The Burden of Attention-Deficit/Hyperactivity Disorder in Adults: A Real-World Linked Data Study

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ABSTRACT

Objective: To assess the humanistic and economic burden of attention-deficit/hyperactivity disorder (ADHD) among adult patients treated with immediate-release (IR) only or extended-release (ER) only stimulants and those unmedicated versus treated with ER + IR stimulants.

Methods: This study analyzed linked data from National Health and Wellness Survey and claims to assess the differences in patient characteristics and outcomes, including health-related quality of life (HRQoL), work productivity and activity impairment, and health care resource utilization (HRU) and associated costs by comparing ADHD patients treated with either IR or ER and those unmedicated for ADHD versus ER + IR.

Results: The burden of ADHD was compared among adults on stimulant medications with different duration of effect (DoE) (ER + IR: n = 34, ER: n = 184, IR: n = 149) and the unmedicated group (n = 114). Bivariate analysis showed the IR ($P = .047$) and unmedicated groups ($P = .01$) had significantly lower Medical Outcomes Study 36-item Short Form physical component summary scores versus ER + IR. The unmedicated group had higher HRU and associated costs versus other groups. Multivariable analysis revealed that the unmedicated group had twice as many outpatient visits ($P = .001$) and higher total annual direct costs than those on ER + IR (risk ratio = 2.20, $P = .016$). Patients with mental health comorbidities had significantly poorer HRQoL mental component summary scores and higher activity impairment versus those without mental health comorbidities ($P = .001$ and $P < .001$, respectively).

Conclusions: Patients with ADHD treated with longer DoE formulations had substantially better economic outcomes versus shorter DoE formulation or unmedicated groups, offering potential cost savings to the health care system and the patient. Furthermore, it is important to consider the effect of mental health comorbidities in the overall management of ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset neurobiological disorder characterized by inattention and/or hyperactivity and impulsivity with difficulties that frequently persist into adulthood.[1–4] According to a meta-analysis of 175 studies, the overall pooled prevalence of ADHD among children and adolescents was 7.2% globally.[5] In recent years, studies[6,7] have shown an increase in prevalence of ADHD among children and adolescents and adults in the United States.

ADHD imposes a substantial humanistic and economic burden on affected individuals and society, especially in adults, even after remission of some symptoms.[2,8,9] Children and adults with ADHD have lower physical, social, mental, and emotional functioning and thus show impaired health-related quality of life (HRQoL).[10–14] The annual costs attributed to adult ADHD in the United States have been estimated at $105 to $194 billion, with ADHD-related work productivity and income losses accounting for the largest share of the economic burden.[9]

Psychostimulants are the most effective and preferred treatment for moderate to severe ADHD,[15] while nonstimulant medications are used in case of lack of efficacy, side effect intolerance, medical contraindications, specific clinical issues (ie, anorexia or risk of substance abuse), or intolerance to stimulant formulations.[15,16] The duration of effect (DoE) for stimulants can have immediate-release (IR) or extended-release (ER) properties based on the formulation. ERs were developed to allow for less frequent dosing, improved tolerability, increased effectiveness, and better treatment adherence and compliance.[17–20] ER stimulants are considered the first-line treatment for adult ADHD.[21,22] ER formulations are well tolerated and more effective,[19,20,23–25] improve QoL,[23,26] and decrease health care resource utilization (HRU)[18] versus IR formulations or placebo in adults with ADHD. Previous studies[18,19] have demonstrated increased treatment adherence and compliance among adults on ER formulations versus IR formulations. ER formulations may be supplemented with another ADHD medication later in the day to extend the duration of coverage to control symptoms throughout the day and into the evening.[27] Studies[28–32] suggest that combining ER stimulants with other ADHD medications lead to greater improvements in clinical and/or cognitive outcomes versus monotherapies in children and adolescents with ADHD.

However, there is a lack of information on assessing the relationship between medication DoE and the burden of ADHD in adult patients. Previous studies used limited data from either only claims databases[33] or only patient surveys.[12] Linking of a data source that is rich in patient-reported outcomes with

Clinical Points

- Longer duration of effect formulations may provide better economic outcomes for adults with attention-deficit/hyperactivity disorder (ADHD).
- The effect of mental health comorbidities should be considered in the overall management of ADHD.

claims data has not been previously applied to the ADHD population. The primary objective of this study was to assess the impact of ADHD on HRQoL, work productivity and activity impairment (WPAI), and HRU and associated costs using linked data sources among adults treated with either IR or ER and those unmedicated for ADHD versus those medicated with ER + IR stimulants.

