# Respiratory care: Why neurology's long-acting therapies could be key

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Respiratory conditions, particularly chronic obstructive pulmonary disease (COPD) and severe asthma, present a significant challenge in long-term management. Despite available therapies, suboptimal adherence to daily or even weekly regimens remains a persistent issue, contributing to exacerbations and progressive lung damage. The field of neurology, specifically in multiple sclerosis (MS), has grappled with similar adherence hurdles and has seen success with ultra-long-acting therapies.

This experience offers a compelling case study for respiratory medicine, exploring how extended dosing intervals could transform patient outcomes by simplifying treatment burdens and ensuring consistent therapeutic exposure. The principles applied in MS, focusing on sustained drug delivery and reduced frequency, hold potential for improving the management of chronic respiratory diseases.

**KEY TAKEAWAYS**

- The Pivot: Neurological conditions like multiple sclerosis have successfully integrated ultra-long-acting therapies, shifting the paradigm from frequent dosing to extended intervals.
- The Data: While no specific respiratory trial data exists for this approach yet, MS therapies demonstrate improved adherence and sustained efficacy with less frequent administration.
- The Action: Clinicians should consider the potential benefits of ultra-long-acting formulations in chronic respiratory diseases, advocating for research and development in this area to address current adherence challenges.

Chronic respiratory diseases, including asthma and COPD, require consistent, often lifelong, pharmacological intervention. The daily burden of inhaled corticosteroids, long-acting beta-agonists, and anticholinergics, or even weekly biologics for severe asthma, can be substantial. This complexity frequently leads to poor adherence, which directly correlates with worse disease control, increased exacerbation rates, and a higher risk of hospitalisation. The challenge is not merely about drug efficacy, but about the practical realities of patient self-management in the face of chronic illness. Patients often struggle with the correct inhaler technique, forget doses, or discontinue therapy when symptoms improve, only to relapse later. This cycle of non-adherence and exacerbation drives significant morbidity and healthcare costs. The unmet need in respiratory care, therefore, extends beyond novel mechanisms of action to novel delivery strategies that simplify regimens and improve patient compliance. The experience in multiple sclerosis provides a valuable analogue. MS is a chronic, progressive neurological disorder requiring continuous immunomodulatory therapy to prevent relapses and slow disease progression. Historically, MS treatments involved frequent injections, often daily or several times a

week, which presented significant adherence barriers and quality of life issues for patients. The development of oral therapies and, more recently, ultra-long-acting injectable or infused agents has fundamentally changed the treatment landscape for MS, offering lessons for other chronic conditions.

## The Evolution of MS Therapy: A Blueprint for Extended Dosing

Multiple sclerosis management has undergone a profound transformation, moving from interferon-beta injections administered multiple times a week to a diverse array of therapies, including oral agents and infusions given every few weeks, months, or even annually. This evolution was driven by a clear understanding that consistent suppression of disease activity is paramount. Early MS therapies, while effective, were often associated with injection site reactions, flu-like symptoms, and the psychological burden of self-injection, leading to suboptimal adherence. The introduction of oral disease-modifying therapies (DMTs) offered a significant step forward, reducing the physical burden of injections. But even daily oral medications can be forgotten or discontinued, particularly in asymptomatic periods.

The true game-changer for adherence in MS has been the advent of ultra-long-acting agents. These therapies, typically monoclonal antibodies or other biologics, are administered intravenously or subcutaneously at intervals ranging from every few months to once a year. For example, some anti-CD20 therapies are given as two infusions a year, while others are administered once every six months. This dramatically reduces the frequency of patient interaction with the healthcare system for drug administration and, critically, minimises the daily cognitive load of remembering to take medication. The sustained presence of the drug in the body ensures continuous therapeutic effect, irrespective of daily patient behaviour. This shift has not only improved adherence but also enhanced patient quality of life, allowing individuals to focus less on their disease management and more on living their lives. The Oxford Handbook of Neurology provides a comprehensive overview of these therapeutic advancements and their impact on patient care.

## Translating Neurological Success to Respiratory Challenges

The principles underpinning the success of ultra-long-acting therapies in MS are directly applicable to chronic respiratory diseases. Many respiratory conditions, like severe asthma, are driven by specific inflammatory pathways, making them amenable to biologic therapies. Currently, biologics for severe asthma are typically administered subcutaneously every two to four weeks. While less frequent than daily inhalers, this still represents a significant ongoing commitment for patients. For patients with severe eosinophilic asthma, for instance, consistent anti-IL-5 or anti-IL-5R therapy is essential to reduce exacerbations and improve lung function. But even with these advanced therapies, adherence can wane over time, particularly if patients perceive their symptoms to be well-controlled.

Imagine a scenario where a patient with severe asthma receives an annual or biannual injection that provides sustained control of their airway inflammation. This would drastically reduce the logistical burden on patients and caregivers, potentially leading to a more consistent therapeutic effect and fewer exacerbations. The development of such therapies would require innovative drug delivery systems, such as sustained-release formulations or gene therapies that enable endogenous production of therapeutic proteins. The challenge lies in achieving a consistent and predictable drug release profile over extended periods, ensuring both efficacy and safety. This is not a trivial undertaking, but the precedent set in MS demonstrates its feasibility and clinical value.

