolution with no worsening of liver fibrosis (OR: 3.18, 95% CI: 1.70 to 5.95, I^2=0%, 2 studies, 301 participants. GRADE: +++O Moderate). - No significant improvement in liver fibrosis stage without worsening of NASH (OR: 0.71, 95% CI: 0.15 to 3.41, I^2=80%, 2 studies, 301 patients. GRADE: ++OO: Low) **Weight related outcomes:** - **Significant reduction of 6.53kg compared to placebo (95% CI: -11.21 to -1.85, I^2=0%, 3 studies, 458 participants).**	clinical heterogeneity, which restricts the generalizability these findings across the spectrum of NAFLD. Additional RCTs with larger sample sizes and longer durations are required to characterize the effects of semaglutide on fibrosis regression and its role in the different phases of NAFLD **Limitations:** Included RCTs are clinically heterogeneous – with patients across the spectrum of NAFLD. This limits applicability of results, as treatment and response across the spectrum of NAFLD may differ. Additionally, a range of doses of Semaglutide was used across trials from 0.1mg once daily to 2.4mg once weekly. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Reference: Wang H, et al. (2024). Optimized strategy among diet, exercise, and pharmacological interventions for nonalcoholic fatty liver disease: A network	**Description of included studies:** This network meta-analysis aimed to assess the relative efficacy of all treatments excluding bariatric surgery for the management of NAFLD. 174 articles included in the review. All articles published between 2005-2022. 103 undertaken in	**Author's conclusions:** Our systematic review and network meta-analysis of RCTs supports that different treatment strategies were associated with different

meta-analysis of randomized controlled trials. *Obesity Reviews.* E13727. DOI: 10.1111/obr.13727 **Study population:** Adults 18+ with ultrasound, CAP, MRS, MRI or histology evidence of NAFLD. **Intervention:** All drug treatments and lifestyle modifications (diet or exercise) **Comparison:** Another treatment plan, or placebo. **Outcomes:** Improvement in fibrosis, as assessed by ballooning degeneration, steatosis, lobular inflammation and/or markers of liver injuries and/or metabolic dysfunctions. Primary and secondary not specified. **Search dates:** Up to February 1, 2023. **Included study types:** RCTs	Asian, 39 Europe, 24 America, 8 Australia. Total of 10,183 participants. 54.68% male and adult, 13.9% had NASH and 28.68% diabetes. Mean age 48.3yrs. Average study duration 12 weeks, with treatment time ranging from 3 weeks to 2 years. Review included trials examining diet interventions, exercise interventions, and drug interventions (including Orlistat, GLP-1s and combinations of GLP-1s + other drugs). Six studies were included that investigated orlistat versus a low-calorie diet or placebo. **Quality of included studies:** Cochrane risk of bias tool was used to evaluate the quality of included studies. The overall research quality was relatively good without obvious bias. **Synthesis:** Network meta-analysis **Findings:** Orlistat was associated with BMI reduction, although not significantly (ME = -3.98 (95% CI: -12.72 to 4.76). This remained the case after removing studies with a short follow-up of less than six months (MD = -1.63, 95% CI: -11.05 to 8.74). Based on the SUCRA curve and the rankogram orlistat was ranked third most effective (56.1%)	improvements of NAFLD varied from weight management, metabolic control, liver fat, liver damages or fibrosis regression. Pan-agonist of PPAR seem to be the most effective in weight control in NAFLD, while GLP-1R agonists were identified to exert the most beneficial effects in reducing the hepatic fat content, which would provide the reference of the optimum choice of treatment plan for NAFLD related abnormalities. **Limitations:** Authors acknowledged several limitations with the evidence base including small sample sizes; diabetes (approximately 32% of patients in the current studies) and obesity coexist, implying that the generalizability of the conclusion to lean individuals remains unclear. Third, the lack of dose comparison in drug-related research and the lack of subgroup analysis of different follow-up time for diet and exercise hinder the applicability of our findings. Some included trials had a relatively small number of participants, which may have affected the outcomes and analysis about the durations and drug dosages for liver endpoints. Our study did not further classify MAFLD patients, however, it is important to

		note that patients with different subtypes have varying long-term risks of developing type 2 diabetes, coronary heart disease and other extrahepatic complications. This suggests the need for personalized management objectives.192 In addition, not all of the selected studies were placebo-controlled, which may increase heterogeneity. Comments: Authors noted that asymmetric distribution of the funnel plot indicated the possibility of publication bias. Please note, the paper does report the findings for additional outcomes not extracted here.
Reference: Ren, Q. et al. (2025). Efficacy of Hypoglycemic Agents in Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD): A systematic review and network meta-analysis. *Journal of Evidence-Based Medicine*. DOI: 10.1111/jebm.70021 Study population: Adults age 18+ with MASLD diagnosed based on liver biopsy histology, imaging or blood biomarkers/scores with one of the following three conditions: overweight or obesity, T2DM, or metabolic dysfunction. Intervention:	Description of included studies: 37 studies involving 2,406 participants were included in the review. This covered 26 interventions including TZDs, SGLT-2is, DPP-4is, GLP-1RAs, sulfonylureas, GLP-1R/ GCGRdual agonist, GLP-1R/GIPR/GCGR triple agonist, metformin, and control. Three of the included studies examined Liraglutide as part of the intervention, with dosages of 0.6-1.8mg/week in two studies (dose not specified in third study). Quality of included studies: ROB assessed using Cochrane ROB2 tool. Five RCTs evaluated as low ROB, 32 as unclear ROB. Synthesis: Network meta-analysis	Author's conclusions: In conclusion, in this comprehensive network meta-analysis, evidence on the efficacy of various hypoglycemic agents, including TZDs, SGLT-2is, DPP-4is, GLP-1RAs, sulfonylurea, GLP-1R/GCGR dual agonists, GLP-1R/GIPR/GCGR triple agonists, and metformin, for the treatment of MASLD was analysed. Although these agents demonstrated improvements in laboratory and imaging markers in adults with MASLD, specific agents showed superior effectiveness in different

thiazolidinediones (TZDs), sodium-glucose co-transporter 2 inhibitor (SGLT-2is), dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), GLP-1 receptor/glucagon receptor (GLP-1R/GCGR) dual agonist, GLP-1 receptor/GIP receptor/glucagon receptor (GLP-1R/GIPR/GCGR) triple agonist, sulfonylurea, metformin or diet therapy or lifestyle modification. **Comparison:** Not specified **Outcomes:** **Primary:** Changes in liver imaging metrics, including LSM and liver-to-spleen CT attenuation ratio (L-S ratio) **Secondary:** Anthropometric measures including BMI, body weight and waist circumference **Search dates:** 31 December 2024 **Included study types:** RCTs	**Findings:** Anthropometrics: *[Note supplementary material for this review includes forest plots of relative effects of Liraglutide vs control for BMI, body weight and waist circumference, however specific numbers are not reported on the plots, so these have not been reported here so as not to misinterpret. However, from the visual, **the 95% CI's do not appear to cross the line of no effect, therefore suggesting a significant effect for Liraglutide compared to control for BMI, body weight and waist circumference**]* Results of network and pairwise meta-analysis for Liraglutide: • BMI: MD -1.77 (95% CI: -5.23 to 1.65) • Body weight: MD -4.02 (95% CI: -11.11 to 3.07) • Waist circumference: MD -4.89 (95% CI: -12.82 to 3.39)	aspects. Liraglutide stood out for its overall efficacy, whereas empagliflozin was particularly effective in reducing LSMs. These findings highlight the importance of targeting MASLD's multifactorial pathophysiology—spanning insulin resistance, lipotoxicity, and inflammatory signalling—through mechanism-specific agents like SGLT-2 inhibitors and GLP-1RAs. **Limitations:** Substantial clinical heterogeneity in the included articles, such as differences in clinical use of hypoglycemic agents and intervention time, and cost was also important, such as the high price of insulin glargine and GLP-1 RAs. However random-effect model used to reduce the impact of these factors. Only English and Chinese literature included, reducing generalizability of findings to diverse populations. **Comments:**
Reference: Park, MJ (2023) Comparison of glucagon-like peptide-1 receptor agonists and thiazolidinediones on treating nonalcoholic fatty liver disease: A network meta-analysis. Clinical and Molecular Hepatology. 29:693-704. DOI: 10.3350/cmh.2022.0330	**Description of included studies:** Twenty-five RCTs with 2,237 overweight or obese patients were included. Eight studies compared GLP-1RA (**6 liraglutide, 1 semaglutide**, and 1 dulaglutide) and placebo; 16 studies, TZD (13 pioglitazone, 3 rosiglitazone) and placebo; one study, GLP-1RA	**Author's conclusions:** The results of this study showed that GLP-1RA was superior to TZD in terms of reducing liver fat content and improving cardiometabolic risk parameters such as BMI and WC in overweight or obese patients with