METHODS

Study Design and Data Source

This study analyzed linked data (between January 1, 2015, and December 31, 2018) from 2 distinct data sources, National Health and Wellness Survey (NHWS) and Komodo Health's medical and pharmacy claims, to assess the study questions in patients with ADHD.

US NHWS (2015–2018)

The NHWS is a self-administered internet-based online survey that includes annually collected data of ~75,000 respondents (≥ 18 years) representative of the general population in the United States.[34–36] Respondents are recruited through a web-based consumer panel that includes opt-in e-mails, co-registration with panel partners, e-newsletter campaigns, banner placements, and affiliate networks. The NHWS information contains data on demographics, behaviors, and outcomes for participating subjects. The NHWS is reviewed and granted exemption status by the Pearl Institutional Review Board.

Medical and Pharmacy Claims

Komodo Health, a health care technology company, provided information on deidentified claims (> 65 billion clinical, pharmacy, and laboratory encounters) for > 320 million patients in the United States between 2012 and 2020.

Medical Claims

The present study included payor-completed data (insurance eligibility and insurer-reported costs) and open medical claims data collected from claims clearing houses (includes patient location, admission/discharge dates of inpatient, diagnosis and procedure codes, and costs of health care visit).

Pharmacy Claims

Pharmacy Benefits Manager provided pharmacy claim data on the patient's enrollment start/end date, age, gender, fill date/number, pharmacy location and national provider identifier and specialty, national drug code number, diagnoses and/or procedures related to the prescription, authorized fills/prescription, units of measure, days' supply, drug costs (covered and copay), and concomitant medications for comorbidities.

Linkage of Databases

The datasets of respondents to NHWS were linked to their corresponding medical/pharmacy claims using Datavant's Health Insurance Portability and Accountability Act certified deidentified linking software. This software uses a proprietary probabilistic matching algorithm (reported to have a 0.2% false positive rate and a 2% false negative rate [Datavant, unpublished data, 2019]) on personally identifiable information (PII) from the NHWS and PII from the claims databases to find matches in the datasets.

Study Eligibility Criteria

Patients were included if they were aged ≥ 18 years with a self-reported physician diagnosis of ADHD in NHWS and linked to either medical or pharmacy claims data or had a billable/specific code or ADHD prescription in the claims databases.

Outcome Measures

All outcome measurements and their sources are provided in Supplementary Table 1.[37–40]

Statistical Analysis

Individual (or all) outcomes (Supplementary Table 1) were assessed by comparing demographics and clinical characteristics between patients in each treatment group based on DoE (IR stimulants, ER stimulants, and ER+IR). The Wilcoxon rank sum test and χ^2 tests were used for continuous variables and categorical variables, respectively. A statistical significance threshold of $\alpha = 0.05$ was used.

Additionally, to control for confounding and between-group differences, multivariable modeling was performed. Each outcome was modeled individually using generalized linear models as a function of treatment (ER, IR, unmedicated vs ER+IR) controlling for covariates. The regression models controlled for the presence of mental health comorbidities (with vs without), which are common in ADHD (ie, depression, anxiety, generalized anxiety disorder, bipolar disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, posttraumatic stress disorder, phobias, and schizophrenia).[41] Other covariates included sociodemographic and health characteristics (age, gender, ethnicity, marital status, education, income, insurance, US census region, Charlson comorbidity index, alcohol consumption, body mass index [BMI], exercise, headache, nicotine dependence, and substance abuse disorder).

RESULTS

Among the 8,432 patients who had a self-reported ADHD diagnosis, 538 patients were linked to claims for analysis. Using the linked cohort, the burden of ADHD was compared

Table 1. Demographics by Treatment Groups Among Patients With a Diagnosis of ADHD (linked sample; NHWS data)

