

Positive Subjective Measures in Abuse Liability Studies and Real-World Non-Medical Use: Potential Impact of Abuse Deterrent Opioids on Rates of Non-Medical Use and Associated Health Care Costs

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[**Under Review, *Journal of Opioid Management***]

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Disclosures: Financial support for this study was provided by Pfizer Inc., which also participated in the study development, interpretation of data, and authorship of this draft. CL Roland and J Mardekian are employees of Pfizer Inc., and own stock/stock options. AG White, J LeCates, W Cheng, and HG Birnbaum are employees of Analysis Group Inc., which has received consulting fees from Pfizer Inc in connection with this project and development of the draft manuscript. Partial results of this research were presented at the 2014 American Academy of Pain Medicine Annual Meeting in Phoenix, Arizona, March 6-9.

ABSTRACT

Objective. The objective of this study was to quantify the potential impact of reductions in positive subjective measures from human abuse liability studies on real-world rates of non-medical use of prescription drugs and associated health care resource utilization and costs.

Design. Positive subjective endpoints “overall drug liking,” in-the-moment “drug liking,” and “drug high” E_{\max} s (peak effects) were recorded from published studies. Non-medical use data were obtained from the 2010 NSDUH and DAWN surveys. Multivariate regressions evaluated the association between the positive subjective endpoints and non-medical use rates, controlling for prescription volume and indicators for opioids and controlled substance schedule. A published budget-impact model was used to assess health care resource utilization and cost impacts of abuse deterrent opioid formulations.

Results. A 5-point reduction in overall drug liking/drug liking/drug high E_{\max} was associated with a 0.25/0.10/0.05 (standard errors: 0.11/0.12/0.07) percentage point decrease in the NSDUH lifetime non-medical use rates. Those decreases yielded a 11.3/4.2/2.1-% reduction compared to the samples’ lifetime non-medical use rates of 2.21/2.38/2.36-%. Based on a number of assumptions, these reductions were associated with private payer cost reductions for a morphine and oxycodone abuse deterrent formulation in the ranges of \$147.9 – 324.1 million and \$230.7 – 958.7 million, respectively.

Conclusions. Reductions in overall drug liking were significantly associated with reduced real-world non-medical use, healthcare utilization and costs. Associations using drug high and drug liking were directionally consistent with this finding though not statistically significant. A reduction in positive subjective measures associated with an abuse deterrent formulation has potential to reduce abuse and associated healthcare utilization and costs.

Key Words: opioid, abuse, human abuse liability, costs, abuse-deterrent formulation

INTRODUCTION

Prescription drug abuse is reported as being the “fastest-growing drug problem” in the United States (US)¹ and the abuse of prescription opioids specifically has reached epidemic proportions.² In 2010, drug overdose was the leading cause of injury death.³ Of the 22,134 overdose deaths involving pharmaceuticals, 75% involved a prescription opioid.⁴ In 2011, nearly one-third of the 1.4 million emergency room visits attributed to the non-medical use (NMU) of pharmaceuticals were related to opioids.⁵ The epidemic of prescription opioid abuse also places an economic burden on society; in 2007, the total societal costs were estimated at \$55.7 billion annually.⁶ More than a third of this burden may be due to opioid poisoning.⁷

Efforts to confront the growing opioid abuse problem are multi-faceted, including clinical education and assessment of patient risk, government implementation of prescription drug monitoring programs, and the recent approval and continued development of new opioid formulations designed to deter abuse, called abuse deterrent formulations (ADFs).^{1,2,8} Recognition of and attention to the role that ADFs may have in addressing the opioid abuse problem has been demonstrated with the issuance of two draft FDA Guidance documents in the past four years.^{9,10} The most recent FDA draft guidance outlines the abuse potential studies that should be conducted for ADFs in development, including in-vitro, in-vivo and post-marketing studies. In particular, considerable guidance has been given to the conduct of clinical abuse potential studies, also known as human abuse liability (HAL) studies.⁹

HAL studies have been conducted since the mid-20th century and are important for assessing the abuse potential of a new drug. Typically, HAL studies use a randomized, double-blind, placebo-controlled and positive comparator-controlled crossover design and recruit participants with a history of recreational drug use. The study participants are administered

specific doses of the study drug, active comparator, and placebo, and then asked to rate their experience with each compound. The experiences include both bad and good drug effects including positive subjective measures (PSMs). The PSM endpoints of “overall drug liking,” “drug liking” assessed in the moment, and “drug high” use visual analog scales where higher values represent a higher degree of drug liking or high. “Overall drug liking” is often asked 12 – 24 hours after the subject has taken the drug of interest, whereas, “drug liking” is assessed at multiple time points after subject has taken the drug. Across participants, a mean maximum effect (E_{max}) is established for each of the study comparator arms for each measure.

