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ORIGINAL ARTICLE

The Use of Neuraminidase Inhibitors in Teenagers May Not Increase the Risk of Neuropsychiatric Adverse Events: A Nationwide Population-based Retrospective Study

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Background: Pandemic influenza virus is a public health issue, and the neuraminidase inhibitors (NIs) "Oseltamivir" and "Zanamivir" are effective treatments. While teenagers use NIs, there are concerns regarding neuropsychiatric adverse events (NPAEs). **Aim:** We aimed to use the Taiwan National Health Insurance Research Database to identify the correlation between NPAEs and NIs use in teenagers aged 13–19 years. **Methods:** The final population between 2000 and 2015 included in this study was 3698 individuals, with 2287 individuals having received "Oseltamivir" and "Zanamivir" (study cohort group) and 9148 individuals not receiving "Oseltamivir" and "Zanamivir" (comparison cohort group). We initially used a multivariate Cox regression analysis during the tracking period to determine the cumulative incidence of NPAEs. **Results:** Our findings revealed no significant increase in the likelihood of developing NPAEs in the study group. The Kaplan–Meier survival curve demonstrated that individuals who received "Oseltamivir" and "Zanamivir" were not associated with statistically significantly increased NPAEs compared with controls (log-rank test, $P = 0.724$). **Conclusion:** No more risk in comparison of the normal population in our study, and the safety of "Oseltamivir" and "Zanamivir" is established treatments for influenza.

Key words: Influenza, neuraminidase inhibitors, neuropsychiatric adverse events

INTRODUCTION

The influenza virus occurs every year worldwide, and children experience attacks that account for between 10% and 40% during the pandemic influenza period.[1] Influenza virus infection in children is correlated with the big burden in social and individual such as hospitalization, missed school days, and parents' missing work days.[2,3] In addition, younger children have the greatest likelihood of sustaining severe complications and mortality. Hence, the importance of influenza immunization has been highlighted.[4] To prevent severe influenza, early administration of antiviral agents in children is of great concern.

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When influenza is diagnosed, antiviral treatment with neuraminidase inhibitors (NIs) is indicated as soon as possible; the ideal time is within 48 h.[5,6] NIs prevent viral release into host cells. "Oseltamivir" and "Zanamivir" are two major NIs available in Taiwan. Oseltamivir is within oral route, and it is indicated in influenzas in individuals ≥2 weeks of age.[5] Zanamivir is taken by inhalation, and it is administrated in individuals ≥ 7 years of age in the United States.[7]

Side effects included nausea and vomiting. However, some postulated neuropsychiatric adverse events (NPAEs) associated with the use of the NIs "Oseltamivir" and "Zanamivir." In the past few years, there was an issue raise a major concern, and the NPAEs such as bizarre behavior, acute confusion, delusions, perceptual disturbances, self-harm, and accidental deaths have been reported with oseltamivir treatment, especially in Japanese teenagers.[8,9] A literature review has mentioned that exposure to NIs is correlated with neuropsychiatric symptoms, especially in teenagers. Most events were seizures, encephalitis, and changes in consciousness. The FDA Adverse Event Reporting System (FAERS) (October 27, 1999, to August 27, 2012) indicated primary suspected cases associated with oseltamivir. Abnormal behavior, psychiatric and behavioral symptoms, delirium, hallucinations, perception disturbances, delusional disorders, and depressed levels of consciousness were observed. Particularly, it has been disproportionately reported in Asian countries. However, the FAERS is considered a passive reporting system after clinical evaluation.[10] Through the data reporting the add ratio, certain NPAEs were observed in Japan, and it was considered that Japan uses more than 75% of manufactured oseltamivir. Due to their widespread use, associated follow-up studies have been performed in Japan. The distributions of age and sex in the relationship between NPAEs and oseltamivir use have not been discussed in detail. However, it is controversial whether other epidemiological and controlled studies have revealed a relationship between NPAEs and oseltamivir use. The occurrence of NPAE is relatively rare but still causes great concern in clinical practice. In this study, we aimed to use a large national population to analyze the correlation between NPAEs and NIs use in teenagers.

