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Advancing Formulation Science in Diabetes and Migraine: From Conventional Therapies to Precision Drug Delivery

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Abstract

The management of diabetes and migraine has witnessed significant advances through innovations in formulation science. Conventional dosage forms such as tablets, capsules, emulsions, suspensions, and parenteral injections remain widely used due to their established clinical efficacy. However, limitations related to delayed onset, patient non-compliance, and invasive administration have shifted focus toward patient-centric and non-invasive drug delivery systems. Recent developments in oral films, inhalation devices, nasal sprays, and microneedles demonstrate the potential for rapid drug absorption, improved adherence, and enhanced therapeutic outcomes. Furthermore, the emergence of GLP-1 receptor agonists highlights a novel therapeutic convergence, with potential applications in both diabetes control and migraine modulation. Advances in smart delivery devices and digital health integration, including wearable injectors and app-connected systems, further enhance personalization of therapy. Despite these promising trends, challenges such as bioavailability barriers, long-term safety concerns of nanocarriers, cost-effectiveness, and regulatory hurdles persist. Overall, the evolution of formulation strategies reflects a paradigm shift toward minimally invasive, patient-friendly, and precision-guided therapies, paving the way for improved clinical outcomes and global accessibility in chronic and episodic disorders.

Keywords: Diabetes mellitus; Migraine; Novel drug delivery; Non-invasive formulations; GLP-1 receptor agonists; Microneedles; Nasal sprays; Patient-centric therapy; Digital health; Drug formulation strategies.

1. Introduction

1.1 Global burden of diabetes and migraine

The prevalence of diabetes has risen dramatically over recent decades: the World Health Organization reported that the number of adults living with diabetes has nearly quadrupled since 1980, with age-standardized prevalence in adults increasing substantially by the mid-2010s (1).
Migraine is also extremely common and a leading cause of neurological disability worldwide; Global Burden of Disease analyses estimated over one billion people with headache disorders and approximately 1.04 billion people with migraine in 2016, with migraine responsible for tens of millions of years lived with disability (2).
Together, these conditions create large individual and societal burdens: diabetes drives substantial direct health expenditure and long-term morbidity (cardiovascular, renal, visual),

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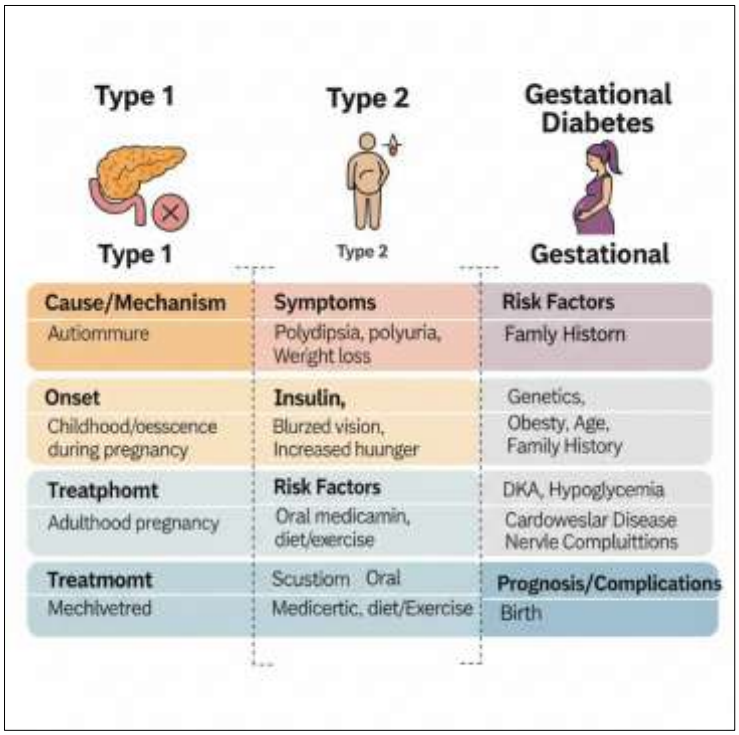
while migraine imposes high productivity losses, reduced quality of life, and marked healthcare utilization—highlighting a major combined public-health and economic load.

