



Management Options for Attention Deficit Hyperactivity Disorder

Public Meeting – June 1, 2012

New England CEPAC

- Goal: To improve the application of evidence to guide practice and policy in New England
- Method:
 - Core evidence: AHRQ review
 - ICER develops supplementary report with information on
 - New published literature
 - Policy landscape: coverage policies, clinical guidelines
 - Cost-effectiveness and budget impact



New England CEPAC

- CEPAC deliberation produces recommendations and votes on:
 - Comparative clinical effectiveness of alternative management options
 - Comparative value of these options
- CEPAC recommendations designed to support:
 - Patient/clinician education
 - Clinical guideline development
 - Medical policy (e.g., benefit design, coverage, payment)



Agenda

- Introductions (10-10:15)
- Evidence presentation, discussion (10:15-12:00)
 - Comparative clinical effectiveness (10:15-11:15)
 - Comparative value (11:15-12:00)
- Public Comment (12:00-12:30)
- Lunch (12:30-1:00)
- Votes and Recommendations (1:00-2:00)
- Roundtable on Implementation (2:00-3:20)
- Close (3:20-3:30)



EVIDENCE PRESENTATION



Outline

- Summary of AHRQ review
- New evidence following AHRQ review
- Clinical guidelines/coverage policies
- Comparative value analyses
 - Budgetary impact
 - Cost-effectiveness



AHRQ Review*

- Three key questions:
 1. Effectiveness and safety of treatment in pre-school children under age 6
 2. Long-term (>12 mo) effectiveness and safety of treatment in patients age 6 years and older
 3. Variation in rates of prevalence, diagnosis, and treatment
- Focus here on #1 and 2 only; *regional* variation data also presented



*Charach A et al. AHRQ Comparative Effectiveness Review #44.

ADHD Management Options

- Parent Behavior Training (PBT)
- Behavioral/Psychosocial Interventions (e.g., educational, counseling, skills training)
- School-based Interventions
- Medications
 - Stimulants (e.g., methylphenidate [MPH], mixed amphetamine salts [MAS])
 - Non-stimulants (e.g., atomoxetine [ATX], guanfacine [GXR])



Effectiveness: Age <6

- PBT vs. usual care
 - Strength of evidence: High
 - Clinically significant improvement in child symptoms and parental stress, irrespective of measures used
- Medication (MPH only) vs. placebo
 - Strength of evidence: Low
 - Single, large RCT (PATS)* showed good efficacy and safety of MPH
- PBT + school/daycare vs. usual care
 - Strength of evidence: Insufficient
 - Note made of findings that daycare intervention not shown to improve outcomes except for low socioeconomic status families related to lack of parental attendance at PBT sessions

*Greenhill L et al. J Am Acad Child Adolesc Psychiatry 2006.



Safety: Age <6

PBT

- No data on adverse outcomes

Medication

- Side effects common in this age group (~30%)
 - Emotional outbursts, difficulty sleeping, appetite decrease
 - 11% of young children discontinued MPH because of drug-attributed side effects
- Serious adverse events are rare
- Preschoolers with long-term stimulant use have growth rates 20% (~1.4cm per year) lower than non-medicated peers



Long-Term Effectiveness: Age 6+

- Medications vs. placebo
 - Strength of evidence: Low
 - Stimulants and ATX provide control of ADHD symptoms and are generally well tolerated over more than 12 months
 - Only one long-term study of GXR is available
 - One prospective head-to-head comparison of osmotically-released MPH to ATX demonstrated better acute (6 weeks) response with MPH (56% vs. 45% for ATX)*
- Medication+/- behavioral therapy vs. usual care
 - Strength of evidence: Low
 - Single, large RCT (MTA)† provides evidence for benefit of medication alone or combo therapy vs. behavioral therapy alone or usual care

*Newcorn. Am J Psychiatry 2008.

†MTA Cooperative Group. Pediatrics 2004.



