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Long-Acting Injectable Medications for Alcohol and Opioid Use Disorders: *Benefit-Cost Findings*

Long-acting injectable medications for alcohol and opioid use disorders were developed with a goal to improve treatment adherence and prevent relapse. These medications are administered monthly, unlike other medication-assisted treatments that are administered daily, and block the euphoric effects of alcohol or opioids.

The Washington State Legislature directed the Washington State Institute for Public Policy (WSIPP) to 1) "review existing research literature," and 2) "begin a four-year study to evaluate outcomes regarding the cost-effectiveness of FDA-approved long-acting injectable medications."[1] The legislation directs WSIPP to focus on the benefits to persons in prison when they are released into the community.

To carry out the first part of this assignment, WSIPP reviewed the research evidence on the effectiveness of these medications. Where possible, we calculated whether the monetary benefits of long-acting injectable medications outweigh the costs.

We are currently unable to conduct an outcome evaluation of injectable medications for persons in prison because, at this time, injectable medications are not prescribed in Washington State prisons to treat misuse of alcohol or opioids.

Summary

The Washington State Legislature directed WSIPP to "review existing literature" and "begin a four-year study to evaluate outcomes regarding the cost-effectiveness of FDA-approved long-acting injectable medications," focusing on the benefits to persons in prison when they are released into the community.

We reviewed the research evidence on the effectiveness of these medications in reducing substance use and recidivism rates. Where possible, we calculated whether the benefits of administering long-acting injectable medications outweigh the costs.

The research evidence shows that injectable naltrexone reduces substance misuse. However, the monetary benefits do not outweigh the costs of the medication. We explain these results in this report and display them in Exhibits 1 and 2.

In this report, we describe our research approach and highlight our findings. Section I provides background, Section II outlines our research approach, Section III reviews our findings, and Section IV discusses the possible next steps for an outcome evaluation.

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[1] Engrossed Substitute Senate Bill 6052, Chapter 4, Laws of 2015.

I. Background

Alcohol and opioid use disorders affect many individuals in Washington State. During 2012 and 2013, 7.6% of individuals age 12 or older in Washington State had an alcohol use disorder, while 3% had an illicit drug use disorder.[2] In 2014, 2,098 Washington State residents died due to drug- or alcohol-induced causes.[3]

A number of treatment options exist to treat alcohol and drug use disorders, including psychosocial and medication-assisted treatments. In this report, we focus on medication-assisted treatment.

Several medication-assisted treatment options can be used to address alcohol and opioid use disorders. These medications are intended to prevent withdrawal symptoms and/or block the euphoric effects of alcohol or opioids. Patients treated with these medications may struggle with adherence, as their doses must be taken daily or several times a week. In some circumstances, such as methadone maintenance treatment, patients must receive the medication daily in specialized clinics.

Long-acting injectable medications for substance use disorders were developed in part to improve treatment adherence. Because these medications are administered as monthly injections, patients do not have to travel to a clinic for treatment every day.

Implantable medications that last for six months have more recently been developed.

In this report, we describe the research evidence on six approaches to medication-assisted treatment for alcohol or opioid use disorder:[4]

- Injectable naltrexone,
- Injectable bromocriptine,
- Naltrexone implants,
- Buprenorphine implants,
- Oral methadone maintenance, and
- Oral buprenorphine/ buprenorphine-naloxone.

All of these medications are typically accompanied by some type of drug counseling. Next, we describe each medication.

Injectable naltrexone for alcohol and opioids

Injectable naltrexone is used as an "antagonist" to treat alcohol and opioid misuse through monthly injections. Antagonists block the euphoric effects of drugs to prevent relapses and reduce further substance misuse. Naltrexone is not a controlled substance and is considered less susceptible to patient abuse because it is not addictive and has no euphoric effects.

Patients do not build tolerance to naltrexone or experience withdrawal symptoms when they stop receiving injections. However,

[2] Substance Abuse and Mental Health Services Administration. (2014). *Behavioral health barometer: Washington, 2014*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

[3] Washington State Department of Health. (2014). *Table E7 – Drug and alcohol-induced causes for residents*. [Data set]. Retrieved from http://www.doh.wa.gov/DataandStatisticalReports/VitalStatisticsandPopulationData/Death/DeathTablesbyTopic.

