Supplementary Table 1: Medication Classes

Benzodiazepines	**Gabanergic**	**Antipsychotic**	**Opiates**	**Antidepressants**
Chlordiazepoxide	Gabapentin	aripiprazole	Oxycodone	citalopram
Diazepam	Pregabalin	chlorpromazine	Morphine	bupropion
Lorazepam		clozapine	Hydromorphone	venlafaxine
Oxazepam		fluphenazine	Codeine	desvenlafaxine
Alprazolam		Haloperidol	Hydrocodone	escitalopram
Clonazepam		lurasidone	Fentanyl	fluoxetine
Eszopiclone		Olanzapine	Methadone	citalopram
Zolpidem		Quietapine		paroxetine
Temazepam		Risperidal		vilazodone
Triazolam		Thioridazine		sertraline
		ziprasidone		duloxetine
				Fluvoxamine
				Mirtazapine
				Nefazodone

Tricyclics	**Statins**	**Diuretic**	**Proton pump inhibitor**	**Beta blocker**
Trazodone	Atorvastatin	Furosemide	Pantoprazole	Nadolol
Amitryptiline	Rosuvastatin	Spironolactone	Omeprazole	Propranolol
Nortryptiline	Pravastatin	Amiloride	Rabeprazole	Carvedilol
Desipramine	Lovastatin	Hydrochlorothiazide	Lansoprazole	
Imipramine	Simvastatin	Epleronone	Esomeprazole	
Doxepin		Chlorthalidone	Deslansoprazole	
		Indapamide		
		Torsemide		

In supplementary table 1, the medication classes explored as exposures for HE risk are detailed by their constituent medications. Both generic and brand names were searched in the clinical data warehouse.

Supplementary Table 2: Incremental Changes After Including Additional Variables in Baseline and Longitudinal Risk Models

	Baseline only AUC (95%CI)	Longitudinal model AUC (95%CI)
Final model (based on Table 2) (albumin, bilirubin, statin, non-selective beta-blocker)	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus proton pump inhibitor use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus benzodiazepine use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus opiate use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus antidepressant use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus gabanergic use	0.68 (0.66-0.70)	0.73 (0.71-0.75)
Plus all meds	0.68 (0.66-0.70)	0.72 (0.70-0.74)

In Supplementary Table 2, the area under the receiver operating curve (AUC) is presented for the variables selected in table 2 for both baseline and longitudinal models. We demonstrate the lack of increased risk discrimination associated with use of selected medication classes either at baseline or during follow-up (longitudinal model)

Supplementary Figure 1