Variable	ER + IR (n = 34)	IR (n = 149)	ER (n = 184)	Unmedicated (n = 114)	*P* Value: ER + IR vs IR	*P* Value: ER + IR vs ER	*P* Value: ER + IR vs Unmedicated
Age, mean ± SD, y	32.0 ± 0.5	35.9 ± 12.5	32.6 ± 11.2	36.6 ± 13.4	.061	.81	.101
Gender, n (%)							
Female	29 (85.3)	101 (67.8)	145 (78.8)	77 (67.5)			
Race/ethnicity, n (%)							
Non-Hispanic White	28 (82.4)	118 (79.2)	141 (76.6)	90 (78.9)	.793	.416	.471
Non-Hispanic non-White	6 (17.6)	31 (20.8)	43 (23.4)	24 (21.1)			
Marital status, n (%)							
Married/living with partner	13 (38.2)	66 (44.3)	68 (37.0)	49 (43.0)	.196	.167	.501
Not married	20 (58.8)	83 (55.7)	116 (63.0)	64 (56.1)			
Decline to answer	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.9)			
Education, n (%)							
Less than high school or equivalent	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.9)	.395	.882	.075
High school or equivalent	14 (41.2)	61 (40.9)	79 (42.9)	66 (57.9)			
More than high school (associate/ bachelor/graduate degree)	20 (58.9)	87 (58.3)	103 (56.1)	47 (41.3)			
Declined to answer	0 (0.0)	1 (0.7)	1 (0.5)	0 (0.0)			
Employment status, n (%)							
Employed full time	18 (52.9)	74 (49.7)	81 (44.0)	38 (33.3)	.129	.19	.011
Employed part time	8 (23.5)	18 (12.1)	30 (16.3)	15 (13.2)			
Unemployed	8 (23.5)	57 (38.3)	73 (39.7)	61 (53.5)			
Household income, n (%)							
< $25,000	5 (14.7)	39 (26.2)	46 (25.0)	39 (34.2)	.152	.26	.193
$25,000 to < $150,000	20 (58.8)	97 (65.2)	117 (63.6)	58 (50.9)			
≥ $150,000	3 (8.8)	6 (4.0)	9 (4.9)	6 (5.3)			
Declined to answer	6 (17.6)	7 (4.7)	12 (6.5)	11 (9.6)			
Insurance status, n (%)							
Commercial	27 (79.4)	84 (56.4)	120 (65.2)	51 (44.7)	.049	.343	.001
Public	6 (17.6)	49 (32.9)	53 (28.8)	53 (46.5)			
Uninsured	1 (2.9)	16 (10.7)	11 (6.0)	10 (8.8)			
Geographic region, n (%)							
Rural	2 (5.9)	21 (14.1)	24 (13.0)	17 (14.9)	.258	.386	.245
Urban	32 (94.1)	128 (85.9)	160 (87.0)	97 (85.1)			
US region, n (%)							
Northeast	8 (23.5)	25 (16.8)	33 (17.9)	22 (19.3)	.268	.419	.878
Midwest	12 (35.3)	39 (26.2)	54 (29.3)	36 (31.6)			
South	8 (23.5)	62 (41.6)	71 (38.6)	35 (30.7)			
West	6 (17.6)	23 (15.4)	26 (14.1)	21 (18.4)			
Alcohol use, n (%)							
Daily	3 (8.8)	6 (4.0)	7 (3.8)	6 (5.3)	.866	.308	.137
Weekly	12 (35.2)	65 (43.6)	49 (26.7)	21 (18.5)			
Monthly	14 (41.2)	51 (34.2)	70 (38.0)	47 (41.3)			
Do not drink alcohol	5 (14.7)	27 (18.1)	58 (31.5)	40 (35.1)			
Smoking status, n (%)							
Never smoker	11 (32.4)	56 (37.6)	88 (47.8)	62 (54.4)	.031	.239	.063
Current smoker	8 (23.5)	59 (39.6)	37 (20.1)	21 (18.4)			
Former smoker	15 (44.1)	34 (22.8)	59 (32.1)	31 (27.2)			
BMI, n (%)							
Underweight: < 18.5 kg/m^2	2 (5.9)	2 (1.3)	5 (2.7)	0 (0.0)	.077	.131	.005
Normal: 18.5–25 kg/m^2	15 (44.1)	54 (36.2)	73 (39.7)	31 (27.2)			
Overweight: > 25–30 kg/m^2	12 (35.3)	42 (28.2)	42 (22.8)	34 (29.8)			
Obese: ≥ 30 kg/m^2	5 (14.7)	50 (33.6)	57 (31.0)	47 (41.2)			
Declined to answer	0 (0.0)	1 (0.7)	7 (3.8)	2 (1.8)			

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BMI = body mass index, CCI = Charlson comorbidity index, ER = extended release, IR = immediate release, NHWS = National Health and Wellness Survey.

with those treated with a longer versus shorter DoE (ER + IR [n = 34], ER [n = 184], IR [n = 149]) and those who were unmedicated (n = 114).