[4] As required in our legislative assignment, we reviewed injectable medications. We also reviewed implant medications because both contain similar chemicals and target similar issues, but with different delivery methods. We included WSIPP findings on buprenorphine and methadone maintenance because these medications are often compared to injectable medications.

patients must abstain from alcohol or opioids before beginning treatment, typically for at least three days or the medication may precipitate withdrawal symptoms.

Injectable bromocriptine

Injectable bromocriptine is a dopamine "agonist" that has been tested in the treatment of alcohol use disorder. Dopamine agonists activate dopamine receptors in the brain. Bromocriptine is intended to alleviate alcohol withdrawal symptoms by imitating the effects of dopamine. Injectable bromocriptine is not approved by the U.S. Food and Drug Administration (FDA) to treat alcohol use disorder.

Naltrexone implants

Implantable naltrexone is used for the same purposes as injectable naltrexone but is administered as a small pellet inserted subcutaneously into the arm every six months. Naltrexone implants have not yet been approved by FDA, and all of the studies reviewed on this medication were conducted in countries outside of the U.S.

Buprenorphine implants

Implantable buprenorphine is a form of opioid substitution treatment, replacing opioids with prescribed medication. Buprenorphine is a partial agonist that suppresses withdrawal symptoms and also blocks the effects of other opioids. Implants are inserted subcutaneously into the arm every six months, releasing a constant level of buprenorphine. Patients may also receive supplemental buprenorphine-naloxone tablets. Buprenorphine implants were approved by the FDA in May 2016.

Pharmacotherapy key terms

The medications in this report fall into three categories of pharmacotherapy:

- Antagonists: Block the euphoric effects of other drugs
- Agonists: Activate certain receptors in the brain to imitate the euphoric effects of other drugs
- Partial agonists: Activate certain receptors in the brain to imitate the euphoric effects of other drugs, but to a lesser extent

Methadone maintenance treatment

Methadone is an opioid substitution treatment used to treat opioid use disorder. It is a synthetic opioid that blocks the effects of opioids, reduces withdrawal symptoms, and relieves cravings. Methadone is dispensed daily in liquid or pill form at outpatient clinics that specialize in methadone treatment.

Buprenorphine/buprenorphine-naloxone

Buprenorphine/buprenorphine-naloxone is an opioid substitution treatment used to treat opioid use disorder. Buprenorphine is a partial agonist that suppresses withdrawal symptoms and blocks the effects of opioids. The addition of naloxone reduces the probability of overdose and reduces misuse by producing severe withdrawal effects if taken any way other than sublingually. Buprenorphine and buprenorphine-naloxone are alternatives to methadone treatments and, unlike methadone, can be prescribed monthly in office-based settings by physicians who have completed special training.

II. Research Methods

When WSIPP carries out study assignments to identify what works in public policy, we implement a set of standardized procedures. We search for all studies on a given topic. Our empirical approach follows a meta-analytic framework to assess systematically all credible evaluations we can locate. Studies with weak research methods are excluded from our analysis, allowing us to confidently estimate causal impacts of a treatment.

Given the weight of the research evidence, we calculate an average effect ("effect size") of a policy or treatment on a particular outcome of interest. An effect size measures the degree to which a program has been shown to change an outcome (such as alcohol misuse) for program participants relative to a comparison group. We describe our methods in detail in WSIPP's Technical Documentation.[5]

To identify all rigorous evaluations that have been undertaken, we searched for studies in PubMed, Google Scholar, and the Cochrane Library. The search was supplemented with citations from published systematic reviews. We located 37 injectable or implant medication studies, of which 16 were rigorous enough to include in the meta-analyses. The remaining studies were excluded due to methodological or reporting issues. The 16 studies involved 1,658 intervention participants in seven different countries.[6]

Next, we consider the benefits and costs of implementing a program or policy by answering two questions.

1) How much would it cost Washington taxpayers to produce the results found in the meta-analysis?
2) How much would it be worth to people in Washington State to achieve these results?

That is, in dollars and cents, what are the benefits and costs of each type of treatment?

