Potential Direct Savings of Implementing Placebo-Controlled Dose Reduction in Psoriasis Treatment

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Abstract

Placebo-controlled dose reduction (PCDR) has the potential to limit topical corticosteroid consumption and expenditure for patients suffering from mild to moderate psoriasis. However, there has been little research into the potential economic benefits of widespread treatment adoption. This study analyzes data representing 2.8 million adults in the 2011-2014 Medical Expenditure Panel Survey to estimate the potential savings in direct out-of-pocket and insurance costs for topical corticosteroids if current dosing regimens were replaced with PCDR. Median individual savings were $42.02 per person (Interquartile Range, 10.71-211.46) for adults under the age of 65, and $53.96 (IR, 12.89-173.38) for adults at least 65. Total savings in these age groups over the four-year period total $684 million (95% CI, $133-$1236 million) and $152 million (95% CI, $58-$247 million) respectively. While widespread adoption of PCDR would provide limited individual savings, there would be significant savings for private and public insurance expenditure. Further study of how the price reduction will impact pharmaceutical prices and markets will clarify the intervention's economic impact.

Introduction

Placebo-controlled dose reduction (PCDR) is a new treatment modality to limit drug consumption that holds large potential savings in medical expenditure. Repeated coadministration of a pharmacologic agent and a neutral placebo has been demonstrated to exhibit the same behavioral conditioning as traditional associations between conditioned and unconditioned stimuli. After a period of associative learning, a placebo alone elicits the same pharmacotherapeutic effect as the active drug and the effect is maintained under a partial reinforcement schedule. Experiments in humans and lower animals support the claim that PCDR allows a portion of an immunosuppressive drug to be replaced by a placebo while maintaining treatment efficacy and limiting side effects.[1,2,3,4]

The treatment's initial success warrants statistical analysis to quantify the potential benefits of implementing PCDR in prescription medication regimens. A preliminary human study found that patients with mild to moderate psoriasis could maintain the therapeutic effects of a standard topical corticosteroid regimen under a partial reinforcement schedule delivering a full dose 25-50%

[1]Castes M, Palenque M, Canelones P, Hagel I, Lynch N. Classic conditioning and placebo effects in the bronchodilator response of asthmatic children. Neuroimmunomodulation 1998;5:70.

[2]Jones RE, Moes NM, Zwickey H, Cunningham CL, Gregory WL, Oken B. Treatment of experimental autoimmune encephalomyelitis with alpha lipoic acid and associative conditioning. Brain Behav Immun 2008;22:538–43.

[3]Exton MS, von Hörsten SB, Schultz M, Vöge J, Strubel T, Donath S, Steinmüller C, Seelinger H, Nagel E, Westermann J, Schedlowski M. Behaviourally conditioned immunosuppression using cyclosporin A: Central nervous system reduces IL-2 production via splenic innervation. J Neuroimmunol 1998;88:182–91.

[4]Klosterhalfen W, Klosterhalfen S. Pavlovian conditioning of immunosuppression modifies adjuvant arthritis in rats. Behav Neurosci 1983;97:663–6.

of the time.[5] These patients also experienced less severe symptoms and incidence of relapse in comparison to patients treated with an equal cumulative amount of corticosteroid delivered under a continuous regimen that mimicked undertreatment. This investigation's success serves as a fitting case study to outline the potential direct economic impact of widespread PCDR adoption in psoriasis treatment.

Psoriasis is a chronic, autoimmune disease that affects 2.6-3.7% of American adults, approximately 7.4 million individuals.[6] The direct cost of psoriasis has been widely studied. Outpatient care, including physician visits and prescription medications, totalled $1.6 to $3.2 billion annually in 1993, with individual costs ranging from $1400 to $6600.[7] Another study reported direct costs of $649.6 million for 1.4 million psoriasis patients in 1997, with 22.7% attributed to prescription medications.[8]

Topical corticosteroids remain a mainstay in treating mild to moderate psoriasis due to their ease of use, safety, and relative affordability.[9] However, approximately half of patients with mild psoriasis and one-quarter of those with moderate psoriasis received no treatment in 2011. A recent study found that only 50-60% of psoriasis patients adhered to treatment.[10] Medication costs and fear of potential side effects are among the top motivations for nonadherence in topical corticosteroid therapy.[11] Additionally, a recent study found that topical corticosteroid prices rose by 290% between 2009-2015, indicate price increases at a rate much higher than general inflation.[12] There is a clear need to offer affordable and safe treatments to improve adherence and reduce individual healthcare expenditure.[13] PCDR might provide a new method that combats patients' concerns and mitigates price increases.

The objectives of this study were to compute the annual cost of prescription topical corticosteroids in psoriasis treatment and estimate the potential savings associated with substituting Placebo-Controlled Dose Reduction for current dosage regimens.

