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GLP1 Agonists Beyond Established Therapeutic Indications: A Narrative Review of Emerging Therapeutic Applications

Dr Usmaan Hafeez Farooq[1]*, Dr Abdalla El Tumi[2]

[1]MbChB MRCGP
[2]MBBCh MRCGP

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***Corresponding author:** Dr Usmaan Hafeez Farooq
MbChB MRCGP

Abstract | **Original Research Article**

Introduction: Since Glucagon-like-Peptide 1 receptor agonists (GLP1-RAs) were first approved as a diabetic drug, their approved indications have considerably expanded and continue to expand. Plausible benefits have been suggested across several other areas including musculoskeletal conditions, liver transplant, kidney transplant, reproductive disease, neurodegenerative conditions substance use disorder, gastrointestinal conditions etc. ***Aim:*** The aim of this review is to summarise what the most up-to-date clinical evidence shows regarding the *other* emerging therapeutic applications of GLP1 receptor agonists beyond their established indications. ***Methods:*** A literature search was undertaken to identify relevant systematic reviews, meta-analyses, randomised controlled trials (RCTs), and other significant clinical studies examining GLP1-RA therapy across emerging therapeutic indications. Particular attention was given to recent evidence and developments not fully represented in earlier reviews. ***Findings:*** Evidence for GLP1-RAs extend across a wide range of conditions including neurodegenerative disease, substance use disorders, musculoskeletal conditions, reproductive disease, and gastrointestinal conditions. The strength of evidence varies considerably between indications. While several areas demonstrate encouraging results and early clinical signals, others remain supported by predominantly by observational data or small studies. There were areas in which there was evidence available but not showing any significant benefit. ***Conclusion:*** GLP1-RAs have evolved from glucose lowering and weight management therapies into broader therapeutic areas. CKD and MASH are examples of some initially exploratory benefits translating into regulatory supported uses. However, this does not apply to all the other emerging areas. In some areas eg Azheimer's and OA the evidence did not show any benefit. Across the other areas, the evidence remains preliminary requiring further study namely randomised trials which are disease specific and adequately powered. There is still scope for further beneficial roles of GLP1-RAs.

Keywords: Glucagon-like peptide-1 receptor agonists, GLP-1RA, Emerging therapeutic indications, Off-label uses, Clinical trial evidence, Narrative review.

INTRODUCTION

Glucagon-like-Peptide 1 receptor agonists (GLP1-RAs) are a group of medications used for various conditions including type 2 diabetes mellitus, obesity and cardiovascular risk reduction. Examples include Byetta, Saxenda, Victoza, Wegovy and Ozempic. [1,2]

They work by mimicking the natural incretin hormone Glucagon-like-Peptide-1 (GLP-1). This is released by intestinal L-cells in response to nutrient ingestion. Their physiological effects include: stimulating glucose-dependent insulin secretion and suppressing glucagon secretion, in the pancreas; slowing gastric emptying; and suppressing hunger and increasing satiety through central appetite-regulating pathways in the brain. Endogenous GLP-1 is very short-lived as it is rapidly degraded, principally by the enzyme dipeptidyl-peptidase-4. However, GLP1-RAs have been developed to resist this rapid degradation resulting in the physiological effects lasting considerably longer and thus making them therapeutically useful. [1]

These physiological effects and the subsequent clinical uses of GLP1-RAs were developed gradually over the past two decades. In 2005 Exenatide became the first GLP1-RA to be approved by the US Food and Drug Administration (FDA) for type 2 diabetes mellitus (T2DM). At the time, it was noted that patients using Exenatide seemed to *lose weight,* distinguishing Exenatide from other diabetic drugs. This led to further investigations namely the SCALE trials. [1,3]

Around the same time in 2007, concerns were raised about the diabetic drug Rosiglitzone, causing cardiovascular problems. This led to the FDA issuing guidance in 2008 recommending manufacturers demonstrate that *all* new treatments for T2DM did not produce adverse cardiovascular events. This led to the Cardiovascular Outcome Trials (CVOTs) which were designed primarily to prove *cardiovascular safety*, but some actually went further and proved to be of actual *cardiovascular benefit*.[4]

The SCALE trials provided evidence for Liraglutide 3mg (Saxenda) for chronic weight management,[3] leading to its FDA approval in 2014. Likewise, the STEP trial provided evidence for Semaglutide 2.4mg (Wegovy),[5] leading to its FDA approval in 2021. The SELECT trial showed Semaglutide reduced major adverse cardiovascular events in adults with established cardiovascular disease and overweight/obesity but without diabetes. [6] This led to Wegovy's approval in 2024 for cardiovascular risk reduction.