In general, except for gender, employment status, health insurance, BMI, and current smoking status, the demographics between the patient groups were similar (Table 1). A higher proportion of patients treated with longer DoE formulations (ER + IR or ER) were female (85.3% and 78.8%, respectively) compared to patients treated with shorter DoE formulations (IR: 67.8%) or those who were unmedicated (67.5%) (Table 1). Compared with the ER + IR group, a lower proportion of those in the unmedicated group were employed full time (33.3% vs 52.9%, $P = .011$), and a lower proportion of individuals had commercial insurance in the IR (56.4% vs 79.4%, $P = .049$) and unmedicated groups (44.7% vs 79.4%, $P = .001$). Moreover, patients who received treatment with a stimulant (ER, IR, or ER + IR) had attained higher levels of education (associate/bachelor/graduate degree) than the unmedicated group (56.1%, 58.3%, 58.9% vs 41.3%).

Table 2. Health-Related Quality of Life and Work Productivity and Activity Impairment Outcomes by Treatment Groups Among Patients With a Diagnosis of ADHD (linked sample; NHWS data)[a]

Outcomes	ER+IR (n=34)	IR (n=149)	ER (n=184)	Unmedicated (n=114)	*P* Value: ER+IR vs IR	*P* Value: ER+IR vs ER	*P* Value: ER+IR vs Unmedicated
SF-36v2							
MCS score	35.4 ± 11.1	36.7 ± 13.1	36.4 ± 13.6	37.5 ± 12.3	.609	.715	.413
PCS score	52.3 ± 10.6	49.3 ± 9.67	52.2 ± 9.96	47.7 ± 10.4	.047	.725	.010
Bodily pain	46.8 ± 11.1	44.7 ± 10.5	47.4 ± 10.7	43.8 ± 11.4	.290	.799	.179
General health	47.1 ± 11.4	44.2 ± 11.5	47.4 ± 11.0	42.9 ± 10.1	.171	.936	.054
Mental health	40.2 ± 9.98	39.3 ± 11.7	39.2 ± 11.7	39.1 ± 11.8	.620	.543	.564
Physical functioning	50.8 ± 9.81	49.7 ± 8.88	51.0 ± 8.84	47.6 ± 10.8	.372	.862	.111
Role emotional	37.1 ± 11.9	39.6 ± 13.4	39.7 ± 13.8	40.0 ± 13.5	.308	.254	.249
Role physical	48.0 ± 11.6	45.3 ± 11.5	47.3 ± 11.1	45.1 ± 11.3	.211	.598	.141
Social functioning	39.4 ± 12.0	39.6 ± 12.4	40.4 ± 11.8	40.1 ± 11.5	.906	.699	.772
Vitality	42.6 ± 9.92	41.2 ± 10.2	42.7 ± 11.0	41.4 ± 10.4	.261	.825	.251
SF-6D health utilities	0.625 ± 0.107	0.630 ± 0.121	0.647 ± 0.123	0.623 ± 0.126	.967	.558	.857
Absenteeism	13.4 ± 23.2	13.3 ± 25.0	8.91 ± 20.9	10.7 ± 24.6	.483	.109	.204
Presenteeism	30.4 ± 26.5	30.7 ± 26.5	26.5 ± 26.4	26.7 ± 26.3	.994	.466	.503
Overall work productivity loss	33.6 ± 28.9	34.5 ± 30.1	29.6 ± 28.3	30.1 ± 29.9	.994	.480	.562
Activity impairment	35.6 ± 30.5	39.6 ± 30.7	33.4 ± 30.0	37.8 ± 30.3	.508	.663	.710

[a]Data are presented as mean ± SD.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ER = extended release, IR = immediate release, MCS = mental component score, NHWS = National Health and Wellness Survey, PCS = physical component score, SF-36v2 = Medical Outcomes Study 36-item Short Form.