1.2 Comorbidity and overlapping mechanisms

Epidemiological data have reported complex associations between diabetes and migraine: some population studies indicate an inverse association (especially for type-1 diabetes) while cohort analyses in adults have suggested a decreased incidence of type-2 diabetes among women with active migraine — findings that point to a non-straightforward, possibly bidirectional relationship. (4).
Mechanistically, several overlapping pathways have been proposed to explain shared risks or interactions. Impaired insulin sensitivity and other metabolic perturbations have been documented in migraineurs, suggesting insulin resistance may link metabolic and cerebrovascular susceptibility (insulin-sensitivity studies, 2005–2013). Neuroinflammatory processes—activation of meningeal nociceptors, cytokine release and glial-immune signalling—are central to migraine pathophysiology and may intersect with systemic metabolic inflammation present in diabetes and metabolic syndrome. Finally, calcitonin gene-related peptide (CGRP), a neuropeptide strongly implicated in migraine generation and vasodilation, represents another mechanistic node: elevated CGRP contributes to trigeminovascular sensitization in migraine and provides a molecular target that conceptually links neurovascular signalling with systemic metabolic influences. (5, 6, 7, 8, 9, 10, 11, 12, 13, 14)

Figure.1 Comparing and contrasting the different types of diabetes.



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1.3 Importance of drug-delivery innovations

Current pharmacotherapies for diabetes and migraine face important, distinct limitations that can be addressed by formulation and delivery innovations. For diabetes, adherence and persistence with injectable insulin remain a major barrier to optimal glycaemic control; device complexity, injection-related anxiety, and regimen burden are repeatedly identified contributors to suboptimal adherence. This motivates user-friendly formulations (pens, patch-like systems), long-acting/prolonged-release approaches, and non-injectable strategies such as oral or inhaled peptide delivery. For migraine, many effective agents (e.g., triptans, NSAIDs) are limited by slow onset when taken orally, variable absorption during migraine-related gastric stasis, or systemic side-effects; nasal, intranasal breath-powered, and transdermal delivery formats have been developed to achieve faster onset, improved bioavailability and better tolerability in acute attacks. Such formulation-specific strategies can also improve patient-reported outcomes and adherence in episodic and chronic migraine. Given the partially overlapping pathophysiology (insulin resistance, neuroinflammation, CGRP signalling) and the distinct delivery challenges of each disorder, rationally designed formulations — for example, rapid-onset CNS-targeted systems for acute migraine or sustained, painless insulin delivery for diabetes — offer a pathway to improving clinical efficacy, safety profiles, and long-term adherence. (5, 6, 7, 8, 9, 10, 11, 12, 13, 14)

2. Overview of Therapeutic Agents Used in Diabetes and Migraine

2.1 Diabetes Medications

Management of diabetes relies on a diverse armamentarium of pharmacological agents, each targeting distinct metabolic pathways. Insulin remains the cornerstone for type 1 diabetes and advanced type 2 diabetes, effectively lowering blood glucose but often limited by hypoglycemia risk and adherence issues (15). Metformin, the first-line oral biguanide, exerts antihyperglycemic effects primarily through suppression of hepatic gluconeogenesis and enhancement of peripheral insulin sensitivity (16). Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, prolong endogenous incretin activity and thereby enhance insulin secretion and reduce glucagon levels with low hypoglycemia risk (17). Glucagon-like peptide-1 (GLP-1) receptor agonists offer additional benefits including weight reduction and cardiovascular protection beyond glycemic control, making them an attractive option for high-risk patients (18). More recently, sodium–glucose cotransporter-2 (SGLT2) inhibitors such as empagliflozin have emerged, providing cardiovascular and renal benefits via glucosuria and blood pressure reduction in addition to their glucose-lowering properties (19).