These cardiovascular benefits appeared not to be fully explained by improved glycemic control and weight loss alone, raising interest in the additional direct and indirect cardiovascular mechanisms of GLP1-RA therapy. [2,6]

GLP1 receptors are expressed in human cardiac tissue, although their precise cellular distribution within the human cardiovascular system remains incompletely defined. [2,7]

Proposed mechanisms contributing to cardiovascular protection include reductions in systemic inflammation, improved endothelial and vascular function, and effects on atherosclerotic plaque biology. [1,2]

The established effects of GLP1-RAs on glucose regulation, appetite and body weight, together with their cardiovascular and renal benefits have stimulated investigation of potential therapeutic effects across multiple other organ systems. [1,2,8] Morello *et al*., in a recent review described emerging or off label applications involving joints, kidney and liver disease, respiratory disease, cognition, bowel function and substance-use disorders.[8] The rapid evolution of the field is illustrated by expansion if GLP1-RA based therapies into additional recognised indications including Obstructive Sleep Apnoea (OSA) and more recently Metabolic-Associated Steatohepatitis (MASH) and chronic kidney disease (CKD). [2,10]

The aim of this narrative review is to summarise, in this rapidly evolving field, what the most up-to-date clinical evidence shows regarding the *other* emerging therapeutic applications of GLP1 receptor agonists beyond their established indications.

METHODS

A narrative review of the published literature was undertaken to evaluate the potential therapeutic applications and clinical benefits of GLP1-RAs specifically in the promising clinical areas, listed above.

Electronic literature searches were conducted using PubMed/MEDLINE and Google Scholar. The search included publications to August 2026.

Separate searches were then performed for each therapeutic area. Search terms included combinations of: "GLP1 receptor agonist"; "GLP1-RA"; "semaglutide"; "liraglutide", "dulaglutide"; "tirzepatide" AND relevant condition-specific terms including: "Kidney transplantation"; "Alzheimer's disease / dementia"; "Parkinson's disease"; "Substances use disorder"; "polycystic ovarian syndrome"; "osteoarthritis"; "Psoriasis"; "respiratory disease"; "rheumatoid / inflammatory arthritis"; "liver transplant" and "high output stoma".

Where available, systematic reviews and meta-analyses were preferentially selected in order to provide the highest levels and most comprehensive summary of available clinical evidence. Where suitable systematic review or meta-analyses were unavailable, or where important subsequent evidence had been published, relevant randomized controlled trials (RCTs) and other major clinical studies were considered.

Priority was given to human clinical studies in peer-reviewed journals and those written in English. Pre-clinical studies, animal studies, case reports, conference abstracts and publications without sufficient clinical outcome data were generally excluded. Studies relating solely to the established conditions (T2DM, obesity, cardiovascular risk reduction, OSA, MASH and CKD) were excluded unless they provided evidence concerning the other therapeutic benefits.

Reference lists of relevant articles and key studies were also examined to identify additional publications of potential relevance. The literature was synthesized narratively according to therapeutic area, with emphasis placed on strength, consistency and clinical relevance of the available evidence.

FINDINGS

Kidney Transplantation

A 2026 meta-analysis (Kanbay *et al*.) included 17 studies involving 54,680 kidney transplant recipients. GLP1-RA use was associated with favorable, metabolic outcomes including lower HBA1c and BMI, while graft function/eGFR was generally preserved. It also reported associations with lower mortality and cardiovascular events, without major signals for disturbance of tacrolimus levels.[9]

A second 2026 systematic review / meta-analysis (Aliyeva *et al*.), looking at kidney transplant recipients with T2DM also reported favorable mortality and major adverse kidney events, without major signal for disturbance of tacrolimus levels.[10]

Even though it seems GLP1-RAs appear metabolically useful and potentially beneficial for kidney transplant patients with T2DM, these results should be treated with caution. Most of the studies included were observational data, as opposed to RCTs, thus susceptible to confounding and treatment-selection bias. Treatment-specific randomised trials are needed before graft or survival benefit effects can be established.

