

Appendix 1: MRCI-A route of administration weighting

	Administration Route	Weight
Oral	Capsules/Tablets	1
	Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders	2
	Sublingual	2
Topical	Creams	2
	Dressings	3
	Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
Ear, Eye, Nose	Ear Drops	3
	Eye Drops	3
	Eye Gels	3
	Nasal Drops	3
	Nasal Sprays	2
Inhalation	Accuhalers	3
	Aerolizers	3
	Metered Dose Inhalers	4
	Nebulizer	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other DPIs	3
Others	Dialysate	5
	Enemas	2

Injections Prefilled	3
Injections Vials	4
Pessaries	3
Patient Controlled Analgesia	2
Suppositories	2
Vaginal Creams	2

Adapted from: *George, J., et al., Development and validation of the medication regimen complexity index. Ann Pharmacother, 2004. 38(9): p. 1369-76.* In cases of uncertain route, the more conservative score was chosen

Appendix 2: Initial endocrine therapy initiation models, with individual components of prior medication regimen factors

Baseline Variables		Mania and Psychoses	MRCI-A Route Complexity	Number Medications Used	Number Pharmacy Visits	Combined Medication & Visit Score	Dementia	Out-Of-Pocket Medication Costs
Parameter		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Bipolar and Psychotic Disorder		-	*0.91 (0.85-0.97)	*0.91 (0.85-0.97)	*0.90 (0.84-0.96)	*0.90 (0.84-0.96)	*0.91 (0.85-0.98)	*0.91 (0.85-0.98)
Adjusted NCI Comorbidity Score (6-month time varying)		1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (0.99-1.01)	0.99 (0.99-1.00)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.01)
Function-related Indicators	1	1.00 (0.96-1.03)	1.00 (0.97-1.04)	1.00 (0.97-1.04)	0.99 (0.96-1.03)	0.99 (0.96-1.03)	0.99 (0.96-1.03)	0.99 (0.96-1.03)
	(ref=0)							
	2	**0.90 (0.85-0.95)	*0.91 (0.86-0.97)	**0.91 (0.86-0.96)	**0.90 (0.85-0.95)	**0.90 (0.85-0.95)	**0.91 (0.86-0.96)	**0.91 (0.86-0.96)
	3+	0.95 (0.89-1.01)	0.96 (0.91-1.02)	0.96 (0.90-1.02)	0.95 (0.89-1.01)	0.95 (0.90-1.01)	0.95 (0.90-1.01)	0.96 (0.91-1.03)
Stage at Diagnosis	2	**1.14 (1.10-1.17)	**1.14 (1.10-1.17)	**1.14 (1.10-1.17)	**1.14 (1.10-1.18)	**1.14 (1.10-1.18)	**1.14 (1.11-1.18)	**1.14 (1.10-1.18)
	(ref=1)							
	3	1.04 (0.98-1.10)	1.04 (0.98-1.10)	1.04 (0.98-1.10)	1.04 (0.98-1.10)	1.04 (0.99-1.10)	1.05 (0.99-1.11)	1.04 (0.99-1.10)
	4	**1.50 (1.30-1.74)	**1.50 (1.30-1.74)	**1.51 (1.30-1.74)	**1.52 (1.31-1.76)	**1.54 (1.33-1.79)	**1.57 (1.35-1.82)	**1.57 (1.36-1.82)
	Unknown	*0.86 (0.77-0.96)	*0.86 (0.77-0.96)	*0.86 (0.77-0.96)	*0.86 (0.77-0.97)	*0.87 (0.77-0.97)	*0.87 (0.78-0.98)	*0.87 (0.77-0.97)
Race	Asian	*1.10 (1.03-1.18)	*1.10 (1.02-1.18)	*1.10 (1.02-1.18)	*1.11 (1.03-1.19)	*1.11 (1.04-1.20)	*1.12 (1.04-1.20)	*1.11 (1.03-1.19)
	(ref=White)							
	Black	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.91-1.03)	0.95 (0.89-1.01)
	Other	0.98 (0.82-1.18)	0.98 (0.82-1.18)	0.98 (0.82-1.18)	0.98 (0.82-1.18)	0.99 (0.83-1.19)	0.98 (0.82-1.18)	0.98 (0.82-1.17)
Ethnicity	Hispanic	1.01 (0.94-1.08)	1.01 (0.94-1.07)	1.00 (0.94-1.07)	1.01 (0.94-1.07)	1.01 (0.95-1.08)	1.01 (0.94-1.08)	1.00 (0.93-1.06)
	(ref=Non-Hispanic)							
Age at Diagnosis	75-84	**0.92 (0.89-0.95)	**0.92 (0.89-0.95)	**0.92 (0.89-0.95)	**0.92 (0.89-0.95)	**0.91 (0.89-0.94)	**0.92 (0.89-0.94)	**0.92 (0.89-0.95)
	(ref=68-74)							
	85-94	**0.65 (0.61-0.68)	**0.64 (0.61-0.68)	**0.64 (0.61-0.68)	**0.64 (0.61-0.68)	**0.64 (0.61-0.68)	**0.64 (0.61-0.68)	**0.65 (0.61-0.68)
	95+	**0.45 (0.34-0.60)	**0.45 (0.34-0.60)	**0.45 (0.34-0.60)	**0.45 (0.34-0.60)	**0.45 (0.34-0.60)	**0.45 (0.34-0.60)	**0.45 (0.34-0.60)
Home Rurality	Metro	**0.82 (0.75-0.91)	**0.83 (0.75-0.91)	**0.82 (0.75-0.91)	**0.83 (0.75-0.91)	**0.83 (0.75-0.92)	*0.83 (0.75-0.92)	**0.83 (0.75-0.92)
	(ref=Rural)							
	Non-metro	*0.85 (0.76-0.94)	*0.85 (0.76-0.94)	*0.85 (0.76-0.94)	*0.84 (0.76-0.94)	*0.85 (0.77-0.94)	*0.85 (0.77-0.92)	*0.85 (0.77-0.95)
	Unknown	1.54 (0.38-6.18)	1.54 (0.38-6.18)	1.52 (0.38-6.11)	1.56 (0.39-6.26)	1.65 (0.41-6.65)	1.53 (0.38-6.16)	1.54 (0.38-6.21)
Year of Diagnosis	2008	0.98 (0.92-1.05)	0.98 (0.92-1.05)	0.98 (0.92-1.05)	0.98 (0.92-1.05)	0.98 (0.92-1.05)	0.98 (0.92-1.04)	0.98 (0.92-1.04)
	(ref=2007)							
	2009	1.01 (0.95-1.07)	1.01 (0.95-1.08)	1.01 (0.95-1.08)	1.01 (0.95-1.08)	1.01 (0.95-1.07)	1.01 (0.94-1.07)	1.01 (0.94-1.07)
	2010	*1.11 (1.04-1.18)	*1.11 (1.04-1.18)	*1.11 (1.04-1.18)	*1.11 (1.04-1.18)	*1.11 (1.04-1.18)	*1.10 (1.04-1.18)	*1.10 (1.04-1.18)