MATERIALS AND METHODS

Data

The Taiwan National Health Insurance Research Database (NHIRD) was established in 1995, and the Taiwan National Health Insurance Administration Ministry of Health and Welfare (Taipei, Taiwan) provides a number of medical services, including inpatient, outpatient, and emergency services, to >99% of the entire population in Taiwan. Data from the NHIRD were used in this study. The investigation protocols were approved by the Institutional Review Board of the Tri-Service General Hospital (Taipei, Taiwan) (TSGHIRB no. E202316008), and this study was conducted in accordance with the Declaration of Helsinki. The patient consent was waived by the IRB. The diagnoses were made according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).[11]

Study cohort

A retrospective cohort study was designed, and we chose outpatient and inpatient data from January 1, 2000, to December 31, 2015, from the NHIRD in Taiwan. These cases involved the use of NIs ("Oseltamivir" and "Zanamivir"). The included case group defined NPAEs as confusion, hallucinations, paranoia, psychosis, schizophrenia, anxiety, restlessness, nervousness, mood disorder, stress symptoms, sleeping disorder, aggression, suicidal ideation, convulsions, encephalitis, ataxia, dizziness, giddiness, and vertigo, in accordance with ICD-9-CM codes [Supplementary Table 1 presents the ICD-9-CM codes of all NPAEs]. Each enrolled case with diagnosed NPAEs was required to have at least one outpatient clinic visit within a year. The exclusion criteria were: (1) subjects aged ≤12 years and (2) unknown sex. The study cohort was required to have been exposed to both "Oseltamivir" and "Zanamivir" at least once during the study period. We excluded patients who used NIs before the index date and study period.

A total of 3698 individuals were included in the study, and 1411 individuals were excluded from the study. The tracking period was 56 days (2 months). Study cohorts with NPAEs were 2 (7 days), 8 (14 days), 21 (28 days), and 37 (56 days). The number of NPAEs events in the comparison cohort was 15 (7 days), 34 (14 days), 72 (28 days), and 140 (56 days) [Figure 1].

Notable variables included sex, age, and comorbidities in accordance with the ICD-9-CM [Supplementary Table 1]. Subanalyses of these two groups were compared by controlling these characteristics during the follow-up period.

At the end of the tracking period, December 31, 2015, we defined the risk of NPAEs at different tracking intervals using the Cox regression analysis [Table 1]. The detailed items of the NPAEs subgroups were further analyzed during the follow-up period [Table 2].

RESULTS

The clinical characteristics of the patients from the present study are shown in Table 3. A total of 2287 (20.00%) patients in the study cohort group and 9148 (80.00%) in the comparison cohort received NIs. After adjusting for the variables, propensity score matching was performed. There were no statistical differences in the clinical characteristics between the study and comparison cohort groups. The mean age was