Alzheimer's Disease / Dementia

Earlier small clinical studies and observational data suggested possible neuroprotective effects. However, a 2026 meta-analysis of RCTs in non-diabetic patients with Alzheimer's disease, mild cognitive impairment and Parkinson's disease found: only a small improvement in global cognition (SMD 0.14; 95%CI 0.01 to 0.27), with an estimated probability of clinically important benefit of only 1%. Functional outcomes were not significantly improved.[11]

Since then, there has been the 2026 EVOKE and EVOKE+ phase III RCTs which enrolled approximately 3808 participants with early Alzheimer's disease and found that oral semaglutide did not significantly slow the disease progression compared with placebo.[12]

Thus the current evidence does not support semaglutide (or GLP1-RAs in general) as a disease-modifying treatment for Alzheimer's disease. This is an example in which initial biological plausibility with early encouraging evidence has not been confirmed by the larger RCTs.

Parkinson's Disease

Several 2026 systematic reviews and meta-analyses have evaluated GLP1-RAs in Parkinson's disease. Chen *et al.,* Pooled eight RCTs involving 850 participants and reported a modest signal for improvement in motor outcomes, together with exploratory mood and cognitive effects. [13]

However, a separate 2026 meta-analysis of five RCTs (708 patients) did not demonstrate a convincing class-wide improvement in motor outcomes, although signals were seen for some individual agents.[14] Similarly, another RCT-only meta-analysis (Mendonca *et al.,*2026) concluded that the evidence remained inconsistent.[15]

A broader 2026 neurological meta-analysis, looking at both Alzheimer's and Parkinson's disease, found that pooled data did not show any statistically significant improvement in Parkinson's related outcomes. It showed a small improvement in depression symptoms in the Parkinsons group (MD -2.09; 95% CI -3.99 to -0.20).[11]

Overall, it can be said that the evidence does not establish a Parkinson's disease-modifying effect but potentially could provide some other benefits. Difference between trials, agents, outcome timing and medication may account for some of the conflicting results.

Substance-use Disorders

A 2026 systematic review and meta-analysis (Sarma *et al*.) included five RCTs involving 764 participants and examined GLP1-RAs across substance-use outcomes particularly alcohol and tobacco use. Pooled analyses did not demonstrate statistically significant improvements in: alcohol-free days; cigarettes smoked per day; or nicotine-dependance scores.[16]

An alcohol-specific 2026 systematic review/meta-analysis identified a possible signal of benefit particularly in people with alcohol-use disorder and obesity but the evidence remained insufficient for a firm therapeutic intervention.[17]

Even though the mechanistic and pre-clinical rationale is strong, human randomised evidence remains small and unconvincing at class level.

Polycystic Ovary Syndrome (PCOS)

Buragohain *et al.,* (2026) was a meta-analysis of eighteen RCTs and Forslund *et al.,* was study of eleven RCTs, both looking at GLP1-RA therapy in women with PCOS. Across both studies the most consistent finding was of reduced body weight/BMI and improvements in insulin resistance along with other metabolic measures. Other outcomes (including androgen concentration, menstrual regularity, ovulation and fertility) showed less consistent benefits. [18,19]

The evidence supports a metabolic role for GLP1-RAs, particularly in women with PCOS who have excessive weight or insulin resistance. It remains uncertain whether they exert a direct PCOS specific reproductive effect independent of weight loss and improved metabolic health.

Osteoarthritis (OA)

Only one significant study was identified relating to GLP1-RAs and OA – this was a large meta-analysis in 2026 using seventy-four RCTs, involving 105,400 patients. Despite the size of the study, no significant difference was found in OA risk between GLP1-RA treatment and placebo, insulin, or oral anti-glycemic drugs (OAD). This absence of statistical significance was also observed across: different GLP1-RA formulations; varying treatment durations; and distinct control groups.[20]

Psoriasis

A 2026 psoriasis specific systematic review (Marani *et al*.) included twenty-six studies and reported improvements in psoriasis severity across several GLP-1 based agents.[21] A further 2026 review from the National Psoriasis Foundation also supported growing interest in GLP1-RAs in psoriatic disease.[22] However much of the clinical literature consists only of case reports, small cohorts and observational studies, with few randomised trials.