Baseline Variables		Mania and Psychoses	MRCI-A Route Complexity	Number Medications Used	Number Pharmacy Visits	Combined Medication & Visit Score	Dementia	Out-Of-Pocket Medication Costs
Parameter		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	2011	**1.17 (1.09-1.24)	**1.16 (1.09-1.24)	**1.16 (1.09-1.24)	**1.16 (1.09-1.24)	**1.16 (1.09-1.23)	**1.16 (1.09-1.24)	**1.16 (1.09-1.23)
	2012	**1.15 (1.08-1.23)	**1.15 (1.08-1.23)	**1.15 (1.08-1.23)	**1.15 (1.08-1.23)	**1.15 (1.08-1.22)	**1.15 (1.08-1.23)	**1.15 (1.08-1.22)
	2013	**1.19 (1.12-1.27)	**1.19 (1.12-1.27)	**1.19 (1.12-1.27)	**1.19 (1.12-1.27)	**1.19 (1.12-1.26)	**1.19 (1.12-1.27)	**1.18 (1.11-1.26)
MRCI-A Route Complexity (ref=0-1)	2-4		1.00 (0.97-1.04)			*0.96 (0.93-0.99)	*0.96 (0.93-0.99)	*0.96 (0.93-0.99)
	5+		1.04 (0.99-1.09)			0.99 (0.94-1.04)	0.99 (0.94-1.04)	1.00 (0.95-1.05)
Number of Medications Used (ref=0-3)	4-8			**1.10 (1.06-1.14)				
	9+			**1.14 (1.09-1.19)				
Number of Pharmacy Visits (ref=0-1)	2-4				**1.17 (1.11-1.23)			
	5-10				**1.22 (1.16-1.28)			
	11+				**1.22 (1.14-1.29)			
Combined Medication & Visit Score (ref=No Meds)	1-3 Meds					**1.31 (1.19-1.43)	**1.31 (1.19-1.43)	**1.34 (1.19-1.50)
	4+ Meds or 2+ Visits					**1.32 (1.22-1.42)	**1.32 (1.22-1.42)	**1.36 (1.23-1.51)
	4+ Meds & 2+ Visits					**1.41 (1.31-1.51)	**1.41 (1.31-1.51)	**1.47 (1.33-1.63)
Dementia Disorder						*0.90 (0.83-0.97)	*0.89 (0.82-0.97)	
Out-of-Pocket Medication Costs (ref=\$0 < \$1)	\$1 < \$50							0.98 (0.91-1.06)
	\$50 < \$500							0.96 (0.89-1.03)
	\$500+							**0.86 (0.79-0.94)

