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POTENTIAL USE OF GLP-1 RECEPTOR AGONISTS IN THE MANAGEMENT OF CHRONIC PAIN SYNDROMES: ANTI-INFLAMMATORY AND NEUROPROTECTIVE PERSPECTIVES

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ABSTRACT

Chronic pain syndromes remain a major clinical and public health challenge because of their multifactorial pathophysiology, frequent refractoriness to standard treatment, and marked effects on quality of life, disability, sleep, psychological well-being, and work capacity. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for type 2 diabetes and obesity, have recently attracted growing interest beyond metabolic medicine because their biological actions appear to extend to anti-inflammatory, antioxidative, neuroprotective, and cytoprotective pathways. These pleiotropic properties are potentially relevant to chronic pain, which is increasingly understood as a condition sustained not only by nociceptive input but also by neuroinflammation, glial activation, oxidative stress, maladaptive neuronal plasticity, mitochondrial dysfunction, and metabolic dysregulation.

This narrative review examines the current biological and translational rationale for GLP-1RAs in chronic pain syndromes, with emphasis on neuropathic pain, diabetic peripheral neuropathy, migraine-related central sensitization, fibromyalgia-related mechanisms, osteoarthritis-associated pain, inflammatory musculoskeletal pain, and visceral pain. Available evidence suggests that GLP-1 receptor activation may modulate several processes implicated in pain chronification, including pro-inflammatory cytokine signaling, microglial activation, oxidative stress, mitochondrial dysfunction, and impaired neuronal resilience. Experimental studies also indicate possible involvement of IL-10-mediated anti-inflammatory signaling, AMPK/NF-kappaB pathway modulation, and broader neuroimmune regulation.

However, the current evidence base remains heterogeneous and is still dominated by preclinical studies, mechanistic reviews, and early observational data. Human evidence in non-diabetic chronic pain populations remains limited, and in many settings it is difficult to separate direct analgesic effects from indirect benefits related to weight loss, improved glycemic control, reduced systemic inflammation, or improved function. At present, GLP-1RAs should therefore be regarded as biologically plausible and clinically promising, but still investigational, candidates in chronic pain management rather than established analgesic therapies. Further translational work and adequately powered prospective clinical studies are required to clarify efficacy, safety, mechanism-specific effects, and phenotype-specific patient selection.

KEYWORDS

GLP-1 Receptor Agonists, Chronic Pain, Neuropathic Pain, Neuroinflammation, Migraine, Fibromyalgia, Osteoarthritis, Neuroprotection

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1. Introduction

Chronic pain syndromes are among the most complex challenges in contemporary medicine because their consequences extend far beyond persistent physical discomfort alone. In addition to somatic suffering, they are commonly associated with impaired sleep, reduced physical activity, diminished psychological well-being, decreased work productivity, social withdrawal, and a substantial decline in overall quality of life. Unlike acute pain, chronic pain is increasingly understood not simply as prolonged nociceptive signaling, but as a multidimensional pathological state sustained by neuroinflammation, maladaptive central sensitization, immune dysregulation, oxidative stress, glial activation, and structural as well as functional alterations involving both the peripheral and central nervous systems (He et al., 2025; Jing et al., 2025).

This broader pathophysiological framework helps explain why conventional analgesic strategies often provide incomplete relief. Many standard treatments reduce symptoms transiently but do not adequately address the upstream cellular and molecular processes that sustain pain persistence and chronification. As a result, growing attention has turned toward therapies capable of modulating neuroimmune, inflammatory, metabolic, and neuroprotective pathways rather than acting exclusively at the level of nociceptive transmission.

Within this context, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a potentially relevant therapeutic class. Initially introduced for the treatment of type 2 diabetes mellitus and later obesity, these agents have demonstrated a range of effects that extend beyond glycemic control and weight

reduction. GLP-1 receptor signaling has been associated with anti-inflammatory, antioxidative, neuroprotective, cytoprotective, and immunomodulatory actions across multiple tissues and disease models (Bendotti et al., 2022; Lu et al., 2024; Zhang, Zhang, & Tian, 2021; Zheng et al., 2024). These broader biological properties are especially relevant to chronic pain syndromes characterized by persistent inflammation, glial reactivity, oxidative injury, neuronal vulnerability, and metabolic dysfunction.