Study population: Adult patients with NAFLD or NASH detected via biopsy or other imaging methods. **Intervention:** TZD or GLP-1RA for at least 3 months **Comparison:** Active control (TZD or GLP-1RA) or placebo control. **Outcomes:** (1) Liver biopsy-based outcomes: NAS, fibrosis stage, and NASH resolution (2) Noninvasive technique-based outcomes: liver fat content on 1H-MRS and CAP (3) Biological outcomes: ALT, AST, HbA1c, FPG, HOMA-IR, T-Chol, LDL-C, and TG. (4) Anthropometric outcomes: BMI and WC **Search dates:** from inception to 26 July 2021. **Included study types:** RCTs	and TZD. Six of the 25 studies included only T2DM patients. Nine studies included only patients without diabetes, and the remaining studies included participants regardless of diabetic status. All interventions were applied for at least 12 weeks, with a maximum duration of 96 weeks. **Quality of included studies:** Risk of bias was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB 2.0). All studies, except six studies, showed a mild to moderate risk of bias due to a risk of incomplete outcome data. **Synthesis:** Network Meta-analysis. **Findings:** Findings compare all GLP-1RAs with TZDs. No individual drugs outcomes are reported. GLP-1RA was significantly superior in reducing liver fat content evaluated using 1H-MRS (MD -2.42, 95% CI -3.84 to -1.00), body mass index (MD -1.60, 95% CI -2.41 to -0.80), and waist circumference (MD -4.89, 95% CI -8.17 to -1.61) than thiazolidinedione. Network graphs, effect estimates of individual studies and pairwise meta-analysis, comparisons of direct and network estimates and forest plots are available as supplementary data on the website.	NAFLD or NASH. Based on the results, GLP-1RA can be considered over TZD for the treatment of overweight or obese patients with NAFLD or NASH in a clinical setting. **Limitations:** Findings of this review incorporate all GLP-1RA's with no individual findings reported for each drug within this classification. No information provided on the limits applied to searching. For example no information was provided on any language limits applied to screening. Authors also acknowledge that caution is required in interpreting findings due to indirect comparisons. In addition, authors noted heterogeneity among the included studies in terms of treatment duration, characteristics of the study population, and medication doses. To address the problem, they adopted a random effects model for analysis and conducted a sensitivity analysis excluding studies with a high risk of bias. Due to the inherent limitations of NMA, this study could not perform a subgroup analysis

		according to the confounding factors of NAFLD, such as race, BMI, or ALT, which could not be obtained from the original article. And, due to the limited number of studies, subgroup analyses were only undertaken for biological and anthropometric outcomes, and the results were inconclusive. These inconsistencies may be due to the small sample size of the included studies, differences in baseline characteristics of study participants, differences in study design such as follow-up duration or control group, and other factors.
Reference: Malik, A, et al. (2023). The effects of liraglutide on liver enzymes and metabolic factors in patients with nonalcoholic steatohepatitis: a meta-analysis of randomized controlled trials. *Gastroenterology Review*, 18(1), pp.100–109. DOI: 10.5114/pg.2022.112775 **Study population:** patients with Nonalcoholic steatohepatitis (NASH) **Intervention:** liraglutide regardless of the dose and the mode of drug administration **Comparison:** no information was provided. **Outcomes:** **Primary:** alanine aminotransferase (ALT) (IU/l), aspartate aminotransferase (AST) (IU/l), alkaline	**Description of included studies:** Five studies met our inclusion criteria. A total of 180 patients were included in these 5. Of 180 patients, 89 received liraglutide in the treatment group, and 91 patients were assigned to the control group. The mean age of the treatment group was 56.2 ±9.18 years, while that of the control group was 57.7 ±9.26 years. The mean BMI of patients in the liraglutide group was 32.97 ±3.8, while that of the control group was 33.41 ±4. **Quality of included studies:** This was assessed using the Cochrane risk of bias (ROB) tool for clinical trials. All studies were at low risk of randomization, except one which was marked as high risk of bias. This study had high risk of bias due to selection, performance and detection bias. **Synthesis:** meta-analysis	**Author's conclusions:** Liraglutide appears to effectively improve lipid profile (HDL and LDL) in patients with NASH. However, its effect is not remarkable in reducing liver enzymes. While there is currently a paucity of data on liraglutide efficacy, further research may prove it to be a potential therapy for the prevention of NASH progression and/or disease reversal. **Limitations:** The small number of studies included and small sample size (180 patients) was considered a limitation by authors and reduces the findings' generalizability.

phosphatase (ALP) (IU/l), and γ-glutamyl transferase (GGT) (IU/l) **Secondary:** body mass index (BMI) (kg/m2), waist circumference (cm), total cholesterol (TC) (mmol/l), triglyceride (TG) (mmoll), high-density lipoprotein (HDL) (mmol/l), low-density lipoprotein (LDL) (mmol/l), and glycated hemoglobin (HbA1c) (%). **Search dates:** from inception until October 2020 **Included study types:** RCTs	**Findings:** **BMI** was reported by all studies. The overall mean difference did not reveal any statistically significant difference between both groups (MD –1.50; 95% CI: –3.95 to 0.95; $p = 0.23$). Pooled analysis was heterogeneous ($p = 0.08$; I^2 79%). To reduce heterogeneity, authors excluded one study ($p = 0.28$; $I^2 = 22\%$). However, the pooled analysis after exclusion still showed no statistically significant difference between either group (MD –0.26; 95% CI: –1.68 to 1.16; $p = 0.72$). Three studies reported the **waist circumference measurements**. The combined mean difference did not reveal a statistically significant difference between both groups (MD –6.19; 95% CI: –14.70, 2.32; $p = 0.15$). Pooled data were heterogeneous ($p = 0.02$; I^2 =75%). %). To reduce heterogeneity, authors excluded one study ($p = 0.94$; $I^2 = 0\%$). The pooled analysis after the exclusion favoured the liraglutide group over the control group (MD -10.96; 95% CI: –16.79, –5.14; $p = 0.02$).	Additionally, the included studies did not report many data about liraglutide side effects, which further necessitates clinical trials providing a detailed safety profile. **Comments:** Authors stated they used GRADE to assess the quality of the systematic review. However, GRADE is used to assess the certainty of outcome findings. These were not reported in the review. please note, paper does report findings for additional outcomes not extracted here.
Reference: Mahmoud, A et al (2024). Efficacy of orlistat in obese patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Proceedings - Baylor University. Medical Center*, 37(4), pp.1–10. DOI: 10.1080/08998280.2024.2335829 **Study population:** patients with NAFLD diagnosed via ultrasound, computed tomography, magnetic resonance imaging (MRI), or liver biopsy. **Intervention:** orlistat **Comparison:** placebo	**Description of included studies:** Four RCTs with a total of 379 patients were included. Two RCTs were conducted in China, one in Iraq, and one in the USA. **Quality of included studies:** The Cochrane ROB2 tool was used to assess study quality. All included studies had some concerns. All had concerns regarding bias arising from the randomization process. Authors could not tell if the allocation was concealed until the patients were assigned to the treatment group. All had some concerns regarding bias in the selection of the reported results, as authors could not find the published protocol to compare it with the study itself. **Synthesis:** meta-analysis.	**Author's conclusions:** This meta-analysis suggests that orlistat may be a beneficial treatment option for NAFLD as it significantly reduces liver fat content and liver enzymes in affected patients. Furthermore, the analysis confirms the established benefits of orlistat in improving anthropometric measures. However, regarding its effects on dyslipidemia in NAFLD patients, orlistat was found to improve total cholesterol and non–high-density lipoprotein levels but increase triglyceride levels. This finding highlights the potential

Outcomes: **Primary:** liver fat content measured by MRI-estimated proton density fat fraction (MRI-PDFF) percentage reduction and liver enzymes. **Secondary:** blood pressure, blood glucose, anthropometric measurements, and lipid profile. **Search dates:** until March 27, 2023. **Included study types:** RCTs	**Findings:** GRADE assessments were also undertaken to assess the overall certainty of the evidence base. Orlistat was significantly associated with reduced waist circumference, BMI, and abdominal circumference. These results were based on pooled studies found to be homogenous, indicating consistent effects of orlistat across different studies. **Waist circumference** Overall certainty of the evidence was low (3 RCTs; 299 participants; MD -3.18; 95% CI -4.25, -2.10; I^2 0%). **BMI** Overall certainty of the evidence was low (4 RCTs, 340 participants; MD -1.03; 95% CI: -1.34, -0.73; I^2 0%). **Abdominal circumference** Overall certainty of the evidence was moderate (2 RCTs, 249 participants; MD -3.41; 95% CI: -1.62, -2.30; I^2 0%).	limitations of orlistat use in patients with hypertriglyceridemia. Analysis did not find any significant improvement in blood pressure or fasting blood glucose levels associated with orlistat treatment. **Limitations:** Authors noted the studies included in the analysis may have had differences in patient populations, dosages, durations of treatment, and concomitant interventions, which could have impacted the response to orlistat treatment and led to variability in outcomes. Second, there may be a lack of long-term data on the effects of orlistat, as most studies had a duration of 12 weeks or less. Third, authors were also limited by a lack of data on patient-centered outcomes, such as quality of life, adverse events, and medication adherence. Finally, the analysis may be subject to confounding factors, such as patients already taking medication for NAFLD, which could have affected the response to orlistat treatment. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Acquired hypothalamic obesity		

Reference: NG, V et al. (2024) The role of glucagon-like peptide 1 receptor agonists for weight control in individuals with acquired hypothalamic obesity—A systematic review. Clinical Obesity. 14:e12642. DOI: 10.1111/cob.12642 **Study population: P**atients of all ages with acquired hypothalamic obesity. **Intervention:** GLP-1RA types included Exenatide, Liraglutide, Dulaglutide in various dosages. All administered subcutaneously. Other intervention details not reported. **Comparison:** Placebo where reported, but in most the comparison was before and after. **Outcomes:** **Primary:** weight, BMI, glycaemic index and appetite **Secondary:** adverse effects of GLP-1RA **Search dates:** inception of the databases until April 2023 **Included study types:** RCTs, case reports and cases series	**Description of included studies:** Ten studies with a total of 54 patients (24 males, 30 females) with hypothalamic obesity, with age range of 13–71 (mean 25.2) years were included At least 32 of the 54 participants were below 25 years old. Craniopharyngioma was the commonest aetiology for HO, affecting 42 patients (77.8%); 8 had other forms of suprasellar tumours including germinoma, 2 had astrocytoma, 1 traumatic brain injury and 1 cerebral aneurysm with hypothalamic involvement. For associated comorbidities, 45 (83.3%) patients had panhypopituitarism, while 13 (24.0%) had concurrent T2DM at the time of initiation of treatment. For the GLP-1RA type, 48 patients received exenatide, 5 patients received liraglutide while 1 received dulaglutide; all GLP-1RA were administered subcutaneously. The mean duration between onset of HO and initiation of GLP-1RA is 13 years (range 2 years to 24 years). The mean duration of GLP-1RA treatment was 12 months (range from 3 to 51 months) in this systematic review. **Liraglutide** was examined in four studies with a dose ranging from 0.3mg, 0.9mg 3mg daily for between eight months and two years or more (exact duration not specified) **Semaglutide** was examined in one clinical trial, where patients were administered an unspecified dose for one year. This trial was ongoing at the time the systematic review was published. **Quality of included studies:** ROB assessed using Joanna Briggs Institute (JBI) Critical Appraisal Tools for Case Reports and Case Series respectively, and Cochrane Risk-of-Bias (ROB) tool for randomized controlled trials. All 6 of the case reports and 3 of the case series were of sufficient quality to be included in the systematic review, while the only RCT was graded as 'low risk of bias'.	**Author's conclusions:** Based on limited published clinical experience, GLP-1RA appears to be a promising therapy for weight control in HO and is generally well-tolerated. This may be a pertinent option for patients who have concurrent T2DM, where there is the additional benefit of improved glycaemic control. We eagerly anticipate the outcomes of the ongoing trial on semaglutide use in patients with HO. As the repertoire of GLP-1RA developed for weight loss continues to expand, its use and potential benefits in HO should be systematically and thoroughly evaluated, in search of an optimal way to manage weight gain and its associated complications in these patients. **Limitations:** In the absence of sufficient RCTs or prospective observational studies, authors opted to include clinical data reported through case reports and series. Authors acknowledge pooling these results has significant limitations due to the heterogenous nature of the patient population, the type, dose and frequency and duration of the GLP-1RA used. However authors have attempted to analyse the outcome data according to these subgroups where data is available, to provide granularity for