P value ** p<0.001, * p<0.05.

Parameter	Initiation		^a Discontinuation		^b Adherence		
	Bipolar and Psychotic Disorder n=1,259	No Diagnosis n=20,635	Bipolar and Psychotic Disorder n=951	No Diagnosis n=16,561	Bipolar and Psychotic Disorder n=951	No Diagnosis n=16,561	
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Estimate (95% CI)	Estimate (95% CI)	
					(0.012, 0.054)	(-0.010, 0.001)	
(ref= 68-74)	85-94	**0.64 (0.50-0.81)	**0.65 (0.61-0.68)	*1.61 (1.04-2.50)	**1.57 (1.42-1.74)	0.012 (-0.027, 0.052)	*0.013 (0.004, 0.021)
	95+	*0.19 (0.06-0.60)	**0.49 (0.36-0.65)	5.09 (0.63-40.94)	**2.58 (1.52-4.39)	-0.022 (-0.081, 0.036)	-0.025 (-0.092, 0.041)
Home Rurality	Metro	0.96 (0.58-1.59)	*0.83 (0.75-0.92)	5.42 (0.75-39.05)	1.17 (0.95-1.44)	-0.007 (-0.065, 0.052)	**0.033 (-0.047, -0.018)
(ref= Rural)	Non-metro	0.97 (0.57-1.66)	**0.85 (0.76-0.95)	4.57 (0.61-34.05)	1.11 (0.89-1.38)	0.007 (-0.056, 0.070)	*0.021 (-0.037, -0.006)
	Unknown	-	1.54 (0.38-6.18)	-	3.15 (0.44-22.72)	-	-0.042 (-0.144, 0.060)
Year of Diagnosis	2008	0.97 (0.73-1.30)	0.98 (0.91-1.04)	*0.61 (0.39-0.96)	0.97 (0.88-1.08)	0.047 (-0.003, 0.097)	0.000 (-0.011, 0.012)
(ref= 2007)	2009	0.99 (0.74-1.31)	1.00 (0.94-1.07)	0.77 (0.50-1.18)	0.92 (0.82-1.02)	*0.065 (0.018, 0.113)	**0.021 (0.010, 0.032)
	2010	1.24 (0.94-1.64)	*1.10 (1.03-1.17)	0.73 (0.47-1.16)	*0.87 (0.77-0.97)	**0.086 (0.038, 0.134)	**0.057 (0.046, 0.068)
	2011	1.22 (0.92-1.62)	**1.15 (1.08-1.23)	*0.47 (0.27-0.80)	0.94 (0.83-1.06)	**0.085 (0.036, 0.133)	**0.069 (0.058, 0.080)
	2012	1.08 (0.82-1.43)	**1.15 (1.08-1.23)	0.91 (0.56-1.47)	0.92 (0.81-1.05)	**0.088 (0.037, 0.138)	**0.084 (0.073, 0.095)
	2013	1.14 (0.87-1.50)	**1.19 (1.11-1.26)	0.82 (0.47-1.42)	0.93 (0.81-1.07)	**0.105 (0.052, 0.158)	**0.081 (0.070, 0.093)
MRCI-A Route Complexity	2-4	1.00 (0.85-1.16)	*0.96 (0.93-1.00)	0.94 (0.69-1.27)	*1.08 (1.00-1.16)	0.007 (-0.018, 0.031)	0.001 (-0.005, 0.006)
(ref= 0-1)	5+	0.97 (0.81-1.17)	1.00 (0.95-1.06)	1.00 (0.69-1.44)	*1.14 (1.02-1.26)	0.016 (-0.013, 0.046)	*0.014 (0.005, 0.022)
Combined Medication & Visit Score	1-3 Meds	0.88 (0.42-1.85)	**1.34 (1.19-1.51)	1.01 (0.25-4.05)	*0.71 (0.56-0.90)	-0.035 (-0.206, 0.136)	0.020 (0.000, 0.040)
(ref= No Meds)	4+ Meds or 2+ Visits	0.87 (0.50-1.50)	**1.37 (1.23-1.52)	0.78 (0.27-2.22)	**0.56 (0.45-0.70)	0.032 (-0.089, 0.153)	**0.044 (0.026, 0.061)
	4+ Meds & 2+ Visits	1.07 (0.64-1.78)	**1.47 (1.33-1.64)	0.64 (0.23-1.73)	**0.49 (0.39-0.61)	0.063 (-0.051, 0.178)	**0.054 (0.037, 0.072)
Out-of-Pocket Medication Costs	\$1 < \$50	1.04 (0.83-1.29)	0.98 (0.90-1.07)	1.18 (0.73-1.90)	1.16 (0.96-1.40)	-0.021 (-0.051, 0.009)	*-0.016 (-0.029, -0.004)