Long-term Effectiveness: Age 6+

- Behavioral therapy alone vs. usual care
 - Insufficient
- PBT alone vs. usual care
 - Insufficient
- School-based interventions alone vs. usual care
 - Insufficient



Safety: Age 6+

Behavioral/Psychosocial/Academic Interventions

- No data on adverse events

Medication

- Discontinuation because of side effects for stimulants and ATX approximately 3% higher for GXR (somnolence, headaches)
- No consistent evidence of increased cardiovascular or cerebrovascular risk with long-term stimulant use
- Evidence of diminished growth rates in long-term studies:
 - In some, rates returned to baseline over time and/or when drug “holidays” initiated



NEW EVIDENCE FOLLOWING AHRQ REVIEW



New Evidence

- Search conducted 1/2010 – 3/2012
- New RCTs of PBT for children < 6 showed findings consistent with meta-analyses in AHRQ review
- No new medication RCTs
- 4 retrospective cohort studies showed no increased cardiovascular or cerebrovascular risks in patients receiving stimulants or ATX



CLINICAL GUIDELINES/ COVERAGE POLICIES



Guidelines (AACAP, AAP, NICE)

- Preschoolers:
 - Behavioral interventions generally considered first line of therapy
 - Medication should be dosed conservatively given effectiveness of lower doses and higher rates of side effects from stimulants
- School-age Children:
 - Stimulants generally recommended as first-line medication; non-stimulants appropriate in patients with comorbidity or risk of abuse
 - Behavioral therapy should be considered as adjunct to medication or for children intolerant of medication
 - School-based interventions recommended in conjunction with primary therapy



Coverage Policies

- PBT: Generally not covered as a manual-based program, but may be billed on an individual session basis
- Behavioral/Psychosocial Interventions: Covered, subject to plan limits on mental health services
- Academic Interventions: Not covered
- Medications :
 - Access generally not restricted for generic stimulants and branded stimulants without generic equivalents
 - Non-stimulants (available as branded agents only) subject to prior authorization and/or step therapy requirements