While HAL research has identified the PSM scores of various drugs, the extent to which a reduction in a PSM score in general translates to the actual reduction of abuse in the real-world has not been established.¹¹ The 2013 FDA Draft Guidance indicates that research is needed in this field.⁹ From a payer’s perspective, the value of a reduced PSM score is the reduction’s impact on the health care resource utilization (HCRU) and costs stemming from abuse. The relationship between opioid abuse or NMU and HCRU and costs has been extensively studied, particularly using health care claims data. These studies demonstrate that diagnosed opioid abuse and dependence are associated with higher HCRU and costs than matched controls.^{6,12–14} The increased costs are driven primarily by the direct medical costs of abuse (e.g., hepatitis, HIV disease, trauma) and events such as emergency department (ED) visits and stays in substance abuse treatment centers.^{12,13} Although informative of the utilization and cost components, claims data measures lack product-specificity so that costs cannot be linked to specific drugs. However, a variety of datasets have been used together to develop a model relating the rate of prescription drug abuse in general to abuse-associated medical events and direct costs,¹⁵ thereby permitting the estimation of the cost implications for a rate of abuse.

Predicting the impact of a PSM score reduction on diminishing actual drug abuse requires estimates of the relationship between the PSM scores and actual abuse rates. This relationship can be assessed by comparing mean values of PSMs — gathered through a post-hoc analysis of HAL studies— to real-world measures of abuse and NMU. Further, translation of the magnitude of the relationship to an economic (cost) measure is possible using a budget impact model of the relationship between rates of NMU and costs of prescription drug abuse.¹⁵ The aim of this study was to assess the relationship between PSMs from HAL studies and real-world prescription drug NMU and evaluate the HCRU and cost impacts of these relationships. The findings of this study are expected to contribute to a greater understanding of the broader impact ADFs may ultimately have on non-medical prescription opioid abuse and misuse and the economic effect of this impact.

METHODS

Data

This study combined data from several data sources: PSMs were obtained from a post-hoc analysis of HAL studies, while NMU data came from the 2010 National Survey on Drug Use and Health (NSDUH) and the 2010 Drug Abuse Warning Network (DAWN) databases. In addition, prescription drug volume data were obtained from IMS Health.

HAL Measure Scores

A post-hoc analysis of 15 HAL studies conducted by INC Research, a large clinical contract research firm, as well as 6 additional HAL studies on file at Pfizer Inc. provided the average peak effects (E_{max}) for the PSMs “overall drug liking,” “drug high,” and “drug liking.”^{16,17} Data came from a compilation of single-dose, randomized, double-blind, crossover

HAL studies which had information on current recreational drug users' reported positive subjective experiences within a range of drug classes (i.e., stimulants, opioids, dissociatives, depressants, cannabinoids, and negative controls). PSMs "overall drug liking" and "drug liking" were predominantly measured on a 100-point bipolar scale, with 0 indicating "strong disliking," 50 indicating a neutral feeling, and 100 indicating "strong liking"; for two studies, "overall drug liking" was measured on a 100-point, unipolar positive liking scale which was mapped to the positive 50-100-point portion of the bipolar liking scale for inclusion in this study. The PSM of "drug high" was universally measured on a unipolar 100-point scale. "Overall drug liking" and "drug liking" PSMs were re-centered in the current study for ease of interpretation, so that 0 represented a neutral effect. Not all HAL studies in the database collected all three of the PSMs of interest here, but all studies with at least one PSM measure were analyzed.

Non-Medical Use

The NSDUH is a computer-assisted, in-person interview conducted annually by the Substance Abuse and Mental Health Services Administration of the Department of Health and Human Services to collect information on the prevalence, patterns, and consequences of alcohol, tobacco, and illegal drug use and abuse in the general U.S. civilian non-institutionalized population, age 12 and older. Each year, approximately 67,500 persons are interviewed, and demographic information is collected, including information on frequency of use of drugs, as well as alcohol, tobacco, and illegal drug use. Populated measures of abuse, misuse, and NMU vary by drug, and are particularly sparse for prescription drugs. Therefore, to obtain the largest possible sample, we used the lifetime rate of NMU defined within the survey questions such as "Have you ever, even once, used any of these pain relievers when they were not prescribed for you or that you took only for the experience or feeling they caused?"¹⁸ This measure therefore includes both

consumption of a drug not prescribed to the user and for the experience produced from consumption; use of over-the-counter (OTC) drugs and legitimate use of prescription drugs are not included. It is worth emphasizing that the concept of NMU differs from other measures of “abuse” such as that associated with ICD-9-CM codes and the DSM-IV criteria. Throughout this paper, we will refer to NMU since this is the measure reported by NSDUH, and the best available source for our analysis.