Materials and Methods

Data

[5] Ader, Robert, Mary Gail Mercurio, James Walton, Deborra James, Michael Davis, Valerie Ojha, Alexa Boer Kimball, and David Fiorentino. 2010. "Conditioned Pharmacotherapeutic Effects: A Preliminary Study". Psychosomatic Medicine 72 (2): 192-197.

[6] Rachakonda, Tara D., Clayton W. Schupp, and April W. Armstrong. "Psoriasis prevalence among adults in the United States." Journal of the American Academy of Dermatology 70, no. 3 (2014): 512-516.

[7] Sander, Hans M., Laura F. Morris, Charles M. Phillips, Paul E. Harrison, and Alan Menter. "The annual cost of psoriasis." Journal of the American Academy of Dermatology 28, no. 3 (1993): 422-425.

[8] Javitz, Harold S., Marcia M. Ward, Eugene Farber, Lexie Nail, and Susan Gillis Vallow. "The direct cost of care for psoriasis and psoriatic arthritis in the United States." Journal of the American Academy of Dermatology 46, no. 6 (2002): 850-860.

[9] Lebwohl, Mark. "A clinician's paradigm in the treatment of psoriasis." Journal of the American Academy of Dermatology 53, no. 1 (2005): S59-S69.

[10] Augustin, M., B. Holland, D. Dartsch, A. Langenbruch, and M. A. Radtke. "Adherence in the treatment of psoriasis: a systematic review." Dermatology 222, no. 4 (2011): 363-374.

[11] Brown, Katherine K., Wingfield E. Rehmus, and Alexa B. Kimball. "Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis." Journal of the American Academy of Dermatology 55, no. 4 (2006): 607-613.

[12] Rosenberg, Miranda E., and Steven P. Rosenberg. "Changes in retail prices of prescription dermatologic drugs from 2009 to 2015." JAMA dermatology 152, no. 2 (2016): 158-163.

[13] Hovstadius, Bo, and Göran Petersson. "Non-adherence to drug therapy and drug acquisition costs in a national population-a patient-based register study." BMC health services research 11, no. 1 (2011): 326.

This was a cross-sectional cohort study using the 2011-2014 Medical Expenditure Panels Survey (MEPS), a nationally-representative database for the civilian, non-institutionalized US population produced by the Agency for Healthcare Research and Quality (AHRQ). The MEPS database is a subsample of households and individuals who participated in the National Health Interview Survey (NHIS), conducted by the National Center for Health Statistics, in the previous year.[14] The MEPS Household Component is a collection of datafiles including self-reported medical conditions, sociodemographic and socioeconomic characteristics, prescription medication events, and associated insurance and out-of-pocket expenditure. Publically available data from the full-year consolidated file, medical condition file, and prescription drug file in the MEPS Household Component were joined via the patient identification variable. The MEPS employs complex survey design, including clustering, stratification, and oversampling of specific subgroups.

Condition and Medication Classification

Psoriasis patients were identified using self-reported medical conditions according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnostic codes. Individuals reporting an ICD-9-CM code of 696 were classified as having psoriasis. This analysis was limited to adults aged 18 years or older due to treatment differences between adults and children. Records of prescription medication acquisition for each psoriasis patient were obtained and topical corticosteroids for psoriasis were identified by a dermatologist. This information was used to obtain direct prescription medication costs for the target patient population.

Expenditure Analysis

Data for a weighted 2,744,329 individuals with psoriasis and corticosteroid expenditure in the 2011-2014 MEPS was analyzed to produce individual and national-level estimates. Multiple prescriptions and refill records within each year were aggregated to determine patients' annual medication use and expenditure. Expenditure was converted to 2014 inflation-adjusted dollars using the Personal Health Care Price Indices for prescription drugs reported by the the Centers for Medicare & Medicaid Services. Potential per person and national savings from implementing PCDR, set at 75% consumption and expenditure reduction, was then calculated at the population level and evaluated by expenditure source. Within each expenditure source, the sample was split into four segments to estimate the median savings if individuals with the largest expenditure adopted PCDR. All calculations were conducted in R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/) using the 'survey' package.[15]

Results

In the 2011-2014 pooled sample, 212 entries matched the inclusion criteria. Summary statistics for the study sample are given in Table 1.

Annual Individual Savings

The median individual savings associated with widespread adoption of placebo-controlled dose reduction were ranged from $14 (interquartile range, 3.58-68.42) to $41.99 (interquartile range, 10.75-205.25). These savings would be shared between the individual and various insurance programs.

[14]Cohen JW, Monheit AC, Beauregard KM, Cohen SB, Lefkowitz DC, Potter DE, Sommers JP, Taylor AK, Arnett RH 3rd. "The Medical Expenditure Panel Survey: a national health information resource." Inquiry 33 (1996):373-89.

