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ORIGINAL RESEARCH ARTICLE

Estimating the National Population of Hospitalized Chronic Baclofen Users: A Cross-Sectional Analysis of a Commercial Claims Database

Natalie Schmitz[1,4] · Margaret Artz[2,5] · Karen Walsh[2,6] · Sandeep Gaudana[2] · James Cloyd[1] · John Schrogie[3] · Robert Kriel[1]

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Abstract

Background Baclofen is an effective treatment for spasticity. Abrupt cessation of intrathecal (IT) or oral baclofen risks the development of withdrawal symptoms; however, the magnitude of the problem is unknown.

Objectives The aims for this study were as follows: (1) using an administrative claims database, estimate the number of patients in the United States on baclofen, and (2) estimate the annual percent hospitalized pediatric and adult populations consequently at risk for interruption of chronic baclofen therapy.

Methods Using 2011–2014 data representing commercially insured individuals, patients were selected based on insurance coverage; evidence of a baclofen claim; and hospitalization. All patients hospitalized while receiving chronic baclofen were assumed to be at risk for baclofen discontinuation. Yearly counts were determined and then extrapolated to national estimates using census data.

Results Extrapolating from the claims database, oral or IT baclofen was prescribed annually to 33,061 or 1486 patients ≤ 18 years, and 654,294 or 7084 patients 19–64 years, respectively. The estimated national mean number of at-risk hospitalizations per year for patients aged 19–64 years on chronic oral or IT baclofen was 31,116 and 3774, respectively; patients ≤ 18 years numbered 4691 and 959, respectively. The mean percent of patients hospitalized per year was 42% in those ≤ 18 years receiving IT baclofen compared with 30% in adults, and 3–10% in the populations receiving oral baclofen.

Conclusions Extrapolation from an administrative claims database was used to estimate the national number and demographics of hospitalized chronic baclofen users. Patients ≤ 18 years receiving IT baclofen were at highest risk of withdrawal due to a high occurrence of hospitalization.

Key Points

A commercial claims database was used to estimate the national population of hospitalized chronic baclofen users, which was used as a surrogate for those at risk for withdrawal.

Patients ≤ 18 years receiving intrathecal baclofen were at highest risk of hospitalization leading to interruption of baclofen therapy and risk of withdrawal.

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✉ Natalie Schmitz
Natalie.schmitz@wisc.edu

Extended author information available on the last page of the article

1 Introduction

Baclofen, available as an oral tablet or intrathecal (IT) solution, is indicated for the treatment of spasticity associated with multiple sclerosis and spinal cord injuries or diseases [1, 2]. Baclofen therapy is also commonly prescribed to patients with cerebral palsy, stroke, neurodegenerative disorders, and alcohol dependence and withdrawal [3–9]. The drug is typically taken on a chronic basis to maintain steady-state blood levels and therapeutic effect; its short half-life of 4–6 h necessitates frequent dosing [10].

Abrupt interruption of oral therapy, either intentional or unintentional, can occur when the patient runs out of medication, is non-adherent, the oral route of administration is not possible, or gastrointestinal absorption is compromised such as with gastroenteritis, ileus, or post-operative ileus after prolonged anaesthesia. IT administration relies on an implanted programmable pump and catheter to deliver baclofen into the intrathecal space. Interruption

of IT baclofen delivery may occur when there is migration of the catheter out of the IT space, breakage or disconnection of the catheter from the pump, failure to refill the pump on schedule, or pump malfunction as well as intentional explantation of the pump due to the need for battery replacement or treatment of infection.

Abrupt interruption of baclofen therapy may lead to exacerbation of spasticity symptoms or, more seriously, a severe withdrawal syndrome [11–16]. Symptoms of baclofen withdrawal include rebound increase in muscle tone and spasms, hallucinations, serotonin syndrome, status epilepticus, malignant hyperthermia, elevated plasma creatine kinase, elevated transaminases, hepatic and renal failure, and in some cases, disseminated intravascular coagulation [11]. In the worst cases, withdrawal may also result in rhabdomyolysis, multisystem organ failure, or death [11].