## The Pharmacokinetic and Pharmacodynamic Considerations

Developing ultra-long-acting therapies for respiratory conditions involves overcoming significant pharmacokinetic and pharmacodynamic hurdles. The goal is to maintain therapeutic drug concentrations within a narrow window for an extended period, avoiding both sub-therapeutic levels that lead to loss of control and supra-therapeutic levels that increase the risk of adverse events. In MS, this has been achieved through various strategies, including the use of monoclonal antibodies with long half-lives, which naturally lend themselves to less frequent dosing. Some formulations also leverage depot technologies, where the drug is encapsulated or formulated to release slowly over time from an injection site.

For respiratory biologics, similar approaches could be explored. Modifying existing antibodies for even longer half-lives, developing novel sustained-release formulations for subcutaneous injection, or even exploring implantable devices that continuously deliver drug at a controlled rate are all avenues for investigation. The target pathways in respiratory diseases, such as IL-5, IL-4/IL-13, or TSLP, are well-characterised, providing clear targets for these extended-release strategies.

The critical aspect is to ensure that the sustained exposure does not lead to increased immunogenicity or unexpected long-term side effects. Rigorous preclinical and clinical development would be essential to characterise the safety and efficacy profile of such novel formulations. The insights from epithelial cytokines linking severe asthma, CRSwNP, and COPD highlight the complex relationship of inflammatory mediators that these therapies would need to modulate consistently.

## Addressing Adherence and Patient Outcomes

The primary driver for ultra-long-acting therapies is improved adherence. For chronic conditions, adherence rates often decline significantly after the first year of treatment, regardless of the disease. In respiratory care, this translates directly to poorer lung function, increased symptoms, and a higher incidence of acute exacerbations requiring hospitalisation. A therapy administered once or twice a year virtually eliminates the daily adherence burden, placing the responsibility on the healthcare system for scheduled administration rather than on the patient for daily self-management. This shift has profound implications for patient outcomes and healthcare resource utilisation.

Beyond adherence, ultra-long-acting therapies could offer a more stable disease course. Fluctuations in drug levels due to missed doses are minimised, leading to more consistent control of inflammation and symptoms. This could translate to fewer emergency department visits, reduced hospitalisations, and a better overall quality of life for patients living with severe asthma or COPD. The economic impact could also be substantial, as the costs associated with managing exacerbations and hospital stays often outweigh the cost of preventive therapies. The potential for these therapies to reduce the overall burden of chronic respiratory disease is compelling, mirroring the benefits observed in MS where sustained disease control has become the norm rather than the exception. Our previous coverage on why benralizumab patients still suffer asthma attacks highlights the ongoing need for improved and more consistent therapeutic strategies.

## The Road Ahead: Challenges and Opportunities

While the conceptual framework is strong, the development of ultra-long-acting respiratory therapies faces several challenges. The initial development costs for novel drug delivery systems are high, and regulatory pathways for such innovative formulations can be complex. Demonstrating non-inferiority or superiority to existing, frequently dosed therapies will be critical, requiring large, well-designed clinical trials. Safety monitoring over extended periods will also be paramount, as any adverse events associated with a long-acting agent would persist for the duration of its action. The potential for immunogenicity, particularly with biologic agents, needs careful evaluation in sustained-release

formulations.

But the opportunities far outweigh these challenges. The potential to transform the lives of patients with chronic respiratory diseases by simplifying their treatment regimens and improving their long-term outcomes is immense. The success in neurology provides a clear roadmap, demonstrating that with scientific innovation and a patient-centric approach, ultra-long-acting therapies are not just a theoretical concept but a clinically achievable reality. The focus should now shift towards investing in the research and development necessary to bring these transformative therapies to respiratory care. The Oxford Handbook of Respiratory Medicine offers a detailed look at current management strategies and the areas ripe for innovation.

**CLINICAL IMPLICATIONS**

The experience from multiple sclerosis with ultra-long-acting therapies provides a clear template for respiratory medicine. The persistent challenge of adherence in chronic respiratory conditions like severe asthma and COPD is not adequately addressed by current daily or even bi-weekly regimens. Simplifying the treatment burden for patients is not merely a convenience; it is a direct pathway to improved disease control and reduced exacerbations.

Pharmaceutical companies developing respiratory biologics should actively explore sustained-release formulations or other long-acting delivery platforms. The investment required for such innovation is substantial, but the long-term benefits in patient outcomes and healthcare cost reduction would be significant. This is a strategic imperative, not just an incremental improvement.

For clinicians, understanding the potential of these future therapies means advocating for their development and recognising the limitations of current adherence strategies. We must acknowledge that even the most effective drug is useless if not taken consistently. The shift towards less frequent administration could fundamentally alter how we manage chronic respiratory diseases, moving the focus from daily compliance to periodic, highly effective interventions.



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