DAWN data provide visit and demographic information for all patients seeking care from sampled hospitals’ emergency departments (ED) (non-Federal, short-stay hospitals in the US with 24-hour EDs) due to substance misuse or abuse, adverse reactions to drugs taken as prescribed, and other drug-related medical emergencies. DAWN data cover emergency department visits for all types of drugs, including prescription drugs, and also provide information on the route of administration. The inferred measure of the NMU rate follows the Substance Abuse and Mental Health Services Administration (SAMHSA) recommendation as the proportion of drug-related emergency department visits categorized for drug misuse as the primary cause and with reference to a particular drug.¹⁹

Prescription Drug Volume

IMS Health collects monthly, national prescription sales and volume data by drug (brand and generic) for its National Prescriptions Audit, covering volume dispensed from retail, mail service, and long-term care pharmacies.

Design

The study involved two components: (1) an econometric model using NMU as the dependent variable and each PSM as the independent variable, controlling for prescription volume and indicators for opioids and controlled substance schedule; and (2) a budget impact

model (BIM) that translates that relationship to an implied measure of HCRU and cost savings. The health care events avoided and cost savings were calculated based on pre-existing research on the hypothetical savings of ADFs based on a number of underlying assumptions, developed by White et al. (2009).¹⁵ The analytical samples consist of those drugs with at least one metric of PSMs as well as rates of NMU from NSDUH and DAWN. In order to determine the relationship between PSMs and rates of NMU, the sample needed observations with variation in rate of NMU. This requirement meant including observations from multiple classes of drugs, including non-opioids, many of which are known to be abused by the general public. As outlined below, several control variables were included in the analysis to ensure the results were broadly robust to the classes of drugs undergoing HAL studies as part of their regulatory approval process.

While the different data sources pertain to different underlying populations, these are the most comprehensive data of the underlying variables.

Model and Imputations

A quantitative evaluation of the association between PSMs and real-world NMU rates was performed using an ordinary least squares (OLS) regression. The unit of observation was a study arm within the HAL studies, i.e., an individual drug with associated PSM and NMU rate information. Equation 1 below presents the multiple linear regression model equation, where Y denotes a measure of the rate of NMU and β_1 is the magnitude of the association between the PSM and NMU rate when holding Opioid, Volume, and Schedule Variable constant.

Equation 1.

$$Y = \beta_0 + \beta_1PSM + \beta_2Opioid + \beta_3\ln(Volume) + \beta_4Schedule\ Variable + \varepsilon$$

As some observations included ADFs not yet on the market, and NMU rates were not known, we imputed a NMU rate for these new drugs based on current literature on the relationship between ADFs and non-ADFs –allowing us to increase our sample size. Specifically, the work of Butler et al. (2013)²⁰ and recent press releases from Endo Pharmaceuticals²¹ suggest that the introduction of ADFs of prescription opioids reduced abuse rates by roughly half (41% and 59%, respectively). We assumed that these reductions in abuse rates could be associated with reductions in NMU rates. Consistent with the Butler et al. result, we imputed NMU rates for the ADFs in the following manner: the NMU rates of the non-ADF opioid counterpart were multiplied by 0.59 (or $1.00 - 0.41$). In addition, to account for the fact that the impact of ADF on NMU may be lower in the real world, we also conducted a sensitivity analysis by assuming a more conservative rate reduction of 25% (rather than 41 percent associated with an ADF from the literature). As such we estimated NMU rates for ADFs by multiplying non-ADF rates by 0.75. When data on number of prescriptions were not available/reported, they were estimated by matching the drug with the post-introduction volume of the most similar drug introduction. All results are presented for the core sample, without imputations, as well as the larger sample sizes including the imputations of NMU for the ADFs.

Data were also analyzed using alternative functional forms in order to reflect real-world data; namely, logarithmic transformations of the NMU rate were used to account for the fact that negative rates have no meaningful interpretation. Results of those regressions were directionally consistent with our main findings below and are available upon request.