Because baclofen is prescribed for multiple conditions, defining the size of the at-risk population by diagnosis is difficult. Hospitalization of patients on oral or IT baclofen can serve as a surrogate for the population considered 'at risk' of interruption of baclofen. As many as 70% of patients either at the time of admission or during hospitalization require intravenous infusions [17]. Further, approximately 20% of hospitalized patients receive nothing by mouth (NPO) for 3 or more days, which can potentially lead to abrupt interruption of therapy [18–25]. Another at-risk group are patients receiving IT baclofen who have problems with their pumps and interruption of drug flow.

Estimating the number of hospitalized patients treated with oral or IT baclofen requires information about the number of patients receiving the drug, the duration of drug therapy and, within that group, the number hospitalized. As an exploratory effort, we employed methodology that allowed us to make clinically reasonable assumptions and to use definitions that would err on the side of over-estimation.

In summary, the primary objectives of this retrospective, cross-sectional, claims-based study were to (i) calculate the number and percent hospitalized of chronic baclofen users within a commercially insured population, and (ii) by extrapolation using census data, estimate the national number and annual percent hospitalized of those patients receiving baclofen at the time of hospitalization and who are consequently at risk of baclofen interruption and a withdrawal syndrome.

2 Methods

2.1 Source Database

Patient counts were derived from medical and pharmacy claims using a commercial claims database, the Optum Research Database (ORD) owned by Optum, a wholly-owned health data and technology subsidiary of UnitedHealth Group (Eden Prairie, MN, USA). The commercial claims database data originates from a larger Optum healthcare data warehouse, the de-identified Normative Health Informatics (dNHI) data asset, which contains longitudinal patient-level healthcare claims and clinical information. dNHI is nationally distributed and represents approximately 19% of the 2014 US commercially insured population under the age of 65 years. Patient counts for the population over 65 years of age were not calculated due to likely under-reporting in a commercially insured population. The covered entities gave permission for de-identified research under applicable business agreements. Medical and pharmacy claims were aligned to enrollment information.

The Optum Research Database member population included commercially insured patients with consistent medical and pharmaceutical coverage during the study year and 3 months prior, hereafter referred to as insurance criteria. For each calendar study year, the population analyzed included 15 months of continuous medical and pharmacy coverage for the study year (12 months of the calendar year and October–December months from the previous year). This population is demographically diverse and can be assumed to be representative of the US population (Table 1).

2.2 Inclusion Criteria

To ensure accurate data extraction, all data for this analysis was collected from 2011 to 2014, prior to the changes in medical classification lists of International Classification of Diseases (ICD) codes in 2015. Yearly counts of patients on oral or IT baclofen from 2011 to 2014 were based on the following characteristics: insurance coverage, evidence of baclofen use, and one or more hospitalizations. The period surveyed included 12 months of continuous medical and pharmacy coverage for the study year and an additional 3 months comprising a lookback period for baclofen prescription coverage. This criterion was applied to insurance coverage only and not to prescription claims. National Drug Codes (NDC) and Healthcare Common Procedure Coding System Level II (HCPCS) drug code-sets were used for oral and IT formulations. NDC reference data were sourced from FDB MedKnowledge™ [26]. As of January 2014, there were 354 NDCs for oral baclofen, 14 NDCs for IT baclofen, and 6 HCPCS for IT baclofen.

2.3 Baclofen Use

A baclofen user was defined as a patient with evidence of one or more oral or IT baclofen prescription claims during the study year. There was no quantity or days' supply constraint on the claim. This patient group represents the total population for whom hospitalization was determined per year.