[5] Washington State Institute for Public Policy (2016). Benefit-cost technical documentation. Olympia, WA: Author. Retrieved from http://www.wsipp.wa.gov/TechnicalDocumentation/WsippBenefitCostTechnicalDocumentation.pdf.

[6] Countries include Canada, France, Norway (two studies), Russia (four), Spain, Sweden, and the United States (11).

Our benefit-cost results are expressed with standard financial statistics: net present values and benefit-cost ratios. We present monetary estimates from the perspective of:

1) program participants,
2) taxpayers, and
3) other people in society.

The sum of these perspectives provides a "total Washington" view on whether a program or policy produces benefits that exceed costs.

Benefits to individuals and society may stem from multiple sources. For example, a treatment that reduces misuse of alcohol or opioids decreases the use of health care resources, thereby reducing taxpayer costs and personal, out-of-pocket costs. In addition, reducing substance misuse increases a person's employment and earnings outlook. Thus, program participants will have higher earnings, on average, in the labor market. WSIPP's benefit-cost model produces estimates of both the health care and labor market effects of reduced alcohol and opioid use disorders.

In addition to these outcomes, some studies also report effects on criminal behavior for opioid-users in the criminal justice system. In these cases, we estimate the monetary benefits from reducing crime, including the reduced use of criminal justice system resources and the avoided costs to victims of crime.

Long-acting injectable medications for alcohol and opioid use disorders were developed with a goal to improve treatment adherence and prevent relapse. We report this outcome in our meta-analytic findings (see Appendix A. II). At this time, however, we are unable to estimate the financial benefits (or costs) associated with this outcome. Thus, treatment engagement and retention is not included in our bottom-line estimates for each intervention presented in the next section.

Costs are calculated as direct Medicaid expenditures for administering these medications. We also apply a factor for the deadweight cost of taxation that applies to any taxpayer-funded program that WSIPP examines. See Appendix A.I for detailed explanations of our benefit-cost results.

We do not assume that the effects of medication-assisted treatment last beyond the period of active treatment. Therefore, we estimate the cost for one year of treatment and the benefits that will accrue over that year.

Any tabulation of benefits and costs involves a degree of uncertainty about the estimates calculated. This is expected in any investment analysis, whether in the private or public sector. To assess the riskiness of our conclusions, we perform a "Monte Carlo simulation" in which we vary key factors in our calculations. The purpose of this analysis is to determine the probability that a particular program or policy will at least have benefits that are equal to or greater than costs ("break even").

Thus, we produce two "big picture" findings: an expected benefit-cost result and, given our understanding of the risks, the probability that the program or policy will at least break even.

III. Key Findings

Exhibit 1 displays the results of our meta-analyses on long-acting injectable and implantable medications for alcohol and opioid use disorders.[7] We also include WSIPP's previous findings on methadone maintenance and buprenorphine/buprenorphine-naloxone, which are alternative forms of medication-assisted treatment commonly prescribed to treat opioid use disorder.[8]

We find that injectable naltrexone for alcohol leads to a small reduction in alcohol use, while injectable bromocriptine does not.

Injectable naltrexone for opioids leads to a reduction in opioid use that is comparable to the effects of naltrexone implants and buprenorphine implants.
Methadone and buprenorphine/buprenorphine-naloxone maintenance have the largest effects of all medication-assisted treatments examined here, reducing the use of opioids by roughly 75% during active treatment.

Two studies examined the effects of injectable naltrexone for opioid-using persons in jail or on parole. We find that injectable naltrexone reduces opioid use for people in the criminal justice system, but does not have a reliable effect on criminal recidivism.

