

# Discussion and Conclusion

## DISCUSSION – ADULTS

One question that arises from the data is whether individual states exhibit consistent prescription utilization patterns across therapy classes. Kentucky, Louisiana, and Mississippi were ranked in the top five for more than ten of the 23 therapy classes studied. In contrast, many of the other Southern states, including Alabama, Arkansas, South Carolina, and Tennessee, ranked in the top five for six or fewer therapy classes. In terms of the lowest-utilizing states, Colorado, Minnesota, Oregon, and Vermont appeared in the bottom five 12 times or more and never appeared among the top 5 for any therapy class. In summary, a small number of states frequently rank at the top (or bottom) for individual therapy classes; but for most states, rankings are less consistent. This finding highlights the complexity of drug use patterns and suggests that multiple factors contribute to the observed variation.

Variation by state for each therapy class and overall is reported in the table below. Three measures of variation are reported, the coefficient of variation (CV), the systematic component of variation (SCV), and the interquartile (IQ) ratio. An important question is whether the observed variability is significant, i.e., whether it is greater than what would be expected by chance. For both the CV and SCV, all therapy classes reached statistical significance.

While the observed variation in overall use (SCV = 2.8) is less than is typically seen for many other medical procedures, it is more appropriate to examine individual therapy classes when making comparisons to other medical services as other studies have focused on individual procedures (e.g., coronary angiography). As would be expected, as one moves from overall use to individual therapy classes, greater variation is observed. For non-chronic classes, the greatest variation was observed for cough/cold/allergy, corticosteroids, antihistamines, and cephalosporins. The penicillins and macrolides demonstrated the least amount of variability across states. Among chronic medications, the greatest variation occurred in the use of calcium channel blockers, diuretics, and estrogen medications. In contrast, the antihyperlipidemic, beta blocker, and antiasthmatic drug classes showed the smallest variation.

**Table 3.1. Key Findings by Therapy Class for Adults**

Therapy Class	PREVALENCE			MEASURES OF VARIATION		
	High	Mean	Low	CV	SCV	Interquartile Ratio
Calcium Channel Blockers	5.3	3.7	1.3	28.2	75.2	1.5
Cough/Cold/Allergy	23.2	17.6	7.5	27.2	65.1	1.5
Corticosteroids	9.2	6.7	3.4	24.5	53.5	1.5
Diuretics	6.7	4.8	2.5	24.6	51.6	1.4
Antihistamines	14.7	10.1	6.0	23.6	48.6	1.4
Estrogens	11.0	7.9	3.6	24.3	46.4	1.3
Cephalosporins	14.2	9.8	5.3	22.5	46.3	1.3
Antihypertensives	10.0	8.1	4.9	19.2	35.3	1.3
Antianxiety Agents	8.4	6.3	3.5	20.6	34.6	1.3
Gastrointestinal Agents	11.7	9.0	5.6	18.8	32.3	1.3
Cardiovascular	17.4	14.6	8.7	17.8	29.8	1.3
Anticonvulsants	3.1	2.2	1.5	18.6	29.3	1.4
Narcotic Analgesics	24.6	18.7	12.6	17.0	28.8	1.3
Antidepressants	16.0	10.7	6.4	17.3	28.8	1.3
Thyroid	5.5	3.6	2.5	17.9	27.4	1.3
Antidiabetics	3.5	3.1	1.7	16.5	23.8	1.3
Antirheumatics	20.4	16.3	10.7	14.7	21.0	1.2
Decongestants	7.9	6.4	3.8	16.2	20.7	1.2
Antiasthmatics	6.9	5.3	3.6	15.1	20.3	1.2
Beta Blockers	5.6	4.5	2.6	15.7	18.3	1.3
Macrolides	16.5	14.1	9.3	12.9	15.0	1.3
Penicillins	19.0	16.4	11.3	11.4	12.1	1.1
Antihyperlipidemics	6.7	6.1	3.9	13.1	11.4	1.2
Ophthalmics	5.6	4.9	2.6	12.0	10.4	1.1
Any Use	70.6	66.7	57.9	5.6	2.8	1.1