POPULATION CHARACTERISTICS & RESOURCE UTILIZATION IN NEW ENGLAND

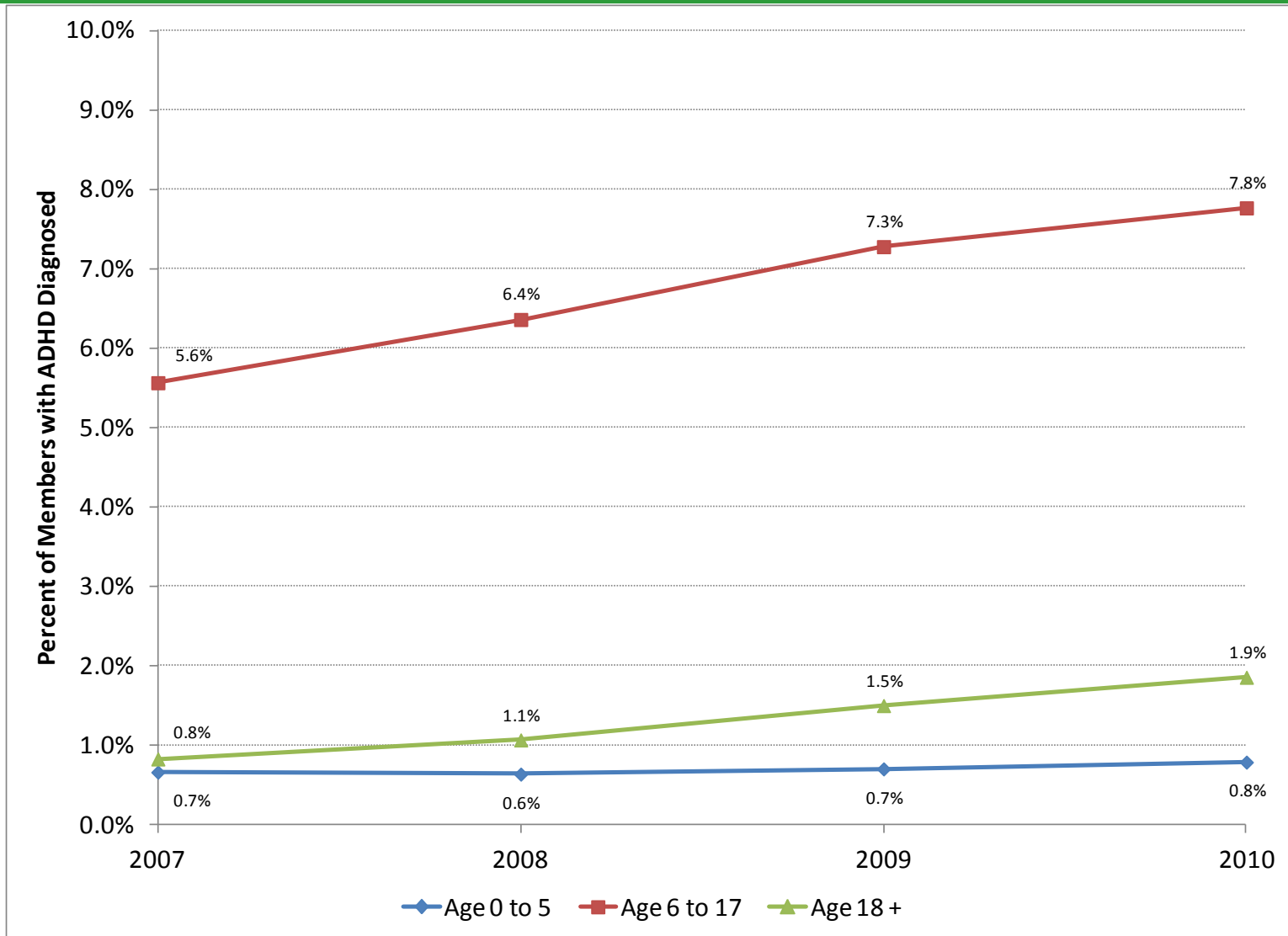


Methods

- Data provided by HealthCore:
 - Integrated Research Database includes claims data from Wellpoint and Anthem plans
- Analyses focused on children with an ADHD diagnosis in 3 New England states (CT, NH, ME)
- Population trends over 4-year span examined
- Treatment patterns following first diagnosis also assessed



Diagnosed Prevalence, 2007-2010



Treatment with Medication, 2007-2010

Measure/Age (per 1000 members)	2007	2008	2009	2010	% Change
Patients with ≥1 ADHD Rx					
0-5 yrs	2.0	1.9	1.8	2.0	---
6-17 yrs	38.8	39.3	40.6	41.4	+6.7
18+ yrs	5.6	6.8	8.9	10.6	+89.3
# Stimulant Rx					
0-5 yrs	8.2	8.2	7.6	6.8	-17.1
6-17 yrs	237.5	227.3	224.5	221.3	-6.8
18+ yrs	40.7	47.7	57.1	61.6	+51.4
# Non-stimulant Rx					
0-5 yrs	1.6	1.1	2.0	2.4	+50.0
6-17 yrs	39.2	36.4	35.4	40.1	+2.3
18+ yrs	3.2	3.5	3.5	3.7	+15.6

Drug Choice, 2010

Drug Type	Age 0-5 years	Age 6-17 years
	% Receiving	
MPH	40.9	50.2
MAS	16.7	21.9
DEX	0.0	0.4
ATX	4.5	6.1
GXR	6.1	2.2
Guanfacine IR*	10.6	3.0
Dexmethylphenidate†	21.2	16.2

*Off-label use for ADHD

†Focalin XR®, approved in 2008, not included in AHRQ review (no long-term data)



COMPARATIVE VALUE ANALYSES: PRESCHOOLERS



Methods

- Budgetary impact analyses of parent behavior training not undertaken
- Cost-effectiveness analyses focused on hypothetical cohorts of 1,000 Medicaid patients
- Pairwise comparisons of cost-effectiveness:
 - PBT vs. usual care (Bor, 2002)
 - Medication only vs. usual care (Ghuman, 2009)
 - PBT+medication vs. PBT only (Greenhill, 2006)