Health Care Resource Utilization and Costs

Predicted HCRU and cost savings associated with a PSM score reduction for a new ADF were calculated based on a BIM by White et al. (2009) to calculate health care events avoided

(e.g., emergency department visits, outpatient visits, hospitalizations) and cost savings associated with the introduction of a theoretical new ADF opioid.¹⁵ In that study, the BIM included information on hypothetical ADF attributes, HCRU and costs associated with prescription opioid abuse, and potential market share capture of the new ADF. Direct medical and pharmaceutical costs and indirect costs associated with prescription opioid abuse, dependence, and misuse were calculated using de-identified employer health care claims data covering more than six million lives. The estimated HCRU and cost savings can be imputed from the model by altering the fundamental underlying assumptions with respect to 1) market penetration of the ADF over targeted drugs; 2) pricing of the ADF; and 3) relative effectiveness of the ADF in deterring abuse. The BIM was used to estimate the number of health care events avoided and cost savings for a one percent reduction in abuse rate following introduction of an extended-release (ER) morphine ADF and ER oxycodone ADF. The effectiveness of the ADF was varied over a range from 20% - 80% to determine the average number of health care events avoided and cost savings. Model assumptions included the ADF being priced at par with the branded opioid, replacing the branded opioid 100%, and prescription volume remaining stable. Generics were assumed to still be available at the same prescription volume.

Using the model, the estimated number of key health care events avoided per percent change in abuse rate for ER morphine ADF and ER oxycodone ADF were determined. The estimated ED visits and hospitalizations avoided per percent change in abuse rate was calculated to be 249.8 and 165.4 for an ER morphine ADF and 1,171.1 and 775.6 for an ER oxycodone ADF, respectively. The estimated cost reduction per percent change in abuse rate was calculated to be \$3.28 million for an ER morphine ADF and \$14.98 million for an ER oxycodone product to a single private national payer.

In this study, we calculated potential health care events avoided and cost savings associated with a given decrease in PSM scores, resulting from the introduction of a new ADF to market, by multiplying the PSM-NMU rate association coefficient (β_1 in Equation 1 above) with the HCRU and cost percentage estimated by the BIM.

RESULTS

A number of variants of the model, both an original and extended sample for each PSM of “overall drug liking,” “drug high,” and “drug liking,” were used to estimate the association between PSMs and rates of drug NMU. Alprazolam, bupropion, dextroamphetamine, ketamine, morphine, oxycodone, and zolpidem were included in all comparisons, but each model variant additionally included other drugs as available when the specific PSM is observed. Table 1 reports sample sizes ranging from 25 to 54 comparator arms with a least one PSM, rate of NMU, and covariate information. HAL studies often use multiple doses of study drugs, making the average number of observations per drug in our sample between 3 and 5. As expected, the samples primarily contained drugs on the Federal Controlled Substances Schedule 2 (with high potential for abuse, possibly leading to severe psychological or physical dependence), with comparator arms generally Schedule 4 (lower likelihood for abuse). Sixty to 76 percent of the samples were comprised of opioids.

Association of HAL Endpoints with Rates of NMU

Table 3 presents our focal OLS regression results using the NSDUH rate of lifetime NMU as the dependent variable and “overall drug liking” E_{\max} as the primary explanatory variable. Model 1 is a simple linear regression, and Models 2 through 4 successively add

covariates: an indicator if the study arm is an opioid, the log-transformed annual prescription volume, and an indicator if the study arm is on the Controlled Substances Schedules 1, 2, or 3. In the final model (Model 4), with an R^2 of 0.62 and F -statistic of 8.06 ($p < 0.05$), the association between overall drug liking E_{\max} and the rate of lifetime NMU is found to be significant ($p < 0.05$); a single point increase in the overall drug liking E_{\max} is associated with a 0.05 percentage point increase in the NMU rate. Given that the sample average rate of NMU is 2.21% (as shown in Table 1), a single point change in the E_{\max} translates to an approximately 2.3% ($0.05/2.21$) change in the overall NMU rate in the sample. Accordingly, an ADF that reduces the overall drug liking E_{\max} by 5 points, all else equal, may therefore be expected to have a rate of NMU 11.3% lower than that of the non-ADF counterpart using the sample average rate of NMU. However, the percent change estimated from an ADF will be dependent upon the NMU rate for the non-ADF opioid. For example, the NMU rate for oxycodone is 2.47% and the NMU rate for morphine is 1.22%. Therefore, an oxycodone ADF that produces a 5-point reduction in overall drug liking E_{\max} compared with the non-ADF would be expected to produce a 10.1% decrease in the NMU rate and a morphine ADF would be expected to produce a 20.5% decrease in the NMU rate. Figure 1 provides an example of this calculation for an ER morphine ADF and ER oxycodone ADF.