CV = coefficient of variation, SCV = systematic component of variation

These findings are consistent with Wennberg's assertion that variations are higher for conditions in which greater uncertainty exists regarding diagnosis and treatment, as the calcium channel blockers (CCBs) and estrogen medications are associated with significant controversy. Consider the case of the CCBs. In the mid-1990s, several well-publicized studies showed an increased risk of myocardial infarction or even death among study participants taking CCBs to control hypertension. High doses of some immediate-release CCBs were more likely to be associated with severe adverse results than controlled-release CCBs or other drugs for hypertension. The information prompted the National Institutes of Health and the American Heart Association to issue statements cautioning physicians about the use of certain short-acting CCBs in specific patient groups. Further investigations revealed that some of the earlier studies had limitations in their designs or implementation. Not all the results were negative, and subsequent trials have not shown similar results.

Similarly for estrogens, preliminary results from large ongoing studies of women receiving hormone replacement therapy (HRT) seemed to dispute its positive cardiovascular effects. The Heart and Estrogen/Progestin Replacement Study (HERS) found that short-term use of HRT neither reduced the risk of death from coronary heart disease nor prevented further heart attacks in postmenopausal women with a history of heart disease.<sup>39</sup> The Estrogen Replacement and Atherosclerosis (ERA) Trial found that HRT did not prevent progression of atherosclerosis in women with established coronary artery disease.<sup>40</sup> In the Women's Health Initiative (WHI), a slightly increased risk of stroke was observed during the first year of HRT.<sup>41,42</sup> ERA and WHI are continuing to examine the long-term cardiovascular effectiveness of HRT in women who have not developed heart disease. Until more conclusive evidence is presented, the National Heart, Lung, and Blood Institute states that the benefits of HRT outweigh its risks, and women should consult with their doctors to individualize the management of menopause.

As the preceding discussion illustrates, significant controversy surrounds the safety and/or effectiveness of the CCBs and the estrogens and hence, their appropriate place in therapy. In contrast, the low variation classes, antihyperlipidemics and antiasthmatics, historically have been associated with far less controversy as clear guidelines for use exist, and safety concerns with these drugs have been minimal.<sup>43,44</sup> That said, a new development has been the recent linking of rhabdomyolysis to at least one of the statin medications.<sup>45</sup>

The variation patterns for the non-chronic therapy classes provide mixed support for the uncertainty hypothesis. The low variation of the penicillins may be linked to well-established indications, demonstrated efficacy, minimal side effects, and low cost, as well as their familiarity to most patients. The macrolide class provides a similar scenario in terms of efficacy, indications, and popularity. Thus, the smaller observed variation is not particularly surprising.

There are a number of potential explanations for the high degree of variability for the cough/cold/allergy class. Climate differences, related to both allergens and temperatures, could contribute to the substantial variation. The fact that some cough/cold products are available over-the-counter, although often at lower strengths, could impact variation if physicians' propensity to recommend OTC versions varies by region of the country. Similarly, the role of patient preferences deserves serious consideration given the significant resources devoted to direct-to-consumer advertising for the non-sedating allergy and decongestant combination products and the availability of OTC products. Are patients in certain regions of the country more likely to visit a physician for colds and allergies and/or more likely to request prescription medications rather than use OTC medications? Corticosteroids may have a similar explanation as the many indications for this class, including asthma exacerbations, allergic reactions, and topical disorders (e.g., poison ivy), could have regional variations in their prevalence. It is interesting to note that further analyses found much smaller variation in corticosteroid use (SCV = 19.8) among patients also taking asthma medications than among those with no claims for prescription asthma medications (SCV = 73.7).