2.2 Migraine Medications

Pharmacological treatment of migraine spans both acute and preventive strategies. Nonsteroidal anti-inflammatory drugs (NSAIDs) remain widely used for mild to moderate attacks due to their ability to inhibit cyclooxygenase-mediated prostaglandin synthesis (20). Triptans, selective 5-HT1B/1D receptor agonists, are considered the gold standard for acute migraine attacks, producing cranial vasoconstriction and inhibiting trigeminal neurotransmitter release (21). Traditional ergot alkaloids, such as ergotamine and dihydroergotamine, also act via serotonergic pathways but are less selective and limited by vascular adverse effects (22). More recently, calcitonin gene-related peptide (CGRP) antagonists—including small-molecule “gepants” and monoclonal antibodies such as

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erenumab—have been developed, targeting CGRP signaling central to migraine pathophysiology (23). By selectively inhibiting this pathway, CGRP-directed therapies represent a significant advance, particularly for patients unresponsive to traditional agents.

2.3 Cross-Therapeutic Insights

Emerging evidence suggests potential cross-utility of agents originally developed for metabolic disorders in neurological diseases. For instance, GLP-1 receptor agonists have demonstrated neuroprotective and anti-inflammatory effects in preclinical studies, with early reports proposing their potential to reduce migraine frequency via modulation of central energy metabolism and inflammation (24). This highlights an intriguing therapeutic convergence between metabolic and neurological pathways. Furthermore, shared formulation needs underscore innovation in drug delivery: both migraine and diabetes therapies demand rapid onset (to abort migraine attacks or correct hyperglycemia), minimal invasiveness (non-injectable or patient-friendly systems), and controlled release (to maintain long-term disease stability). Thus, formulation science offers opportunities to improve efficacy, adherence, and patient-centered outcomes across these two seemingly distinct disorders.

3. Formulation Approaches in the Treatment of Diabetes and Migraine

3.1 Suspension

Pharmaceutical suspensions are heterogeneous systems in which insoluble solid particles are dispersed in a liquid vehicle (25). In diabetes management, the exenatide extended-release suspension provides once-weekly glycemic control by embedding drug-loaded microspheres into an aqueous medium, thereby improving adherence (26). For migraine, intranasal suspensions have been explored to achieve rapid drug absorption across the nasal mucosa, while pediatric compounding of suspensions is sometimes used when solid dosage forms are unsuitable (27).

3.2 Tablets

Tablets are compressed solid dosage forms intended for oral administration, widely regarded for their stability, dosing accuracy, and patient convenience (25). In diabetes, metformin, sitagliptin, and glipizide tablets remain first-line or adjunctive therapies for type 2 diabetes (28,29). In migraine, sumatriptan tablets are a standard acute treatment, while orally disintegrating tablets (ODTs) such as rimegepant ODT offer rapid dissolution and improved tolerability for patients with migraine-related nausea (30).

3.3 Capsules

Capsules are gelatin or polymer-based shells enclosing powders, pellets, or liquids, providing flexibility in formulation and drug release kinetics (Cole et al., 2008). In diabetes, extended-release (XR) capsule formulations of metformin and empagliflozin are available to improve dosing convenience and gastrointestinal tolerability (Owens et al., 2001). In migraine, naproxen capsules and fixed-dose combination triptan–NSAID formulations have

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demonstrated enhanced therapeutic outcomes by targeting multiple pain pathways simultaneously (Silberstein & McCrory, 2003).

3.4 Oral Films

Oral films are thin polymeric strips that rapidly disintegrate in the oral cavity, enabling buccal or sublingual absorption (31). For diabetes, oral film platforms are under investigation for peptide delivery, including insulin, to bypass gastrointestinal degradation and first-pass metabolism (32). In migraine, rizatriptan oral dispersible films (ODF) have been studied as an alternative to ODTs, with advantages in patients suffering from migraine-associated nausea or vomiting (33).

3.5 Emulsions

Pharmaceutical emulsions are biphasic systems of oil and water stabilized by surfactants, useful for solubilizing lipophilic drugs and enabling controlled release (34). In diabetes, nanoemulsion systems are being investigated for oral peptide delivery, showing promise for enhancing insulin bioavailability (35). In migraine, intranasal dihydroergotamine (DHE) emulsions have been developed to improve mucosal absorption and therapeutic onset compared to traditional parenteral forms (36).