As a robustness check, we estimated a number of sensitivities. Results using the DAWN rate of NMU and NSDUH extended samples demonstrate the general robustness of the association between rates of NMU and overall drug liking E_{\max} . The first results column of Table 3 provides the final model (i.e. Model 4) estimates of the association between overall drug liking E_{\max} and the measured rates of NMU. When using the DAWN rate, the magnitude of the impact is roughly 1.8% ($p > 0.05$), which is similar to the NSDUH rate despite explaining a

different measure of NMU. When explaining the extended samples' NMU rates – those using 0.59 and 0.75 multiples of the NSDUH NMU rate – the results remain consistent with the focal NSDUH findings, though the magnitude of the impact is marginally smaller.

The remaining columns in Table 3 present the final model (Model 4) results for drug high E_{\max} and drug liking E_{\max} . Despite strong correlations between the three PSMs (correlation coefficient $r > 0.87$ in sample Group A), no statistically significant associations between drug high E_{\max} and drug liking E_{\max} were found. Additionally the measures of model fit (R^2) were lower in these regressions than for overall drug liking E_{\max} . This may be explained by the smaller sample sizes associated with some of these alternative models.

Using the model and HAL studies conducted with an ER morphine ADF and ER oxycodone ADF, the overall drug liking reduction for the ADF relative to the non-ADF comparator in each study was determined and the decrease in NMU rate was estimated. There were three HAL studies conducted for each ADF; an oral crushed, intranasal, and intravenous administration HAL study. Using the model for the ER morphine ADF, the NMU rate is estimated to decrease by 45.1% to 98.8% to a predicted NMU rate of 0.01% to 0.67% compared with the NSDUH NMU rate of 1.22% for a non-ADF morphine. Using the model for the ER oxycodone ADF, the NMU rate is estimated to decrease by 15.4% to 64.0% to a predicted NMU rate of 0.89% to 2.09% compared with the NSDUH NMU rate of 2.47% for a non-ADF oxycodone.

Health Care Utilization and Cost impacts of HAL endpoints

The HCRU and cost impact of the relationship between PSM scores and rates of misuse was estimated using White et al.'s (2009) BIM of the potential cost savings for a hypothetical

ADF, based on the overall U.S. population covered by a single private payer.¹⁵ Based on different assumptions with respect to 1) market penetration of the ADF over targeted drugs; 2) pricing of the ADF; and 3) relative efficacy of the ADF we find the estimated health care events avoided for an ER morphine ADF ranging from 11,262 to 24,673 emergency department (ED) visits and from 18,017 to 74,913 ED visits for an ER oxycodone ADF using the overall drug liking measure. The estimated hospitalizations avoided for an ER morphine ADF were 7,457 to 16,337 and 11,932 to 49,613 for an ER oxycodone ADF. The cost savings for an ER morphine ADF were estimated to be in the range of \$147.7 million to \$323.6 million and \$230.5 million to 958.5 million for an ER oxycodone ADF using the overall drug liking measure.

DISCUSSION

This study provides evidence that reductions in overall drug liking E_{\max} scores are associated with decreases in rates of NMU. Further, these decreases are associated with significant reductions in healthcare utilization and costs. In our main analyses, our estimated models showed that a 5 point reduction (re-centered to a bipolar scale) in overall drug liking E_{\max} , drug high E_{\max} , or drug liking E_{\max} was associated with a 0.25, 0.10, and 0.05 percentage point decrease in the NSDUH lifetime rates of NMU, respectively. Whether this reduction is meaningful is not known. Eaton et al. (2012) determined that an approximately 10-point reduction (unipolar scale) in the “drug high” PSM represented a clinically meaningful difference,²² for which our results implied a 0.20 ($p>0.05$) percentage point reduction in the NMU rate. In 2011 the White House Office of National Drug Control Policy issued its Prescription Drug Abuse Plan Goals that included a 15 percent reduction in the non-medical use of prescription psychotherapeutic drugs and a 15 percent reduction in the number of