Due to the lack of randomised controlled trials, the evidence remains weak. Large psoriasis specific RCT are needed to establish whether benefit is independent of other factors.

Respiratory Disease

A couple of small systematic and meta-analytic reports had indications of fewer asthma/COPD related outcomes. This included Esmaeel *et al.,*in 2026 which reviewed five RCTs involving 1034 participants, and a 2025 meta-analysis of six observational studies including 62,678 participants. [23,24]

There was a large 2026 network meta-analysis of glucose-lowering therapies incorporating 128 RCTS and 316,832 participants which suggested reduced airway-disease risk with some GLP1-RA regimens. A separate pooled analysis of twenty-eight randomised trials (77,485 participants) reported lower overall risk of respiratory disease with GLP1-RAs (RR 0.86; 95% CI 0.81 - 0.93).[25]

Overall, the respiratory signal is promising but remains difficult to interpret as direct pulmonary therapeutic effect. Weight-loss, improved metabolic health and reduced systemic inflammation may mediate some of the apparent benefit. Dedicated asthma or COPD specific RCTs are required to assess this further.

Rheumatoid / Inflammatory arthritis

The notable finding regarding this potential therapeutic indication is the stark lack of any significant evidence compared to the other indications. Potential benefits have been suspected from observational studies but even from the most recent review from 2025-2026, they could only describe plausible anti-inflammatory mechanisms as opposed to any robust clinical evidence.[26] It would be fair to say that benefit of GLP1-RA use in rheumatoid/inflammatory arthritis is still very much in the hypothesis-generating stage.

Liver Transplantation

A 2025 systematic review identified 12 retrospective studies evaluating GLP1-RAs and/or SGLT2 inhibitors after liver transplantation, including 402 liver transplant recipients exposed to one or both drug classes. GLP1-RA containing treatment was associated with improved glycemic control, lower body weight and reduced insulin requirements with favorable signals for graft stenosis, renal function and cardiovascular outcomes.[27]

Given there has only been retrospective studies, the benefits of GLP1-RAs in liver transplant remains only plausible. Especially as some of the analyses combined GLP1-RAs with SGLT-2 inhibitors, which puts into doubt the benefit is due to GLP1-RA alone. Prospective controlled studies are required to further assess this relationship.

High-output Stoma

A 2026 scoping review of GLP1-RAs for high output stoma identified only three small clinical studies. Reductions in stoma output were reported, in some studies approaching 50%, providing a physiological rationale for benefit through slowing gastrointestinal transit and secretion. [28]

Again, prospective controlled trials are required to explore GLP1-RA benefits in high output stoma.

DISCUSSION

This review demonstrates that interest in the therapeutic potential of GLP1-RAs now extends considerably beyond their original metabolic indications. Across the therapeutic areas examined, however, the quantity and quality of supporting evidence varied considerably. Some indications are supported by increasingly robust clinical data, whereas others remain based on relatively small studies, observational findings or early signals of benefit. The recent progression of CKD and MASH from areas of emerging interest to recognised approved indications provide important examples of how initial interesting, promising observations may, when supported by adequately powered trials, ultimately translate into changes in clinical practice.

At the same time, the findings of this review reiterate that biological plausibility is not always equated with proven clinical efficacy. GLP1 receptors and their downstream pathways have effects extending beyond glycemic control, including effects on appetite and body weight, inflammation, vascular function and potentially neuronal pathways. These mechanisms provide plausible explanations for benefits across a diverse range of conditions. However, encouraging, mechanistic, pre-clinical or observational findings do not necessarily predict a clinically meaningful treatment effect. This distinction is particularly relevant when considering the latest evidence in Alzheimer's disease and OA, which do not show any significant benefit of GLP1-RA use. Studies in Parkinson's disease have produced mixed findings, while early signals in substance use disorders remain promising but have not yet translated into consistent evidence of benefit in pooled randomised data.