Recent reviews suggest that GLP-1RAs may have potential relevance in several pain conditions, including inflammatory pain, osteoarthritis-associated pain, visceral pain, neuropathic pain, diabetic peripheral neuropathy, headache, and cancer pain (He et al., 2025; Jing et al., 2025). Experimental findings further indicate that GLP-1 receptor activation may influence pain hypersensitivity through mechanisms extending beyond classical analgesia, including suppression of microglial activation, attenuation of inflammatory signaling, reduction of oxidative stress, preservation of mitochondrial function, and modulation of processes implicated in central sensitization (Jing, Zou, Wang, Cai, & Tang, 2021; Ma et al., 2021; Zhang et al., 2021). In addition, emerging literature raises the possibility that GLP-1RAs may be particularly relevant in multimorbid pain populations in whom obesity, insulin resistance, low-grade inflammation, fatigue, or sleep dysfunction overlap with altered pain processing (Alfaro-Martinez et al., 2026; Bilgin et al., 2025).

Despite these promising signals, the current evidence base remains preliminary. Much of the available literature is preclinical, mechanistic, observational, or extrapolated from adjacent inflammatory and central nervous system disorders rather than derived from dedicated randomized studies in chronic pain populations. Accordingly, discussion of GLP-1RAs in pain medicine should remain cautious, critical, and hypothesis-driven.

2. Aim and Scope of the Review

The aim of this narrative review is to synthesize the current evidence regarding the potential role of GLP-1 receptor agonists in chronic pain syndromes, with particular emphasis on the anti-inflammatory, neuroprotective, antioxidative, neuroimmune, and metabolic mechanisms through which GLP-1 receptor activation may influence pain pathophysiology. Given the heterogeneity of the available literature and the predominance of mechanistic, preclinical, and translational studies over large controlled trials, a narrative rather than systematic approach was considered the most appropriate format.

The review focuses on selected pain phenotypes and related mechanistic domains, including neuropathic pain, diabetic peripheral neuropathy, migraine-related central sensitization, fibromyalgia-related mechanisms, osteoarthritis-associated pain, inflammatory musculoskeletal pain, and visceral pain. Particular attention is given to studies addressing neuroinflammation, glial activation, cytokine signaling, oxidative stress, mitochondrial dysfunction, neuronal injury, metabolic dysregulation, and pain hypersensitivity. Supportive evidence from adjacent fields, including broader central nervous system disease models and inflammatory rheumatologic conditions, is also discussed when relevant to mechanistic plausibility, while clearly distinguishing such evidence from direct chronic pain data.

This review is not intended to establish clinical recommendations. Rather, it aims to assess whether the currently available literature provides a coherent biological and translational rationale for further investigation of GLP-1RAs in chronic pain medicine.

3. Biological Rationale for GLP-1 Receptor Agonists in Chronic Pain

The potential relevance of GLP-1RAs in chronic pain is supported by several converging biological mechanisms that extend substantially beyond metabolic regulation. In addition to their established effects on appetite, glycemic control, and insulin secretion, GLP-1 receptor signaling has been linked to anti-inflammatory, antioxidative, neuroprotective, and cytoprotective actions across both peripheral tissues and the central nervous system (Bendotti et al., 2022; Zhang, Zhang, & Tian, 2021; Zheng et al., 2024). This broader mechanistic profile is highly relevant to chronic pain, which is increasingly understood not as simple persistence of nociceptive input, but as a multifactorial pathological state sustained by neuroinflammation, maladaptive neuronal plasticity, oxidative stress, glial activation, mitochondrial dysfunction, and mechanisms contributing to central sensitization.