Table 1 Age and sex for commercially insured members in commercial claims database compared with the 2014 US population [36]

	Optum members 2014 (%) (n = 6,158,173)	US population 2014 (%) (n = 274,327,481)
Sex		
Males	50.8	50.2
Females	49.2	49.8
Unknown	0.0*	
Age, years		
0–18	24.8	29.3
19–34	22.9	25.5
35–44	16.8	14.9
45–54	18.1	15.9
55–64	17.3	14.4
Unknown	0.1	

*Optum members of unknown sex represent 0.017% of the population

Patients on chronic baclofen therapy are at the highest risk for withdrawal following abrupt cessation; however, no minimum dose or days' supply has been established [27, 28]. Given that use of baclofen over the study year could vary for reasons including discontinuation of therapy or poor adherence, we identified a subgroup of patients within the baclofen user population for whom there was claims evidence of high, consistent use of oral or IT baclofen. We categorized this cohort as chronic baclofen users, which included all those who had 70% fixed-duration medication possession ratio (FMPR) of the oral drug within 90 days prior to hospitalization. Seventy percent FMPR was selected as a clinically reasonable cut-off for chronic baclofen use. Using the hospitalization date as the index date, the days' supply and fill dates of oral baclofen were used to calculate FMPR using the following equation: FMPR = total day supply/90 days. Due to a lack of days' supply information on IT claims, all individuals on IT baclofen were considered chronic baclofen users.

2.4 Hospitalizations

The at-risk populations for baclofen withdrawal are patients on chronic oral or IT baclofen whose therapy is abruptly interrupted. Hospitalizations per year were used as a surrogate for the at-risk group because abrupt interruption of chronic oral or IT baclofen therapy is often associated with hospitalization. If these patients are admitted to a hospital for other reasons, they may experience an abrupt interruption of therapy due to illness, surgery, procedures prohibiting oral intake, or complications associated with IT pump management as noted above. Furthermore, the IV product under development is intended for use only in the inpatient setting.

Hospitalization was defined as a hospital stay determined by confinement place-of-service, admit date, and discharge date. The hospitalization definition excluded outpatient procedures and observation stays. No constraints were placed on the reason for hospitalization or procedures conducted during the hospitalization. Since it is difficult to precisely determine the number of hospitalized patients in whom bridging therapy would be required in the case of a baclofen interruption, for simplicity, all hospitalized patients meeting the definition of chronic baclofen use within 90 days of hospitalization were assumed to be at risk for baclofen interruption. The first hospitalization was used if a patient had more than one hospitalization in the year. There were patients who had evidence of both IT and oral baclofen use within the same study year. To eliminate counting a patient twice, those on both IT and oral baclofen during the same 90 days before the hospitalization index date were included only in the oral baclofen count.

2.5 Data Analysis

Data were analyzed using SAS v9.4 and Microsoft Excel Version 2010. National estimates were determined using the percentage of patients 18 years of age and younger (children) and those 19–64 years (adults) who fulfilled all inclusion criteria. These percentages were then applied to the comparable, sex- and age-stratified population for the corresponding year, based on US Census Data from the CDC [29]. For example, in Table 4, year 2014, the projected count of oral baclofen users for 18 years and under was 36,635. This number is derived from the number of patients 18 years and younger using oral baclofen in the commercial claims database (696) and the total number of members 18 years and younger in the Optum database (1,528,260) (Table 2). This ratio (696/1,528,260) is multiplied by the 2014 US Census data population for ages 18 years and under (80,443,567) (Table 4). Patient counts for those 65 years and older were not included within the commercial claims database and therefore, not extrapolated to a national estimate. For all analyses, arithmetic means were calculated for each route of administration. Estimates <0.5 were rounded down and estimates ≥ 0.5 were rounded up.

3 Results

3.1 Population Demographics

In 2014, the Optum members in the commercial claims database totaled 28,244,388. The yearly number of patients with consistent medical and pharmaceutical coverage during the study period ranged between 6.1 and 7.0 million from 2011 to 2014. The commercial claims database population was

demographically similar to the US population for each study year (2011–2014). Table 1 displays the sex and age of the commercial claims database population compared with the US population for the 2014 study period.