Methods

- Effectiveness measured as “treatment response”:
 - Based on standardized measures of clinically-significant change on multiple behavior rating scales
 - Number needed to treat (NNT): number of patients needed to treat to obtain 1 additional treatment response
- Payment estimates for interventions:
 - Medication: MPH 5 mg 3x daily, \$163 per year
 - PBT: \$844 for 10 sessions (Triple-P Program)



Key Assumptions

- Interventions NOT assumed to impact patterns of resource utilization or payments for usual care
 - Marginal costs only related to medication and/or PBT
- Noncompliance and therapy switching were not explicitly modeled:
 - No data to inform impact of these phenomena on outcomes
- Outcomes and payments modeled over 1 year



Key Model Outcomes: PBT vs. Usual Care

Measure (per 1,000 patients with ADHD)	Usual Care	PBT	Difference (PBT – Usual Care)
Treatment responses	230	620	390
NNT			3
Total costs	\$1,287,955	\$443,635	\$844,320
Cost per add'l treatment response			\$2,165



Key Model Outcomes: Medication vs. Usual Care

Measure (per 1,000 patients with ADHD)	Usual Care	MPH	Difference (MPH – Usual Care)
Treatment responses	71	500	429
NNT			2
Total costs	\$443,635	\$606,682	\$163,048
Cost per add'l treatment response			\$380



Key Model Outcomes: PBT+MPH vs. PBT Alone

Measure (per 1,000 patients with ADHD)	PBT	PBT+MPH	Difference (PBT +MPH – PBT)
Treatment responses	130	220	90
NNT			11
Total costs	\$1,287,955	\$1,451,002	\$163,048
Cost per add'l treatment response			\$1,812



COMPARATIVE VALUE ANALYSES: SCHOOL-AGE CHILDREN



Methods: Budgetary Impact

- Budgetary impact estimated for Medicaid across region and for each state
- Assumed prevalence of ADHD (literature-based*):
 - Boys: 16.3%
 - Girls: 6.6%
 - Corresponds to ~95,000 school-age children in NE
- Analyses focused on impact of increasing % of MPH used as first-line therapy

*Pastor. Vital Health Stat 2008.



Methods: Budgetary Impact

- Baseline estimates of first-line use and annual costs (literature-based*):
 - MPH 10 mg: 51%
 - MAS: 32%
 - ATX: 17%
- Analyses focused on 1-year impact of changing MPH % to 75% and 100% alternatively

*Christensen. CMRO 2010.



One-Year Budgetary Impact: Medicaid Population

Estimate	Baseline (51% MPH)	Scenario 1 (75% MPH)	Net Δ	Scenario 2 (100% MPH)	Net Δ
<u>Medication Use</u>					
MPH	48,955				
ATX	15,968				
MAS	30,310				
<u>Payments Per Child</u>					
ADHD Medication	\$955				
Medication Visits	\$173				
Total Payments	\$107,422,889	\$75,366,123	(\$32,056,766)	\$41,399,592	(\$66,023,297)
Payments PMPM	\$9.36	\$6.56	(\$2.79)	\$3.61	(\$5.75)

Methods: Cost-Effectiveness

- Used MTA study to evaluate meds only, behavioral therapy only, and combination therapy
 - All compared to “community care”
 - 2-year time horizon
- Some crossover assumed based on data from MTA
- Treatment:
 - MPH 10 mg 3x daily (\$262 per year)
 - 27 group and 8 individual behavioral therapy sessions (\$1,838)
 - Costs adjusted downward to reflect compliance in RCT



Key Model Outcomes: Meds/Behavioral Therapy/Combo Therapy vs. Community Care

Measure (per 1,000 patients with ADHD)	Behavioral Therapy	Medication	Combination Therapy	Community Care (referent)
Treatment responses	320	370	482	280
NNT	25	11	5	---
Cost per child with ADHD:				
ADHD medication				
Behavioral therapy				
Other resource utilization				
Total population cost				
Net population cost (vs. CC)	\$1,122,809	\$13,156	\$1,386,742	---
Net treatment response (vs. CC)	40	90	202	---
Cost per additional treatment response	\$28,070	\$146	\$6,865	---