A major component of this rationale is the effect of GLP-1RAs on inflammatory signaling. Bendotti et al. (2022) emphasized that GLP-1 receptor agonists can attenuate pro-inflammatory cytokine production, reduce oxidative stress, modulate immune-cell recruitment, and suppress inflammatory signaling pathways in multiple tissues. Complementing this view, Zhang, Zhang, and Tian (2021) described the GLP-1/GLP-1R axis

as a pleiotropic regulator of intracellular homeostasis in central nervous system disorders, highlighting effects on oxidative stress, inflammation, excitotoxicity, apoptosis, and neuronal injury. Taken together, these findings suggest that GLP-1RAs may be relevant to chronic pain not only because they improve systemic metabolic status, but also because they may modify the inflammatory and cellular environment in which persistent pain is maintained.

This interpretation is strengthened by evidence that GLP-1 receptor signaling may regulate neuroimmune and glial mechanisms. Zheng et al. (2024) noted that GLP-1RAs may alleviate neuroinflammation and exert tissue-protective effects in nervous-system disorders, which is particularly relevant because neuroinflammation contributes to peripheral sensitization, glial reactivity, impaired neuronal resilience, and central pain amplification. Jing et al. (2025) similarly concluded that GLP-1 receptor activation may influence a broad range of pain conditions, including inflammatory pain, osteoarthritis-associated pain, visceral pain, neuropathic pain, diabetic peripheral neuropathy, headache, and cancer pain. This breadth suggests that GLP-1RAs may function less as conventional analgesics and more as biological modulators of the molecular and cellular processes that sustain pain persistence.

Additional support for this concept comes from inflammatory joint disease models and rheumatoid arthritis literature. A recent scoping review in rheumatoid arthritis reported that, in experimental synovial-cell models, GLP-1RAs reduced pro-inflammatory cytokine production, oxidative stress, and matrix-degrading enzymes while suppressing NF-kappaB and MAPK signaling. The same review summarized early observational clinical data describing reductions in inflammatory markers, disease activity, and pain scores, with some analgesic and anti-inflammatory improvements not fully correlated with weight loss, suggesting that at least part of the benefit may be weight-independent. Although rheumatoid arthritis should not be conflated with chronic pain syndromes broadly, these findings strengthen the mechanistic plausibility that GLP-1RAs may influence pain through direct anti-inflammatory and tissue-protective effects in conditions characterized by systemic or local inflammatory activation (Wu et al., 2026).

Overall, the available evidence supports a coherent biological rationale for considering GLP-1 receptor agonists as candidate agents in chronic pain management. Their potential relevance lies in the convergence of several mechanisms, including suppression of pro-inflammatory signaling, attenuation of oxidative stress, modulation of glial and neuroimmune activation, preservation of mitochondrial and neuronal function, and possible modification of processes contributing to central sensitization. Although clinical validation remains limited, these pleiotropic actions provide a plausible mechanistic basis for further translational and clinical investigation.

4. Selected Pain Phenotypes and Translational Relevance

4.1. Neuropathic Pain

Neuropathic pain is among the most biologically plausible candidate indications for future GLP-1RA repurposing because it is closely linked to neuroinflammation, glial activation, oxidative injury, and long-term neuronal dysfunction. Experimental work suggests that GLP-1 receptor signaling may modulate these processes at both spinal and supraspinal levels.

Ma et al. (2021) showed that microglial activation of GLP-1R signaling in neuropathic pain was associated with adaptive changes in inflammatory gene expression and attenuation of pain-related responses. This observation is particularly relevant because microglial activation is increasingly recognized as a key mechanism in the initiation and maintenance of neuropathic pain.

Zhang et al. (2021) reported that GLP-1R activation ameliorated novel-object recognition memory dysfunction in neuropathic pain mice through regulation of the hippocampal AMPK/NF-kappaB pathway. This finding is notable because neuropathic pain often involves cognitive dysfunction, altered central processing, and neuronal stress in addition to abnormal nociceptive signaling. Therapies with both neuroprotective and anti-inflammatory properties may therefore offer broader benefit than purely symptomatic analgesics.