Table 3. Health Care Resource Utilization by Treatment Groups Among Patients With a Diagnosis of ADHD (linked sample; claims data)

Variable	ER+IR (n=34)	IR (n=149)	ER (n=184)	Unmedicated (n=114)	*P* Value: ER+IR vs IR	*P* Value: ER+IR vs ER	*P* Value: ER+IR vs Unmedicated
Inpatient visits (annual), mean ± SD	0.111 ± 0.339	0.266 ± 0.883	0.272 ± 1.24	0.629 ± 2.69	.303	.617	.059
Missing, n (%)	0 (0)	0 (0)	2 (1.1)	0 (0)			
Outpatient visits (annual), mean ± SD	2.30 ± 1.89	3.43 ± 3.19	3.69 ± 6.43	4.59 ± 3.86	.109	.150	.001
Missing, n (%)	0 (0)	0 (0)	2 (1.1)	0 (0)			
ED visits (annual), mean ± SD	0.380 ± 0.621	0.425 ± 0.823	0.300 ± 0.492	0.862 ± 2.16	.821	.617	.241
Missing, n (%)	0 (0)	0 (0)	2 (1.1)	0 (0)			
Total annual direct cost (US$), mean ± SD	5,460 ± 9,120	9,190 ± 16,500)	8,970 ± 20,600	18,200 ± 51,100	.102	.204	.001
Missing, n (%)	0 (0)	0 (0)	2 (1.1)	0 (0)			

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ED = emergency department, ER = extended release, IR = immediate release.

HRQoL Outcomes (SF-36v2 in NHWS Data)

In general, the entire study population scored below the standardized norm score for the US population for most of the domains in the Medical Outcomes Study 36-item Short Form (SF-36v2), and higher scores were observed among patients in the longer DoE group compared with those in the shorter DoE or unmedicated group. There were no significant differences on mental component summary (MCS) scores among all groups; however, the mean MCS scores were below the standardized US population norm of 50 in all groups (35.4–37.5), indicating poorer mental health. Compared with the ER + IR group, significantly lower physical component summary (PCS) scores were observed in the IR group (mean: 49.3 vs 52.3, $P = .047$), indicating a poorer physical QoL; differences in the PCS scores also met the minimal important difference of 3 points. The unmedicated group also had significantly lower PCS scores than the ER + IR group (mean: 47.7 vs 52.3, $P = .01$) (Table 2). Additionally, in the ER + IR group, PCS scores were observed to be higher than the standardized US population norm.

WPAI

There were no significant differences across all groups on all WPAI metrics (Table 2). However, across the groups, the overall work productivity loss was ~30% of the time (ER + IR group: 33.6, IR: 34.5, ER: 29.6, unmedicated: 30.1), and general activity impairment was reported by > 30% of all subjects included in the study. In contrast, among the NHWS-only respondents who did not have a diagnosis of ADHD, overall work impairment was lower (~20%). In patients with ADHD, all WPAI metrics were higher across the groups, demonstrating greater impairment when compared with the non-ADHD population (Supplementary Table 2).

HRU and Direct Costs

The unmedicated group experienced numerically higher annual inpatient visits versus those treated with stimulants (unmedicated: 0.629, ER+IR: 0.111, ER: 0.272, IR: 0.266). The ER + IR group had the lowest number of inpatient visits versus other groups (Table 3). The unmedicated group had significantly higher annual outpatient visits versus the ER + IR group (4.59 vs 2.30, $P = .001$). Moreover, the ER + IR

Table 4. Multivariable Results

Variable	Level	RR	SE	*P* Value
Mental component summary score (continuous)				
Presence of mental health comorbidities	No*			
	Yes	−4.78	1.39	.001
Physical component summary score (continuous)				
Mental health	No*			
	Yes	−1.24	0.92	.179
Health utilities index (continuous)				
Mental health	No*			
	Yes	−0.04	0.01	.003
Absenteeism (% impairment, continuous)				
Mental health	No*			
	Yes	1.04	0.33	.893
Presenteeism (% impairment, continuous)				
Mental health	No*			
	Yes	1.10	0.17	.534
Overall work productivity impairment (%)				
Mental health	No*			
	Yes	1.04	0.16	.824
Activity impairment (%)				
Mental health	No*			
	Yes	1.48	0.15	< .001
Inpatient visits (continuous)				
Mental health	No*			
	Yes	3.16	1.42	.011
Outpatient visits (continuous)				
Treatment	ER+IR*			
	IR	1.59	0.35	.034
	ER	1.55	0.33	.040
	Unmedicated	2.06	0.46	.001
Mental health	No*			
	Yes	1.70	0.20	< .001
Emergency department visits (continuous)				
Mental health	No*			
	Yes	2.36	0.49	< .001
Annual direct costs (continuous)				
Treatment	ER + IR*			
	IR	1.40	0.45	.295
	ER	1.45	0.45	.229
	Unmedicated	2.20	0.71	.016
Mental health	No*			
	Yes	2.15	0.38	< .001