[15]T. Lumley (2016) "survey: analysis of complex survey samples". R package version 3.31-5.

Table 1: Summary of adults with psoriasis and reporting corticosteroid acquisition in study period.

	Persons less than 65 Years of Age		Persons greater than 65 Years of Age	
	unweighted n	weighted percentage	unweighted n	weighted percentage
Sex				
Female	98	41.49	29	13.23
Male	53	29.14	32	16.14
Race				
Asian or other	12	4.8	6	1.53
Black	18	3.91	5	0.66
Hispanic	27	6.73	5	1.21
White	94	55.19	45	25.98
Age (years)				
18-29	19	7.61	–	–
30-39	25	13.29	–	–
39-49	33	11.95	–	–
49-64	74	37.76	–	–
64-74	–	–	39	17.53
>74	–	–	22	11.85
Education Level				
High School or Less	101	44.24	38	16.43
College	44	23.05	13	8.23
Post-College	6	3.33	10	4.72
Insurance Status				
<65 Any Private	104	55.43	–	–
<65 Any Public	30	7.7	–	–
<65 Uninsured	17	7.49	–	–
65+ Medicare Only	–	–	17	8.6
65+ Medicare and Private	–	–	35	18.93
65+ Medicare and Other Public	–	–	8	1.55
65+ No Medicare	–	–	1	0.29

Individual savings estimates are presented in Table 2. For each savings type, only individuals with non-zero savings values are included. Thus, a low number of individuals with disproportionately high cost in a given expenditure category will result in unreliable median estimates.

For adults over age 65, total median savings associated with widespread adoption of PCDR at 75% expenditure reduction were $53.96 (interquartile range, 12.89-173.38). For adults under age 65, total median savings associated with widespread adoption of PCDR at 75% expenditure reduction were $39.73 (interquartile range, 8.29-208.33).

The following results consider scenarios in which individuals in the top 25% of corticosteroid expenditures within a given expenditure method (private insurance, out-of-pocket, medicare, and medicaid) choose to implement PCDR in their treatment regimens and witness 75% expenditure reductions. The median estimates in the following scenarios exclude individuals reporting no expenditure within the expenditure method under discussion.

Among individuals in the highest quarter of total corticosteroid expenditure, potential median individual savings was $435.63 (IQR, $241.26-875.4), representing 28.29% of total drug expenditure. Among individuals in the highest quartile of private insurance corticosteroid spending, median private insurance savings were $718.74 (IQR, $442.82-1573.89), representing 4.66% of total private insurance pharmaceutical spending. Median out-of-pocket drug expenditure savings was $71.57

Table 2: Individual median savings among individuals with non-zero expenditures within each savings type, including interquartile range.

Savings Type	Savings among Persons less than 65 YOA	Savings among Persons greater than 65 YOA
Total	42.02 (10.71-211.46)	53.96 (12.89-173.38)
Personal	14.79 (7.18-36.99)	13.04 (5.42-39.42)
Private Insurance	89.51 (18.52-406.49)	153.59 (33.19-366.25)
Medicare	120.08 (18.14-167.89)	22.2 (9.12-132.12)
Medicaid	57.04 (34.38-371.32)	4.71 (4.45-23.71)

(IQR, $42.35-98.2), representing 2.31% of total out-of-pocket pharmaceutical spending. Median medicare drug expenditure savings due to PCDR was $338.4 (IQR, $269.55-488.07), or 0.26% of total medicare pharmaceutical expenditure, among individuals in the the highest 25% of medicare corticosteroid expenditure. Finally, among individuals in the top quartile of medicaid corticosteroid expenditure, PCDR savings would be $516.28 (IQR, $383.34-1364.88), representing 1.11% of total medicaid pharmaceutical spending.

National Savings

From a national perspective, the total potential savings associated with PCDR adoption over the four-year study period ranged from $279 million (CI, 84 - 474) to $837 million (CI, 251 - 1423).

Discussion

These analyses indicate that implementing placebo-controlled dose reduction in topical corticosteroid psoriasis treatment could save approximately $200 million, or 14.2% of prescription medication spending, annually. The individual savings would help patients and insurance programs manage costs as drug prices continue to increase at rates higher than inflation. Despite small sample size when analyzed across demographic characteristics, investigating individuals with spending quartiles by expenditure source gives a more realistic understanding of the populations that might adopt PCDR for financial reasons. Targeting PCDR towards individuals with the highest corticosteroid expenditure would yield large savings for patients and insurance programs. There is a strong incentive for individuals and insurance programs to encourage additional research into PCDR to fully illustrate its medical and economic impacts.

