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A Transparent and Consistent Approach to Assess US Outpatient Drug Costs for Use in Cost-Effectiveness Analyses

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ABSTRACT

Background: Assessment of drug costs for cost-effectiveness analyses (CEAs) in the United States is not straightforward because the prices paid for drugs are not publicly available and differ between payers. CEAs have relied on list prices that do not reflect the rebates and discounts known to be associated with these purchases. **Objectives:** To review available cost measures and propose a novel strategy that is transparent, consistent, and applicable to all CEAs taking a US health care sector perspective or a societal payer's perspective. **Methods:** We propose using the National Average Drug Acquisition Cost (NADAC), the Veterans Affairs Federal Supply Schedule (VAFSS), and their midpoint as the upper bound, lower bound, and base case, respectively, to estimate net drug prices for various payers. We compare this approach with wholesale acquisition cost (WAC), the most common measure observed in our literature review. The minimum WAC is used to provide the most conservative comparison. **Results:** Our sample consists of 1436 brand drugs and 1599 generic drugs. On

average, the upper bound (NADAC) is 1% and 9.8% lower than the WAC for brand and generic drugs respectively, whereas the lower bound (VAFSS) is 48.3% and 54.2% lower than the WAC. The NADAC is less than the WAC in 89.6% of drug groups. The distributions of these relationships do not show a clear mode and have wide variation. **Conclusions:** Our study suggests that the WAC may be an overestimate for the base case because the minimum WAC is higher than the NADAC for most drugs. Our approach balances uncertainty and lack of data for the cost of pharmaceuticals with the need for a transparent and consistent approach for valid CEAs.

Keywords: cost-effectiveness analysis, drug cost, health economic methods, United States.

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Introduction

Prescription drug costs, which totaled more than \$300 billion in the United States in 2015, are an essential input for cost-effectiveness analyses (CEAs) [1–5]. A lack of transparency in actual transacted amounts complicates the process of obtaining reasonable drug cost estimates for US-based CEAs [6,7]. Traditionally, the drug manufacturer's list price or the wholesale acquisition cost (WAC) of pharmaceuticals published in commercially available drug pricing compendia has been used in CEAs [8,9]. These list prices do not reflect the actual cost paid for drugs, because there are numerous discounts and rebates known to be granted to various entities throughout the drug supply chain [7,10,11]. Accounting for these rebates and discounts is necessary to reflect costs from any payer's perspective [8].

The goal of this work was to describe a consistent, transparent, and empirically based approach for estimating a plausible range of drug costs for US-based CEAs taking an all-payer's perspective such as the US health care sector perspective or the

societal perspective. We then compare our approach with standard practice. Our approach relies on two publicly available price measures, the National Average Drug Acquisition Cost (NADAC) and the Department of Veterans Affairs Federal Supply Schedule (VAFSS), which are used to form the bounds of our drug cost parameter estimates. The range of net costs excludes pharmacy dispensing fees, which, although relevant for CEA, are not easily estimated. Our method does not incorporate dispensing fees, but does suggest assigning a separate parameter in the final analysis.

Our approach diverges from current practice that specifies a base case on the basis of either a list price or a prespecified fixed percent reduction from the list price, and then adds and subtracts a percent of the base case to cover the range of likely transaction costs for sensitivity analyses [12,13]. We focus instead on defining plausible extremes of the range and assign the base case as the midpoint of this interval. We compare our approach to using the WAC for more than 3000 drugs covered by Medicaid and examine subsets of highly used and costly drugs.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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To provide some background, we review existing recommendations for best practices in assessing drug costs for CEAs, and then we conduct a systematic review of recent CEAs to understand whether, and how, the recommendations are being followed. Next, we summarize the drug supply chain and highlight vital features including the discounts available to pharmacies and rebates available to payers (health insurers or pharmacy benefit managers) that reduce the cost of pharmaceuticals compared with their list prices to motivate our approach.

Current Recommendations and Current Practice

To promote quality and uniformity in drug costing for CEA studies, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published a series titled Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses [8,14–16]. ISPOR guidelines for costing drugs adopt the perspective of five different types of payers: societal, managed care organizations, US government, industry, and international. The guidelines state that “CEAs performed from a payer’s perspective should use drug prices actually paid by the relevant payer net of all rebates, co-pays, or other adjustments [discounts]” [8]. The ISPOR guidelines provide limited guidance as to how to account for these discounts and rebates, but suggest a generic average discount by some percent of the list price. In the chapter on the managed care organization perspective, the guidelines suggest a range of 5% to 25% for the manufacturer’s rebate [15]. This suggestion, however, is based only on a subset of highly used drugs from calendar year 2003 [11,17].

To assess the impact of the recommendations, we conducted a literature search of US-based CEAs published between 2011 and 2015 that explicitly estimated cost for at least one outpatient drug. Forty-four of 81 studies adopted a US health system or generic third-party payer’s perspective, whereas 19 of 81 adopted the broader societal perspective.

Of the 81 studies, 43 used full nondiscounted WAC for the base case, 17 studies used nondiscounted average wholesale price (AWP), and 9 studies accounted for rebates/discounts by applying some discount to the AWP or the WAC. Twenty of the 81 studies used measures other than the AWP or the WAC for the base case, 19 studies used the VAFSS, and 1 study used the NADAC. Uncertainty of these estimates for sensitivity analyses was typically reflected by some percentage addition and subtraction, with a mode of $\pm 25\%$ ($n = 19$). Nevertheless, studies varied greatly, from as low as $\pm 5\%$ to as high as $\pm 100\%$.