	Synthesis: Narrative synthesis **Findings:** **Liraglutide:** All 5 patients had weight reduction post-therapy, with mean weight loss of 12.4 (SD 9.9) kg and mean weight change of -10.2% (SD 5.0) from baseline. **Semaglutide:** As this trial was ongoing at the time of publication, no findings were available.	the effects of different GLP-1RA use in acquired hypothalamic obesity. Only English publications were included, reducing generalisability of findings to diverse populations. Authors note that one of the case series was not of sufficient quality to be included in the review, however do not provide any justification for excluding. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Chronic kidney disease		
Reference: Natale, P et al. (2025) Glucagon-like peptide 1 (GLP-1) receptor agonists for people with chronic kidney disease and diabetes. *Cochrane Database of Systematic Reviews*, Issue 2. Art. No.: CD015849. DOI: 10.1002/14651858.CD015849.pub2. **Study population:** participants with diabetes and chronic kidney disease (stages 1 – 5). **Intervention**: GLP-1 receptor agonist, placebo, standard care or a second glucose-lowering agent **Comparison:** as above **Outcomes:**	**Description of included studies:** Forty-two studies involving 48,148 participants were included. All studies were conducted on people with type 2 diabetes, and no studies were carried out on children. The median study age was 66 years. The median study follow-up was 26 weeks. Six studies were conducted in people with CKD stages 1-2, 11 studies in people with CKD stages 3-5, one study in people on dialysis, and the remaining studies included people with both CKD stages 1-2 and 3-5. Although the review looked at GLP-1RAs overall, several studies included examined the effects of semaglutide and liraglutide. **Quality of included studies:** Risk of bias was assessed using the Cochrane risk of bias assessment tool 2 (ROB-2).	**Author's conclusions:** GLP-1 receptor agonists probably reduced all-cause death but may have little or no effect on cardiovascular death in people with CKD and diabetes. GLP-1 receptor agonists probably lower major cardiovascular events, probably have little or no effect on kidney failure and composite kidney outcomes and may have little or no effect on the risk of severe hypoglycaemia in people with CKD and diabetes. **Limitations:** Authors noted It was possible that some potential studies have been missed due to publication bias (e.g. conference abstracts, dissertations).

Primary: Death (all-cause and cardiovascular), 3- and 4-point major adverse cardiovascular events (MACE), kidney failure, composite kidney outcome, and severe hypoglycaemia **Secondary:** non-fatal or fatal myocardial infarction (MI) or stroke, non-fatal peripheral arterial events, heart failure, hospitalisation due to heart failure, estimated glomerular filtration rate or creatinine clearance, doubling of serum creatinine, urine albumin-to-creatinine ratio, albuminuria progression, vascular access outcomes, body weight, body mass index, fatigue, life participation, peritoneal dialysis infection, peritoneal dialysis failure, adverse events, serious adverse events, withdrawal due to adverse events, HbA1c, sudden death, acute MI, ischaemic stroke, and coronary revascularisation. **Search dates:** to 10 September 2024 **Included study types:** RCTs and quasi-RCTs	Risks of bias in the included studies for all the primary outcomes in studies that compared GLP-1 receptor agonists to placebo were low in most methodological domains, except one study that was assessed at high risk of bias due to missing outcome data for death (all-cause and cardiovascular). The overall risk of bias for all-cause and cardiovascular death in studies that reported the treatment effects of GLP-1 receptor agonists compared to standard care, dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT2) inhibitors were assessed as unclear or at high risk of bias due to deviations from intended interventions or missing data. For GLP-1 receptor agonists compared to insulin or another GLP-1 receptor agonist, the risk of bias for all-cause and cardiovascular death was low or unclear. **Synthesis:** meta-analysis **Findings:** Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. **Analysis included all GLP-1RAs, and no sub-group analysis in individual pharmacotherapies appears to have been undertaken.** **GLP-1 receptor agonists versus placebo** **Body weight** • GLP-1 receptor agonists may decrease body weight compared to placebo (MD -5.34 kg, 95% CI -8.72 to -1.96; 1 study, 80 participants; low-certainty evidence) in people with CKD stages 1-2. • GLP-1 receptor agonists may decrease the change in body weight compared to placebo (MD -2.50 kg, 95% CI -3.33 to -1.67; 1 study, 324 participants; low-certainty evidence) (MD -0.86 kg, 95% CI -1.46 to -0.26; IQ = 51%; 3 studies; low certainty evidence) in people with all CKD stages	Some assumptions on classification for author-self-reported outcomes (3- or 4-point MACE and a composite kidney outcome) or CKD subgroups extracted from studies reporting mixed populations or from those where only GFR values have been reported may underestimate our confidence in reporting. Despite efforts to minimise missing results in specific syntheses, authors note this may prevent the generalisability of their results. **Comments:** Cochrane reviews are noted for their rigorous methodology please note, paper does report findings for additional outcomes not extracted here.

	and type 2 diabetes. Similar results were seen in the subgroups for CKD stages 1-2, CKD stages 3-5 and people on dialysis. Body mass index • GLP-1 receptor agonists may decrease BMI compared to placebo (MD -2.47 kg/m2, 95% CI -3.35 to -1.59; 1 study, 80 participants; low-certainty evidence) in people with CKD stages 1-2. • GLP-1 receptor agonists may decrease the change in BMI compared to placebo (MD -0.71 kg/m2, 95% CI -1.10 to -0.32; IQ = 74%; 2 studies, 572 participants; low-certainty evidence) (MD -0.51 kg/m2, 95% CI -0.83 to -0.19; 1 study; low-certainty evidence) in people with CKD stages 3-5 and type 2 diabetes. GLP-1 receptor agonists versus standard care *Body mass index* One study reported GLP-1 receptor agonists may decrease BMI compared to standard care alone (MD -1.61 kg/m2, 95% CI -3.00 to -0.22; 1 study, 84 participants; low-certainty evidence) in people with all CKD stages and type 2 diabetes. GLP-1 receptor agonists versus insulin *Change in body weight* It was uncertain whether GLP-1 receptor agonists had any effects on change in body weight compared to insulin (MD -1.68 kg, 95% CI -3.72 to 0.36; IQ = 95%; 2 studies, 630 participants; very-low-certainty evidence) (MD -3.80 kg, 95% CI -4.80 to -2.80; 1 study; very-low-certainty evidence) in people with all CKD stages and type 2 diabetes. *Body weight increase* GLP-1 receptor agonists had uncertain effects on body weight increase compared to insulin (RR 0.57, 95% CI 0.30 to 1.10; 1 study, 576 participants; very-low-certainty evidence; in people with CKD stages 3-5 and type 2 diabetes.	

	GLP-1 receptor agonists versus SGLT2 inhibitors *Body weight* One study reported GLP-1 receptor agonists may increase body weight compared to SGLT2 inhibitors (MD 7.43 kg, 95% CI 4.41 to 10.45; 1 study, 80 participants; low-certainty evidence). *Body mass index* One study reported GLP-1 receptor agonists may increase BMI compared to SGLT2 inhibitors (MD 1.53 kg/m2, 95% CI 0.63 to 2.43; 1 study, 80 participants; low-certainty evidence).	
Reference: Krisanapan P, et al (2024b). Safety and Efficacy of GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus with Advanced and End-Stage Kidney Disease: A Systematic Review and Meta-Analysis. Diseases, 12(1), pp.14. DOI: 10.3390/diseases12010014 **Study population:** adults aged 18 years or older with type 2 diabetes mellitus (T2DM) with advanced chronic kidney disease (CKD) defined as CKD stage 5 (estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2) or ESKD undergoing haemodialysis or peritoneal dialysis. **Intervention:** GLP-1RAs **Comparison:** a control group, which were defined as placebo, standard glucose-lowering medications, or lifestyle modification. **Outcomes:** All-cause mortality, cardiovascular events (including cardiovascular death, myocardial infarction, stroke, and heart failure), the change in blood pressure or left ventricular hypertrophy, the change in blood glucose, the change in weight or body composition, renal outcomes (the rate of	**Description of included studies:** Eight studies (five trials and three cohort studies) consisting of 27,639 patients were included in this meta-analysis. These studies comprised of 4 non-randomized controlled studies, 3 retrospective cohorts, and 1 RCT. Seven studies were conducted in Asia and only 1 from Europe. Liraglutide was the most frequently used GLP-1RAs across 5 studies, with doses ranging from 0.3 to 1.8 mg daily. Dulaglutide was also commonly reported in 3 studies with a fixed weekly dose of 0.75 mg, while lixisenatide was only reported in 1 study without dose description. All 8 studies evaluated ESKD patients undergoing dialysis, while only 2 studies included a subgroup of stage 5 nondialysis (ND) CKD patients. Overall, 54.4% of the patients were male, with a mean age of 64.8 ± 13.0 years and a mean body mass index (BMI) of 24.7 ± 4.6 kg/m^2. The mean duration of DM and RRT were 9.6 ± 7.4 and 1.4 ± 2.4 years, respectively. Baseline HbA1c was 7.1 ± 1.5%, and glycated albumin was 23.8 ± 7.5%. Notably, 21% of patients had preexisting coronary artery disease in 3 studies. **Quality of included studies:** The Risk of Bias In Non-randomized Studies—of Interventions (ROBIN-I) tool was used in cohort and non-randomized	**Author's conclusions:** Our study summarizes the safety and efficacy size of GLP-1RAs among T2DM patients with advanced CKD and ESKD. While GLP-1RAs might increase the risk of GI side effects, GLP-1RAs demonstrate significant improvements in blood glucose control, weight reduction, and potential benefit in cardiovascular outcomes. **Limitations:** Authors acknowledged several imitations in this review including the inclusion of a few studies with a limited number of patients in each analysis resulted in significant heterogeneity among the included studies on certain outcomes of interest, including SBP, HbA1c, and hypoglycemia. Secondly, the short-term follow-up period of the included studies, most of which were within one year, limits our ability to assess long-term outcomes such as