Exhibit 1

Summary of Meta-Analytic Findings for Medication-Assisted Treatment for Alcohol and Opioid Use Disorders

Medication	Outcome	Percent change	# of effect sizes	Average adjusted effect size	Standard error	p-value	# in treatment group
Injectable naltrexone for alcohol	Alcohol use	-12.8%	5	-0.133	0.044	0.003	627
Injectable naltrexone for opioids	Opioid use	-55.6%	5	-0.566	0.152	0.000	329
Injectable naltrexone for opioid users in the criminal justice system	Crime	-21.6%	2	-0.218	0.208	0.294	169
	Opioid use	-59.0%	2	-0.594	0.248	0.017	169
Injectable bromocriptine	Alcohol use	7.1%	2	0.077	0.181	0.672	212
Naltrexone implants	Opioid use	-56.2%	4	-0.734	0.046	0.000	247
Buprenorphine implants	Opioid use	-53.0%	2	-0.538	0.156	0.001	222
Methadone maintenance for opioid users	Opioid use	-75.0%	8	-0.945	0.304	0.002	623
Buprenorphine/buprenorphine-naloxone	Opioid use	-74.8%	9	-0.941	0.181	0.000	793

[7] When calculating treatment effects and costs, we assume that all study participants, whether in the treatment or control group, were receiving some kind of drug counseling, as per treatment standards for these forms of medication-assisted treatment.

[8] See Miller, M., Goodvin, R., Grice, J., Hoagland, C., & Westley, E. (2016). *Updated Inventory of evidence-based, research-based, and promising practices prevention and intervention services for adult behavioral health.* (Doc. No. 16-09-4101). Olympia: Washington State Institute for Public Policy.

Exhibit 2 displays our benefit-cost results on long-acting injectable medications and other medication-assisted treatments. The costs of injectable medications are roughly three to four times higher than orally administered medications. The total benefits for injectable medications are negative after accounting for the deadweight costs of taxation (displayed under non-taxpayer benefits). In other words, the benefits of injectable medications do not outweigh the costs.

We were unable to calculate the costs of injectable bromocriptine, naltrexone implants, and buprenorphine implants. Injectable bromocriptine and naltrexone implants have not been approved by the FDA. The FDA recently approved buprenorphine implants, but cost estimates are not yet available.

Exhibit 2

Benefit-Cost Results for Medication-Assisted Treatment for Alcohol and Opioid Use Disorders

Program name	Benefits				Costs	Summary		
	Total benefits[1]	Taxpayer benefits	Non-taxpayer benefits	Deadweight cost of the program	Program costs	Benefits minus costs (net present value)	Benefit to cost ratio	Chance benefits will exceed costs
Methadone maintenance for opioid users	$8,280	$1,153	$8,962	($1,835)	($3,727)	**$4,554**	$2.22	**89%**
Buprenorphine/buprenorphine-naloxone	$8,054	$1,174	$8,996	($2,116)	($4,579)	**$3,475**	$1.76	**86%**
Injectable naltrexone for opioids for persons in the criminal justice system	($305)	$1,331	$6,555	($8,192)	($16,359)	**($16,665)**	($0.02)	**0%**
Injectable naltrexone for opioids	($948)	$823	$6,448	($8,218)	($16,349)	**($17,297)**	($0.06)	**0%**
Injectable naltrexone for alcohol	($7,188)	$269	$654	($8,111)	($16,375)	**($23,563)**	($0.44)	**0%**

Notes:
These results are current as of December 2016. More recent results may be available on WSIPP's website http://www.wsipp.wa.gov/BenefitCost?topicId=7
[1] The total benefits include the monetary benefits of reduced substance use disorders but also include the deadweight cost of taxation. See the detailed tables in Appendix II of the report for more information.

IV. Next Steps

The Washington State Legislature also directed WSIPP to "begin a four-year study to evaluate outcomes regarding the cost effectiveness of FDA approved long-acting injectable medications focused on potential benefits to prison offenders being released into the community."[9] However, we are unable to conduct such an outcome evaluation because Washington does not currently prescribe injectable medication to persons leaving prison.

In order for WSIPP to complete an outcome evaluation of long-acting injectable medications, we need to observe outcomes for two groups in a prison setting.

In an ideal research design, eligible persons in prison would choose to participate in the study and then be randomly assigned to a treatment or control group. Participants in the treatment group would receive injectable medications and drug counseling, and those in the control group would receive drug counseling only. With this kind of experimental design, any differences in outcomes could be confidently attributed to the injectable medications.