3.6 Parenteral Formulations

Parenteral systems involve injectable routes (IV, SC, IM) that bypass the gastrointestinal tract, allowing for immediate systemic action (37). In diabetes, insulin formulations (rapid-acting analogs such as lispro, and long-acting analogs such as glargine) remain essential for glycemic control, alongside injectable GLP-1 analogs such as liraglutide and semaglutide (38). In migraine, subcutaneous triptans (e.g., sumatriptan) provide rapid relief, while CGRP monoclonal antibodies such as erenumab represent long-acting injectable preventives (39).

3.7 Inhalation Delivery

Inhalation formulations exploit the large pulmonary surface area for systemic drug absorption (40). In diabetes, inhaled insulin demonstrated rapid onset of action and reduced postprandial hyperglycemia compared with injectable insulin (41). In migraine, inhaled dihydroergotamine (was designed to deliver rapid relief during early migraine phases by avoiding gastric absorption delays (36).

3.8 Nasal Delivery

Nasal formulations facilitate drug absorption across the richly vascularized nasal mucosa, offering rapid systemic effects (42). In diabetes, intranasal insulin has been studied for ultra-rapid glucose regulation and potential neurocognitive benefits (43). In migraine, sumatriptan

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nasal sprays provide faster relief than tablets, and novel CGRP antagonist nasal sprays such as zavegepant have been investigated for acute attacks (45).

Table.1. Formulation Approaches in the Treatment of Diabetes and Migraine

Dosage Form	Definition	Diabetes Examples	Migraine Examples	Key Notes
Suspension	Solid particles dispersed in a liquid vehicle	Exenatide extended-release suspension (Bydureon) for weekly dosing improves patient compliance (Kim et al., 2017)	Intranasal suspensions developed for pediatric migraine patients (Krymchantowski et al., 2014)	Useful for poorly soluble drugs
Tablets	Solid oral dosage forms	Metformin, Sitagliptin, Glipizide are standard first-line therapies (Bailey, 2017)	Sumatriptan, Rimegepant ODT improve ease of use during migraine attacks (Dodick, 2018)	ODTs bypass swallowing difficulties and nausea
Capsules	Gelatin shells containing powders, liquids, or pellets	Empagliflozin and Metformin XR capsules enhance controlled release (Inzucchi, 2015)	Naproxen and triptan combinations in capsules offer synergistic relief (Silberstein, 2017)	Flexible for modified release
Oral Films (ODF/ODT)	Thin polymer films dissolving rapidly in oral cavity	Investigated for peptide delivery like insulin films (Gupta et al., 2016)	Rizatriptan oral films under development to improve patient compliance (Shrewsbury et al., 2017)	Non-invasive, fast onset
Emulsions	Oil–water dispersions stabilized by surfactants	Nanoemulsions improve oral peptide stability and absorption (Fonte et al., 2015)	Dihydroergotamine (DHE) nasal emulsions in trials for acute migraine (Halker Singh et al., 2017)	Enhance solubility and stability
Parenteral	Injectable routes (IV, SC, IM)	Insulin analogs (Liraglutide, Semaglutide) for sustained glycemic control (Garber, 2011)	SC triptans and CGRP antibodies (Erenumab) provide rapid migraine relief (Goadsby et al., 2017)	High bioavailability

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Inhalation	Delivery via pulmonary route	Afrezza (inhaled insulin) offers non-invasive alternative (Rosenstock et al., 2015)	Inhaled DHE (Levadex) provides rapid symptom relief (Krymchantowski & Bigal, 2006)	Fast systemic absorption
Nasal Delivery	Absorption via nasal mucosa	Intranasal insulin investigated for rapid onset and CNS targeting (Benedict & Frey, 2011)	Sumatriptan nasal spray and CGRP nasal sprays enhance compliance (Cady et al., 2014)	Avoids first-pass metabolism

(76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91)