GFR or proteinuria reduction), or any adverse events. **Primary:** **Secondary:** **Search dates:** from inception through 25 October 2023. **Included study types:** clinical trials and cohort studies.	controlled studies, and the Cochrane Risk of Bias (RoB 2) tool was used in randomized controlled trials (RCTs). **Synthesis:** meta-analysis **Findings:** Three trials evaluated GLP-1RAs treatment effect on weight at 3–12 months. From this meta-analysis, GLP-1RAs significantly reduced weight from baseline as compared to controls with an SMD of −2.2 kg (95% CI −2.9, −1.5; I^2 = 0%).	mortality and MACE. Thirdly, the included studies predominantly involved Asian populations, which may limit the generalizability of findings to other ethnic groups. This study did not include patients with ESKD who were transplanted, nor did it have sufficient numbers to perform a subgroup analysis on the type of dialysis modality and the associated impact of GLP-1RAs. Finally, only a few studies evaluated blood glucose levels with CGM, and none of them reported self-monitoring blood glucose, which is more reliable than HbA1c in patients with advanced CKD and ESKD. **Comments:** please note, paper does report findings for additional outcomes not extracted here.
Obstructive sleep apnoea		
Reference: Altobaishat O, et al., (2025) Safety and efficacy of glucagon-like peptide-1 receptor agonists in patients with obstructive sleep apnea: a systematic review and meta-analysis of randomized controlled trials. European Clinical Respiratory Journal, [online] 12(1). DOI: 10.1080/20018525.2025.2484048. **Study population:** Non-diabetic patients with obstructive sleep apnea (OSP) **Intervention:** GLP-1 agonists: tirzepatide and liraglutide	**Description of included studies:** Two studies – (Blackman et al. 2016 and Malhorta et al. 2024) – describing three RCTs were included in the systematic review and meta-analysis. Of the three RCTs included, two involved tirzepatide (a combined GLP-1 and GIP agonist) and one involved a GLP-1 agonist (liraglutide). Therefore, for clarity, in the pooled analysis, the intervention group was referred to as the GLP-1/tirzepatide group. The final analysis included 828 patients: 414 in the GLP-1/tirzepatide group and 414 in the control group.	**Author's conclusions:** Although GLP-1 agonists improved the AHI, hypoxia burden, weight, and systolic blood pressure in adults with moderate-to-severe obstructive sleep apnea, the evidence remains limited to only two randomised controlled trials using different pharmacological agents. Consequently, further studies are needed before firm conclusions can be drawn. **Limitations:**

Comparison: Placebo **Outcomes:** Efficacy outcomes, change in Apnea/Hypopnea Index, systolic blood pressure, diastolic blood pressure, body weight **Primary:** Change in Apnea/Hypopnea Index (AHI) per hour **Secondary:** ≥50% reduction in AHI at week 52, AHI of < 5 (no sleep apnea) or AHI of 5 to 14 (mild sleep apnea) with Epworth sleepiness scale (ESS) ≤10 at week 52, Change sleep apnea-specific hypoxic burden (SASHB, %/min), Change in body weight (%), Change in blood pressure (mmHg), Change in the level of hsCRP (mg/dl) at 52 weeks **Search dates:** Up to 24 June 2024 **Included study types:** Randomised controlled trials	Blackman et al. (2016) was a double-blinded RCT clinical trial where non-diabetic patients with obesity and moderate (AHI 15–29.9 events h – 1) to severe (AHI > 30 events h – 1) OSP without treatment with continuous positive airway pressure at baseline were allocated to receive either 32-week liraglutide 3.0 mg or placebo. Malhorta et al. (2024) was a two-phase three, multicentre, double-blinded RCT (Trial 1 and 2) involving non-diabetic patients with obesity with moderate to severe OSP. Patients who did not receive positive airway therapy at baseline were enrolled in Trial 1, and patients who received positive airway therapy were enrolled in Trial 2. Patients in both trials were allocated in a 1:1 ratio to receive either the maximum tolerated dose of tirzepatide 10 mg or 15 mg subcutaneously once weekly or placebo for 52 weeks. Finally, each trial in the study has its distinct, independent control group, so there was no fear of potential unit of analysis errors. **Quality of included studies:** Cochrane Risk of Bias 2 tool was used. The included studies were of high quality in all domains. No biases were detected regarding the selection (randomisation) process, such as random sequence generation and concealment of allocators. All studies included double-blinding for both patient treatment and assessment. No study has limited the reporting of any key outcomes like Apnea/Hypopnea Index (AHI). All trials analysed patients using intention-to-treat analysis to deal with lacking outcome data. All outcomes had a moderate overall certainty of evidence, except for changes in AHI and changes in body weight. **Synthesis:** Meta-analysis and narrative synthesis **Findings:** Change in Apnea/Hypopnea Index (AHI, events per hour)	This meta-analysis includes only two valid studies (one with two trial arms). Although 828 participants were initially enrolled, only 743 completed the tests (354 in the Blackman et al. study and 389 in the Malhotra et al. study). Second, different medications were used in these studies; tirzepatide is generally more effective than liraglutide in reducing body weight and may consequently have a greater impact on OSA treatment. The test durations also differed (32 vs. 52 weeks). In the Malhotra et al. study, an additional CPAP intervention was provided in one trial arm, whereas in the Blackman et al. study, liraglutide was combined with a 500 kcal/day diet and exercise regimen. These differences make it difficult to isolate the specific effects of GLP-1 agonists alone. Searches were limited to English-language publications, and high heterogeneity was observed in some outcomes, particularly AHI changes and body weight, initially lowering the certainty of evidence. However, sensitivity analyses resolved this heterogeneity without altering the main findings. In addition, the included studies focused on patients with moderate to severe OSA, so our

	The overall mean change in AHI favoured the GLP-1/tirzepatide group over the placebo group, showing a significantly greater mean reduction in AHI in the intervention (MD −16.57 events per hour, 95% CI [−27.41,−5.73], p = 0.003,3 RCTs,803 patients, with very low certainty evidence. The pooled studies in AHI change were significantly heterogeneous (I2 = 91%). To investigate the source of this heterogeneity, we performed a sensitivity analysis and found that excluding the Blackman 2016 study showed a significant reduction in heterogeneity I2 = 0%. Excluding the Blackman study, tirzepatide over the placebo group (MD −21.89 events per hour,95% CI [−26.00, −17.77], p < 0.00001) Change in body weight (%) The studies enrolled in the pooled analysis for change in body weight were substantially heterogeneous (I2 = 99%). The GLP-1/tirzepatide group showed a significant reduction in body weight (%) compared to the placebo group (MD −12.71%, 95% CI [−21.38, −4.03], p = 0.004, 3 RCTs, 822 patients, with very low certainty evidence. Heterogeneity significantly reduced (I2 = 0%) when the Blackman et al. 2016 study was excluded in a sensitivity analysis maintaining the significant benefit of body weight reduction (MD −12.71%, 95% CI [−21.38, −4.03], p = 0.0000. Tirzepatide is generally more effective than liraglutide in reducing body weight and may consequently have a greater impact on OSA treatment.	results may not be generalisable to those with mild disease. Comments: GLP-1/tirzepatide shows strong potential for improving sleep apnea (AHI reduction) and weight loss. However, the overall evidence is rated "very low", which could mean that the true effect may be substantially different from the observed one. Therefore, more high-quality, consistent research is needed. Also, one study (Blackman 2016) seemed to be an outlier contributing to heterogeneity and removing it improved consistency across studies and strengthened the results. There were other outcomes reported by the paper which have not been extracted here.
Reference: Li M, et al (2024). Glucagon-like Peptide 1 Receptor Agonists for the Treatment of Obstructive Sleep Apnea: a meta-analysis. *SLEEP*, [online] 48(4). DOI: 10.1093/sleep/zsae280	Description of included studies: Six studies with seven arms were included in our meta-analysis with a total of 1067 participants enrolled. The mean age of the participants was 50 years. The mean BMI ranged from 26.7 to 39.1, and the follow-up duration ranged from 4 to 52 weeks.	Author's conclusions: In summary, GLP-1RA, as an important treatment for T2D and obesity, could significantly reduce the severity of OSA, and also lead to weight loss and lower blood