Recent reviews have reinforced this interpretation. He et al. (2025) and Jing et al. (2025) both argue that GLP-1RAs may influence neuropathic pain through suppression of oxidative stress, attenuation of inflammation, improvement in mitochondrial function, and preservation of neural structure and function. Collectively, these findings suggest that neuropathic pain remains one of the strongest mechanistic candidates for future translational development.

4.2. Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy represents a particularly important translational setting because GLP-1RAs may offer both metabolic and direct neurobiological benefit. In principle, they could improve the pathophysiological environment in which neuropathy develops while also modulating inflammatory, oxidative, and neurodegenerative mechanisms relevant to neuropathic pain.

Recent literature suggests that GLP-1 receptor activation may improve neuronal function in diabetic peripheral neuropathy through inhibition of inflammation, oxidative stress, and mitochondrial dysfunction, while supporting neural homeostasis and recovery (He et al., 2025). This distinction is clinically relevant because it raises the possibility that any benefit may not be explained solely by improved glycemic control. However, direct clinical evidence specifically targeting painful diabetic neuropathy remains limited, and further studies are needed to distinguish symptom-modifying effects from broader metabolic improvement.

4.3. Migraine and Central Sensitization-Related Headache

Migraine is increasingly understood as a disorder involving neuroinflammation, glial activation, trigeminal sensitization, and altered neuronal excitability rather than a purely vascular phenomenon. This has increased interest in therapies that can modulate inflammatory and neuroimmune processes within pain-processing networks.

Jing, Zou, Wang, Cai, and Tang (2021) demonstrated that activation of microglial GLP-1R in the trigeminal nucleus caudalis suppressed central sensitization in a chronic migraine model induced by recurrent nitroglycerin stimulation. In a later study, Jing, Zou, and Pu (2023) found that liraglutide attenuated pain hypersensitivity in a nitroglycerin-induced chronic migraine mouse model by stimulating IL-10 release. Together, these findings provide mechanistic support for the idea that GLP-1 receptor signaling may act directly within structures relevant to migraine chronification.

Jing et al. (2025) summarized these data and concluded that GLP-1RAs may modulate migraine-related pathophysiology by attenuating neuroinflammation and suppressing neuronal hyperexcitability. Although current evidence remains predominantly preclinical, the mechanistic coherence is notable and supports further translational study.

4.4. Fibromyalgia-Related Mechanisms and Chronic Widespread Pain

Fibromyalgia is a complex syndrome characterized by widespread pain, fatigue, sleep disturbance, cognitive symptoms, and altered central pain processing. Although its pathogenesis remains incompletely understood, central sensitization, neuroimmune signaling, metabolic burden, impaired physical function, and low-grade inflammation are increasingly discussed as contributing factors.

Alfaro-Martinez et al. (2026) reviewed the potential indirect impact of GLP-1RAs in fibromyalgia and argued that these agents may influence several pathways relevant to the disorder, including inflammatory signaling, oxidative stress, altered pain processing, and metabolic dysregulation. However, the authors also emphasized that the current support remains largely indirect and that direct interventional evidence is still lacking.

This hypothesis is consistent with the broader multimorbidity-oriented framework proposed in the chronic pain literature. In patients with obesity, fatigue, sleep disturbance, low physical activity, or metabolic dysfunction, GLP-1RAs may theoretically influence symptoms not only through weight reduction but also through anti-inflammatory and neurobiological mechanisms. Nevertheless, the present evidence does not justify clinical recommendations for fibromyalgia itself, and any interpretation should remain cautious and exploratory.

4.5. Osteoarthritis and Inflammatory Musculoskeletal Pain

Osteoarthritis-associated pain is increasingly recognized as involving more than mechanical joint degeneration alone. Low-grade inflammation, synovial activation, macrophage-mediated cytokine signaling, obesity-related metabolic burden, and neuroimmune interactions all appear to contribute to symptom severity and structural progression.