Doering and Rief found that implementing PCDR in psoriasis treatment using dermatologic prescription drugs would amount to $73 million (2002 USD) in cost reduction, assuming the active medication was replaced by a placebo 50% of the time.[16] Updating their assessment using the Personal Health Care Price Indices suggests annual savings of $101.9 million (2014 USD). The prescription medications they included in their assessment encompassed various non-corticosteroid dermatologic treatments, suggesting the difference between their estimate and our $220 million figure is larger. Our estimate is higher because we assume a 75% cost reduction based on the findings from Ader, et al. that corticosteroid use only one-quarter as frequently as normally prescribed is sufficient to treat psoriasis. This finding should be interpreted as the highest potential savings within the context of the current literature, however further studies of the optimal medication reinforcement schedule will determine more accurate potential savings. Investigations into whether

[16]Doering, Bettina K., and Winfried Rief. "Utilizing placebo mechanisms for dose reduction in pharmacotherapy." Trends in Pharmacological Sciences 33, no. 3 (March 2012): 165-72.

PCDR is applicable to other dermatologic treatments will uncover the range of therapies available for psoriasis patients.

Pilot studies in patients with asthma and ADHD have indicated similar therapeutic outcomes, suggesting that PCDR might be applied to a large subset of medical conditions following a more complete understanding of the placebo response.[17,18] This economic analysis indicates that PCDR might yield more affordable therapies that encourage patients to improve medication adherence, further enhancing therapeutic outcomes. PCDR might be considered a tool to help individuals and insurance programs manage high drug prices, similar to generic substitution. Other human trials have produced promising results by leveraging classical conditioning in treating Multiple Sclerosis, Asthma, and ADHD, indicating that the placebo response might yield therapeutic and economic benefits in numerous diseases.[19,20,21]

This analysis has several limitations. Primarily, our analyses are constrained by small sample sizes. Approximately fifty individuals fit the inclusion criteria each year, below the minimum sample size for national estimates suggested by AHRQ. Pooling data over a larger timeframe and utilizing datasets that provide more comprehensive expenditure figures for psoriasis patients would improve our estimates.

We do not have information on copayments or other cost-sharing methods for health plans, critical factors that would impact patients' decision to undergo PCDR treatment to reduce their medical expenditure. Adults over the age of 65 might witness larger savings as drug expenditure falls below the coverage gap and social programs and supplemental private insurance cover a larger proportion. While we cannot precisely estimate the savings for individuals or insurance programs, PCDR treatment presents important savings because they reduce unnecessary medication consumption in comparison to current dosage regimens.

A number of patients in our analysis also have prescription medication acquisition events for systemic and biologic treatments. Combination therapy with these treatments might exhibit more complex biochemical interactions that negate the partial reinforcement schedule and require full-dose regimens. Further studies should examine whether PCDR is applicable to all dermatologic agents, as well as combination therapies in psoriasis.

Furthermore, our analysis does not consider the clinical considerations that might arise in delivering PCDR treatment. Modelling individual rational expectations would indicate how patient perceptions of PCDR treatment impact therapeutic outcomes and medication expenditure. Estimating the added economic cost of delivering PCDR in outpatient treatment would also refine the estimated total economic savings for individual spending and pharmaceutical expenditure. More broadly, these findings serve as a case study for the potential direct economic impact of PCDR on drug expenditure. Further studies to determine the optimal acquisition and reinforcement schedule,

[17]Castes, M. et al. (1998) Classic conditioning and placebo effects in the bronchodilatator response of asthmatic children. Neuroimmunomodulation 5, 70

[18]Olness, K. and Ader, R. (1992) Conditioning as an adjunct to the pharmacotherapy of lupus erythematosus. J. Dev. Behav. Pediatr. 13, 124–125

[19]Giang, DW, AD Goodman, RB Schiffer, DH Mattson, M Petrie, N Cohen, and R Ader. 1996. "Conditioning Of Cyclophosphamide-Induced Leukopenia In Humans". The Journal Of Neuropsychiatry And Clinical Neurosciences 8 (2): 194-201. doi:10.1176/jnp.8.2.194.

[20]Kemeny, Margaret E., Lanny J. Rosenwasser, Reynold A. Panettieri, Robert M. Rose, Steve M. Berg-Smith, and Joel N. Kline. 2007. "Placebo Response In Asthma: A Robust And Objective Phenomenon".

[21]Sandler, Adrian D., Corrine E. Glesne, and James W. Bodfish. 2010. "Conditioned Placebo Dose Reduction: A New Treatment In Attention-Deficit Hyperactivity Disorder?". Journal Of Developmental & Behavioral Pediatrics 31 (5): 369-375.

in addition to the range of applicable medical conditions and therapeutic drug classes will yield new insight into this cost-saving tool.