*Reference groups: treatment: ER + IR; presence of mental health comorbidities: no mental health comorbidities. Presence of mental health comorbidities include any of the following: depression, anxiety, generalized anxiety disorder, bipolar disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, posttraumatic stress disorder, phobias, or schizophrenia.

Abbreviations: ER = extended release, IR = immediate release, RR = risk ratio, SE = standard error, SF-36v2 = Medical Outcomes Study 36-item Short Form.

group (2.3) had numerically lower annual outpatient visits versus the IR (3.43) and ER (3.69) groups. Compared with the ER + IR group, the total annual direct costs were significantly higher in the unmedicated group (US $5,460 vs $18,200, $P = .001$, Table 3). Of note, the ER + IR group had the lowest total annual direct costs (US $5,460), followed by the ER ($8,970), IR ($9,190), and unmedicated ($18,200) groups. In general, all HRU and associated costs were higher among unmedicated versus the treated groups; inpatient (0.629 vs 0.111, $P = .06$), outpatient (4.59 vs 2.30, $P = .001$), emergency department visits (0.862 vs 0.380, $P = .241$), and total annual direct cost ($18,200 vs $5460, $P = .001$) were higher among the unmedicated versus ER + IR groups.

Multivariable Analysis: HRQoL and WPAI

No significant differences were observed by ADHD treatment on the SF-36v2. However, significant differences were observed for presence of mental health comorbidity. Specifically, those with mental health comorbidities scored 5 points lower on the MCS versus those without ($P = .001$), indicating poorer QoL (Table 4). Additionally, other health domains, including general health, mental health, physical functioning, role emotional, role physical, social functioning, and vitality were also significantly lower among those with mental health comorbidities than those without (all $P < .05$) (data not shown in the table). Further, those with mental health comorbidities had about 50% higher activity impairment ($P < .001$) than those without (Table 4).

HRU and Cost

Patients with mental health comorbidities had 3.16 times more inpatient visits than those without ($P = .011$) (Table 4). Although nonsignificant, the size of the rate ratios for inpatient visits was highest among the unmedicated (risk ratio

[RR] = 2.14), followed by ER (RR = 1.41) and IR (RR = 1.14) versus ER + IR. A significant difference was observed among treatment regimen for outpatient visits. Patients unmedicated for ADHD had twice as many outpatient visits than those on ER + IR ($P = .001$). Furthermore, compared with those on ER + IR, those on IR ($P = .034$) and ER ($P = .040$) had 59% and 55% higher outpatient visits, respectively. Those with mental health comorbidities had 70% higher outpatient visits and more than twice the number of emergency department visits compared to those without mental health comorbidities ($P < .001$ for both, Table 4). Those patients who were unmedicated had higher total annual direct costs than those who were on ER + IR (RR = 2.20, $P = .016$). Total annual direct costs were observed to be 2.15 times higher in those with mental health comorbidities compared to those without. Although statistically nonsignificant, ER and IR had 40%–45% higher costs versus the ER + IR group (Table 4). Thus, presence of mental health comorbidities increases most HRU (inpatient, outpatient, and emergency department) and associated costs.

DISCUSSION

This study compared the demographics, health characteristics, and humanistic and economic burden of patients with ADHD who were unmedicated and those who were treated with IR, ER, and ER + IR stimulants. This study allowed for simultaneous examination of NHWS self-reported data and medical/pharmacy claims data for the same individuals.

A retrospective analysis of claims database data demonstrated that early intervention of methylphenidate-ER was associated with lower emergency department visits versus methylphenidate-IR.[18] In our study, we also observed trends of less HRU for patients with ADHD treated with longer DoE (ER or ER + IR). Specifically, those on ER + IR had fewer outpatient visits than those on IR or who were unmedicated, possibly indicating better symptom management with stable treatment with longer DoE.