A similar spectrum of evidence is apparent across the other conditions reviewed. In PCOS, the evidence for improvements in weight and metabolic parameters is relatively encouraging, although the extent to which GLP1-RAs provide disease-specific reproductive or hormonal benefits remains less certain. Kidney transplantation represents another potentially important area, but much of the available evidence remains observational. In inflammatory and musculoskeletal conditions, including OA, psoriasis and respiratory disease, preliminary findings suggest possible benefit, but the evidence base remains relatively early-stages. Evidence in rheumatoid arthritis and high output stomas is particularly limited, while findings following liver transplantation are also constrained by the small and predominantly retrospective evidence base. These differences are important: the absence of convincing evidence should not necessarily be interpreted as evidence of no effect, but it does indicate that clinical enthusiasm should remain proportionate to maturity of available data.

Interpretation is further complicated by difficulty in separating direct disease specific actions of GLP1-RAs from secondary effects of weight loss and improved metabolic health (eg better glycemic control). This is particularly relevant in conditions associated with obesity, insulin resistance or chronic low-grade inflammation. Future studies should therefore attempt, where possible, to distinguish weight-loss-mediated effects from independent GLP1-receptor mediated actions. This would help determine whether the medication is modifying the underlying disease process or predominantly improving associated metabolic risk factors.

The evidence also highlights several recurring methodological limitations. For many emerging indications, the studies were small, of short duration or observational in design, thus clinically meaningful endpoints not always available. Further limitations were related to inconsistency in: the GLP1-RA studied; dose used; study population and outcome measures; all of which limit direct comparisons. Conversely, the development of the evidence of CKD and MASH highlights the importance of progression from mechanistic and preliminary clinical observations to large, appropriately-powered randomised trials using clinically relevant outcomes. For the more promising emerging indications, this should be the priority. Future trials should include where possible, analyses capable of distinguishing direct therapeutic effects from those due to weight reduction or better metabolic control.

The findings should therefore be interpreted cautiously in relation to current clinical practice. Evidence of possible therapeutic benefit is not equivalent to evidence sufficient to support routine prescribing for a new indication. Nevertheless, identifying areas in which independent studies show consistent signals of benefit is valuable in prioritising future research. The expanding indications for semaglutide in CKD and MASH demonstrate this point. Equally, other proposed benefits may fail to demonstrate meaningful efficacy when subjected to larger randomised studies. The key clinical question is therefore not simply whether GLP1-RAs exert a biological effect across multiple organ systems, but which of these effects are sufficiently large, reproducible and clinically relevant to justify disease-specific treatment.

This review has several limitations. It was designed as a focused narrative review rather than a systematic review or meta-analysis and was intended to provide clinically relevant overview of a broad and rapidly developing field. Around twenty key publications were considered across multiple therapeutic areas, with the emphasis placed on recent systematic review, meta-analyses and pivotal clinical trials where available. Consequently, the review does not represent an exhaustive assessment of every published study, and the depth of the appraisal necessarily varied according to the maturity of the evidence within each condition. The rapid pace of research in this field is an additional limitation, as new trial results and regulatory decisions may alter the relative strength for individual indications. These limitations notwithstanding, consideration of multiple therapeutic areas within a single review allowed the differing stages of evidence development to be compared and highlights both the most promising directions and the substantial gaps that remain.

Conclusion

GLP1-RAs are evolving from glucose lowering and weight management therapies into a broader therapeutic class with potential applications across multiple organ systems. The progression of CKD and MASH into recognised indications demonstrates that some initially exploratory benefits can translate into clinically meaningful and regulatory supported uses. However, the evidence across most other emerging indications remain heterogeneous and, in several areas preliminary. Current findings support continued investigation rather than widespread extension of routine clinical use. Future research requires adequately powered randomised trials with clinically meaningful, disease-specific endpoints and greater clarification of whether observed benefits are independent of weight loss and metabolic improvement. The next phase of GLP1-RA research will determine which of the many biologically plausible therapeutic effects represent genuine disease-modifying opportunities and which do not translate into meaningful clinical benefit.

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