Key Transactions in the Drug Supply Chain

In a CEA, the relevant entities in the drug supply chain include drug manufacturers, drug wholesalers, pharmacies, and payers. Manufacturers produce drugs and sell these drugs to wholesalers, who, in turn, sell the drugs to pharmacies. Pharmacies dispense the drugs to patients and are usually paid by a health insurer or pharmacy benefit manager (herein “payer”) [18]. The manufacturer’s sale to the wholesaler is represented by the manufacturer’s suggested list price known as the WAC. These purchases, however, are often made at less than the WAC, because manufacturers grant discounts to wholesalers [19].

The second transaction is the sale from the wholesaler to the pharmacy. In theory, this purchase is also represented by a manufacturer-reported number, the AWP. It is well documented that discounts are often available for this purchase, for larger quantity and prompt pay [1,7,20,21].

The third transaction is payer purchases of the drug from the pharmacy on behalf of the patient. This amount is negotiated between the pharmacy and the payer and is supposed to capture the amount the pharmacy paid to acquire the drug plus a

dispensing fee. After the payer pays the pharmacy, the payer receives a rebate from the manufacturer independent of what they paid the pharmacy [22,23]. This rebate, the final key transaction, effectively lowers the price of the drug to the payer below what they paid the pharmacy. The details of the manufacturer rebate or final negotiated price for almost all payers are confidential and vary not only by different drugs and manufacturers but also by different payers and their market power to negotiate these rebates [7].

Cost Measures

Our method proposes two cost measures to represent the range of plausible net costs likely encountered by all payers. The NADAC defines the upper bound, whereas the VAFSS defines the lower bound. We describe these measures in sufficient detail to motivate why they can represent these respective bounds for CEA.

National Average Drug Acquisition Cost

The amount that fee-for-service Medicaid (distinct from Medicaid managed care) spends for a certain outpatient drug has two components—the payment to the pharmacy, which itself comprises ingredient costs and dispensing fee, and the rebates Medicaid eventually receives from the drug manufacturer [24]. The ingredient cost estimation varies by state, but is generally a fixed percent reduction or addition to the drug list price (either the AWP or the WAC) [25]. The second component comprises the rebates that are received by the state from the manufacturers after the drug has been dispensed and the pharmacy has been paid. The Medicaid Drug Rebate Program sets the amount and grants these rebates automatically, although the rebates can be larger if the state has negotiated an additional supplements rebate for individual drugs [24,26].

In 2012, in an effort to aid state Medicaid agencies in modernizing their reimbursement, to pharmacies, the Centers for Medicare & Medicaid Services conceived of the NADAC as a new price measure for use in fee-for-service Medicaid [19,27,28]. The goal of the NADAC is to estimate what pharmacies pay to acquire all outpatient pharmaceuticals reimbursed by Medicaid to better estimate their ingredient costs [27]. To compute the NADAC, an accounting firm contracted by the Centers for Medicare & Medicaid Services (CMS) conducts a monthly nationwide survey of a random sample of pharmacies to assess their drug acquisition cost for purchases using invoices from the last 30 days. A weighted average is computed using the number of times each product, by unique National Drug Code (NDC), is observed in the sample. NDCs are grouped into therapeutically equivalent “drug groups,” that is, the same active ingredient, strength, and formulation. The survey yields a single weighted average cost for each drug group that may be used by states as the basis for reimbursement. Of the roughly 67,000 pharmacies in the United States, approximately 2000 to 2500 are sampled monthly [19,27,28].

We define the NADAC as an upper bound for sensitivity analyses, because it is an estimate of the net amount paid by payers before manufacturer rebates. We assume that the amount paid by the pharmacy to acquire the drug is the amount the payer will pay to acquire it, excluding the dispensing fee. The details of the NADAC are presented in Table 1.

Veterans Affairs Federal Supply Schedule

The US Department of Veterans Affairs (VA) Health Administration, an integrated care system with roughly 9 million enrollees, is able to negotiate the price of drugs with manufacturers. Unlike virtually all other US payers, these contract details, including the final negotiated prices, are publicly available [13,21,26,29]. The pricing process for the VA is complex, because the VA is charged

Table 1 – Drug cost measures’ descriptions and suggestions to inform CEA.

Cost measure	Description	Suggestion for inclusion in CEA
National Average Drug Acquisition Cost (NADAC)	<ul style="list-style-type: none"> • Guides Medicaid on what to reimburse pharmacies • Weighted average pharmacies pay to acquire a unit of a given drug group (unique combination of active ingredient, strength, and formulation) • Based on monthly national survey that collects invoices from pharmacies, made publicly available online • The NADAC does not reflect the payers’ dispensing fee or rebates provided by drug manufacturers • The NADAC is updated weekly and published online; it lists only one cost for NDCs that contain identical ingredients. 	<ul style="list-style-type: none"> • Use the NADAC as the upper bound of drug cost
Veterans Affairs Federal Supply Schedule (VAFSS)	<ul style="list-style-type: none"> • The FSS is the price negotiated by the Department of Veterans Affairs (VA) with drug manufacturers on behalf of all federal direct payers • For certain drugs the VA receives additional rebates on behalf of the Big 4 public payers (Big 4 price) • In addition, in some cases the VA can achieve even lower prices for the VA only on the basis of preferred placement on the VA formulary; this is called the national contract price (the NC price) • We define the VAFSS as the lowest price available to the VA (i.e., minimum FSS, Big 4, or the NC price) of any drug in a drug group (VAFSS)* • Believed to be one of the lowest if not the lowest final price any payer (public or private) pays • Contracts are publicly available and published online • Prices can vary within drug group depending on the NDC 	<ul style="list-style-type: none"> • Use the VAFSS as the lower bound of drug cost

CEA, cost-effectiveness ratio; NDC, National Drug Code.

