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Long-Term Systemic Corticosteroid Exposure: A Systematic Literature Review

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ABSTRACT

Purpose: While corticosteroids are relatively inexpensive and commonly used as treatment for a variety of conditions, long-term use is known to be associated with certain toxicities. Prior systematic reviews have revealed an increased risk for costly adverse events (AEs), including bone fracture, infection, and gastrointestinal bleeding. The objective of this study was to conduct a systematic literature review of recent publications on the burden of long-term corticosteroid exposure, specifically, to summarize the AEs and economic impact of long-term corticosteroid use and to reveal data gaps for additional research.

Methods: The Ovid search platform was used to access scientific literature databases. The search strategy targeted the use of corticosteroids and economic outcomes research. Articles were restricted to those published between 2007 and 2016 to cover publications since prior reviews; conference abstracts and articles assessing pediatrics were excluded. Titles and abstracts resulting from inclusion criteria were screened, and reviewers independently extracted relevant information from the relevant full-text articles.

Findings: The literature review included 32 articles, with 75% focusing on autoimmune diseases, asthma, or lung diseases. Included articles were 14 database analyses, 6 simulations, 6 clinical trials, 3 systematic literature reviews, 2 patient surveys, and 1 chart review. Commonly-cited AEs associated with long-term corticosteroid exposure included hypertension (prevalence >30%); bone fracture (21%–30%); cataract (1%–3%); nausea, vomiting, and other gastrointestinal conditions (1%–5%); and metabolic issues (eg, weight gain, hyperglycemia, and type 2 diabetes; cases had 4-fold the risk of controls). Association of dose and duration with increased AE risk is not well-quantified. AEs like peptic ulcer and myocardial infarction are particularly costly to payers (1-year cost of $21,825 and $26,472, respectively, in year-2009 USD). The few articles assessing the economic impact of corticosteroid use have found dose-related increases in health care resource utilization and costs, with per-annum incremental costs relative to nonusers ranging from $5700 in low-dose users (<7.5 mg/d) to $29,000 in high-dose users (>15 mg/d). Adherence to treatment guidelines on avoiding AEs (eg, prescribing of oral bisphosphonates, calcium, and vitamin D) remains low.

Implications: Although doses of long-term corticosteroids have fallen over the past several decades in response to AEs, dose reduction may not be a sufficient solution. Numerous AEs, some very costly, persist among long-term corticosteroid users, suggesting a need for further research to fill current data gaps, as well as a potential need for alternative treatment options. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: adverse events, corticosteroids, costs, economic burden, long-term corticosteroid exposure.

INTRODUCTION

Systemic (oral or parenteral) corticosteroids (eg, prednisone, prednisolone, methylprednisolone, dexamethasone) possess potent anti-inflammatory, immunomodulatory, and antineoplastic properties and are integral in the treatment of numerous conditions, including autoimmune diseases, allergic reactions, asthma exacerbations, chronic obstructive pulmonary disease, and select malignancies.[1] However, despite the potentially beneficial clinical effects of these agents, such use is also

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associated with serious risks, especially at high doses for extended periods.[2] Well-known adverse events (AEs) associated with systemic corticosteroid use include osteoporosis, cardiovascular disease, impaired immune response and wound healing, alterations in glucose and lipid metabolism, and psychiatric disturbances.[1,2] Such complications may decrease a patient's quality of life and can also be costly to manage.[3,4]

As shown in **Figure 1**, systemic corticosteroid therapy has been used to treat various ailments for decades. Exogenous corticosteroids were first proposed for use in the 1950s.[5] However, beginning in the later part of the decade, the initial enthusiasm surrounding the then-novel therapy was tempered as findings of toxicity and AEs associated with longer-term corticosteroid use arose.[7] As research on corticosteroid therapy progressed in the 1980s, several studies popularized treatment using lower-dose corticosteroids (<15 mg/d),[8] including a double-blind study that found that patients' conditions improved, with minimal AEs.[6] Use of even lower doses of corticosteroids (<5 mg/d) gained recognition by primary care providers and rheumatologists as both a "bridge" and an alternative to slow-acting antirheumatic drugs, disease-modifying antirheumatic drugs, and NSAIDs.[6]

Previous studies have taken a first look at the burden of long-term corticosteroid exposure. Manson et al[3] reported on a systematic literature review on the burden of AEs and the economic implications of oral corticosteroid use. The article covered a period spanning from January 1990 to March 2007 and focused primarily on asthma, estimating that the costs in 2007 associated with selected AEs arising from long-term corticosteroid exposure were £165 per patient taking oral corticosteroids; a comprehensive estimate of the economic burden of long-term corticosteroid exposure more broadly was not provided. Sarnes et al[9] built on that earlier work, covering literature published between April 2007 and October 2009 and arriving at similar conclusions regarding AEs and building on those findings with respect to the costs of AEs.

The objective of the present study was to conduct a systematic literature review on the burden of long-term corticosteroid exposure, specifically: (1) to update prior work conducted by Manson et al[3] covering publications between 1990 and 2007 by compiling articles published during the period from 2007 to 2016 to (a) reflect current medical thinking and (b) identify gaps in research on the use of corticosteroids; and (2) to focus on economic outcomes to better capture the implications of long-term use to payers. Specific end points collected included AEs associated with long-term systemic corticosteroid use, health care resource utilization (eg, visits for the treatment of AEs), health care costs, and patients' quality of life. In addition to articles focusing on oral and parenteral corticosteroids, articles focusing on inhaled corticosteroids were included in the review to bridge this study with the existing literature.

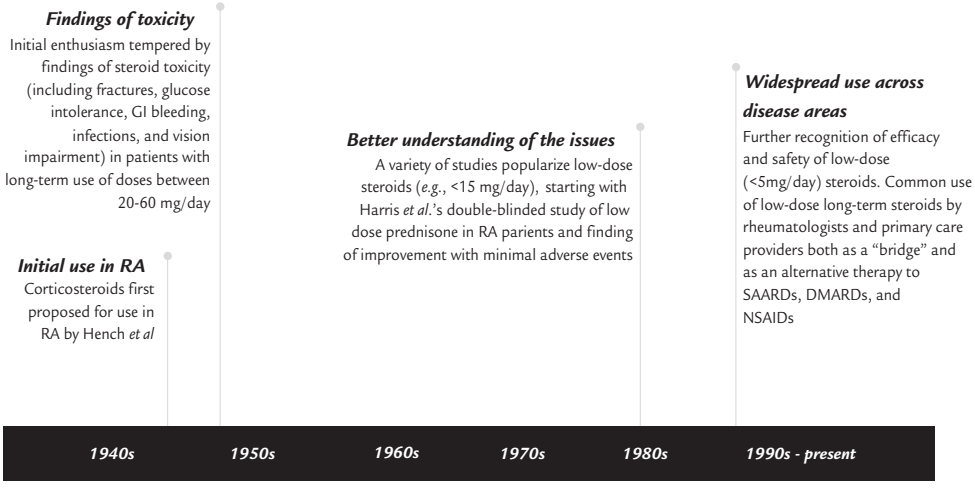

Figure 1. Evolution of corticosteroid use.[5–8] DMARDs = disease-modifying antirheumatic drugs; GI = gastrointestinal; RA = rheumatoid arthritis; SAARDs = slow-acting antirheumatic drugs.