Zheng et al. (2024) noted that GLP-1RAs may reduce macrophage-mediated inflammatory responses in osteoarthritis and thereby alleviate symptoms such as pain and joint stiffness. Jing et al. (2025) similarly included inflammatory pain and osteoarthritis among the pain modalities in which GLP-1 receptor activation may have therapeutic relevance.

Additional support comes from rheumatology literature. Bilgin et al. (2025) summarized evidence suggesting that GLP-1RAs may influence inflammatory pathways, oxidative stress, and immune regulation across rheumatic and musculoskeletal diseases, including osteoarthritis. The rheumatoid arthritis scoping review further reported reductions in inflammatory markers and pain scores in early observational studies, while in vitro data supported suppression of cytokine signaling, oxidative stress, and tissue-degrading pathways (Wu et al., 2026). Although rheumatoid arthritis is not directly equivalent to osteoarthritis or chronic pain syndromes more broadly, this evidence offers supportive translational insight for pain states characterized by inflammatory and metabolic overlap.

The role of weight loss should also be considered carefully in this context. In musculoskeletal pain populations, symptom improvement may partly reflect reduced mechanical load and better function. However, the observation that some anti-inflammatory and pain-related improvements may not correlate fully with weight loss suggests that direct biological effects also warrant investigation.

4.6. Visceral Pain

Visceral pain represents another area of potential interest because GLP-1 signaling is closely linked to gastrointestinal regulation and gut-brain communication. Jing et al. (2025) reviewed evidence suggesting that GLP-1 receptor agonists may reduce visceral hypersensitivity and improve bowel dysfunction in experimental models. This is clinically relevant because visceral pain syndromes are often difficult to manage and frequently involve interactions among autonomic regulation, immune activation, stress physiology, and altered central sensory processing.

At present, however, this literature remains limited, and dedicated clinical evidence is still sparse. Visceral pain should therefore be regarded as a promising but early-stage translational field rather than an established clinical application.

5. Mechanisms Potentially Underlying Analgesic Relevance

The potential analgesic relevance of GLP-1RAs appears to arise from their capacity to modulate several converging pathways involved in pain initiation and maintenance.

A central mechanism is attenuation of neuroinflammation. Chronic pain is associated with activation of spinal and supraspinal glial cells, increased production of pro-inflammatory cytokines, and enhanced neuronal excitability. By suppressing microglial overactivation and inflammatory gene expression, GLP-1 receptor activation may reduce neuroimmune amplification that contributes to persistent pain (Jing, Zou, Wang, Cai, & Tang, 2021; Ma et al., 2021). A second major mechanism involves oxidative and metabolic stress. In conditions such as diabetic neuropathy, obesity-associated pain, and inflammatory pain, oxidative burden and altered cellular metabolism may contribute directly to nerve dysfunction and pain chronification. GLP-1RAs may interrupt this cycle by improving metabolic regulation while simultaneously exerting anti-inflammatory, antioxidative, and mitochondrial-protective effects (Bendotti et al., 2022; He et al., 2025; Zhang, Zhang, & Tian, 2021). Neuroprotection represents a further plausible mechanism. Experimental and review literature suggests that GLP-1 receptor activation may support neuronal survival, preserve neural integrity, and improve functional recovery in settings characterized by inflammatory or neural stress (Lu et al., 2024; Ma et al., 2021; Zhang et al., 2021; Zheng et al., 2024). Such effects may be especially relevant in neuropathic pain syndromes, where persistent symptoms reflect not only altered nociception but also progressive neural dysfunction. Finally, GLP-1 signaling may exert broader systems-level effects through interactions among metabolism, inflammation, sleep-related dysfunction, physical capacity, and central neural regulation. This integrative perspective is important because the severity and persistence of chronic pain often depend on the interaction between biological, behavioral, and metabolic factors rather than on isolated nociceptive mechanisms alone. Taken together, these mechanisms suggest that GLP-1RAs may have relevance in pain medicine not simply by reducing pain signaling, but by modifying the inflammatory, metabolic, mitochondrial, and neuroimmune environment in which chronic pain develops and persists.