To conduct this experiment as assigned by the legislature, persons in prison would need to be prescribed long-acting injectable medications within the prison setting. Recidivism outcomes could then be tracked following release. If the assignment is to also measure treatment retention and substance use, new data would need to be collected.[10] Currently, no agency tracks released persons' substance misuse or treatment.[11]

If these conditions were met, it would be possible to conduct an evaluation of the outcomes of long-acting injectable medications for persons in prison after they are released into the community.

[9] Engrossed Substitute Senate Bill 6052, Chapter 4, Laws of 2015.

[10] DOC does not currently track formerly incarcerated persons' substance use treatment in the community, according to personal communication with Dr. Steven Hammond, Chief Medical Officer, Dawn Williams, Program Administrator of Substance Abuse Recovery Unit, and Paige Harrison, Director of Research, Data & Analytics, of the Department of Corrections, on April 11, 2016.

[11] Substance use treatment data are available for Medicaid recipients, but during the first half of fiscal year 2015, only 17 patients per month were using injectable naltrexone through Medicaid. Even if we were able to identify which of these patients were formerly incarcerated, we would not have the statistical power to detect any meaningful impact on alcohol or opioid misuse or crime.

Appendices

Long-Acting Injectable Medications for Alcohol and Opioid Use disorder: Benefit-Cost Findings

Appendix

I. Detailed Benefit-Cost Results

All results are also available on WSIPP's website: http://www.wsipp.wa.gov/BenefitCost?topicId=7

The estimates shown in the benefit-cost summaries below are present-value, life-cycle benefits and costs. All dollars are expressed in the base year chosen for this analysis (2015). The chance the benefits exceed the costs are derived from a Monte Carlo risk analysis. The details on this, as well as the economic discount rates and other relevant parameters, are described in our Technical Documentation.[12]

In the detailed monetary estimate tables, "others" are people other than taxpayers and participants. Depending on the program, it could include reductions in crime victimization, the economic benefits from a more educated workforce, and the benefits from employer-paid health insurance. "Indirect benefits" include estimates of the net changes in the value of a statistical life and net changes in the deadweight costs of taxation.

The annual cost estimates displayed below reflect costs to implement programs in Washington. The comparison group costs reflect either no treatment or treatment as usual, depending on how effect sizes were calculated in the meta-analysis. The cost range reflects potential variation or uncertainty in the cost estimate.

[12] WSIPP (2016), http://www.wsipp.wa.gov/TechnicalDocumentation/WsippBe nefitCostTechnicalDocumentation.pdf.

Injectable naltrexone for alcohol

Benefit-Cost Summary Statistics Per Participant			
Benefits to:			
Taxpayers	$269	Benefits minus costs	($23,563)
Participants	$560	Benefit to cost ratio	($0.44)
Others	$18	Chance the program will produce benefits greater than the costs	0 %
Indirect	($8,035)		
Total benefits	($7,188)		
Net program cost	($16,375)		
Benefits minus cost	($23,563)		

The estimates shown are present value, life cycle benefits and costs. All dollars are expressed in the base year chosen for this analysis (2015). The chance the benefits exceed the costs are derived from a Monte Carlo risk analysis. The details on this, as well as the economic discount rates and other relevant parameters are described in our Technical Documentation.

Detailed Monetary Benefit Estimates Per Participant					
Benefits from changes to:	Benefits to:				
	Taxpayers	Participants	Others	Indirect	Total
Crime	$0	$0	$0	$0	$0
Earnings associated with alcohol use disorder	$253	$556	$0	$68	$877
Health care costs associated with alcohol use disorder	$17	$3	$16	$8	$44
Property loss associated with alcohol use disorder	$0	$1	$2	$0	$2
Adjustment for deadweight cost of program	$0	$0	$0	($8,111)	($8,111)
Totals	**$269**	**$560**	**$18**	**($8,035)**	**($7,188)**

[1]In addition to the outcomes measured in the meta-analysis table, WSIPP measures benefits and costs estimated from other outcomes associated with those reported in the evaluation literature. For example, empirical research demonstrates that high school graduation leads to reduced crime. These associated measures provide a more complete picture of the detailed costs and benefits of the program.
[2]"Others" includes benefits to people other than taxpayers and participants. Depending on the program, it could include reductions in crime victimization, the economic benefits from a more educated workforce, and the benefits from employer-paid health insurance.
[3]"Indirect benefits" includes estimates of the net changes in the value of a statistical life and net changes in the deadweight costs of taxation.