QUESTIONS FOR DELIBERATION



ROUNDTABLE DISCUSSION



Closing

- Further public comments accepted until COB June 15, 2012
- Dissemination plans
- Next meeting: XXX
- Next topic: To be posted by XXX



BACKUP SLIDES



NNT in Context

Condition	Comparison	Time Horizon	Outcome	NNT
Localized Prostate Cancer	Radical prostatectomy vs. watchful waiting	10 yrs	PCa mortality - Low risk - High risk	42 13
Schizophrenia	Combined training vs. functional skills only	24 wks	Functioning (10-50% improvement)	3-18
Major Depressive Disorder	Vilazodone vs. placebo	8 wks	50% Δ MADRS Remission	8 14
Depression	AD+AP vs AD AD+AP vs AP	4-16 wks	Inefficacy /lack of improvement	7 5
Bipolar Disorder (pilot)	Olanzapine vs placebo	1 wk	Remission	4
ADHD (ICER estimates) – Preschool	Triple P vs Usual Care Medication vs Usual Care PBT w/Medication vs PBT alone	1 yr	Clinically significant improvement	3 2 11
ADHD (ICER estimates) – School-age	Behavioral intervention vs CC Medication vs CC Medication + Behavior vs CC	2 yrs	Clinically significant improvement	25 11 5

Cost/Response in Context

Condition/Circumstance	Comparison	Time Horizon	CEA Measure	ICER
Major depressive disorder	Antipsychotic medication w/antidepressant vs. antidepressant only	6 wks	Cost per additional response	\$3,447-8,725
Severe chronic obstructive pulmonary disease (COPD)	Roflumilast/tiotropium vs. tiotropium only	5 yrs/ Lifetime	Cost per exacerbation avoided Cost per <u>severe</u> exacerbation avoided	\$589/\$962 \$5,869/\$8,674
Obese diabetes mellitus	Surgical intervention vs. conventional therapy	2 yrs	Cost per case of diabetes remitted	AUS\$16,600 (\$12,284 USD)
Low-income students eligible for school free-lunch programs	Small class size vs. regular class size	Lifetime	Cost per additional graduate	\$196,266
ADHD (ICER estimates) – Preschool	Triple P vs Usual Care Medication vs Usual Care PBT w/Medication vs alone	1 yr	Cost per additional response	\$2,165 \$380 \$1,812
ADHD (ICER estimates) – School-age	Behavioral intervention vs CC Medication vs CC Medication + Behavior vs CC	2 yrs	Cost per additional response	\$28,070 \$146 \$6,865



Evidence Quality

- Key Question 1:
 - Greatest amount of RCT evidence with parent behavior training
 - Follow-up limited to 3-6 mo in most cases
 - Variation in interventions used and outcomes of interest
 - Wait-list used as control in most cases
 - Single large, good-quality RCT on effects of medication following PBT (PATS*):
 - Long-term follow-up data not available

*Greenhill L et al. J Am Acad Child Adolesc Psychiatry 2006.



Evidence Quality

- Key Question 2:
 - Long-term data on medication available primarily from uncontrolled extension studies
 - Single study provides good data for methylphenidate, behavioral intervention, and combination therapy (MTA Study*)
 - Studies of academic interventions vary on domains and outcomes assessed, measurement of maintenance vs. growth in skills, and other factors

*MTA Cooperative Group. Pediatrics 2004.