* According to a 2011 report, the VA uses the FSS in 78% of prescriptions, a Big 4 price in 15%, and 7% in other negotiated situations that include the NC price.

with negotiating prices, called the Federal Supply Schedule (FSS), for all federal direct health care payer agencies (notably not Medicare and Medicaid). The FSS price is no more than the price manufacturers charge their most favored nonfederal customers under similar market conditions [30]. In addition to the FSS, the VA can receive additional statutorily defined rebates through their shared purchasing power with other large agencies (the Big 4 price) and additional rebates for themselves through preferred formulary placement (national contract price) [31].

We define the VAFSS as the lowest of all these prices available to the VA for every covered drug. A recent Department of Health and Human Services report to Congress described the large rebates the VA receives: “The national formulary allows the VA to purchase prescription drugs at some of the lowest prices available to any buyer in the US based on its ability to drive utilization to the most cost-effective drugs” [32]. The other key feature of the VAFSS is that it is excluded from the computation of the statutorily defined best price used in computing Medicaid’s manufacturer rebates [32]. Thus, the VAFSS exclusion from the computation of best price allows manufacturers to offer larger rebates to the VA without having to allow a larger rebate to Medicaid [32,33]. A 2005 Congressional Budget Office report found that the VA paid on average 42% of the AWP, whereas the average best price of all pharmaceuticals was 63% of the AWP [17,31].

The VAFSS price can vary by the NDC within drug groups if more than one therapeutically equivalent product is reimbursed. The details of VA pricing are presented in Table 1.

Methods

Approach

Our approach focuses on defining plausible values of the minimum and maximum net price [34]. We define the NADAC as an

upper bound estimate of the net price for payers. We define the minimum VAFSS price by drug group as the lower bound estimate of the lowest net price available to any US payer. The midpoint between the upper and lower bounds is designated as the base case. The tutorial in Appendix I in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2017.06.013> provides further details with two completed examples using our approach. Appendix II in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2017.06.013> details how to make adjustments if the cost metrics do not follow their anticipated ordering, that is, if the NADAC is lower than the VAFSS. This reverse ordering may occur because VAFSS prices are updated less frequently than NADACs [35].

Comparison

We compared a wide range of pharmaceuticals using the current approach represented by the WAC and our approach represented by the NADAC and the VAFSS. We selected the WAC as our comparator because it was revealed to be the most prevalent strategy currently being used in CEAs. The minimum WAC by drug group was used to be as conservative as possible in our comparisons [3].

The WAC, NADAC, and VAFSS databases were accessed on April 1, 2015. To select our set of drug groups (unique ingredient, strength, and formulation), we used the NDCs representing each drug group reported in the NADAC. We included NDCs of single- and multi-ingredient tablet and capsule formulated drugs as well as single-ingredient non-tablet and capsule formulated drugs that had a reported cost in all three databases. We converted the unit cost for each NDC into the units used by the NADAC drug group for each product.

Data Analysis

We calculated the following ratios: 1) the NADAC to the WAC, 2) the VAFSS to the WAC, and 3) the base case to the WAC. The ratio

Table 2 – Average unit cost and average ratio between price measures by brand designation.

	Brand (N = 1436)	Generic (N = 1599)
Unit cost		
WAC	67.42	4.47
NADAC	65.22	3.58
VAFSS	34.05	1.69
Ratio of price measure to the WAC		
NADAC (upper bound)	0.991	0.902
VAFSS (lower bound)	0.517	0.458
Proposed base case	0.754	0.680
NADAC, National Average Drug Acquisition Cost; VAFSS, Veterans Affairs Federal Supply Schedule; WAC, wholesale acquisition cost.		

of the NADAC to the WAC explains how much the WAC fails to account for discounts pharmacies receive when acquiring the drug. The ratio of the VAFSS to the WAC explains how much using the WAC fails to account for the maximum rebate available to any payer. The ratio of the midpoint to the WAC compares our strategies' base case with the most common approach for CEAs. We examined these ratios separately for brand and generic drugs and created histograms to examine the consistency of the relationships between price measures.

Finally, we examined the unit cost of each price measure for 20 drug groups with the highest utilization and 20 drug groups with the highest overall spending as identified in the 2015 utilization report published by IMS Health [36].

Results

We included 3035 drug groups with a reported NADAC, VAFSS, and WAC. The average unit costs by the NADAC, the VAFSS, and the WAC for 1436 brand drug groups and 1599 generic drug groups are presented in Table 2. As expected, these average unit costs show that the WAC is the highest and the VAFSS is the lowest.