Parameter		Initiation		^a Discontinuation		^b Adherence	
		Bipolar and Psychotic Disorder n=1,259	No Diagnosis n=20,635	Bipolar and Psychotic Disorder n=951	No Diagnosis n=16,561	Bipolar and Psychotic Disorder n=951	No Diagnosis n=16,561
		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Estimate (95% CI)	Estimate (95% CI)
^c Year of Endocrine Therapy Use (ref= 1)	(ref= \$0 < \$1)						
	\$50 < \$500	0.96 (0.78-1.16)	0.96 (0.89-1.04)	1.43 (0.93-2.18)	*1.28 (1.07-1.54)	** -0.069 (-0.098, -0.039)	** -0.036 (-0.048, -0.024)
	\$500+	*0.73 (0.57-0.93)	*0.88 (0.80-0.97)	1.36 (0.83-2.23)	1.22 (1.00-1.50)	** -0.065 (-0.101, -0.030)	** -0.029 (-0.044, -0.015)
	2	-	-	-	-	**0.057 (0.041, 0.074)	**0.067 (0.063, 0.071)
	3	-	-	-	-	**0.076 (0.056, 0.095)	**0.090 (0.085, 0.095)
	4	-	-	-	-	**0.100 (0.073, 0.128)	**0.120 (0.114, 0.126)
	5	-	-	-	-	**0.115 (0.077, 0.153)	**0.132 (0.124, 0.140)

P value * < 0.05, ** < 0.001, 95% confidence interval. "Combined Medication & Visit" variable created from each variable's significant response levels in separate adjusted models (Appendix 2). Models adjusted for stage, age, race, ethnicity, NCI comorbidity score, function-related indicators, rurality, year of diagnosis. ^{a,b}Follow-up began the day of endocrine therapy initiation, concluding at censoring or a maximum five years of endocrine therapy use. ^aDiscontinuation analysis censored after five years continuous use. ^bAdherence measured with the proportion of days covered (PDC), for patients with one or more years of observation with over half of this time outside hospitals and skilled nursing facilities. Estimate of 0.01 corresponds to 1%. ^cApplicable to adherence only.