Table 2 Hospitalizations in baclofen users ≤ 18 years (commercial claims database)*

Year	Optum members ≤ 18 years (insurance criteria applied)	Baclofen patients (with any baclofen use)		Baclofen patients with hospitalizations (with chronic baclofen use)			
				Oral		Intrathecal	
		Oral	Intrathecal	Admit count	Patient count	Admit count	Patient count
2011	1,792,310	708	41	115	72	25	16
2012	1,752,349	709	34	120	76	15	11
2013	1,728,914	698	31	93	69	25	15
2014	1,528,260	696	22	75	55	17	11
Arithmetic mean (95% CI)	1,700,458 (1,585,071–1,815,846)	703 (696–709)	32 (24–40)	101 (80–121)	68 (59–77)	21 (15–26)	13 (11–16)

*The total number of Optum members in 2014, without restrictions, was 6,158,173. There was 'unknown' age information for 53 members in the 18 years and under category and 1013 members in the 19 years and older category, and 5 members with unknown sex and unknown age. This accounts for the missing 1071 members in Tables 2 and 3

Table 3 Hospitalizations in baclofen users 19–64 years (commercial claims database)*

Year	Optum members 19–64 years (insurance criteria applied)	Baclofen patients (with any baclofen use)		Baclofen patients with hospitalizations (with chronic baclofen use)			
				Oral		Intrathecal	
		Oral	Intrathecal	Admit count	Patient count	Admit count	Patient count
2011	5,244,601	14,613	195	891	601	113	61
2012	5,272,381	16,702	207	807	522	125	67
2013	5,220,859	18,377	184	849	540	90	50
2014	4,628,842	18,987	164	743	505	74	46
Arithmetic mean (95% CI)	5,091,671 (4,788,592–5,394,750)	17,170 (15,250–19,090)	188 (170–205)	823 (761–884)	542 (501–583)	101 (78–123)	56 (46–66)

*The total number of Optum members in 2014, without restrictions, was 6,158,173. There was 'unknown' age information for 53 members in the 18 years and under category and 1013 members in the 19 years and older category, and 5 members with unknown sex and unknown age. This accounts for the missing 1071 members in Tables 2 and 3

Table 4 Estimated national yearly counts of hospitalizations in baclofen users (≤ 18 years)

Year	US population (≤ 18 years)	National baclofen patients (with any baclofen use)		National baclofen patients with hospitalizations (with chronic baclofen use)			
				Oral		Intrathecal	
		Oral	Intrathecal	Admit count	Patient count	Admit count	Patient count
2011	79,051,412	31,225	1810	5073	3176	1104	707
2012	79,416,116	32,129	1543	5444	3448	681	499
2013	79,893,606	32,253	1433	4299	3189	1155	693
2014	80,443,567	36,635	1158	3947	2895	895	579
Arithmetic mean (95% CI)	79,701,175 (79,110,030–80,292,321)	33,061 (30,682–35,439)	1486 (1,221–1,751)	4691 (4,016–5,365)	3177 (2,956–33,98)	959 (746–1,171)	620 (523–716)
Percent patients hospitalized (patient count/total patients × 100)					10% (3177/33,061)		42% (620/1486)

3.2 Analysis of Patient Populations

Tables 2 and 3 present the number of children and adult patients in the commercial claims database who met the criteria as oral or IT baclofen users from 2011 to 2014. Sex differences are summarized in the electronic supplementary material (ESM). Over the 4 years of the study, the mean count for oral and IT use in children was 703 and 32 patients, respectively. In adults, it was 17,170 for oral use and 188 for IT use. Tables 2 and 3 also show that the number of hospitalizations (admission count) was greater than the patient count, indicating that some patients had more than one hospitalization during a given year. In the commercial claims database, an average of 68 children taking chronic oral baclofen and 13 receiving IT baclofen, along with 542 adults taking oral and 56 receiving IT baclofen, were hospitalized annually over the 4 study years. Although oral baclofen use among children was comparable between males and females, IT use was consistently higher for males < 18 years (Table A-1 in the ESM). In contrast, adult IT baclofen use was similar for males and females, but oral baclofen use was higher in females (Table A-2, see ESM). Of these patients, there were an average of 101 and 21 hospitalizations for children on chronic oral and IT baclofen, respectively, and 823 and 101 hospitalizations for adults on oral and IT baclofen, respectively. Additionally, there was a trend towards hospitalization being more frequent in male children and adult females (Tables A-1 and A-2 in the ESM).