Thus far, this discussion has highlighted some possible reasons for greater uncertainty around the high variation classes and for less uncertainty for the low variation classes. These assertions will require additional investigation in order to fully understand their merit. Furthermore, there is currently no formal mechanism for categorizing therapy classes by degree of uncertainty. This is a criticism which has been made of previous discussions of the association between uncertainty and variation and which clearly applies to this discussion as well.<sup>46</sup>

Another potential explanation for the observed variation in prescription use is differences in the underlying disease prevalence across states. As one would expect, the underlying burden of disease within a particular state is associated with the variation in drug use for certain therapy classes. Twenty-one percent of the variation in use of diabetes drugs is related to the prevalence of diabetes, and the risk of heart disease by state explained 62% of the variation in the use of cardiovascular medications. Keep in mind that one would not expect the variation explained to achieve anything close to 100% because the prevalence of disease is based on a sample of all state residents whereas the prevalence of drug use is based on members of Express Scripts. Furthermore, not everyone with diabetes will be taking a prescription medication. Unfortunately, prevalence data by state is not readily available for other diseases for which such a comparison would be relevant. That said, the correlations are significant and suggest that differences in diabetes prevalence and risk for heart disease are contributing to differences in drug use for diabetes and cardiovascular medications, respectively.

Finally, results can be compared to those found in the Dartmouth Atlas of Michigan by limiting our comparison to the drugs included in both studies and measured consistently (antihistamines, antianxiety, and beta blockers). For those three classes, both studies found the greatest variation for antihistamines and the lowest for beta blockers (Table 3.2).

**Table 3.2. Comparison of Express Scripts and Blue Cross Blue Shield of Michigan Findings**

Therapy Class	COEFFICIENT OF VARIATION	
	Express Scripts	BCBSM*
Antihistamines	23.6	21.2
Antianxiety	20.6	20.0
Beta Blockers	15.7	17.0

\*BCBSM = Blue Cross Blue Shield of Michigan, Source: Dartmouth Atlas of Health Care in Michigan

## DISCUSSION – CHILDREN

Comparing the weighted Coefficient of Variation (CV), the Systematic Component of Variation (SCV), and the Interquartile Ratio, the therapy categories with the greatest variation among children were cough/cold/allergy products followed by ADHD stimulant therapy, and cephalosporins (Table 3.3). The therapy category with the least variation across states was penicillins. These findings are consistent with those observed for adults.

Generally speaking, the same factors that potentially influence variation in adult prescription use could also explain variation in children, including variation in the prevalence of a particular condition and physician practice style. However, given that children are typically dependent upon adult caregivers to access the health care system, another factor that would influence prescription use in children are the beliefs/preferences/values of their adult caregivers.

Similar to adults, variation in cough/cold/allergy use among children could be the result of regional variation in environmental factors, such as allergens and pollutants that would trigger these symptoms. Additionally, variation across regions in the propensity of physicians to recommend and/or parents to accept OTC products rather than prescription medications for their child's cold and allergy symptoms could account for variation in the use of these products.

The higher variation for use of ADHD stimulants likely reflects the uncertainty around the diagnosis and treatment for ADHD. During the 1990s, concerns were expressed over the increased use of these medications among school-aged children,<sup>47 48</sup> the implications of long-term use in children, and evidence of geographic variation.<sup>26 27</sup> While diagnostic criteria for ADHD exist, how these criteria are applied or the extent to which physicians apply these criteria is not known.<sup>49</sup> Differences in adult caregivers' perceptions of need, both parents and teachers, may also play an important role.

The higher variation in the use of cephalosporins may relate to differences in physicians' propensity to reserve these medications for second line use although differences in bacterial resistance cannot necessarily be ruled out.