Detailed Annual Cost Estimates Per Participant				
Annual cost		Year dollars	Summary	
Program costs	$16,356	2015	Present value of net program costs (2015 dollars)	($16,356)
Comparison costs	$0	2015	Cost range (+ or -)	10 %

We estimate the per-participant costs of providing injectable naltrexone treatment for alcohol or opioid use disorders for 12 months. From January through June of 2015, Washington State Medicaid spent an average of $1,363.03 per patient per month on injectable naltrexone for alcohol and opioid use disorder, according to personal communication with Donna Sullivan, Chief Pharmacy Officer of the Washington Health Care Authority, on February 4, 2016.

Injectable naltrexone for opioids

Benefit-Cost Summary Statistics Per Participant			
Benefits to:			
Taxpayers	$823	Benefits minus costs	($17,297)
Participants	$1,168	Benefit to cost ratio	($0.06)
Others	$326	Chance the program will produce	
Indirect	($3,265)	benefits greater than the costs	0 %
Total benefits	($948)		
Net program cost	($16,349)		
Benefits minus cost	($17,297)		

Detailed Monetary Benefit Estimates Per Participant					
Benefits from changes to:	Benefits to:				
	Taxpayers	Participants	Others	Indirect	Total
Crime	$0	$0	$1	$0	$1
Property loss associated with problem alcohol use	$0	$0	$0	$0	$0
Earnings associated with opioid use disorder	$498	$1,098	$0	$4,787	$6,384
Health care costs associated with opioid use disorder	$324	$71	$325	$166	$886
Adjustment for deadweight cost of program	$0	$0	$0	($8,218)	($8,218)
Totals	**$823**	**$1,168**	**$326**	**($3,265)**	**($948)**

Detailed Annual Cost Estimates Per Participant				
Annual cost		Year dollars	Summary	
Program costs	$16,356	2015	Present value of net program costs (2015 dollars)	($16,356)
Comparison costs	$0	2015	Cost range (+ or -)	10 %

We estimate the per-participant costs of providing injectable naltrexone treatment for alcohol or opioid use disorders for 12 months. From January through June of 2015, Washington State Medicaid spent an average of $1,363.03 per patient per month on injectable naltrexone for alcohol and opioid use disorder, according to personal communication with Donna Sullivan, Chief Pharmacy Officer of the Washington Health Care Authority, on February 4, 2016.

Injectable naltrexone for opioid-using persons in prison

Benefit-Cost Summary Statistics Per Participant			
Benefits to:			
Taxpayers	$1,321	Benefits minus costs	($16,712)
Participants	$839	Benefit to cost ratio	$0.02
Others	$1,667	Chance the program will produce benefits greater than the costs	0 %
Indirect	($4,176)		
Total benefits	($349)		
Net program cost	($16,363)		
Benefits minus cost	($16,712)		

Detailed Monetary Benefit Estimates Per Participant					
Benefits from changes to:	Benefits to:				
	Taxpayers	Participants	Others	Indirect	Total
Crime	$715	$0	$1,417	$358	$2,490
Earnings associated with opioid use disorder	$356	$784	$0	$3,538	$4,679
Health care costs associated with opioid use disorder	$249	$54	$250	$124	$678
Adjustment for deadweight cost of program	$0	$0	$0	($8,196)	($8,196)
Totals	**$1,321**	**$838**	**$1,667**	**($4,176)**	**($349)**

Detailed Annual Cost Estimates Per Participant				
Annual cost		Year dollars	Summary	
Program costs	$16,356	2015	Present value of net program costs (2015 dollars)	($16,356)
Comparison costs	$0	2015	Cost range (+ or -)	10 %

We estimate the per-participant costs of providing injectable naltrexone treatment for alcohol or opioid use disorder for 12 months. From January through June of 2015, Washington State Medicaid spent an average of $1,363.03 per patient per month on injectable naltrexone for alcohol and opioid use disorder, according to personal communication with Donna Sullivan, Chief Pharmacy Officer of the Washington Health Care Authority, on February 4, 2016.