Study population: participants with Obstructive sleep apnea (OSA) and who had been exposed to treatment with GLP-1RA. **Intervention:** GLP-1RA treatment **Comparison:** not mentioned **Outcomes:** **Primary:** apnea-hypopnea index (AHI) **Secondary:** weight, BMI, systolic blood pressure (SBP), and diastolic blood pressure. **Search dates:** until July 1, 2024. **Included study types:** controlled trials	Four studies included participants with moderate-to-severe OSA and obesity. GLP-1RA plus CPAP as intervention strategies were reported in two studies. **Quality of included studies:** The scale of Jadad and Newcastle-Ottawa Scale were used for quality assessment and risk of bias. However, findings do not appear to have been discussed. **Synthesis:** meta-analysis **Findings:** **BMI or weight** In four studies with 585 participants using BMI as the measurement outcome, the difference of means was −1.60 (95% CI: −1.63 to −1.57, I^2 = 0%). The change in weight was reported in four studies with 842 participants, the difference of means was −10.99 kg (95% CI: −19.28 to −2.70, I^2 = 99%). Compared with the control, GLP-1RA can significantly reduce body weight. Tirzepatide significantly reduced AHI more than liraglutide with an estimated treatment difference of −21.86 events per hour (95% CI = −25.93 to −17.79) vs −5.10 events per hour (95% CI = −6.95 to −3.26). Liraglutide 3.0 mg showed a more pronounced reduction in the severity of OSA compared to lower doses. The application of CPAP and the duration of follow-up did not affect the therapeutic effect.	pressure. The efficacy varies among different GLP-1RAs and dosages. Participants in non-obese and not using CPAP can still benefit. Due to the quality of the included studies, further high-quality RCT studies are needed to explore GLP-1RA therapies and duration and identify participant subgroups that may benefit the most. **Limitations:** Significant heterogeneity was detected among studies in AHI. Meta-regression showed that the type of medication and study design might be sources of heterogeneity, whereas follow-up duration, baseline AHI, BMI, and study sample size did not influence the outcomes. First, although there was no significant publication bias, the funnel plot was limited in this situation if the included studies were less than 10. Furthermore, due to the limited number of existing studies, two non-RCT studies were included. Our subgroup analysis suggested that the type of study had a statistically significant impact on the treatment effect, which warrants well-designed prospective cohort studies in the future. Additionally, the studies included did not comprehensively evaluate the effects of all Food and Drug Administration-

		approved GLP-1RA medications on OSA. Tirzepatide in the SURMOUNT-OSA study demonstrated significantly better outcomes compared to liraglutide in other studies. All of the above might contribute to overestimation of the test performance. Comments: please note, paper does report findings for additional outcomes not extracted here.
Reference: Dutta D, et al. (2025). Efficacy and Safety of Glucagon Like Peptide-1 Receptor Agonism Based Therapies in Obstructive Sleep Apnoea: A Systematic Review and Meta-Analysis. *Indian journal of endocrinology and metabolism*, [online] 29(1), pp.4–12. DOI: 10.4103/ijem.ijem_365_24 Study population: people living with obstructive sleep apnoea (OSA). Intervention: the use of GLP1R agonism-based therapies (liraglutide, semaglutide, tirzepatide and any other medication of this class) for managing OSA Comparison: either on placebo or any other approved treatment for OSA. Outcomes: Primary: apnea–hypopnea index (AHI) Secondary: percent change in AHI, Epworth Sleepiness Score, body weight, blood pressure, and side-effect profile.	Description of included studies: Data from four publications were analysed in this SRM, involving 937 patients. Interventions involved Tirezepatide and Liraglutide. Quality of included studies: Two authors independently assessed the risk of bias in RCTs using the risk of bias assessment tool in Review Manager (Revman) Web software. Random sequence generation (selection bias), attrition bias, and reporting bias were found to be low risk in all the study cohorts (100%). Allocation concealment, performance bias, and detection bias were found to be at low risk in 60% of the study cohorts. Another bias which looks at pharmaceutical industry funding and the presence of one or more authors from the pharmaceutical industry was found to be at low risk in 40% of the study cohort. Synthesis: meta-analysis Findings: Effect of GLP1R agonism-based therapies compared to placebo	Author's conclusions: To conclude, it may be said that this first SRM evaluating the impact of GLP1R agonism-based therapies provides us with encouraging data on improvement in different respiratory aspects of OSA along with a reduction in body weight and blood pressure. Limitations: There are several limitations of this SRM, as noted by the authors. This includes the analysis of data from different GLP1R agonism-based therapies together. This SRM highlights the current paucity of work in this area and intends to promote more active research on the role of GLP1R agonism-based therapies on different aspects of OSA. Comments:

Search dates: June 2024 **Included study types:** RCTs, cohort studies, and case-control studies.	Data from 3 different cohorts of patients (803 patients) were analysed. Patients on GLP1R agonism-based therapies had a significantly greater percent reduction in body weight from baseline as compared to PCG [MD -12.46% (95% CI: -22.54 – -2.39); P < 0.001; I^2 = 99%]. The considerable heterogeneity was because of the difference in the weight-loss outcomes between liraglutide and tirzepatide. Sub-group analysis revealed that percent reduction in body weight was significantly better with tirzepatide [MD -16.67% (95% CI: -18.04 – -15.30); P< 0.001; I^2 = 0%] as compared to liraglutide [MD -4.10% (95% CI: -4.18 – -4.02); P < 0.001]. **Effect of GLP1R agonism-based therapies compared to CPAP (active control group)** Data from one study was analysed. Liraglutide was superior to CPAP with regards to percent reduction in body weight [MD -8.90% (95% CI: -12.5 – 46.26); P < 0.001].	please note, paper does report findings for additional outcomes not extracted here.
Polycystic Ovary Syndrome		
Source details:	Results:	Conclusions:
Reference: Austregésilo B et al., (2024) The efficacy and safety of GLP-1 agonists in PCOS women living with obesity in promoting weight loss and hormonal regulation: A meta-analysis of randomized controlled trials. Journal of Diabetes and its Complications, [online] 38(10), pp.108834–108834. DOI: 10.1016/j.jdiacomp.2024.108834 **Study population:** PCOS women living with obesity **Intervention:** GLP1 agonist: semaglutide, liraglutide, exenatide, lixisenatide **Comparison:** Placebo	**Description of included studies:** A total of four RCTs were selected for the meta-analysis. Semaglutide was the GLP1 agonist in Jensterle et al., (2021) and Jensterle et al., (2022). Liraglutide was the agonist in Frossing et al., (2018) and Elkind-Hirsh et al., (2022). **Quality of included studies:** Cochrane Risk of Bias assessment tool (RoB 2) **Synthesis:** Meta-analysis **Findings:** Pooled analysis *BMI and waist circumference* GLP1-RAs was associated with a reduction in BMI (MD: -2.42; 95 %CI: - 3.10 to - 1.74; p < 0.00001; I2: 55 %) and waist	**Author's conclusions:** GLP1-RAs can reduce waist circumference, BMI, serum triglycerides and total testosterone in women with polycystic ovarian syndrome (PCOS). This study provides evidence that GLP1 receptor agonists are a safe and effective adjunct treatment for weight reduction in women with PCOS. **Limitations:** The limited number of RCTs published up to date as well as a modest number of patients included in these studies. Some important outcomes such as menstrual and

Outcomes: Body mass index (BMI), Triglycerides, Waist circumference, Total testosterone, Total cholesterol, Homeostatic Model Assessment for Insulin Resistance test (HOMA-IR). **Search dates:** Date limits for searches were from inception to November 2023 **Included study types:** Randomised controlled trials	circumference (MD: -5.16 cm; 95 % CI: - 6.11 to - 4.21; p < 0.00001; I2: 7%) when compared to placebo. *Total testosterone levels* Total testosterone levels were significantly lower in women who were treated with GLP1-RAs when compared with placebo (MD: - 1.33; 95 % CI: - 2.55 to - 0.12; p = 0.03; I2: 93%). *HOMA-IR index* There was no significant difference between GLP1-RAs and the placebo group in the HOMA-IR index (MD: - 0.30; 95 % CI: - 0.92 to 0.32; p = 0.35; I2: 74 %). *Serum triglycerides* There was a significant reduction in serum triglycerides (MD: - 0.20; 95 % CI: - 0.30 to - 0.11; p < 0.00001; I2:13 %) in participants who received GLP1-RAs compared to placebo. *Total cholesterol levels* There was no difference in total cholesterol levels (MD: - 0.04; 95 % CI: - 0.10 to 0.01; p = 0.15; I2 = 12%). GLP1-RAs were associated with mild side effects in 49 out of 112 patients in the intervention group and 9 out of 60 patients in the control group (RR: 2.97; 95 % CI: 1.64 to 5.37; p = 0.0003; I2: =5 %). Although predominantly gastrointestinal, with 43 out of 112 patients (38 %) reporting nausea, diarrhoea, vomiting, reflux, indigestion, heartburn, abdominal pain, and constipation, only two patients discontinued treatment due to these side effects (1.78 %). This demonstrates that the side effects were manageable compared to the treatment benefits.	ovulatory abnormalities as well as insulin resistance were not evaluated due to a lack of information in the individual trials. Finally, it was also not possible to evaluate Liraglutide and Semaglutide effects individually for the same reason. **Comments:** The results reported are the pooled findings as GLP1 agonists and not individually reported. However, the individual results can be found in the paper (2 papers on Semaglutide and 2 on Liraglutide). Also, there were other outcomes reported by the paper which have not been extracted here.
Reference: Bader S, et al. (2024) A systematic review of GLP-1 on anthropometrics, metabolic and endocrine parameters in patients with PCOS. Women's	**Description of included studies:** Eight studies out of the 403 identified by the searches were included in this systematic review.	**Author's conclusions:** Several studies highlighted the potential superiority of GLP-1 RAs, particularly liraglutide, over