The extrapolated national estimates of oral and IT baclofen use and hospitalizations for children and adults are shown in Tables 4 and 5, respectively. The 4-year arithmetic mean annual estimates for children are 33,061 and 1486 for oral and IT baclofen users, respectively, and for adults, 654,294 and 7084 patients, respectively. Annual hospitalizations (admission count) in the chronic oral and IT baclofen populations were 4691 and 959 in children and 31,116 and 3774 in adults, respectively. This equates to a total of 40,540 average hospitalizations annually. In children, mean annual percent hospitalized was 42% for the IT group and 10% for the oral therapy group; in adults, 30% were hospitalized annually from the IT group and 3% from the oral therapy group.

4 Discussion

A search of peer-reviewed literature revealed no information on the number of patients on oral or IT baclofen, hospitalization rates, or baclofen withdrawal. The present study offers initial estimates of these populations and indicates that the size of this 'at-risk' target population is relatively small. Higher risk subpopulations were also identified. Children receiving IT baclofen had the highest risk of hospitalization, while both children and adults on oral baclofen were hospitalized less often. These differences are attributable to the likely increased morbidity associated with conditions requiring IT baclofen and are consistent with clinical experience. We also found that hospitalization risk was greater for males than for females in those < 18 years. In contrast, hospitalization risk was greater for females than for males in those 19–64 years. The reasons for these sex differences warrant further study.

Due to the lack of a priori data on the number of potential at-risk baclofen users, we chose to identify baclofen users via pharmacy and HCPCS codes and to define chronic use and hospitalization. We intentionally assumed that all hospitalized patients would be subject to baclofen interruption. While information about procedures during hospitalization was not available, clinical experience indicates that only a portion of these patients would actually be subject to therapy interruption. We recognize that most hospitalizations would not result in interruption of baclofen therapy, and we accept that these results would represent an overestimate of the actual at-risk population [25].

Table 5 Estimated national yearly counts of hospitalizations in baclofen users (19–64 years)

Year	US population (19–64 years)	National baclofen patients (with any baclofen use)		National baclofen patients with hospitalizations (with chronic baclofen use)			
				Oral		Intrathecal	
		Oral	Intrathecal	Admit count	Patient count	Admit count	Patient count
2011	191,428,415	531,501	7120	32,425	21,853	4110	2222
2012	192,313,594	608,170	7543	29,399	19,007	4546	2440
2013	193,104,954	679,156	6804	31,377	19,955	3327	1848
2014	193,883,914	798,350	6867	31,262	21,253	3112	1936
Arithmetic mean (95% CI)	192,682,719 (191,650,138–193,715,300)	654,294 (543,168–765,420)	7084 (6755–7412)	31,116 (29,883–32,349)	20,517 (19,262–21,772)	3774 (3117–4430)	2112 (1846–2377)
Percent patients hospitalized (patient count/total patients × 100)					3% (20,517/654,294)		30% (2112/7084)

Calculating hospitalizations by diagnoses may underestimate the at-risk population because not all possible medical conditions for which baclofen is prescribed would be included. Another approach is an analysis based on chart reviews; however, for our research question this was not feasible due to the volume of charts needed and cost. We surveyed clinicians to estimate baclofen use and their perceptions of withdrawal incidence, but regional differences in patient populations and prescribing patterns limited the usefulness of this method [17].

At the present time, there is no established way to bridge an interruption in oral or IT therapy. A recent survey found that nearly all responding physicians who manage patients on baclofen are concerned about the potential for baclofen withdrawal. However, among clinic sites, approximately 75% and 35% lack protocols for managing anticipated interruption of oral or IT baclofen therapy, respectively [30]. To address this gap in therapy, an intravenous (IV) formulation of baclofen is being developed for use in patients whose oral baclofen therapy has been abruptly interrupted [10, 31–33]. Administration of IV baclofen will require extended and repeated infusions on a schedule similar to a patient's previous oral administration regimen. The route of administration and monitoring requirements limits its use to hospitalized patients [10].