Results: Effectiveness (Age <6)

PBT

- 28 RCTs (8 good, 20 fair)
- Comparisons to wait-list, no treatment, and usual care
- Findings suggest statistically significant reductions in oppositional behavior, discipline problems and parental stress regardless of training program used
- Meta-analysis:
 - Standardized mean difference (SMD): -0.68 (95% CI: -0.88, -0.47, $p < .0001$)



Results: Effectiveness (Age <6)

Medication

- 8 RCTs (2 good, 6 fair)
- MPH alone vs. placebo (7 RCTs):
 - Outcomes favored MPH in 6; no difference in 1
- MAS alone vs. placebo (1 RCT):
 - Outcomes favored MAS



Results: Effectiveness (Age <6)

Medication+PBT

- 3 RCTs (1 good, 2 fair)
- Combination therapy vs. PBT alone (1 RCT):
 - Outcomes favored combination therapy
- Combination therapy vs. placebo (2 RCTs):
 - Outcomes favored combination therapy in 1, no differences in clinic ratings in 1 (only in parent-reported behavior)



Results: Harms (Age <6)

PBT

- No data on adverse events

Medication

- Adverse events commonly reported with MPH in this age group (~30%)
- Serious adverse events are rare
- Preschoolers with long-term stimulant use have growth rates 20-50% lower than non-medicated peers



Results: Effectiveness (Age 6+)

Medication: Stimulants

- 3 RCTs (all good)
- MPH vs. placebo (1 RCT)
 - Outcomes favored MPH at up to 5 yr, but many patients remained symptomatic
- MPH/DEX vs. placebo (1 RCT)
 - Outcomes favored MPH/DEX with maintenance dose (1 yr)
- Amphetamine vs. placebo (1 RCT)
 - Outcomes favored amphetamine at 15 mo
- Improvement in symptoms also maintained in 5 add'l open-label extension studies



Results: Effectiveness (Age 6+)

Medication: Non-stimulants

- 1 RCT (good)
- ATX vs. placebo:
 - Outcomes favored ATX at 18 mo (lower rate of symptom relapse)
- Improvement in symptoms also maintained in 3 add'l open-label extension studies of ATX/GXR



Results: Effectiveness (Age 6+)

Behavioral Therapy

- 1 RCT (fair)
- Behavioral therapy vs. wait-list control:
 - Outcomes favored behavioral therapy at 12 mo



Results: Effectiveness (Age 6+)

Combination Therapies

- 3 RCTs (all good)
- MPH vs. intensive behavioral treatment vs. combination vs. “community care” (MTA study):
 - Outcomes favored all active treatments vs. control at 2 yrs; benefits greatest for combination therapy
- MPH vs. MPH+multimodal treatment vs. MPH+attention control therapy (Abikoff et al.):
 - No differences between groups in level of improvement
- MPH vs. MPH+behavioral therapy (So et al.):
 - No overall differences at 18 mo; outcomes favored combination therapy among patients with ODD



Results: Effectiveness (Age 6+)

Academic Interventions

- 3 RCTs (1 good, 2 fair)
- MTA study (1 RCT):
 - Homework completion improved in all groups; greater improvement in reading on standardized tests for combination therapy vs. other groups
- Challenging Horizon Program vs. control (1 RCT):
 - No differences between groups
- Traditional vs. intensive data-based academic intervention (1 RCT):
 - No differences between groups
- 2 add'l RCTs showed benefits of stimulant medication on academic outcomes



Results: Harms (Age 6+)

Behavioral/Psychosocial/Academic Interventions

- No data on adverse events

Medication

- Some indication that cardiac ER visits and transient ischemic attacks higher in children on stimulants than gen'l population, but findings not consistent across studies
- Evidence of diminished growth rates in long-term studies:
 - In some, rates returned to baseline over time and/or when drug “holidays” initiated



Other Population-Based Findings

- MPH most common stimulant (~60% of stimulant Rx)
- ATX most common non-stimulant
- 40-50% of children on medications “managed” by pediatricians, 25-30% by psychiatrists



Additional Analyses

- Some evidence from retrospective studies that extended-release formulations may improve adherence/outcomes
- Assessment of level of effectiveness required with extended-release MPH (Concerta®) to generate similar cost/response to immediate-release MPH:
 - Difference in cost (\$4.80 vs. \$0.72 per day) so great, no equivalent cost/response identified
 - Cost/response at arbitrary effectiveness thresholds (vs. 37% for immediate-release MPH):
 - 50%: \$3,612
 - 75%: \$1,691
 - 90%: \$1,282