The lower panel of Table 2 indicates that on average the NADAC is 99.1% of the WAC for brand drugs and 90.2% of the WAC for generics. The VAFSS cost is 51.7% of the WAC for brand drugs and 45.8% of the WAC for generics. Finally, the ratio of the base case to the WAC is on average 75.4% for brand drugs and 68% for generics. The smaller ratios for generics than for brand drugs suggests that the extent of discounts and rebates available to pharmacies and payers from wholesalers and manufacturers is greater for generic drugs than for brand drugs.

The histograms of these ratios are shown in Figures 1 to 3. The left-hand panel of Figure 1 shows strong concentration around 97% and few observations above 100% (n = 75). There is much greater uncertainty for generics, with a mode of 95% and a surprisingly large number of drug groups over 100% (n = 238).

Figure 2 displays the ratio of the VAFSS to the WAC. Most ratios for brand drugs fall between 40% and 60%, with a mode of 50% and few observations over 100% (n = 16). The relationship for generics is much less consistent with an almost uniform distribution between 15% and 35%, and more drug groups above 100% (n = 62).

Finally, Figure 3 compares the ratio between base case estimates. A single mode of 75% for brand drugs is found with few observations above 100% (n = 56). Generic drugs indicate a

mode of 50% with larger uncertainty and more ratios above 100% (n = 171).

Top Drug Groups

We identified the top 20 prescription drugs by total US spending and by overall utilization per number of prescriptions written. Table 3 presents the unit price reported in each price measure for the top 20 drugs by frequency (all generics) and the top 20 drugs by total spending (all brand drugs).

The most used drug, 50 µg levethroxine, has an NADAC of \$0.375, a minimum VAFSS of \$0.021, and a minimum WAC of \$0.413. Our approach sets the base case as \$0.198, with a range of \$0.021 to \$0.375. Compared with using the WAC as the base case, our value is half of the WAC. We see a similar pattern in the rest of the table. In all but hydrocodone-acetaminophen, the base case using our approach is lower than the WAC. The WAC is generally closer to the NADAC than the midpoint between the NADAC and the VAFSS. The VAFSS of omeprazole is larger than its NADAC. Appendix II in Supplemental Materials offers our suggested adjustment.

Table 4 presents the subset of the top 20 drugs by spending in the United States, except for 3 drugs that are physician-administered and not included in the NADAC. The WAC for Harvoni is \$1125 per tablet and the range using our approach is \$675 to \$1091 per tablet with a base case of \$883. All the drugs have the expected rank orderings by price measure; the proportional differences, however, vary by drug.

Discussion

Our new method for estimating drug costs for CEAs adopting a US health care sector or a societal payer's perspective relies on two measures—the NADAC and the VAFSS. These metrics represent the plausible range of drug costs likely experienced by payers in the United States. When conducting a CEA, we propose the midpoint between the NADAC and the VAFSS as the base case and the NADAC and the VAFSS form the bounds used for deterministic sensitivity analysis and probabilistic sensitivity analysis. For probabilistic sensitivity analysis, we advocate using a uniform distribution between the bounds, because there is not a strong theoretical basis for selecting a different distribution.

We compared our approach with the WAC, because it is currently the most commonly used measure for assessing drug costs in US-based CEAs. We used the minimum WAC by drug group to compare our approach with a conservative choice of the base case. Our analysis showed that using the WAC as the base case overstates net drug costs. In 94.7% of brand drugs and 85.1% of generics, the minimum WAC is larger than our proposed upper bound. Thus, we proposed the NADAC, instead of the WAC, as the upper bound. The variation observed in the ratios of the NADAC to the minimum WAC indicates that a single discount rate is not appropriate when applied to all drugs to account for the impact of rebates and discounts.

Assumptions of Approach

Our approach relies on several assumptions, which should be communicated clearly in any analysis adopting this approach. By proposing the NADAC as an upper bound, we assume that the pharmacy average acquisition cost is a proxy for the highest net cost paid by some payers. The NADAC is an average cost, with some pharmacies paying more than the average. Nevertheless, all payers receive rebates that effectively lower their final price below what they pay the pharmacy.

We also assume that the VAFSS price is the lowest price likely paid by any payer. We supported this assumption with details of