6. Clinical Implications

The emerging literature suggests that GLP-1RAs may represent a promising adjunctive direction in chronic pain management. Their therapeutic appeal lies in the possibility of addressing several interconnected dimensions of pain pathophysiology simultaneously, including neuroinflammation, metabolic dysfunction, oxidative injury, impaired neuronal resilience, and processes contributing to sensitization.

From a clinical perspective, GLP-1RAs may be particularly relevant in patients with chronic pain and coexisting obesity, type 2 diabetes, insulin resistance, sleep disturbance, fatigue, or systemic inflammatory burden. In such populations, pain often develops within a broader network of metabolic and functional dysregulation. A therapy capable of influencing multiple components of that network may offer advantages over narrowly symptom-focused strategies. At the same time, this promise should not be overstated. Improvements in pain-related outcomes may reflect weight loss, improved glycemic control, reduced systemic inflammation, better sleep, enhanced mobility, or lower mechanical stress rather than a specific analgesic action. This does not diminish the possible clinical value of the therapy, but it complicates mechanistic interpretation and has important implications for trial design and phenotype-specific patient selection. If future studies confirm clinically meaningful benefits, GLP-1RAs could broaden the therapeutic landscape of chronic pain by introducing a more mechanism-oriented and multimorbidity-aware treatment concept. Their greatest utility may ultimately lie not in replacing conventional analgesics, but in complementing them within carefully selected patient groups.

7. Limitations and Future Directions

Despite growing interest in this field, the current evidence supporting GLP-1RAs in chronic pain remains preliminary and methodologically constrained. Much of the literature consists of animal studies, mechanistic analyses, narrative reviews, and early observational findings. Randomized clinical trials specifically designed to assess pain outcomes remain scarce, and many currently available human data derive from populations treated primarily for diabetes, obesity, or related metabolic disorders.

Another major limitation is the heterogeneity of the pain phenotypes under discussion. Neuropathic pain, diabetic peripheral neuropathy, migraine, osteoarthritis-associated pain, inflammatory musculoskeletal pain, visceral pain, and fibromyalgia-related symptoms differ substantially in pathophysiology, clinical expression, and treatment responsiveness. Broad conclusions about GLP-1RAs in chronic pain as a unified category are therefore not yet justified. Mechanistic attribution also remains uncertain. It is not yet clear to what extent apparent benefits are driven by direct effects on neuroinflammation, microglial activity, oxidative stress, mitochondrial function, and neural integrity, as opposed to indirect effects mediated by weight loss, improved metabolic regulation, reduced systemic inflammation, or improved function and sleep. This question is especially important in multimorbid populations with substantial metabolic comorbidity.

Future studies should include adequately powered randomized controlled trials, stratified analyses by pain phenotype and metabolic status, and mechanistic endpoints capable of distinguishing peripheral, central, inflammatory, and metabolic contributors to treatment response. Where feasible, such studies should also assess outcomes beyond pain intensity alone, including function, sleep quality, fatigue, quality of life, and analgesic consumption.

In summary, GLP-1RAs should currently be regarded as promising but investigational agents in chronic pain management. Their mechanistic profile and early translational signal justify continued study, but robust clinical validation remains necessary before any clear therapeutic role can be established.

8. Conclusions

GLP-1 receptor agonists represent a biologically plausible and potentially important emerging therapeutic strategy in chronic pain syndromes. Their possible value appears to derive from anti-inflammatory, antioxidative, neuroprotective, mitochondrial-supporting, and neuroimmune-modulating effects rather than from conventional analgesic action alone.

The strongest current mechanistic rationale exists for neuropathic pain, diabetic peripheral neuropathy, and migraine-related central sensitization, while osteoarthritis-associated pain, inflammatory musculoskeletal pain, fibromyalgia-related mechanisms, and visceral pain remain promising but still exploratory areas of investigation. Supportive evidence from broader central nervous system and inflammatory disease literature further strengthens the biological plausibility of this therapeutic concept, but should not be mistaken for direct proof of clinical efficacy in chronic pain populations.