Health, [online] 20, p.17455057241234530. DOI: 10.1177/17455057241234530 **Study population:** Patients with PCOS **Intervention:** Glucagon-like peptide-1 receptor agonist (GLP-1 RA) **Comparison:** Metformin or placebo **Outcomes:** Changes in anthropometric measurements, insulin resistance, hyperandrogenism, and metabolic and endocrine parameters. **Search dates:** Searched on 15 November 2022 and updated on 10 June 2023 **Included study types:** RCT studies, such as randomized open-label trials, prospective randomized trials, double-blind controlled trials, and single-blind controlled trials.	One study (Jensterle et al. 2015) compared metformin versus liraglutide, three studies (Jernsterle M, et al., 2016; 2017) and (Salamun V, et al., 2018) compared combination treatment of metformin and liraglutide versus liraglutide, two studies (Elkin-Hirsch KE et al. 2022 and Frossing S, et al. 2018) compared between liraglutide and placebo, one study (Liu et al. 2017) compared between exenatide and metformin, and one study (Ma et al. 2021) compared combination exenatide and metformin versus metformin. These studies were conducted in women with PCOS aged between 18 and 45 years. The mean follow-up time ranged between 12 and 32 weeks. **Quality of included studies:** The authors report conducting a risk of bias assessment. However, the tool used is not reported, neither is the quality of included studies. **Synthesis:** Narrative **Findings:** Ma et al. (2021) showed that waist circumference reduced by 4.63 ± 4.4 cm (combination group) versus 1.72 ± 3.07 cm (metformin-only group). On the contrary, Jensterle et al. (2017) showed that waist circumference in the liraglutide group exhibited a greater reduction compared with the combination group. Four studies showed weight reduction in nearly 5%. It was seen in 59.1% in the combination group (liraglutide and metformin) versus 42.9% of patients in the liraglutide-only group (Jernsterle et al. 2016) It was also seen in about 69.2% in combination group (liraglutide and metformin) versus 57.1% metformin-only group (Salamun et al. 2018). Frossing et al., (2018) showed similar achievement in 55% and 14% of participants in the liraglutide and placebo groups, respectively. In addition, 47% of patients achieved more than 5% weight loss with exenatide therapy within the initial 12 weeks, contrasting	metformin in reducing body weight, BMI, and waist circumference. These physical improvements indicate a potential impact for GLP-1 RAs in managing the metabolic outcomes of PCOS. Given that insulin resistance stands as the primary driver for metabolic and endocrine dysfunction in PCOS, the therapeutic advantages of GLP-1 agonist therapy in this population appear logical. Although the primary effect of GLP-1 is not to stimulate insulin secretion, these agonists may indirectly enhance insulin sensitivity through their weight-reducing effects. This dual mechanism of action positions GLP-1 RAs as potentially advantageous in tackling the intricate interplay of factors contributing to PCOS. By not only addressing physical metrics but also potentially influencing insulin sensitivity, GLP-1 RAs present a multifaceted approach to managing the complexities of PCOS. On the contrary, several articles revealed that the combination treatment of GLP-1 RA and metformin has demonstrated promising results enhancing metabolic and endocrine parameters compared with monotherapy. In conclusion, GLP-1 RAs, especially liraglutide, exhibit potential superiority over metformin in addressing physical and metabolic aspects of PCOS. However, further research is needed to determine the

	with the metformin group where a similar weight loss was not observed. Notably, the reduction in WC was more pronounced in patients treated with exenatide compared with those on metformin (Liu et al. 2017)	optimal treatment approach and ultimately discover the long-term safety of combined therapy in women with PCOS and obesity. Limitations: The primary limitation lies in the selection of studies with short duration of follow-up and the number of participants in the studies. Another limitation is that all studies didn't include all the anthropometrics, and endocrine and metabolic parameters. Comments: There were other outcomes reported by the paper which have not been extracted here.
Reference: Goldberg A, et al. (2024). Anti-obesity pharmacological agents for polycystic ovary syndrome: A systematic review and meta-analysis to inform the 2023 international evidence-based guideline. *Obesity reviews*, 25(5). DOI: 10.1111/obr.13704 Study population: individuals with PCOS diagnosed by Rotterdam, original National Institutes of Health (NIH) or Androgen Excess and Polycystic Ovary Syndrome society (AE-PCOS) criteria of any age, ethnicity or weight. Intervention: anti-obesity pharmacological agents (including, but not limited to, orlistat, GLP-1 RAs, phentermine/topiramate, lorcarserin, or naltrexone/bupropion), provided for a minimum	Description of included studies: Seventeen manuscripts, representing 11 trials and 996 participants were included, with four trials included in meta-analyses. Six trials were conducted in China, two in the United States, one in Slovenia, one in Iran, and one in Denmark. Sample sizes for arms relevant for this study ranged from 2,547 to 24,031 with a mean sample size of 91 participants. Mean age ranged from 26.2 to 31.4 years and mean baseline BMI from 28.0 to 43.9 kg/m^2. Mean baseline BMI was in the overweight category (BMI ≥ 25 kg/m^2) in 5/11 studies, Class I obesity category in 3/11 studies, Class II obesity (BMI 35 to <40 kg/m^2) category in 2/11 studies, and Class III obesity (BMI ≥ 40 kg/m^2) category in one study. Five studies trialled exenatide, three trialled	Author's conclusions: Findings support the need for further investigations of anti-obesity agents in PCOS. On the basis of the analyses, authors cannot provide definitive recommendations at this time due to the small number of trials, short follow-up periods, and overall high or unclear risk of bias in the majority of trials. Given the association of metabolic and reproductive benefits that appear to have a dose response with degree of weight loss, anti-obesity medications including liraglutide, semaglutide, GLP-1 RAs, and orlistat could be considered, in addition

of 3 months, alone or in combination with lifestyle, metformin, the combined oral contraceptive pill (COCP) or anti-androgens. **Comparison:** placebo or any other intervention listed in the intervention or combinations of those listed in the intervention. **Outcomes:** hormonal, metabolic, lipids, psychological, or anthropometric outcomes, and adverse effects. **Primary:** **Secondary:** **Search dates:** Between July 2002 and July 22, 2022 **Included study types:** Only RCTs, and crossover trials were included only for the phase before the crossover.	orlistat, two trialled liraglutide, one trialled semaglutide, and one trialled phentermine-topiramate as well as exenatide. Lifestyle interventions were provided in six studies and the COCP in four studies. All interventions were provided for at least 12 weeks. **Quality of included studies:** Trial integrity was assessed using the Trustworthiness in Randomised Controlled Trials (TRACT) checklist, an integrity assessment tool based on the Cochrane Research Integrity Assessment tool which classifies studies on multiple domains related to integrity. Low-risk studies were included, and authors for moderate- and high-risk studies were contacted to clarify integrity concerns. Where a satisfactory response was received, those studies were subsequently "included." Studies with no response were "not included". Authors also used the Cochrane Risk of Bias 1 tool to assess study quality. The majority of trials were at unclear risk of selection bias, mainly due to failure to specify if or how allocation was concealed. More than half of the trials were at high risk of performance bias due to lack of blinding of participants and personnel. Three quarters of the trials were at unclear risk of detection bias, and more than half were at high or unclear risk for reporting bias. Greater than a quarter of trials were at high risk of other biases, mainly due to conflicts of interest. **Synthesis:** meta-analysis **Findings:** The quality of the evidence at the outcome-level was assessed using the GRADE approach. **Liraglutide versus placebo**	to active lifestyle intervention, for the management of higher weight in adult women with PCOS as per general population guidelines. Weight management is an important outcome for those with PCOS, and further studies in this area need to be prioritized. **Limitations:** Limitations noted by authors included that only published studies, available in English, were included, and due to resource and time limitations, grey literature was not searched. Despite little to no integrity concerns identified in the included studies, the quality of these studies (in terms of risk of bias) and small sample sizes decreased the level of certainty of the evidence presented. Data on adolescents were not available, and due to time limitations, grey literature or clinical trial registries were not searched. **Comments:** Please note, other outcomes were reported by the paper which have not been extracted here.

	One trial (n = 65) compared liraglutide 1.8 mg daily versus placebo for 26 weeks in individuals with a BMI ≥ 25 kg/m^2 and/or insulin resistance. Liraglutide was reported to be superior to placebo for most anthropometric outcomes including weight (mean change -5.2 kg ± 0.7 vs. 0.2 ± 0.9 kg, p < 0.001), BMI (mean change _1.9 kg ± 0.3 vs. 0.1 ± 0.3 kg/m2, p < 0.001), WHR (mean change 0.01 ± 0.01 vs. 0.04 ± 0.01, p = 0.048), WC (mean change _4.1 ± 1.1 vs. 1.1 ± 1.5 cm, p = 0.01), and fat mass (mean change _2.6 ± 0.5 vs. 0.3 ± 0.7 kg, p = 0.02) but also resulted in more lean body mass loss compared with placebo (mean change -2.4 ± 0.4 vs. 0.1 ± 0.4 kg, p < 0.001). There was no difference between groups for percentage body fat. One trial (n = 67) reported on the comparison of liraglutide 3 mg/daily versus placebo for 32 weeks in individuals with a BMI ≥ 30 kg/m^2**.** Liraglutide + lifestyle was superior to placebo + lifestyle for most anthropometric outcomes including weight (104.7 ± 2.9 vs. 117.9 ± 5 kg, p = 0.002), BMI (39.1 ± 1.1 vs. 43.4 ± 1.8 kg/m^2, p = 0.001), WHR (0.81 ± 0.01 vs. 0.83 ± 0.02, p = 0.038), WC (101 ± 2.0 vs. 110 ± 3.3 cm, p = 0.011), percentage with 5% weight loss (57% vs. 22%, p = 0.09), % with 10% weight loss (29.5% vs. 8.7%, p = 0.046), and percentage body fat (46.0 ± 0.9 vs. 47.9 ± 0.9%, p = 0.028). Semaglutide versus placebo One trial (n = 25) compared semaglutide 1 mg weekly versus placebo for 16 weeks. Semaglutide was superior to placebo for all anthropometric outcomes including body weight (95.6 ± 13.3 vs. 100.7 ± 14.8 kg, p = 0.001), BMI (34.8 ± 3.2 vs. 36.1 ± 4.2 kg/m^2, p = 0.001), waist circumference (99.7 ± 10.7 vs. 109.8 ± 14.6 cm, p = 0.002), and visceral body fat (632 ± 215 vs. 766 ± 237 g, p < 0.001). Orlistat versus placebo One trial (n = 86) compared orlistat 120 mg three	