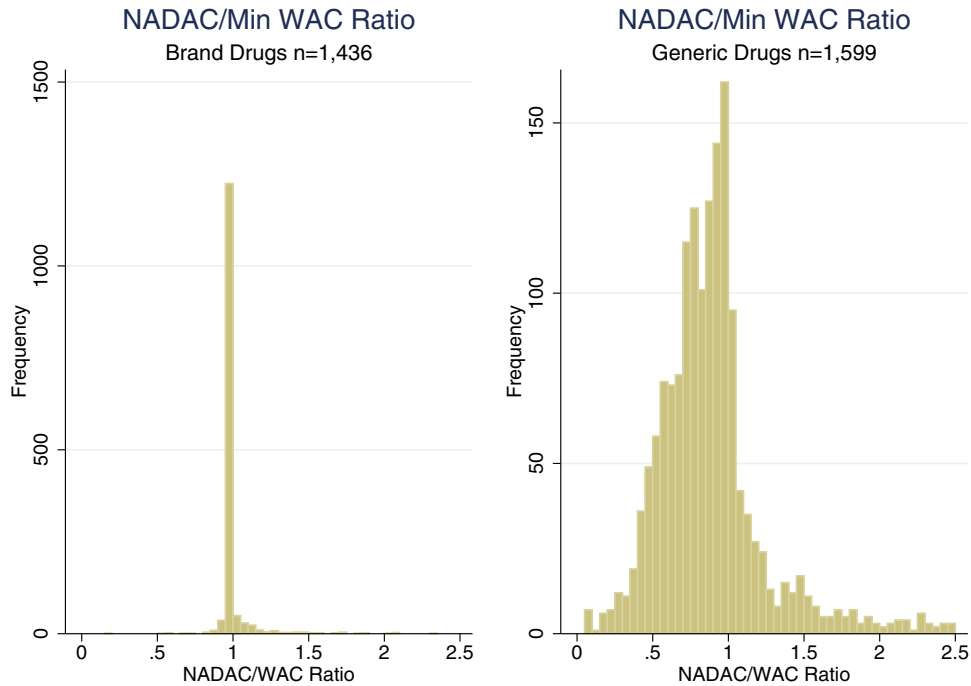


Fig. 1 – Histograms of NADAC/Minimum WAC Ratio.

the computation of federally mandated manufacturer rebates for fee-for-service Medicaid purchases as well as previous work from the Congressional Budget Office that used proprietary data on prices paid by private payers.

We define the base case as the midpoint between the NADAC and the WAC. This measure was simply defined, because there is no other obvious metric to represent the base case. More transparency in net price paid by all payers, both public and private,

and their relative market share would help us improve how we select the base case.

Study Limitations

A limitation of the NADAC is the extent to which it accurately represents the pharmacy acquisition cost. During the public comments phase of the NADACs release, several individuals

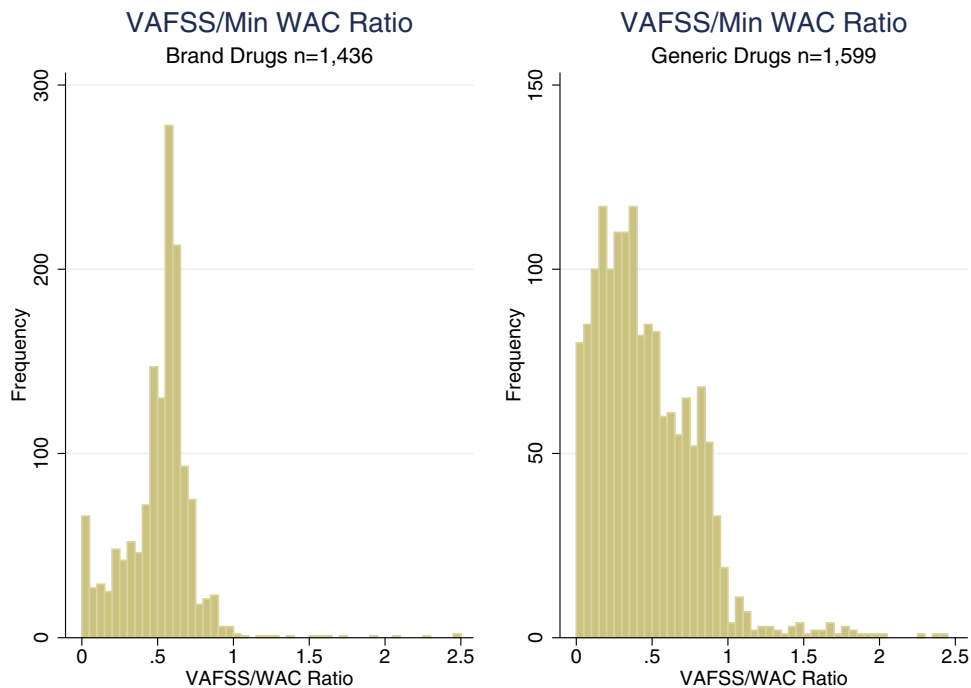


Fig. 2 – Histogram of VAFSS/Minimum WAC Ratio.