Accordingly, GLP-1RAs should not yet be considered established treatments for chronic pain syndromes. Their role is best described as investigational and hypothesis-generating. Further translational studies and prospective clinical trials are needed to clarify efficacy, safety, mechanism-specific effects, optimal patient selection, and the feasibility of integrating GLP-1RAs into multidisciplinary chronic pain management.

Conflicts of interest: The authors declare no conflicts of interest.

REFERENCES

1. Alfaro-Martinez, J. J., Lopez-Gomez, J. J., Ahmed, S. S., Motallebzadeh, R., McVeigh, N. M., Parekh, S., McVeigh, C. M., Kaye, A. D., Thaker, J. S., Yong, R. J., Kaye, A. M., Urits, I., & Viswanath, O. (2026). The potential indirect impact of GLP-1 receptor agonists in the management of fibromyalgia. *Journal of Clinical Medicine*, 15*(9), 3330.
2. Bendotti, G., Montefusco, L., Lunati, M. E., Uselli, V., Pastore, I., Lazzaroni, E., Assi, E., Seelam, A. J., El Essawy, B., Jang, J., Loretelli, C., D'Addio, F., Berra, C., Ben Nasr, M., Zuccotti, G. V., & Fiorina, P. (2022). The anti-inflammatory and immunological properties of GLP-1 receptor agonists. *Pharmacological Research*, 182*, 106320. <https://doi.org/10.1016/j.phrs.2022.106320>
3. Bilgin, E., Venerito, V., & Bogdanos, D. P. (2025). Glucagon-like peptide-1 receptor agonists in rheumatology: A review of current evidence and future directions. *Autoimmunity Reviews*, 24*(9), 103864. <https://doi.org/10.1016/j.autrev.2025.103864>
4. Bliddal, H., Bays, H. E., Czernichow, S., Deanfield, J., Flint, A., Gibson, S., Haluzik, M., Jensen, T. J., Kamiya, K., Lau, D. C. W., le Roux, C. W., McGowan, B. M., O'Neil, P. M., Rubino, D. M., Wiese, R. J., & Gudbergensen, H. (2024). Once-weekly semaglutide in persons with obesity and knee osteoarthritis. *The New England Journal of Medicine*, 390*(15), 1394-1408.
5. Bendotti, G., Montefusco, L., Lunati, M. E., Uselli, V., Pastore, I., Lazzaroni, E., Assi, E., Seelam, A. J., El Essawy, B., Jang, J., Loretelli, C., D'Addio, F., Berra, C., Ben Nasr, M., Zuccotti, G. V., & Fiorina, P. (2022). The anti-inflammatory and immunological properties of GLP-1 receptor agonists. *Pharmacological Research*, 182*, 106320. <https://doi.org/10.1016/j.phrs.2022.106320>
6. Drucker, D. J. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metabolism*, 27*(4), 740-756. <https://doi.org/10.1016/j.cmet.2018.03.001>
7. He, Y., Xu, B., Zhang, M., Chen, D., Wu, S., Gao, J., Liu, Y., Zhang, Z., Kuang, J., & Fang, Q. (2025). Advances in GLP-1 receptor agonists for pain treatment and their future potential. *The Journal of Headache and Pain*, 26*(1), 46. <https://doi.org/10.1186/s10194-025-01979-4>
8. Holst, J. J. (2019). The physiology of glucagon-like peptide 1. *Physiological Reviews*, 99*(3), 1405-1430. <https://doi.org/10.1152/physrev.00034.2018>
9. Jing, F., Zeng, Y., Yu, Q.-L., Fu, C.-J., Zhang, F., & Tang, Y. (2025). The role of GLP-1 receptor in pain disorders and its pharmacological properties. *European Journal of Pharmacology*, 178345. <https://doi.org/10.1016/j.ejphar.2025.178345>
10. Jing, F., Zou, Q., Pu, Y., Wang, Y., & Tang, Y. (2023). GLP-1R agonist liraglutide attenuates pain hypersensitivity by stimulating IL-10 release in a nitroglycerin-induced chronic migraine mouse model. *Neuroscience Letters*, 812*, 137397. <https://doi.org/10.1016/j.neulet.2023.137397>
11. Jing, F., Zou, Q., Wang, Y., Cai, Z., & Tang, Y. (2021). Activation of microglial GLP-1R in the trigeminal nucleus caudalis suppresses central sensitization of chronic migraine after recurrent nitroglycerin stimulation. *The Journal of Headache and Pain*, 22*(1), 86. <https://doi.org/10.1186/s10194-021-01302-x>
12. Lu, C., Xu, C., & Yang, J. (2024). The beneficial effects of GLP-1 receptor agonists other than their anti-diabetic and anti-obesity properties. *Medicina*, 61*(1), 17. <https://doi.org/10.3390/medicina61010017>
13. Ma, L., Ju, P., Wang, W., Wei, J., Wang, W., Zhao, M., Ahmad, K. A., Wang, Y., & Chen, J. (2021). Microglial activation of GLP-1R signaling in neuropathic pain promotes gene expression adaptation involved in inflammatory responses. *Neural Plasticity*, 2021*, 9923537. <https://doi.org/10.1155/2021/9923537>
14. Müller, T. D., Finan, B., Bloom, S. R., D'Alessio, D., Drucker, D. J., Flatt, P. R., Fritsche, A., Gribble, F., Grill, H. J., Habener, J. F., Holst, J. J., Langhans, W., Meier, J. J., Nauck, M. A., Perez-Tilve, D., Pocai, A., Reimann, F., Sandoval, D. A., Schwartz, T. W., Seeley, R. J., Stemmer, K., Tang-Christensen, M., Woods, S. C., DiMarchi, R. D., & Tschöp, M. H. (2019). Glucagon-like peptide 1 (GLP-1). *Molecular Metabolism*, 30*, 72-130. <https://doi.org/10.1016/j.molmet.2019.09.010>
15. Nauck, M. A., & Quast, D. R. (2021). Cardiovascular safety and benefits of glucagon-like peptide-1 receptor agonists. *The Lancet Diabetes & Endocrinology*, 9*(10), 653-662. [https://doi.org/10.1016/S2213-8587\(21\)00169-0](https://doi.org/10.1016/S2213-8587(21)00169-0)
16. Si, J., Yu, K., Hao, J., Wang, J., & Zhang, L. (2025). The therapeutic effects and mechanisms of glucagon-like peptide-1 receptor agonists in neurocognitive disorders. *Therapeutic Advances in Chronic Disease*, 16*, 20406223251332035. <https://doi.org/10.1177/20406223251332035>