	times per day + lifestyle versus placebo + lifestyle for 3 months. Orlistat + lifestyle was reported to be superior to placebo + lifestyle for all anthropometric outcomes including weight (76.25 ± 4.3 vs. 79.15 ± 4.51 kg, p < 0.01), BMI (27.16 ± 1.93 vs. 28.57 ± 1.90 kg/m^2, p < 0.01), and WHR (0.76 ± 0.03 vs. 0.86 ± 0.03, p < 0.01) and for TT (63.95 ± 1.63 vs. 81.60 ± 4.64 ng/mL, p = 0.01). Two trials reported on orlistat (120 mg three times/day) + lifestyle + COCP versus lifestyle + COCP. In descriptive analyses from single trials, orlistat + lifestyle was superior to lifestyle and COCP alone for body weight (69.9 ± 7.86 vs. 72.52 ± 9.35 kg, p = 0.001),35 BMI (26.26 ± 3.12 vs. 27.02 ± 3.31 kg/m2, p = 0.001),35 and % body fat (43.13 ± 8.89 vs. 43.3 ± 5.71%, p < 0.001).35 There was no difference between groups for waist circumference. One study reported on orlistat (120 mg three times/day) versus metformin (1.5 g/day), together with the co-interventions of lifestyle and COCP, with no between-group differences for any outcomes in this comparison that included anthropometric (body weight, BMI, WC, fat mass, % body fat). The same study also compared a combination of orlistat + metformin versus metformin alone (together with cointerventions of the COCP and lifestyle in both arms). Orlistat + metformin was superior to metformin for body fat percent reduction. However, no between-group differences were noted for anthropometric (body weight, BMI, WC, fat mass).	
Reference: Bo Y, et al. (2025) Comparative efficacy of pharmacological interventions on metabolic and hormonal outcomes in polycystic ovary syndrome: a Network Meta-Analysis of Randomized	Description of included studies: The included studies were published between 2000 and 2022, with a median publication year of 2014. Sample sizes varied from 20 to 143 participants, with a median of 40 participants per study. The mean age of participants ranged from 23.9 to 34.3 years, with a median of 27.9 years. Baseline BMI was	Author's conclusions: Our comprehensive network meta-analysis underscores the superior efficacy of combining standard therapy with GLP-1 receptor agonists in improving a spectrum of metabolic

controlled trials. BMC Women's Health, 25(1). DOI: 10.1186/s12905-025-03594-6. **Study population:** Participants diagnosed with PCOS **Intervention:** Metformin, Pioglitazone, Orlistat, standard care, GLP-1 therapy, SGLT-2 therapy, Roflumilast and a combination of treatment therapies such as Standard + SGLT-2, Standard + DPP-4 inhibitors, Standard + Flutamide and Standard + GLP-1 therapy **Comparison:** Placebo **Outcomes:** Metabolic or hormonal outcome including body weight (BW), body mass index (BMI), waist circumference (WC), testosterone, sex hormone-binding globulin (SHBG), total cholesterol (TC), HDL-C, LDL-C, triglycerides (TG), HOMA-IR, fasting blood glucose (FBG), or fasting insulin (FINS) **Primary:** **Secondary:** **Search dates:** Databases and websites were searched from inception through October 20, 2024. **Included study types:** Randomised controlled trials	reported in 27 studies, ranging from 27.1 to 40.8 kg/m², with a median of 35.9 kg/m². Regarding treatment strategies, 24 studies investigated Standard therapies (e.g., Metformin, Pioglitazone), 9 studies utilised GLP-1 receptor agonists, 6 studies examined Orlistat, and 4 studies assessed combinations of Standard + GLP-1 therapy. Additionally, Flutamide and SGLT-2 inhibitors were each evaluated in 2 studies, as were Standard + Flutamide regimens. Roflumilast, Standard + DPP-4 inhibitors, and Standard + SGLT-2 combinations were each examined in 1 study. Placebo was used as a control in 14 studies. **Quality of included studies:** The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool. **Synthesis:** *Meta-analy*sis **Findings:** **Body weight** The network meta-analysis for body weight included 19 studies with 1,091 patients. Based on SUCRA rankings, the top three treatments for body weight reduction were Standard + GLP-1 (81.6%), GLP-1 (75.2%), and Standard + Flutamide (58.7%). **Standard + GLP-1** (MD = −3.44, 95% CI: −6.20 to −0.67) and GLP-1 (MD= −2.91, 95% CI: −5.04 to −0.78) significantly reduced body weight compared to standard alone. Additionally, compared to Placebo: • **Standard + GLP-1** (MD = −6.18, 95% CI: −8.78 to −3.57), • **GLP-1** (MD = −5.65, 95% CI: −7.44 to −3.86), • **SGLT-2** (MD = −4.06, 95% CI: −6.82 to −1.29), • **Orlistat** (MD = −3.41, 95% CI: −5.19 to −1.62), and • Standard (MD = −2.74, 95% CI: −4.54 to −0.94)	and hormonal outcomes in women with PCOS. The combination therapy significantly enhances weight loss, insulin sensitivity, and lipid profiles, addressing key components of PCOS pathophysiology. Orlistat emerges as a particularly effective agent for reducing androgen levels, offering an additional therapeutic avenue for patients with pronounced hyperandrogenism. These findings advocate for a personalised, multifaceted treatment approach in PCOS management, tailored to individual patient profiles and clinical manifestations. Clinicians should weigh the benefits of combination therapies against potential side effects and patient preferences, aiming to optimise both metabolic and reproductive health outcomes. **Limitations:** First, the heterogeneity among included studies regarding diagnostic criteria, intervention protocols, and patient characteristics may affect the robustness of our conclusions. Despite using random-effects models to mitigate between-study variability, residual confounding factors may persist. Second, the potential for publication bias exists, as indicated by asymmetrical funnel plots for some outcomes. This bias may result from the underreporting of negative or non-significant findings in the

	showed significant body weight reductions. Body Mass Index (BMI) The BMI network meta-analysis included 26 studies with 1,393 patients. According to SUCRA rankings, the top treatments for BMI reduction were: • Standard + GLP-1 (72.3%), • Orlistat (71.4%), and SGLT-2 (63.1%). Orlistat significantly reduced BMI compared to Standard (MD = −1.31, 95% CI: −2.49 to −0.12). Furthermore, • Standard + GLP-1 (MD = −2.05, 95% CI: −3.55 • to −0.55), Orlistat (MD = −2.02, 95% CI: −3.35 to −0.69), • and GLP-1 (MD = −1.72, 95% CI: −2.91 to −0.53) significantly • reduced BMI compared to Placebo. Waist circumference The waist circumference network meta-analysis included 17 studies with 942 patients. Based on SUCRA rankings, the top treatments for waist circumference reduction were: • Standard + GLP-1 (88.9%), • GLP-1 (86.0%), and • Flutamide (64.9%). • Standard + GLP-1 significantly reduced WC compared to SGLT-2 (MD = −2.85, 95% CI: −5.54 to −0.16), • Orlistat (MD = −3.74, 95% CI: −5.98 to −1.49), • Standard (MD = −4.39, 95% CI: −6.75 to −2.02), • Standard + Flutamide (MD = −4.88, 95% CI: −8.46 to −1.31), and • Placebo (MD = −5.34, 95% CI: −7.49 to −3.19).	literature. Third, the relatively short duration of most included studies (minimum of 12 weeks) limits our ability to assess the long-term efficacy and safety of the interventions. Longitudinal studies with extended follow-up periods are necessary to evaluate the sustainability of therapeutic benefits and to monitor potential adverse effects. Lastly, our analysis focused on surrogate metabolic and hormonal outcomes without incorporating patient-centred endpoints such as quality of life, ovulation rates, or pregnancy outcomes. Future research should aim to include these clinically relevant outcomes to provide a more comprehensive assessment of treatment efficacy. Comments: Please note, other outcomes were reported by the paper which have not been extracted here.

	GLP-1 also showed a significant reduction in waist circumference compared to SGLT-2 (MD = −2.50, 95% CI: −4.75 to −0.25), • Orlistat (MD = −3.39, 95% CI: −4.96 to −1.82), • Standard (MD = −4.04, 95% CI: −5.99 to −2.09), • Standard + Flutamide (MD = −4.54, 95% CI: −7.75 to −1.32), and • Placebo (MD = −4.99, 95% CI: −6.17 to −3.82). • Flutamide significantly reduced waist circumference compared to Placebo (MD = −3.26, 95% CI: −6.38 to −0.14).	
Reference: Machado M.F, et al. (2024). Clinical Effects of Glucagon-Like Peptide-1 Agonist Use for Weight Loss in Women With Polycystic Ovary Syndrome: A Scoping Review. *Cureus*, [online] 16(8). DOI: 10.7759/cureus.66691 **Study population:** Women aged between 18 and 65 years of age who were not postmenopausal with a formal diagnosis of PCOS. **Intervention:** GLP-1 **Comparison:** not stated **Outcomes:** not listed **Primary:** **Secondary:** **Search dates:** published between 2012 and September 2023. **Included study types:** RCTs and quasi-experimental designs	**Description of included studies:** The eight included studies spanned from 2014 to 2022 and were conducted in the United States (n = 1), China (n = 2), Denmark (n = 3), the United Kingdom (n = 1), and the Netherlands (n = 1). Methodologically, the selected studies included interventional RCT (n = 5) and quasi-experimental study methods (n = 3). These studies investigated the use of GLP-1 RAs, specifically exenatide (EXE) (n = 3) and liraglutide (LIRA) (n = 5), in patients diagnosed with PCOS. The average age of study participants ranged from 27.69-35.5 years while body mass index (BMI) ranged from 28.29 to 40.4 kg/m^2 across the studies. **Quality of included studies:** Joanna Briggs Institute Appraisal Tools were used to critically appraise each selected study. **Synthesis:** narrative **Findings:** All studies utilising liraglutide as an intervention reported weight loss among PCOS patients. Notably, reductions in various anthropometric measures, such as waist circumference, were observed in two studies. However, the impact on blood pressure following LIRA administration showed no significant improvement in one study. Furthermore, across three studies,	**Author's conclusions:** In conclusion, while GLP-1 RAs hold promise as a therapeutic option for PCOS management, further research is warranted to validate their efficacy, safety, and long-term outcomes in this population. As PCOS continues to pose significant clinical challenges, exploring innovative pharmacological strategies remains crucial in improving outcomes and quality of life for affected individuals. **Limitations:** Authors noted several limitations that warranted acknowledgment. The limited number of studies included may restrict the generalizability of findings. Additionally, the exclusion of studies involving combination therapies and the non-diabetic PCOS population may have influenced the comprehensiveness of our results. Moreover, the recent FDA approval