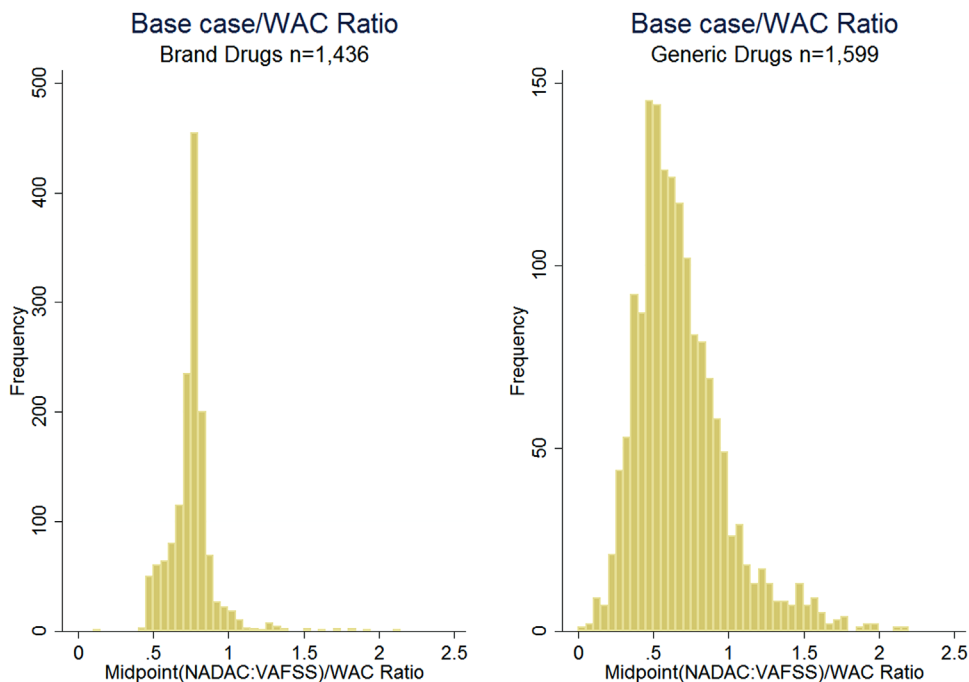


Fig. 3 – Histogram of Basecase/Minimum WAC Ratio. NADAC, National Average Drug Acquisition Cost; VAFSS, Veterans Affairs Federal Supply Schedule; WAC, wholesale acquisition cost

and organizations identified discounts that are not included in the NADAC computation, such as discounts tied to achieving certain volumes purchased over time [28]. Similarly, because participation in the NADAC survey is not mandatory, pharmacies

that are receiving a lower price than the current NADAC price may be disincentivized from participating, because it could lower the amount they are reimbursed by Medicaid in certain states [25]. Although we cannot evaluate the impact of these two

Table 3 – Unit cost of top 20 drug groups by the number of prescriptions in the United States in 2015.

Drug group	Proposed approach			Standard
	NADAC (upper bound) (\$)	VAFSS (lower bound) (\$)	Base case (\$)	WAC (\$)
Levothyroxine 50 µg tablet	0.375	0.021	0.198	0.413
Lisinopril 20 mg tablet	0.026	0.020	0.023	0.037
Hydrocodone/acetaminophen 10 mg/325 mg tablet	0.273	0.081	0.177	0.137
Atorvastatin 40 mg tablet	0.180	0.059	0.120	0.294
Metoprolol tartrate 25 mg tablet	0.027	0.016	0.022	0.027
Amlodipine besylate 10 mg tablet	0.027	0.014	0.021	0.030
Metformin hydrochloride 500 mg tablet	0.016	0.012	0.014	0.028
Omeprazole DR 20 mg capsule	0.063	0.080	NA*	0.224
Albuterol sulfate 2.5 mg/3 ml solution	0.044	0.034	0.039	0.053
Simvastatin 20 mg tablet	0.028	0.020	0.024	0.031
Gabapentin 300 mg capsule	0.049	0.024	0.037	0.067
Amoxicillin 500 mg capsule	0.070	0.017	0.044	0.079
Fluticasone propionate 50 µg spray	0.354	0.103	0.229	1.375
Hydrochlorothiazide 25 mg tablet	0.013	0.008	0.011	0.011
Alprazolam 1 mg tablet	0.024	0.008	0.016	0.045
Azithromycin 250 mg tablet	0.605	0.363	0.484	1.287
Furosemide 40 mg tablet	0.011	0.006	0.009	0.012
Sertraline hydrochloride 100 mg tablet	0.062	0.077	0.070	0.086
Losartan potassium 50 mg tablet	0.064	0.060	0.062	0.115
Tramadol hydrochloride 50 mg tablet	0.030	0.014	0.022	0.045

NA, not applicable; NADAC, National Average Drug Acquisition Cost; VAFSS, Veterans Affairs Federal Supply Schedule; WAC, wholesale acquisition cost.

* VAFSS > NADAC (see Appendix II in Supplemental Materials for further explanation).

Table 4 – Unit cost of top 20 drug groups by spending in the United States in 2015^{*}.

Drug group	Proposed approach			Standard
	NADAC (upper bound) (\$)	VAFSS (lower bound) (\$)	Base case (\$)	WAC (\$)
Harvoni 90/400 mg tablet	1,091.23	675.00	883.12	1,125.00
Humira 40 mg/0.8 ml pen	1,415.19	687.54	1,051.37	1,456.82
Enbrel 50 mg/ml SureClick syringe	728.67	415.66	572.16	743.41
Crestor 20 mg tablet	6.73	2.65	4.69	13.72
Lantus solostar 100 units/ml	24.06	8.58	16.32	24.85
Remicade 100 mg vial	890.37	532.89	711.63	973.72
Advair diskus 250/50 µg (60 doses)	4.87	3.23	4.05	4.97
Abilify 5 mg tablet	28.72	17.12	22.92	29.73
Copaxone 20 mg/ml syringe	196.34	124.34	160.34	203.68
Januvia 100 mg tablet	10.82	5.91	8.36	11.02
Neulasta 6 mg/0.6 ml syringe	7,248.35	2,341.98	4,795.17	7,808.67
Lyrica 150 mg capsule	4.71	2.92	3.82	5.04
Lantus 100 units/ml vial	24.22	7.16	15.69	24.85
Nexium DR 40 mg capsule	7.64	4.86	6.25	7.89
Spiriva 18 µg CP-handihaler (30 doses)	9.61	5.60	7.61	9.93
Sovaldi 400 mg tablet	981.50	593.57	787.54	1,000.00
Atripla 600 mg/200 mg/300 mg tablet	68.71	43.08	55.90	70.89

NADAC, National Average Drug Acquisition Cost; VAFSS, Veterans Affairs Federal Supply Schedule; WAC, wholesale acquisition cost.