Studies[12,42] have reported greater work difficulties in adults with ADHD versus those without ADHD. While we found no significant differences across treatment groups in any of the WPAI metrics by ADHD treatment, individuals with ADHD were experiencing work productivity loss at least 30% of the time. In contrast, among NHWS respondents (unlinked) who did not have a diagnosis of ADHD, reported work productivity loss was 20%, thus supporting the existing literature (Supplementary Table 2). To assess potential improvement in work productivity, the Permanent Product Measure of Performance (PERMP) total scores (which assess sustained attention and ability to initiate and stay on task and do effortful work throughout the simulated adult workplace environment [AWE] session) have been used as a proxy for work productivity. Several simulated AWE studies as well as adult laboratory classroom studies using the PERMP have demonstrated efficacy up to 16 hours with different long-acting stimulant medications versus placebo.[43–47] Although these measures cannot be directly correlated with WPAI scales, better work productivity indicated by better PERMP scores after treatment with ER medications may be considered.

In the current study, we found no significant differences in HRQoL between groups except for the PCS domain of the SF-36v2 (IR or unmedicated vs ER + IR), yet high scores close to the standardized norm score of the US population in the majority of SF-36v2 parameters was indicative of overall better QoL in patients treated with longer DoE formulations. Previous research examining the burden of illness and impact on HRQoL in older adults with ADHD reported that HRQoL suffered from the cumulative negative impact of ADHD that impairs many aspects of daily life and overall well-being.[48]

In a previous study by Goodman et al,[49] adherence to ADHD medications was increased with once-daily dosing of long-acting stimulant formulations, such as mixed amphetamine salts-ER and modified-release methylphenidate. The study[49] also reported significant improvements in ADHD symptoms and QoL with the use of mixed amphetamine salts-ER following 10 weeks of treatment.[49] Regardless of treatment regimen, we did not observe significant differences in all domains of HRQoL measures most likely due to the study design. Specifically, HRQoL was only measured as one point in time, thus we do not know baseline measures of these patients, which may differ by disease duration and severity. It may be that patients who were on longer DoEs have more severe symptoms, higher Charlson comorbidity index scores, and a lower HRQoL at baseline than those who were on shorter DoEs.

Multivariable analyses indicated that those with mental health comorbidities had significantly lower scores on the SF-36v2 MCS and other health domains than those without such comorbidities. Furthermore, mental health comorbidities were associated with higher HRU and costs. Likewise, previously published studies have also indicated that ADHD patients with physical or mental health comorbidities had significantly higher outpatient and inpatient costs, drug costs, and total medical costs versus non-ADHD cohorts[50] or ADHD patients with no additional health concerns.[51–53] A retrospective study[50] of a large claims database reported that ADHD adults with comorbidities had 2.5 times higher inpatient costs and 2 times higher outpatient and total medical costs versus non-ADHD patients. Hence, it is important to consider management of adult mental health comorbidities in the overall management of ADHD. In this regard, focus should be on providing consistent care over the lifespan of the patient to prevent comorbidities with progressing age. Although neurodevelopmental comorbidities and associated impairments have been commonly observed in routine clinical practice, only a few studies[12,53] have evaluated the impact of ADHD in adults. Furthermore, identifying concurrent comorbidities would help create a diagnostic prioritization for treatment and the development of a pharmacologic/psychotherapeutic algorithm.

Strengths and Limitations

Linking a data source that is rich in patient-reported outcomes with claims data was not previously applied to the ADHD population. Our study has several strengths; linkage of NHWS and claims complement each other and resulted in a more robust dataset. NHWS (representative of the US general population) provides real-world data on patient characteristics, patient-reported outcomes, HRU, and treatment, which may not be captured through controlled clinical trials or pharmacy claims. The linkage allowed more comprehensive understanding of the burden, treatment, and health care costs all within one study for patients with ADHD.