5. Clinical and Regulatory Considerations

5.1 Bioavailability and Pharmacokinetics

Inter- and intra-subject variability in absorption is a major clinical concern for both oral small molecules and especially for peptide therapeutics, which are susceptible to enzymatic degradation and poor epithelial permeability in the gastrointestinal tract (47,48). The Biopharmaceutics Classification System (BCS) underscores that aqueous solubility and membrane permeability are primary determinants of oral bioavailability and helps predict when formulation strategies (e.g., solubilization, permeability enhancers, or modified release) are required to reduce pharmacokinetic variability (47). For peptides and proteins, enzymatic cleavage in the stomach and intestine, first-pass hepatic metabolism, and size-limited paracellular transport dramatically limit oral exposure; consequently, developers frequently rely on parenteral routes or advanced carriers (lipid-based systems, enzyme inhibitors, nano-carriers) to achieve therapeutically relevant systemic levels (48,49). Pulmonary and nasal routes can provide rapid systemic uptake and avoid first-pass degradation, but device performance, particle size distribution, and mucosal condition introduce additional sources of PK variability that must be characterized in clinical studies (50).

5.2 Patient-Centric Formulation Design

Patient adherence and real-world effectiveness depend heavily on formulation attributes such as ease of administration, dosing frequency, and tolerability. The World Health Organization highlighted that poor adherence to long-term therapies is multi-factorial and often driven by regimen complexity, route of administration, and side effects, making patient-centred design (less frequent dosing, non-invasive routes, simplified devices) a key objective for chronic indications like diabetes and recurrent conditions such as migraine (51). For example, long-acting injectables or once-weekly GLP-1 receptor agonists improve persistence versus daily injections, and orally disintegrating or intranasal forms for acute migraine increase the likelihood of timely administration during an attack (49,51).

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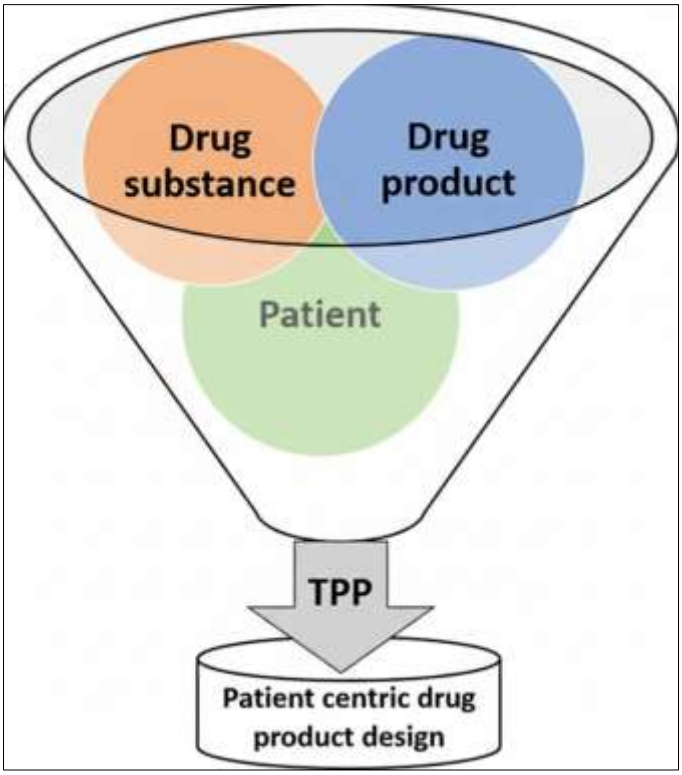
Figure.2. illustrating the funneling of "Drug substance," "Drug product," and "Patient" considerations through a "TPP" (Target Product Profile) to achieve "Patient centric drug product design."



(92)

5.3 Regulatory Challenges

Novel delivery systems and combination products (drug + device) face complex, multi-faceted regulatory pathways because jurisdictions must evaluate both the pharmacology of the active substance and the performance and safety of the delivery device. Regulatory agencies have therefore issued specific frameworks and guidances for bioavailability/bioequivalence assessment and for combination products, requiring early engagement to determine the primary mode of action, applicable center (drug, device, biologic), and appropriate clinical and manufacturing expectations (52,53). Demonstrating consistent in-vivo performance for user-operated delivery devices (e.g., inhalers, autoinjectors, nasal sprays) also necessitates human factors/usability studies and device-specific clinical endpoints in addition to traditional pharmacokinetic/pharmacodynamic and safety data (52,53).