unintentional overdose deaths related to opioids within the next 5 years.¹ Compared to the sample average NSDUH NMU rates, a 5-point reduction in the PSMs of an ADF would amount to a 2.3% - 11.2% decrease in the NMU rate for that ADF relative to the non-ADF comparator. However, the percent reduction is dependent upon the baseline rate of NMU and the effectiveness of the ADF in reducing the PSM relative to the non-ADF in HAL studies. Using the results from HAL studies conducted with an ER morphine and ER oxycodone ADF, the model predicts these products would reduce the NMU rate by 45.1% - 98.8% and 15.4% - 64.0%, respectively. These reductions are all greater than the National Drug Control Policy's goal. The predicted reduction from the ADF varies based on the difference observed in the HAL study. In these studies, the oral crushed HAL study produced the smallest reduction in the PSM score and the intravenous HAL study produced the largest reduction in the PSM score.

Using the model's estimated reduction in NMU rate based on the HAL studies of the ER morphine ADF and ER oxycodone ADF, a BIM was used to estimate the number of health care events avoided and cost savings that may result. Our results imply an avoidance of ED visits ranging from 11,262 to 74,913, avoidance of hospitalizations ranging from 7,457 to 49,613, and cost reductions ranging from \$147.7 to \$958.5 million annually for a for which an ADF is used by the covered population (here the U.S. population covered by a single private payer) rather than the non-ADF. Using the CDC estimate that there are 24.8 ED visits for every overdose death for prescription opioid misuse or abuse,³ our results imply that 454 to 3,021 deaths would be avoided with an ADF demonstrating reduced overall drug liking relative to a non-ADF opioid as demonstrated in the HAL studies performed with these ADFs. Together these results mean that reductions in overall drug liking E_{max} are associated with reductions in real world NMU rates resulting in lower healthcare utilization and cost savings to payers.

To the best of our knowledge, our predictive analysis is the first study to attempt to quantify HCRU and cost savings based on existing HAL data and rates of NMU. The primary strength of this analysis was the combining of a variety of different datasets and making them consistent from an analytic perspective. Although the budget impact of abuse of prescription drugs has been thoroughly documented, no known study to date has confirmed the predictive power of any PSM for abuse rates, HCRU and costs. While our analysis focuses on changes in NMU rates, to the extent that the same relationship holds true for measures of abuse, the implications for HCRU and cost reductions arising from reduced abuse rates are important from a societal perspective.

Limitations

The nature of the study data and methods limits the conclusions this study may draw. Although analyses using the NSDUH past-year or past-month measures of NMU would provide more direct evidence of abuse, these measures are less populated than the lifetime measure. Both the NSDUH and DAWN usage of lifetime NMU potentially includes the situation of someone taking the medication prescribed to someone else, even on a single occasion, but for legitimate purposes. The small sample size limits the generalizability of the results. Because statistical methods are limited by the degrees of freedom (a result of sample size) available, our consideration of a causal model of PSM scores on real-world abuse rates using statistics will necessarily be of limited inference. Care should be taken in extrapolating and interpreting the results in different sample settings, and larger samples covering a broader set of potential drugs, including ADFs currently on the market would greatly improve the strength of this model.

A limitation to our model's consistency is the inability to control for the route of administration in each of the HAL studies. Both the initial composition of the study arm drug as well as the route of administration in a HAL study can affect the PSM measurements. For example, oral ingestion of an opioid is likely to produce lower PSMs than injection or intranasal consumption. Our data lack this degree of specificity with respect to the conduct of each study so that we cannot account for route within the statistical analysis or utilization calculations. Neither can we model the difference in response to misusing an ADF versus a generic formulation of an opioid.

Two further concerns arise from combining data from multiple sources. First, in the construction of the primary PSM database, we incorporate measurements from multiple HAL studies. Though this convenience sample from INC Research and Pfizer, Inc. offers an efficient source of many drug-specific measurements, the database is unlikely to approximate a random sample of drugs measured, and within studies of the database, there is potential for correlated measures either site- or study-group-specific which may bias sample results away from the population values.

Second, as observations in the INC database are combined with NMU measurements from NSDUH and DAWN, measurement error may be introduced. Though we merge information based on the international nonproprietary name of the drug, PSM observations are dose-specific, and are generated from a sample of recreational drug users. NMU rates, however, represent the general population and are not dose-specific. If that measurement error is "classical" in the statistical sense, our estimate of the association between drug liking measures and abuse rates will be attenuated, providing a conservative estimate.