17. Wu, X., Li, Y., Chen, H., Zhao, M., Zhang, J., & Liu, Q. (2026). Glucagon-like peptide-1 receptor agonists in rheumatoid arthritis: A scoping review of metabolic, anti-inflammatory, and cardioprotective effects. *Journal of Personalized Medicine*, 16*(6), 284. <https://doi.org/10.3390/jpm16060284>
18. Zhang, L.-Q., Zhang, W., Li, T., Yang, T., Yuan, X., Zhou, Y., Zou, Q., Yang, H., Gao, F., Tian, Y., Mei, W., & Tian, X.-B. (2021). GLP-1R activation ameliorated novel-object recognition memory dysfunction via regulating hippocampal AMPK/NF-kappaB pathway in neuropathic pain mice. *Neurobiology of Learning and Memory*, 182*, 107463. <https://doi.org/10.1016/j.nlm.2021.107463>
19. Zhang, L., Zhang, W., & Tian, X. (2021). The pleiotropic of GLP-1/GLP-1R axis in central nervous system diseases. *International Journal of Neuroscience*, 133*(5), 473-491. <https://doi.org/10.1080/00207454.2021.1924707>
20. Zheng, J., Lu, Y., Chen, W., Li, F., Chen, G., Wang, X., & Zhang, Y. (2024). Glucagon-like peptide-1 receptor: Mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy*, 9*, 88. <https://doi.org/10.1038/s41392-024-01745-9>