5.4 Cost and Accessibility

Balancing innovation with affordability is crucial in chronic disease management: advanced formulations and biologics often carry high development and manufacturing costs that translate into elevated prices and can limit patient access and health-system adoption (54). Policymakers, payers, and manufacturers are therefore exploring value-based pricing,

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biosimilars/generics pathways, and technology design choices that reduce complexity and cost without compromising clinical benefit (54). For globally prevalent conditions such as diabetes and migraine, scalable and cost-effective delivery solutions (e.g., stable formulations that reduce cold-chain dependence, simplified single-use devices) can materially improve population health outcomes by widening accessibility and adherence.

6. Future Perspectives

6.1. Dual-Target Formulations

The development of dual-target formulations represents a promising avenue for addressing comorbid conditions such as diabetes and migraine. Glucagon-like peptide-1 (GLP-1) receptor agonists, originally developed for glycemic control, have shown emerging potential in modulating central nervous system pathways implicated in migraine pathophysiology, particularly through effects on neuroinflammation and satiety regulation (55). Their ability to influence appetite, vascular tone, and neuronal excitability suggests that carefully engineered GLP-1 analog-based formulations may provide therapeutic benefits in both metabolic and neurological domains (56).

6.2. Personalized and Precision Delivery

Future formulation strategies must align with the principles of personalized medicine, where treatments are tailored to patient-specific characteristics, including genetics, biomarkers, and lifestyle factors (57). Advances in pharmacogenomics and biomarker discovery have paved the way for precision drug delivery systems capable of optimizing therapeutic efficacy while minimizing adverse effects (58). For chronic conditions like diabetes and migraine, personalized delivery platforms—such as controlled-release oral systems or self-regulated insulin pumps—could enable more targeted management strategies (59).

6.3. Integration with Digital Health

Digital health technologies are increasingly being integrated with drug delivery systems to improve patient adherence and therapeutic outcomes. Innovations such as smart insulin pens, continuous glucose monitors, and wearable drug-delivery patches have demonstrated significant promise in diabetes care (60). Similarly, smartphone-connected devices and app-based symptom tracking are being explored in migraine management, enabling real-time monitoring and personalized dosing adjustments (61). The convergence of digital health and advanced formulations may allow for closed-loop systems that optimize treatment based on real-time physiological data (62).

6.4. Research Gaps

Despite significant advancements, several research gaps remain. The long-term safety and biocompatibility of nanocarrier-based formulations for peptide and protein delivery are not

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fully established, necessitating extended toxicological evaluations (63). Similarly, scalable and cost-effective manufacturing techniques for microneedle-based systems are still under development (64). Moreover, comorbid populations—such as individuals with both diabetes and migraine—remain underrepresented in clinical trials, highlighting the need for more inclusive study designs that capture the complexities of real-world patient scenarios (65). Addressing these gaps will be crucial for translating innovative delivery systems into widespread clinical practice.

7. Conclusions

The management of chronic diseases such as diabetes and episodic conditions like migraine has advanced considerably with innovations in formulation science. Traditional approaches—including suspensions, tablets, capsules, emulsions, and parenteral injections—remain the backbone of therapy for both conditions, with established agents such as metformin and triptans continuing to dominate treatment regimens (67,68). However, the growing emphasis on non-invasive and patient-centric formulations has led to significant progress in the development of oral films, inhalation systems, and nasal sprays, offering faster onset of action and improved patient adherence (69, 70).

Emerging research highlights the potential cross-therapeutic utility of agents such as GLP-1 receptor agonists, which may serve dual roles in diabetes control and migraine modulation, although further validation is required (68, 71). Moreover, digital health–enabled delivery platforms, including smart pens, wearable injectors, and app-connected devices, provide opportunities to personalize therapy and improve self-management in patients (72).

Despite these advances, challenges remain regarding bioavailability of peptides, long-term safety of nanocarriers, scalable microneedle fabrication, and regulatory complexities for novel delivery systems (73,74). Cost-effectiveness and equitable access also continue to be pressing concerns in ensuring that innovative formulations translate into clinical practice worldwide (75).

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