Finally, the cost calculations used in this report are drawn from White et al. (2009).¹⁵ This paper looked at a narrower set of abuse-related costs, such as emergency room visits, hospitalizations, substance abuse treatment stays, and diseases related to abuse via injection. These costs do not include other more general medical costs that may be associated with prescription drug abuse. These costs are based on a national population insured by a single payer, and may not be generalizable to other populations such as Medicaid or Medicare, for example. Further, our use of the model requires several assumptions, including fixing the price of the hypothetical ADF at the price of the current branded version. Analyzing the impact of different pricing schemes would require modeling market-wide pricing dynamics that are beyond the scope of this paper.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Ryan Andrews, BS; Tyler Paul, BS; and Romaine Campbell, BA, for excellent research assistance, and Ana Bozas, PhD, for contributing to the preparation and editing of the manuscript. We also thank INC Research for their assistance with the data and information on PSMs.

DISCLOSURES

Financial support for this study was provided by Pfizer Inc., which also participated in the study development, interpretation of data, and authorship of this draft. CL Roland and J Mardekian are employees of Pfizer Inc., and own stock/stock options. AG White, J LeCates, W Cheng, and HG Birnbaum are employees of Analysis Group Inc., which has received consulting fees from Pfizer Inc in connection with this project and development of the draft manuscript.

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Table 1. Summary Statistics of Regression Group Samples

	Overall Drug Liking Samples				Drug High Samples				Drug Liking Samples			
	Original Sample (n=25)		Imputed Abuse Rates (n=39)		Original Sample (n=31)		Imputed Abuse Rates (n=51)		Original Sample (n=34)		Imputed Abuse Rates (n=54)	
	Group A ¹		Group B ²		Group C ³		Group D ⁴		Group E ⁵		Group F ⁶	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
Non-Medical Use Rates												
NSDUH ⁷	2.21	[1.67]			2.36	[1.69]			2.38	[1.74]		
DAWN ⁸	1.97	[1.5]			2.21	[1.65]			2.13	[1.64]		
NSDUH_59 ⁹			1.87	[1.42]			1.86	[1.47]			1.90	[1.53]
NSDUH_75 ⁹			1.99	[1.39]			1.98	[1.43]			2.01	[1.49]
Positive Subjective Measures												
Overall Drug Liking E _{max} ¹⁰	21.72	[10.86]	19.34	[9.81]								
Drug High E _{max} ¹¹	73.83	[21.45]	67.95	[19.99]	72.89	[19.8]	66.77	[19.01]				
Drug Liking E _{max} ^{10,11}	30.12	[11.39]	27.00	[10.4]	27.41	[12.14]	24.02	[11.69]	27.93	[11.92]	24.53	[11.7]
Average Number of Obs Per Drug	3.13	[2.42]	3.90	[2.98]	3.44	[2.95]	4.64	[3.67]	3.09	[3.09]	4.15	[3.78]
Controlled Substances Schedule (Obs)												
1	0		0		0		0		0		0	
2	17		31		23		43		24		44	
3	1		1		1		1		1		1	
4	6		6		6		6		7		7	
Non-scheduled	1		1		1		1		2		2	
Opioid, % of All Obs	60%		74%		61%		76%		59%		74%	
2010 Volume, Millions of Rx¹²	20.43	[16.66]	13.21	[16.45]	18.21	[16]	11.17	[15.22]	17.71	[15.46]	11.25	[14.87]
Log of Volume	16.15	[1.74]	14.87	[2.23]	15.74	[2.27]	14.43	[2.43]	15.78	[2.18]	14.53	[2.4]

Notes:

- Group A drugs: Alprazolam, Bupropion, Dextroamphetamine, Hydromorphone, Ketamine, Morphine, Oxycodone, Zolpidem.
- Group B drugs: Alprazolam, Bupropion, Dextroamphetamine, Hydromorphone, Ketamine, Morphine, Morphine/Naltrexone, Oxycodone, Oxycodone/Naltrexone, Zolpidem.
- Group C drugs: Alprazolam, Bupropion, Dextroamphetamine, Hydromorphone, Ketamine, Methamphetamine, Morphine, Oxycodone, Zolpidem.
- Group D drugs: Alprazolam, Bupropion, Dextroamphetamine, Hydromorphone, Ketamine, Methamphetamine, Morphine, Morphine/Naltrexone, Oxycodone, Oxycodone/Naltrexone, Zolpidem.
- Group E drugs: Alprazolam, Bupropion, Dextroamphetamine, Diazepam, Diphenhydramine, Hydromorphone, Ketamine, Methamphetamine, Morphine, Oxycodone, Zolpidem.
- Group F drugs: Alprazolam, Bupropion, Dextroamphetamine, Diazepam, Diphenhydramine, Hydromorphone, Ketamine, Methamphetamine, Morphine, Morphine/Naltrexone, Oxycodone, Oxycodone/Naltrexone, Zolpidem.
- NSDUH: National Survey on Drug Use and Health 2010, Lifetime Misuse
- DAWN: Drug Abuse Warning Network 2010, Unspecified ER Visits
- NSDUH_59 and NSDUH_75 include imputed abuse rates for drugs with an Abuse Deterrent Formulation (ADF). The implied reduction is 59% (Butler et al. 2013) and 75% (as a sensitivity), respectively, of the original rate.
- The original HAL endpoint had a bipolar scale. It was recentered to take values in the range of -50 to 50, with 0 as the neutral score.
- Groups C, D, E and F do not have an Overall Drug Liking E_{max} value for every observation, so their averages were removed. Groups E and F do not have a Drug High E_{max} value for every observation, so their averages were removed.
- Volume information comes from 2010 IMS total prescriptions. Volume for ADFs not yet marketed was imputed using market penetration rates for existing ADFs.

Table 2. OLS Regression of Lifetime NSDUH Non-Medical Use Rate on Overall Drug Liking E_{\max} and Control Variables

Explanatory Variables	Model 1	Model 2	Model 3	Model 4
Intercept	1.46 [0.76]	1.95 [0.73]*	-7.56 [2.14]*	-7.63 [4.59]
Overall Drug Liking E_{\max}	0.03 [0.03]	0.05 [0.03]	0.05 [0.02]*	0.05 [0.02]*
Opioid		-1.48 [0.65]*	-1.56 [0.47]*	-1.58 [1.2]
Log of Volume			0.60 [0.13]*	0.60 [0.26]*
Schedule123				0.03 [1.55]
Number of Observations	25	25	25	25
R-Squared	0.05	0.23	0.62	0.62
Adjusted R-Squared	0.01	0.16	0.56	0.54
F-statistic	1.23	3.36	11.29	8.06
Prob>F	0.28	0.05	0.00	0.00

Drugs Used In this Analysis: Oxycodone, Alprazolam, Hydromorphone, Morphine, Dextroamphetamine, Zolpidem, Bupropion, Ketamine.

Notes:

1. Models 1, 2, 3, and 4 represent successive addition of independent variables.
2. Standard error in brackets. * denotes p-value < 0.05.
3. The original liking score had a bipolar scale. It was recentered to take values in the range of -50 to 50, with 0 as the neutral score.
4. Opioid is a dummy variable which takes the value 1 if a drug is an opioid; 0 otherwise.
5. Log of Volume is the log value of the 2010 total volume of prescriptions dispensed for the drug.
6. Schedule123 is a dummy variable which takes the value 1 if a drug is either schedule 1, 2, or 3; 0 otherwise.
7. In this analysis there were 25 observations, consisting of 8 drugs. Of these, 18 observations and 5 drugs were either schedule 1, 2, or 3.

Table 3. OLS Regression Coefficients of Non-Medical Use Rates across Model Specifications

Dependent Variable	Overall Drug Liking E_{\max}	Drug High E_{\max}	Drug Liking E_{\max}
NSDUH Lifetime Non-Medical Use (NMU)	0.05 [0.02]* {0.62}	0.01 [0.01] {0.26}	0.02 [0.02] {0.22}
DAWN Proportion ED Visits	0.03 [0.02] {0.57}	0.01 [0.01] {0.06}	0.02 [0.02] {0.10}
NSDUH Lifetime NMU, Imputed ADF Rate (59%)	0.04 [0.02]* {0.58}	0.01 [0.01] {0.39}	0.02 [0.02] {0.36}
NSDUH Lifetime NMU, Imputed ADF Rate (75%)	0.04 [0.02]* {0.53}	0.01 [0.01] {0.34}	0.02 [0.02] {0.30}

Notes:

1. All estimates from models controlling for opioid, log of 2010 prescription volume, and Schedule123.
2. Standard error in brackets. * denotes p-value < 0.05. Model R^2 values in braces.
3. Sample sizes varied across specifications; see Table 1 for corresponding sample sizes.

Figure 1. Example Impact of ADF-induced Overall Drug Liking E_{max} Reduction on Predicted Abuse Rates