**Table 3.3. Key Findings By Therapy Class for Children**

Therapy Class	PREVALENCE			MEASURES OF VARIATION		
	High	Mean	Low	CV	SCV	Interquartile Ratio
Cough/Cold/Allergy	26.7	14.6	3.5	42.6	147.0	1.9
ADHD Stimulant Therapy (5-14 years)	6.5	4.2	1.9	29.4	78.1	1.5
Cephalosporins	19.5	12.8	7.2	26.4	60.6	1.5
Macrolides	19.1	13.6	9.9	17.7	25.4	1.3
Penicillins	34.1	29.5	23.0	9.9	9.5	1.2
Any Prescription Use	64.5	58.9	48.5	7.2	5.1	1.1

CV = Coefficient of Variation, SCV = Systematic Component of Variation

In comparison to adults, variation was greater for children in overall prescription use, cephalosporins, macrolides, and cough/cold/allergy products. In particular, cough/cold/allergy products showed much higher variation among children than among adults (SCV: 147.0 versus 65.1, respectively). While the difference in the magnitude of variation among children and adults was quite dramatic, the state rankings mirrored each other, with 8 of the top 10 states for children also in the top 10 for adult use for this class.

## CONCLUSIONS

The Express Scripts Prescription Drug Atlas is the first nationwide evaluation of variation in prescription use. The atlas findings demonstrate significant variations in prescription use across the United States among Express Scripts members, even with adjustment for differences in age and gender. The geographic pattern of variation changed by therapy class; but for many of the therapy classes, the South demonstrated the highest prevalence of medication use among adults. The magnitude of variation among adults was greater for some therapy classes than others with calcium channel blockers and cough/cold/allergy medications showing the greatest variation, and ophthalmics, antihyperlipidemics, and penicillins exhibiting the least variation.

As with adults, total prescription use among children was highest in the Midwest and segments of the South. While exceptions were noted, use across the specific therapy categories showed a similar regional pattern to overall use (i.e., higher in many Southern and Midwestern states and lower in Northeastern and Western states). Consistent with adults, variation was greatest for cough/cold/allergy products and lowest for penicillins. Children exhibited greater variation than adults for most therapy classes. Whether greater variation is warranted for children and/or whether it is reflective of greater uncertainty by physicians or caregivers in the treatment of childhood ailments is an important area for future research.

While the Express Scripts Prescription Drug Atlas provides some explanation for the observed prescription use patterns, it inevitably raises many questions. First, what are the reasons for the observed variation? When data were available, a significant association was found between prescription drug use and disease prevalence, suggesting that at least some of the observed variation can be explained by underlying disease prevalence. However, the limited prevalence data by state prevents any strong conclusions on this regard. Furthermore, the greater variation for calcium channel blockers, estrogens, and ADHD stimulants than for other therapy classes provides support to the hypothesis that greater variation is seen when greater uncertainty exists around diagnosis and/or treatment. However, both explanations warrant further examination.

The atlas controlled for differences in age and gender across states and disease prevalence when possible but did not examine other potentially important predictors of prescription use. Separate studies of these data have found statistically significant regional patterns of prescription use, controlling for various sociodemographic and pharmacy benefit design characteristics.<sup>59</sup> However, whether there were systematic and significant differences in physician office visit copays by state or region is unknown. As receiving a prescription is strongly related to physician office visit use, and office visit use may be influenced by physician office visit copay amount, this will be an important area for future study of geographic variation in prescription use.

In terms of understanding reasons for the variation in use, the roles of both patient and physician factors need to be explored. Numerous factors can influence physician prescribing, ranging from the type of training to the practice setting to the patient's ability to pay.<sup>51</sup> For patients, multiple factors have been identified that influence prescription use yet many remain understudied. Of particular interest in understanding geographic variation is the interplay between physician and patient demand, especially given the rise in direct-to-consumer advertising. Related is the question of whether social and cultural differences across regions lead to differences in the "stage of illness at which patients seek health care."<sup>52</sup> In other words, the rate at which people seek care for a given symptom cannot be assumed to be constant across geographic regions of the country. The role played by uneven diffusion of medical technology, in this case pharmaceuticals, should be explored. Are variations greatest when new drugs hit the market and how long do variation rates take to stabilize?