Our study also has some limitations. Self-reported data may introduce bias, inconsistencies, or inaccuracies.[54,55] Moreover, NHWS may not be truly representative of the ADHD population at large. Survey data may have selection bias due to disorder-related treatment. For example, treated patients might have better symptom control and thus completed the survey, whereas diagnosed but unmedicated patients or patients with severe levels of attention deficit might not be able to complete the survey. Additionally, the patient-reported outcomes from NHWS were only collected at one point in time. Thus, comparing HRQoL or WPAI by treatment groups may be challenging, as patients on these treatments could have different baseline levels for these metrics. Although, we have not considered the likely effect of executive dysfunction on the daily functioning of adults with ADHD, its presence cannot be ruled out as one of the contributing factors, and further research on this aspect is warranted. Importantly, pharmacy claims data reflect only fill patterns and assume that patients take the medication as prescribed; however, that may not always be the case.[56]

CONCLUSION

Based on this linked study, the DoE was found to be a significant predictor of HRU. In the overall management of ADHD, it is important to consider negative impact on HRQoL activity impairment and a higher HRU in patients with mental health comorbidities. Further, patients with ADHD treated with longer DoE formulations had substantially better economic outcomes versus shorter DoE formulation or unmedicated groups, offering potential cost savings to the patient and the health care system. Thus, as reflected by economic indicators (HRU and costs), treatment compared to no treatment is beneficial. Furthermore, comorbidities, especially mental health, present a challenge when treating these patients.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

Article Title: The Burden of Attention-Deficit/Hyperactivity Disorder in Adults: A Real-World Linked Data Study

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List of Supplementary Material for the article

1. Supplementary Table 1
2. Supplementary Table 2

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Outcome measures

Outcomes	Description	Data Source
Medication use	• Information on medication use for ADHD (IR, ER, combination [ER+IR] and unmedicated ADHD) and concomitant medications for associated comorbidities	Pharmacy claims database
Demographics/Socioeconomic/Health characteristics	• Assessed factors like age, gender, race/ethnicity, marital status, education, household income, employment status, insurance status, region, CCI[37], BMI[38], smoking and alcohol consumption, and exercise behavior	NHWS
Health and economic outcomes		
HRQoL	• Assessed using SF-36v2[39] • Comprised of 36 questions mapped onto eight health domains* and two component summary scores** • A norm-based scoring algorithm was used to calculate each domain and summary score so that all measures were interpreted relative to the US general population value†	NHWS

WPAI	• Assessed using WPAI questionnaire[40] – a six-item validated instrument used to measure work productivity and activity impairment • Consists of four metrics: absenteeism‡, presenteeism§, overall work productivity loss¶, and activity impairment#	NHWS (Data on absenteeism, presenteeism, and overall work impairment included only NHWS respondents who reported being full-time or part-time; activity impairment included all NHWS respondents)
HRU	• Assessed number of traditional healthcare provider visits and specialist visits (i.e., psychologists, psychiatrists, neurologists), the number of visits for behavior therapy, the number of emergency room visits, and the number of	Claims database

	times hospitalized per year of follow-up • Direct economic costs were estimated using medical claims data (based on diagnosis codes and procedure codes) and MEPS) data.	

*Physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health.

**Mental component summary scores (MCS) and physical component summary scores (PCS).

†The mean of 50 was considered as the population mean for the US population where the deviation from this mean was tested with one-sample t-test, when relevant comparator groups were unavailable.

‡Percentage of work time missed because of one's health in the past seven days

§Percentage of impairment experienced while at work in the past seven days because of one's health

¶An overall impairment estimate that is a combination of absenteeism and presenteeism

#Percentage of impairment in daily activities outside of work because of one's health in the past seven days

ADHD, attention deficit hyperactivity disorder; BMI, body mass index, CCI, Charlson Comorbidity Index, ER, extended release; IR, immediate release; HRQoL, health-related quality of life; HRU, health resource utilization; MEPS, medical expenditure panel survey; NHWS, National Health and Wellness Survey; SF-36v2, medical outcomes study 36-item short form; WPAI, work productivity and activity impairment.

Supplementary Table 2. Work productivity and activity impairment outcomes in respondents not reporting diagnosis of ADHD vs. respondents self-reporting diagnosis of ADHD – NHWS Sample

Variables	Overall	
	Respondents not reporting diagnosis of ADHD (n=273,936)	**Respondents self-reporting diagnosis of ADHD (n=8432)**
Absenteeism, Mean (SD)	5.87 (±16.7)	10.7 (±22.2)
Presenteeism, mean (SD)	18.0 (±26.1)	28.4 (±27.7)
Overall work Productivity loss, mean (SD)	19.9 (±28.3)	31.6 (±30.3)
Activity impairment, mean (SD)	23.3 (±28.2)	36.5 (±30.2)

ADHD, attention deficit hyperactivity disorder; NHWS, National Health and Wellness Survey; SD, standard deviation.