* Three physician-administered drugs are excluded because they are not included in the NADAC.

potential biases directly, both result in an overestimate of the NADAC. The NADAC represents an upper bound. Because the NADAC remains lower than the minimum WAC for most drugs and is based on actual transactions instead of list prices, the NADAC, although imperfect, is an improvement over current practice to represent the upper bound of drug cost.

The comparison with minimum WAC revealed several issues that warrant discussion. We chose the minimum WAC as our comparator to define the most conservative comparison. As a result, there are instances when the minimum WAC by drug group was lower than the NADAC. Had we chosen the median WAC within drug group, there would have been only 4.7% as compared with 10.4% of WAC drug groups below the NADAC. The difficulty in choosing a representative WAC or whether it is appropriate to take some summary of the distribution of WACs (mean, median, minimum, etc.) is a further limitation of using the WAC to estimate cost parameters.

Our analysis revealed cases of the NADAC being lower than the VAFSS. Although it happened in relatively few cases (84 of 3035 drug groups), this discrepancy occurred once among the top 20 prescribed generics. The NADAC is updated weekly on the basis of survey updates and list price changes. For a VAFSS price change to occur, a manufacturer needs to submit a proposal, which can take several months to be approved.

Our approach does not account for dispensing fees or fees paid to pharmacy benefit managers, because they are nonpublic and best practices do not exist for their estimation [37,38]. Dispensing fees are recommended for inclusion in CEAs and we suggest including a separate parameter in the model independent of the unit cost of the drug.

A final limitation of our methodology is that it is unable to address an unresolved issue in CEA—that analysis from a true societal perspective, costs of drugs or otherwise, should represent opportunity costs. Opportunity costs of drugs are distinct and lower than what the market price of patented drugs represents because patented drugs are granted patent exclusivity, allowing manufacturers to extract producer surplus. Our method only improves the estimates of the market price and does not suggest

an additional reduction to approach social marginal costs of brand drugs. The ISPOR Drug Cost Task Force Report—Part II contains a detailed discussion of this problem [16].

Conclusions

Our article provides a clear methodology that improves on current practice to specify metrics that do not rely on a particular NDC list price. Overall, our approach improves transparency in drug cost estimates, because we rely on two publicly available reasonable extremes. This is in contrast to the WAC, in which selection of a single NDC is hard to justify, and ranges for sensitivity analysis are frequently based on best guesses and arbitrary assumptions about uncertainty rather than on data.

Our method is consistent with the 2016 recommendations of the Second Panel on Cost Effectiveness in Health and Medicine that advocate that all CEAs conduct analysis from two reference cases, the societal and the health care sector perspectives [5]. For each reference case, drug costs are meant to represent the costs most likely to be paid by various payers, but some consideration should be given to estimating the opportunity cost when using the societal perspective [16]. The panel further recommends the use of sensitivity analysis to account for uncertainty in this parameter estimate. This is exactly what our method has captured, with the ranges available for various types of sensitivity analyses.

The true distribution of US drug costs is not known. Our approach relies on publicly available data. Although our method is not perfect, it is well defined and transparent. Embedding consistency and transparency in the definition of the base case and the bounds of drug costs bolsters the credibility of CEA findings and aids comparability between studies. Our approach represents the current best available recommendations to measure drug costs in the United States and provides consistency in computing results to inform decision makers.

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Supplemental Materials

Supplemental data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jval.2017.06.013>.