A second and closely related question is whether greater use equates to greater inappropriate use. In contrast, does lower use represent greater underuse? This study alone cannot establish the appropriateness of use but highlights the need to undertake research in this area. Previous researchers have extrapolated savings from variations in other medical procedures by assuming that high use areas would experience the rates in low use areas.<sup>53</sup> Not surprisingly, they have found the potential savings to be substantial. While such an approach is intuitively appealing, it risks assuming that the lowest observed rate is the right rate without sufficient empirical evidence.

In this study, we demonstrate the potential fallacy of this approach using the antihyperlipidemic class. The reported prevalence of high cholesterol in the United States is nearly 19%. Yet, we found that only about 6% of our sample of adults were being treated with an antihyperlipidemic (Table 3.4). This finding is consistent with the assertion that high cholesterol is an undertreated condition.<sup>54 55</sup> Furthermore, were we to assume that the lowest observed rate of use (3.9%) was appropriate, we would be advocating drug therapy for only 21% of patients with high cholesterol (3.9%/19%), which is low even considering that not all patients with high cholesterol will be treated with drug therapy.

**Table 3.4. Reported Prevalence and Drug Use Prevalence in Adults For Selected Diseases/Conditions**

Disease/Condition	Reported Prevalence	EXPRESS SCRIPTS	
		Overall Drug Use	Range Across States
Anxiety	13.3*	6.3	3.5-8.3
Asthma	5.4•	5.3	3.6-6.9
Diabetes	2.9•	3.1	1.7-3.5
Hyperlipidemia	19.0†	6.1	3.9-6.7
Thyroid Disease	2.2§	3.6	2.5-5.5

\* Narrow WE, Rae DS, Regier DA. NIMH epidemiology note: prevalence of anxiety disorders. One-year prevalence best estimates calculated from ECA and NCS data. Population estimates based on U.S. Census estimated residential population age 18 to 54 on July 1 1998, unpublished. Available at [www.nimh.gov/publicatnumbers.cfm](http://www.nimh.gov/publicatnumbers.cfm), Accessed 2001.

• Calculated as the weighted average of number of reported chronic conditions per 100 persons for the age groups 18 to 44 and 45 to 64 years. Current Estimates From the National Health Interview Survey, 1996 National Center for Health Statistics Vital Health Stat 10(200), 1999, Table 57, page 82.

† Defined as percent of persons reporting serum cholesterol levels of 240mg/dL or higher among people 20 to 74 years of age. National Health and Nutrition Examination Survey, 1994 CDC, National Center for Health Statistics. As referenced in Healthy People 2000 Review, 1998-99.

§ Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association Guidelines for Detection of Thyroid Dysfunction. Archives of Internal Medicine 2000;160;1573-75.

Two studies have examined the relationship between appropriateness of use and rates of use for coronary angiography, carotid endarterectomy, and upper gastrointestinal tract endoscopy.<sup>52-56</sup> Looking at both large and small geographic areas, researchers did find significant rates of inappropriate use for these procedures but found no relationship between inappropriateness and total rate of use. More of this type of research is needed for medical care in general and for pharmaceuticals specifically.

Finally, the treatment expansion effect is a relatively unstudied phenomenon that is central to the understanding of variation in and appropriateness of pharmaceutical use.<sup>57</sup> While new drug therapies may substitute for older drug therapies, new drugs often expand the number of people who are treated. When newer drugs are more effective and/or safer, there is the potential for doctors to diagnose and treat the disease more frequently and for patients to be more aware of the disease. The value of the treatment expansion depends on whether the benefits to these newly treated patients (or marginal patients as some have stated) merit the cost of the medication. This is the key challenge for managed care in general and for pharmacy benefit managers and their clients specifically in upcoming years.

Understanding the reasons for and appropriateness of observed variations in the use of prescription medications across the United States will require information beyond prescription or medical claims data. Prescription medications have become an increasingly central component of medical care treatment. Their growing use and popularity, combined with ever-increasing costs and potential for adverse events, warrants that significant and rigorous efforts be devoted to understanding the extent to which pharmaceuticals are being used in the safest, most effective, and cost-effective manner.