Methadone maintenance for opioids

Benefit-Cost Summary Statistics Per Participant			
Benefits to:			
Taxpayers	$1,153	Benefits minus costs	$4,554
Participants	$1,623	Benefit to cost ratio	$2.22
Others	$469	Chance the program will produce	
Indirect	$5,036	benefits greater than the costs	89 %
Total benefits	$8,280		
Net program cost	($3,727)		
Benefits minus cost	$4,554		

Detailed Monetary Benefit Estimates Per Participant					
Benefits from changes to:	Benefits to:				
	Taxpayers	Participants	Others	Indirect	Total
Crime	$3	$0	$9	$1	$13
Labor market earnings associated with opioid use disorder	$691	$1,523	$0	$6,664	$8,858
Health care associated with opioid use disorder	$459	$100	$460	$226	$1,245
Adjustment for deadweight cost of program	$0	$0	$0	($1,835)	($1,835)
Totals	**$1,153**	**$1,623**	**$469**	**$5,036**	**$8,280**

Detailed Annual Cost Estimates Per Participant				
Annual cost		Year dollars	Summary	
Program costs	$3,613	2012	Present value of net program costs (in 2015 dollars)	($3,727)
Comparison costs	$0	2012	Cost range (+ or -)	20 %

We estimate the per-participant costs of providing methadone in addition to standard substance use treatment for 12 months. Costs reflect the average of costs reported in numerous cost-effectiveness studies (Rosenhack and Kosten, 2001; Jones et al., 2009; Nordlund et al., 2004; Masson et al, 2004). Costs included vary by study but generally include costs of medication, dispensing, toxicology screens, medical care related to methadone treatment, and when available, costs of equipment, administration, and clinic space. Jones, E.S., Moore, B.A., Sindelar, J.L., O'Connor, P.G., Schottenfeld, R.S., & Fiellin, D.A. (2009). Cost analysis of clinic and office-based treatment of opioid use disorder: Results with methadone and buprenorphine in clinically stable patients. *Drug and Alcohol Use disorder, 99*(1), 132-140. Masson, C.L., Barnett, P.G., Sees, K.L., Delucchi, K.L., Rosen, A., Wong, W., & Hall, S.M. (2004). Cost and cost-effectiveness of standard methadone maintenance treatment compared to enriched 180-day methadone detoxification. *Addiction, 99*(6), 718-726. Nordlund, D.J., Estee, S., Mancuso, D., & Felver, B. (2004). *Methadone treatment for opioid addiction lowers health care costs and reduces arrests and convictions.* Olympia, Wash.: Washington State Dept. of Social and Health Services, Research and Data Analysis Division. Rosenheck, R., & Kosten, T. (2001). Buprenorphine for opioid addiction: potential economic impact. *Drug and Alcohol Use disorder, 63*(3), 253-262.

Buprenorphine/Buprenorphine-naloxone

Benefit-Cost Summary Statistics Per Participant			
Benefits to:			
Taxpayers	$1,174	Benefits minus costs	$3,475
Participants	$1,653	Benefit to cost ratio	$1.76
Others	$472	Chance the program will produce benefits greater than the costs	86 %
Indirect	$4,756		
Total benefits	$8,054		
Net program cost	($4,579)		
Benefits minus cost	$3,475		

Detailed Monetary Benefit Estimates Per Participant					
Benefits from changes to:	Benefits to:				
	Taxpayers	Participants	Others	Indirect	Total
Crime	$0	$0	$1	$0	$2
Labor market earnings associated with opioid use disorder	$704	$1,551	$0	$6,803	$9,058
Health care associated with opioid use disorder	$466	$102	$467	$230	$1,265
Health care associated with emergency department visits	$3	$1	$3	$1	$8
Adjustment for deadweight cost of program	$0	$0	$0	($2,279)	($2,279)
Totals	**$1,174**	**$1,653**	**$472**	**$4,756**	**$8,054**

Detailed Annual Cost Estimates Per Participant				
Annual cost		Year dollars	Summary	
Program costs	$4,431	2012	Present value of net program costs (in 2015 dollars)	($4,579)
Comparison costs	$0	2012	Cost range (+ or -)	30 %