	both EXE and LIRA treatments were associated with improvements in menstrual cycle frequency and rates of spontaneous pregnancy.	of some GLP-1 RAs for weight management may have limited the availability of eligible studies within authors time frame. Furthermore, a reliance on peer-reviewed original articles may have overlooked relevant grey literature and unpublished data. Comments: Please note, other outcomes were reported by the paper which have not been extracted here.
Reference: Tong X, et al. (2024). Efficacy and safety of glucagon-like peptide-1 receptor agonists in the treatment of polycystic ovary syndrome- A systematic review and meta-analysis. *The Journal of Metabolic Diseases*, 130(6). DOI: 10.1080/13813455.2024.2380422 Study population: Patients with a diagnosis of PCOS Intervention: GLP-1 RA Comparison: Any other treatment Outcomes: Changes in menstrual frequency (MFR), serum total testosterone (tt), the free androgen index (FAI), homeostasis model assessment of insulin resistance (HOMI-IR), BMI, abdominal circumference, LDL-C	Description of included studies: Eight RCTs were included in this meta-analysis. The included studies were published between 2008 and 2021. Two studies were conducted in USA (Elkind-Hirsch et al. 2008, 2021), three (Jensterle et al. 2014, Jensterle et al. 2015a, Jensterle et al. 2015b) in Slovenija, and three (Liu et al. 2017, Siyuan Zheng et al. 2017, Tao Tao et al. 2021) in China. There were 7 RCTs that compared GLP-1RAs with metformin and 1 that compared GLP-1RAs with dapagliflozin. A total of 519 women with PCOS were included, and the intervention duration ranged from 8 to 16 weeks. Quality of included studies: The Cochrane Risk of Bias tool was used to perform quality assessment. Synthesis: Meta-analysis and narrative review Findings: Serum total testosterone concentration No significant difference was found between the GLP-1 RAs group and the control group in terms of decreasing serum total	Author's conclusions: The meta-analysis showed that even though there was no significant difference between GLP-1RA and control group in improving menstrual frequency, lowering serum total testosterone and FAI, GLP-1RA was superior compared to controls in improving insulin resistance and lowering BMI, key factors for PCOS women. Moreover, there was no significant difference in adverse events between the two groups. Considering the current evidence of efficacy and safety, GLP-1RA may be a novel and effective medicine for the treatment PCOS among obese women. Limitations:

Primary: Menstrual frequency (MFR), serum total testosterone (tt), the free androgen index (FAI), homeostasis model assessment of insulin resistance (HOMI-IR), BMI, abdominal circumference, LDL-C **Secondary:** BMI, abdominal circumference, LDL-C **Search dates:** Databases were searched from inception to June 2023 **Included study types:** Randomised controlled trial	testosterone concentration (WMD 0.04, 95% CI −0.12 to 0.20; I2 = 18.7%, P < 0.05). According to the funnel diagram and Egger's test, no obvious asymmetry or publication bias was found. **Menstrual frequency** A total of five RCTs reported menstrual frequency. The results showed that there were no significant differences between the GLP-1 receptor agonist group and the control group in terms of improving menstrual frequency (WMD 0.04, 95% CI −0.08 to 0.16; I2 = 41.1%; P < 0.05). **Free androgen index and homeostasis model assessment of insulin resistance (HOMA-IR)** A total of seven RCTs reported the free adndrogen index. The results also showed that there was no significant difference between the GLP-1 receptor agonist group and the control group in terms of decreasing the free androgen index (WMD 0.19, 95% CI −0.77 to 1.16; I2 = 0%, P < 0.05). However, regarding HOMA-IR, the results showed that GLP-1RAs had a greater effect on improving insulin resistance than control treatments (WMD −0.59, 95% CI −0.95 to −0.24; I2 = 0%. **BMI and abdominal circumference** The results showed that GLP-1RAs had a greater effect on reducing BMI (WMD −1.57, 95% CI −2.22 to −0.91; I2 = 0%, P < 0.05) and abdominal circumference (WMD −3.33, 95% CI −5.31 to −1.34; I2 = 0%, P < 0.05) than control treatments. **LDL-C** There were no significant differences in LDL-C; however, the results suggest that GLP-1RAs exerted slightly beneficial effects on HDL-C compared to control treatments P < 0.05).	First, aggregated data was included rather than patient-level data. Second, due to the limited number of identified RCTs, the number of patients included in our study was small, and only one study used dapagliflozin in the control group, while the remaining trials used metformin. Third, the duration of these studies was short, and PCOS is a long-term chronic metabolic disease; thus, there is some impact on the results. Finally, some of the included studies were not blinded or did not describe the blinding method, which may have biased the reliability of the results. Hopefully, additional large-scale, high-quality, long-term follow-up clinical trials with diverse ethnic populations are needed to confirm the long-term efficacy and safety of these treatments. **Comments:** Individual risk of bias of included studies were not reported. However, the cumulative RoB result show that the main concerns were blinding (unclear/high risk of bias rating) and allocation concealment. Randomisation, outcome completeness, and reporting had a relatively low risk of bias rating.

Prediabetes		
Reference: Alsanea S, et al. (2024) Liraglutide's Effect on Weight Management in Subjects With Pre-diabetes: A Systematic Review & Meta-Analysis. Endocrine Practice, 30(8), pp.737–745. DOI: 10.1016/j.eprac.2024.05.009 **Study population:** People living with pre-diabetes **Intervention:** Liraglutide **Comparison:** Placebo, lifestyle intervention, diet **Outcomes:** Change in bodyweight, BMI, waist circumference, HbA1c, LDL-C levels **Primary:** **Secondary:** **Search dates:** Searched databases from inception till December 2023 **Included study types:** Randomised controlled trials	**Description of included studies:** Five RCT studies were included in this review. These studies included 1604 subjects in the liraglutide arm and 859 subjects in the control arm. **Quality of included studies:** Assessment of bias was performed using the Cochrane risk of bias tool for RCTs, evaluating domains such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Studies that score high for risk of bias in at least 1 domain were considered of low quality. **Synthesis:** Meta-analysis **Findings:** **Change in Bodyweight** Four of the included RCTs reported on a change in body weight from baseline. Three out of these 4 studies used a placebo as the control arm, and 1 study used diet. The MD in change in body weight from baseline was -4.95 kg with (95% CI -5.16 to -4.73), and I^2 = 93% using a fixed-effect model. A sensitivity analysis using the random-effects model was conducted and the overall effect size remained similar (MD = -3.05 kg; 95% CI -5.93 to -0.17; I^2 = 93%). We repeated the analysis by excluding 1 study that used diet as the control arm and included only those with a placebo arm and the results were similar to the main analysis (MD = -4.99; 95% CI -5.21 to -4.77; I^2 = 90%). **Change in BMI** Four of the included RCTs reported on change in BMI from baseline. The MD in change in BMI from baseline was -2.06 kg/m^2 (95% CI -2.22 to -1.89; I^2 = 97%) using a fixed-effect model. We ran a sensitivity analysis using the random-effects	**Author's conclusions:** In conclusion, without a proper and timely intervention for prediabetes, the development of diabetes, cardiovascular diseases, and death in severe cases may occur. An effective method of early intervention and prevention of disease progression is weight management, which may be achieved by the administration of liraglutide. When compared to the control arm, liraglutide showed some benefit in decreasing the body weight, BMI, waist circumference, HbA1c, and LDL-C levels. Although the rate of adverse events was higher with liraglutide when compared to the control, the rate of dropouts was relatively lower with the former. Nonetheless, these results should be interpreted cautiously considering the limited number of published studies in individuals with prediabetes and the high heterogeneity among the studies included in this meta-analysis. Furthermore, studies on long-term outcomes are warranted to confirm the benefits of liraglutide in subjects with prediabetes. **Limitations:** The studies included exhibited heterogeneity, as indicated by the high I^2 statistics in all study outcomes. Several factors may

	model, and the overall difference in effect size crossed the non-significance threshold (MD = -1.57 kg/m^2; 95% CI -3.20 to 0.05; I^2 = 97%). Change in Waist Circumference Four of the included RCTs reported on change in waist circumference from baseline. The MD in change in waist circumference from baseline was -4.61 cm (95% CI -4.79 to -4.43; I^2 = 82%) using a fixed-effect model. We ran a sensitivity analysis using the random-effects model and the results remained similar (MD = -4.28 cm; 95% CI -5.02 to -3.53; I^2 = 82%)	account for the heterogeneity observed in this study, including variations in the control arm, follow-up durations, and the use of structured diets in both the liraglutide and control groups. However, the limited number of studies meeting the eligibility criteria precluded the performance of subgroup analyses to explore the underlying causes of this heterogeneity. Also, most of the included studies were of short duration in terms of follow-up and small sample size. It is important to note that our study has several strengths, including the comprehensive search strategy employed in this review. In addition, we performed several sensitivity analyses, and the results consistently support the positive effect of liraglutide on body weight in subjects with prediabetes. Comments: Please note, other outcomes were reported by the paper which have not been extracted here.

ISBN: 978-1-83766-666-9