Appendix 4: Usage of psychiatric medications in the four months prior to breast cancer, by bipolar and psychotic disorder subgroups

Medication class used	Patients with diagnosed bipolar and psychotic disorders	Patients without bipolar and psychotic disorders	Chi-square p value
Antidepressants	63.0%	17.5%	<0.001
Antipsychotics	27.6%	<1.0%	<0.001
Anxiolytics, sedatives, and hypnotics	33.4%	20.7%	<0.001
Medications typically used for bipolar disorder	11.8%	<1.0%	<0.001
Misc. medications with psychiatric uses	17.4%	7.2%	<0.001
Stimulants	1.3%	<1.0%	<0.001

Description of generic medications included in each class can be found in Appendix 5.

Appendix 5: Generic medications included in each psychiatric medication class

Medication class	Generic medications
Antidepressants	Amitrip HCL/Chlordiazepoxide, amitriptyline HCL, amoxapine, bupropion HCL, citalopram hydrobromide, clomipramine HCL, desipramine HCL, desvenlafaxine succinate, duloxetine HCL, escitalopram oxalate, fluoxetine HCL, fluvoxamine maleate, imipramine HCL, maprotiline HCL, milnacipran HCL, mirtazapine, nefazodone HCL, nortriptyline HCL, paroxetine HCL, paroxetine mesylate, perphenazine/amitriptyline HCL, phenelzine sulfate, protriptyline HCL, sertraline HCL, trazodone HCL, trimipramine maleate, venlafaxine HCL
Antipsychotics	Aripiprazole, clozapine, fluphenazine decanoate, fluphenazine HCL, haloperidol, haloperidol decanoate, haloperidol lactate, loxapine succinate, lurasidone HCL, olanzapine, paliperidone, pimozide, quetiapine fumarate, risperidone, risperidone microspheres, thioridazine HCL, thiothixene, trifluoperazine HCL, vilazodone hydrochloride, ziprasidone HCL, ziprasidone mesylate
Anxiolytics, sedatives, and hypnotics	Alprazolam, atenolol, atenolol/chlorthalidone, buspirone HCL, chloral hydrate, chlordiazepoxide HCL, clonazepam, clonidine, clonidine HCL, clorazepate dipotassium, diazepam, estazolam, eszopiclone, flurazepam HCL, hydroxyzine HCL, hydroxyzine pamoate, lorazepam, meprobamate, oxazepam, prazosin HCL, propranolol HCL, propranolol/hydrochlorothiazid, ramelteon, sodium oxybate, temazepam, triazolam, zaleplon, zolpidem tartrate
Medications typically used for bipolar disorder	Carbamazepine, divalproex sodium, lamotrigine, lithium carbonate, lithium citrate, olanzapine/fluoxetine HCL, oxcarbazepine
Misc. medications with psychiatric uses	Gabapentin, levetiracetam, memantine HCL, pregabalin, tiagabine HCL, topiramate, valproate sodium, valproic acid, zonisamide
Stimulants	Amphet asp/amphet/d-amphet, armodafinil, atomoxetine HCL, dextroamphetamine sulfate, dextroamphetamine/amphetamine, methylphenidate HCL, modafinil

Generic medication names identified in Medicare Part D claims, with classes based on Cerner Multum drug database (<https://www.cerner.com/solutions/drug-database>). Spellings and abbreviations not changed from original data. Any medications not prescribed to the cohort were not listed.

Appendix 6: List of Function-related Indicators (FRIs)

Function-related Indicators
Mobility limitation
Blood transfusion
Oxygen at home
Supplemental nutrition at home
Hip or Pelvic fractures
Urinary catheter at home
Chronic skin ulcer
Pneumonia
Bone marrow failure
Depression
Respiratory failure
Sepsis
Malnutrition/unintentional weight loss
Fall-related injury
Syncope

Code adapted from: Chrischilles, E., et al., Beyond comorbidity: expanding the definition and measurement of complexity among older adults using administrative claims data. *Med Care*, 2014. 52 Suppl 3: p. S75-84.