REFERENCES

- [1] Glick HA, Doshi JA, Sonnad SS, et al. *Economic Evaluation in Clinical Trials*. Oxford, UK: Oxford University Press, 2014.
- [2] Briggs AH, Claxton K, Sculpher MJ. *Decision Modelling for Health Economic Evaluation*. Oxford, UK: Oxford University Press, 2006.
- [3] Levy JF, Meek PD, Rosenberg MA. US-based drug cost parameter estimation for economic evaluations. *Med Decis Making* 2015;35:622–32.
- [4] Keehan SP, Poisal JA, Cuckler GA, et al. National health expenditure projections, 2015–25: economy, prices, and aging expected to shape spending and enrollment. *Health Aff (Millwood)* 2016;35:1522–31.
- [5] Neumann PJ, Sanders GD, Russell LB, et al. *Cost-Effectiveness in Health and Medicine*. Oxford, UK: Oxford University Press, 2016.
- [6] Glick HA. What's in a perspective? *Value Health* 2010;13:2.
- [7] Willke RJ. Beyond AWP ... way beyond. *Value Health* 2010;13:1.
- [8] Hay JW, Smeeding J, Carroll NV, et al. Good research practices for measuring drug costs in cost effectiveness analyses: issues and recommendations: the ISPOR Drug Cost Task Force Report-Part I. *Value Health* 2010;13:3–7.
- [9] Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA* 2016;316:858–71.
- [10] Gottlieb S. How Congress can make drug pricing more rational. *Forbes* 2016. <https://www.forbes.com/sites/scottgottlieb/2016/09/12/how-congress-can-make-drug-pricing-more-rational/#6f35710d3e3b>. [Accessed June 22, 2017].
- [11] Somers J, Cook A. *Prescription Drug Pricing in the Private Sector: A CBO Study*. Washington, DC: US Congressional Budget Office, 2007.
- [12] Frank RG. Prescription drug prices: Why do some pay more than others do? *Health Aff (Millwood)* 2001;20:115–28.
- [13] Kirkwood JB. *Buyer Power and Healthcare Prices*. Washington Law Review 2016;91:253–93.
- [14] Mullins CD, Seal B, Seoane-Vazquez E, et al. Good research practices for measuring drug costs in cost-effectiveness analyses: Medicare, Medicaid and other US government payers perspectives: the ISPOR Drug Cost Task Force Report-Part IV. *Value Health* 2010;13:18–24.
- [15] Mansley EC, Carroll NV, Chen KS, et al. Good research practices for measuring drug costs in cost-effectiveness analyses: a managed care perspective: the ISPOR Drug Cost Task Force Report-Part III. *Value Health* 2010;13:14–7.
- [16] Garrison LP Jr, Mansley EC, Abbott TA III, et al. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force Report-Part II. *Value Health* 2010;13:8–13.
- [17] Somers J, Cook A. Prices for brand-name drugs under selected federal programs. *Regul Aff. Focus* 2006;11:13.
- [18] Hakim A, Ross JS. High prices for drugs with generic alternatives: the curious case of Duexis. *JAMA Intern Med* 2017;177:305–6.
- [19] Centers for Medicare & Medicaid Services. *Methodology for calculating the National Average Drug Acquisition Cost (NADAC) for Medicaid covered outpatient drugs 2013*. Available from: <https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/ful-nadac-downloads/nadacmethodology.pdf>. [Accessed June 22, 2017].
- [20] Curtiss FR. What is the price benchmark to replace average wholesale price (AWP)? *J Manag Care Pharm* 2010;16:492–501.
- [21] Academy of Managed Care Pharmacy. *AMCP Pharmaceutical Payment Guide 2013*. Alexandria, VA: Academy of Managed Care Pharmacy, 2013.
- [22] US Department of Health and Human Services. *Medicaid Rebates for Brand-Name Drugs Exceeded Part D Rebates by a Substantial Margin*. Report OEI-03-13-00650. Washington, DC: US Department of Health and Human Services, 2015.
- [23] Howard DH, Bach PB, Berndt ER, et al. Pricing in the market for anticancer drugs. *J Econ Perspect* 2015;29:139–62.
- [24] Medicaid and CHIP Payment and Access Commission. *Medicaid Payment for Outpatient Prescription Drugs*. Issue Brief. Washington, DC: Medicaid and CHIP Payment and Access Commission, 2017.
- [25] Center for Medicare & Medicaid Services. *Medicaid covered outpatient prescription drug reimbursement information by state 2017*. Available from: <https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/downloads/xxxreimbursement-chart-current-qtr.pdf>. [Accessed June 22, 2017].
- [26] US Department of Health and Human Services. *Office of Inspector General. States' Collection of Offset and Supplemental Medicaid Rebates*. Report No. OEI-03-12-00520. Washington, DC: US Department of Health and Human Services, 2014.
- [27] Centers for Medicare & Medicaid Services. *Draft methodology for calculating the National Average Drug Acquisition Cost (NADAC) 2012*. Available from: <https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/ful-nadac-downloads/nadacdraftmethodology.pdf>. [Accessed June 22, 2017].
- [28] Centers for Medicaid & Medicare Services. *National Average Drug Acquisition Cost (NADAC) questions and responses 2011*. Available from: <https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/ful-nadac-downloads/nadacqa.pdf>. [Accessed June 22, 2017].
- [29] US Department of Veterans Affairs. *National Acquisition Center. Office of Acquisition and Logistics*. Available from: <http://www.va.gov/nac/>. [Accessed June 22, 2017].
- [30] US Government Accountability Office. *Prescription drugs: comparison of DOD and VA direct purchase prices 2013*. Available from: <http://www.gao.gov/assets/660/654019.pdf>. [Accessed June 22, 2017].
- [31] Congressional Budget Office. *Prices for Brand-Name Drugs under Selected Federal Programs*. Washington, DC: Congressional Budget Office, 2005.
- [32] US Department of Health and Human Services. *Prescription Drugs: Innovation, Spending, and Patient Access*. Washington, DC: US Department of Health and Human Services, 2016.
- [33] Frank RG, Newhouse JP. Should drug prices be negotiated under Part D of Medicare? And if so, how? *Health Aff (Millwood)* 2008;27:33–43.
- [34] Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics* 2008;26:781–98.
- [35] US Department of Veterans Affairs. *Federal Supply Schedule Modification Request Forms*. https://www.va.gov/oal/docs/business/nac/fssWebinarContractorGuide-RequestForModification_20130522.pdf. [Accessed June 22, 2017].
- [36] IMS Institute for Healthcare Informatics. *Medicines use and spending in the US 2016*. <http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/medicines-use-and-spending-in-the-us-review-of-2016-outlook-to-2021#form>. [Accessed June 22, 2017].
- [37] Lyles A. Pharmacy benefit management companies: Do they create value in the US healthcare system? *Pharmacoeconomics* 2017;35:493–500.
- [38] McRae J, Vogenberg FR, Beaty SW, et al. A review of US drug costs relevant to Medicare, Medicaid, and Commercial Insurers Post-Affordable Care Act Enactment, 2010–2016. *Pharmacoeconomics* 2017;35:215–23.