There are several limitations inherent in our study design that affect our estimation of the at-risk population. It is likely the number of hospitalized patients on IT therapy is greater than that reported by us. A high percentage of these patients have associated disabilities and are covered by public health insurance; therefore, they are unlikely to be fully represented in a study population drawn from a commercially insured database. Supporting this possibility, information from the major provider of IT baclofen pumps estimates that there are approximately 40,000 patients nationally using baclofen pumps in the US [34]. Alternatively, the commercial claims database did not allow discrimination between the number of hospitalized patients on IT baclofen whose pumps remained functional and those with malfunctioning pumps. Therefore, this estimate includes hospitalized patients whose pumps remained functional and, hence, would not be at risk for withdrawal symptoms. Finally, use of a commercial database may not be applicable for those populations 65 years of age and older and therefore it could have resulted in an underestimation of the national at-risk population.

5 Conclusions

By using a commercial claims database, this study was able to estimate the size and age characteristics of a hospitalized, chronic baclofen user population. The highest hospitalization rate, and therefore highest risk for withdrawal, was found in children on IT baclofen, while both children and adults on oral therapy were at a much lower risk.

An estimation of the number of patients at risk has several potential benefits. Such information can assist hospitals in evaluating if IV baclofen is needed on their formularies. Also, this estimate could be useful in determining if the target population meets the requirement of $\leq$200,000 people in the United States in order to qualify for orphan product designation [35]. Understanding the size of the intended patient population for a drug in development can also inform clinical trial design, product marketing programs, and manufacturing needs among other operational considerations. This report demonstrates the value of using a representative claims database to calculate a national estimate of hospitalized chronic baclofen users who might benefit from availability of an intravenous baclofen formulation.

Although there are limitations to this approach, using liberal assumptions throughout the methodology enabled estimation of the largest possible at-risk population. Using commercial claims databases to estimate the prevalence of rare conditions or the incidence of clinical events can be an important, underutilized tool in clinical care and the drug development process.

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Declarations

Conflict of interest This study was primarily funded by contracts from Allaysis, LLC awarded to the University of Minnesota and to Optum. Should the investigational intravenous baclofen formulation being developed by Allaysis LLC be commercialized, the University of Minnesota and James Cloyd may receive royalty payments.

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Ethics approval Data used in this study were de-identified and in full compliance with the Health Insurance Portability and Accountability Act (HIPPA); Declaration of Helsinki, and ICH GCP. This study did not require review or approval by ethics committees or informed consent.

Consent to participate Not applicable.

Consent for publication All authors of this manuscript and agree with its publication in Drugs–Real World Outcomes.

Availability of data and material The data that support the findings of this study are available from Optum, Inc. and Allaysis LLC. but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Data are, however, available from the authors upon reasonable request and with permission from Optum, Inc. and Allaysis LLC.

Code availability Not applicable.

Author Contributions NS study conception, data interpretation, and writing (drafted original manuscript and substantial edits); MA data acquisition, analysis, and interpretation, and writing (contributed substantial edits); KW data acquisition and analysis; SG data acquisition and analysis; JC study conception, data interpretation, and writing (contributed substantial edits); JS study conception, data interpretation, and writing (contributed substantial edits); RK study conception, data interpretation, and writing (contributed substantial edits).

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Authors and Affiliations

Natalie Schmitz[1,4] · Margaret Artz[2,5] · Karen Walsh[2,6] · Sandeep Gaudana[2] · James Cloyd[1] · John Schrogie[3] · Robert Kriel[1]

Margaret Artz
Margaret.b.artz@gmail.com

Karen Walsh
Karen.Walsh@jefferson.edu

Sandeep Gaudana
Sandeep.gaudana@optum.com

James Cloyd
cloyd001@umn.edu

John Schrogie
Johnschrogie@allaysis.com

Robert Kriel
kriel001@umn.edu

1 Department of Experimental and Clinical Pharmacology, College of Pharmacy, Center for Orphan Drug Research, University of Minnesota, Minneapolis, MN, USA

2 Optum, Eden Prairie, MN, USA

3 Allaysis LLC, Marlton, NJ, USA

4 School of Pharmacy, University of Wisconsin, 1037 Rennebohm, Hall 777 Highland Ave, Madison, WI 53705, USA

5 Blackstone Artz Solutions LLC, Minneapolis, MN, USA

6 College of Population Health, Thomas Jefferson University, 901 Walnut, St. Philadelphia, PA 19107, USA