We estimated the per-participant costs of providing buprenorphine/buprenorphine-naloxone in addition to standard substance use treatment for 12 months. Costs reflect the average of costs reported in numerous cost-effectiveness studies (Polsky et al., 2010; Rosenheck and Kosten, 2001; Schackman et al., 2012). Costs included vary by study but generally include costs of medication, dispensing, toxicology screens, and when available, costs of medical care related to methadone treatment, equipment, administration, and clinic space. Polsky, D., Glick, H.A., Yang, J., Subramaniam, G.A., Poole, S.A., & Woody, G.E. (2010). Cost-effectiveness of extended buprenorphine-naloxone treatment for opioid-dependent youth: data from a randomized trial. *Addiction, 105*(9), 1616-1624. Rosenheck, R., & Kosten, T. (2001). Buprenorphine for opioid addiction: potential economic impact. *Drug and Alcohol Use disorder, 63*(3), 253-262. Schackman, B.R., Leff, J.A., Moore, B.A., Moore, B.A., & Fiellin, D.A. (2012). Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid use disorder in primary care. *Journal of General Internal Medicine, 27*(6), 669-676. Polsky, D., Glick, H.A., Yang, J., Subramaniam, G.A., Poole, S.A., & Woody, G.E. (2010). Cost-effectiveness of extended buprenorphine-naloxone treatment for opioid-dependent youth: data from a randomized trial. *Addiction, 105*(9), 1616-1624. Rosenheck, R., & Kosten, T. (2001). Buprenorphine for opioid addiction: potential economic impact. *Drug and Alcohol Use disorder, 63*(3), 253-262. Schackman, B.R., Leff, J.A., Moore, B.A., Moore, B.A., & Fiellin, D.A. (2012). Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid use disorder in primary care. *Journal of General Internal Medicine, 27*(6), 669-676.

II. Detailed Meta-Analysis Results

Exhibit A. II

Summary of Meta-Analytic Findings for Medication-Assisted Treatment for Alcohol and Opioid Use Disorders

Medication	Outcome	# of effect sizes	Average adjusted effect size	Standard error	p-value	# in treatment groups
Injectable naltrexone for alcohol	Alcohol use	5	-0.133	0.044	0.003	627
	Substance misuse (alcohol and/or drugs)	2	0.04	0.270	0.989	71
Injectable naltrexone for opioids	Crime	2	-0.218	0.208	0.293	169
	Death	1	0.000	0.211	1.000	153
	Opioid use	5	-0.566	0.152	0.000	329
	Problem alcohol use	1	-0.049	0.364	0.893	153
	Retention/engagement in treatment	1	0.299	0.106	0.005	126
	STD risky behavior	1	-0.047	0.211	0.825	153
Injectable naltrexone for opioid-using persons in prison	Crime	2	-0.218	0.208	0.294	169
	Death	1	0.000	0.211	1.000	153
	Opioid use	2	-0.594	0.248	0.017	169
	Problem alcohol use	1	-0.49	0.364	0.893	153
	STD risky behavior	1	-0.47	0.211	0.825	153
Injectable bromocriptine	Alcohol use	2	0.077	0.181	0.672	212
Naltrexone implants	Opioid use	4	-0.734	0.046	0.000	247
Buprenorphine implants	Opioid use	2	-0.538	0.156	0.001	222
	Retention/engagement in treatment	1	0.981	0.253	0.000	114
Methadone maintenance for opioids	Alcohol use	2	-0.281	0.250	0.261	223
	Crime	3	-0.672	0.112	0.001	259
	Death	3	-0.236	0.261	0.365	137
	Hospitalization	3	0.242	0.464	0.602	286
	Opioid use	8	-0.945	0.304	0.002	623
	STD risky behavior	3	-0.559	0.242	0.021	492
Buprenorphine/buprenorphine-naloxone for opioids	Emergency department visits	1	-0.026	0.263	0.920	46
	Opioid use	9	-0.941	0.181	0.001	793
	Psychiatric symptoms	1	-0.156	0.201	0.437	51

III. Studies Used in the Meta-Analyses

Injectable naltrexone for alcohol

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