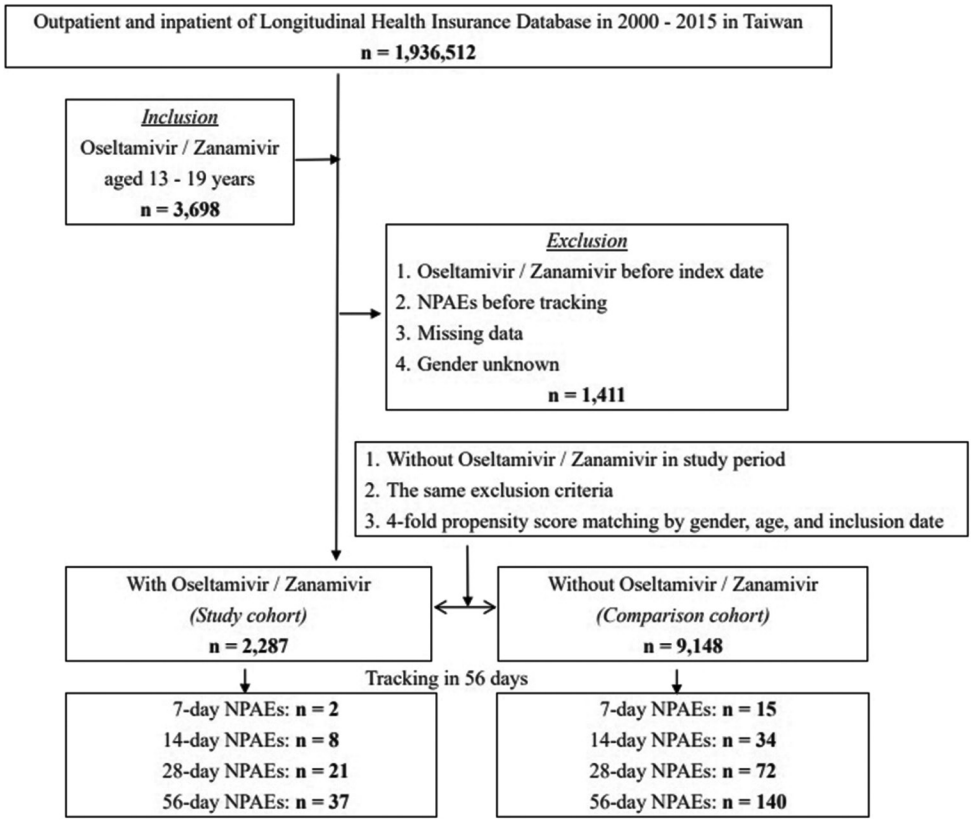

Figure 1: Flowchart of the study sample selection. NPAEs: Neuropsychiatric adverse events

Table 1: The risk of neuropsychiatric adverse events associated with oseltamivir/zanamivir use in different interval of tracking period

Tracking period (days)	Oseltamivir/ zanamivir	Adjusted HR	95% CI	*P*
7	Without	Reference		
	With	1.111	0.881–1.264	0.498
14	Without	Reference		
	With	1.085	0.862–1.238	0.502
28	Without	Reference		
	With	1.077	0.838–1.236	0.536
56	Without	Reference		
	With	1.066	0.819–1.224	0.599

HR=Hazard ratio; CI=Confidence interval

15.78 ± 6.85 years in those with NIs and 15.94 ± 6.91 in those without. Considering the comorbidities of asthma, ischemic heart disease, other heart diseases, diabetes mellitus, metabolic disorders/immunosuppressive disorders, renal disease, cancer, and neurologic/neurodevelopmental conditions, there were no significant differences in these variables.

To explore the risk of NPAE associated with NIs use at different intervals during the tracking period, further analysis was performed using multivariate Cox regression in Table 1. Compared to those without NIs use, a higher adjusted hazard ratio (HR) was found in those using NIs. The observation of NPAE at 2 months was used as a time-point reference, and we observed that a relatively higher risk at 7 days was associated with a higher risk of NPAE (adjusted HR = 1.111, $P = 0.498$). With increasing time, the adjusted HR tended to decrease; the P value obtained on days 14, 28, and 56 was 0.502, 0.536, and 0.599, respectively. This revealed no significance in the overall tracking period; however, the adjusted HR for NPAE was still higher in the NIs groups.

The NPAE subgroups are presented in Table 2. After 7 days, the items of NPAEs were relatively lower, and mood disorders (adjusted HR = 2.128, $P = 0.329$) showed a relatively higher adjusted HR than the others. Serious NPAEs such as aggression, suicidal ideation, convulsions, encephalitis, ataxia, dizziness, giddiness, and vertigo were not noted during the 56 days of follow-up.

DISCUSSION

In our study, we used a nationwide population to explore the time interval of neuropsychiatric symptoms after NIs use, especially in teenagers. There were no statistically significant

Table 2: Factors of neuropsychiatric adverse events subgroups using Cox regression

Tracking (days)	Oseltamivir/zanamivir NAPEs subgroups	With versus without		
		Adjusted HR	95% CI	*P*
7	Overall	1.111	0.881–1.264	0.498
	Confusion	0.000	-	0.994
	Hallucinations, paranoia	0.000	-	0.975
	Psychosis, schizophrenia	0.000	-	0.986
	Anxiety, restlessness, and nervousness	0.000	-	0.986
	Mood disorder	2.128	0.770–3.222	0.329
	Stress symptoms	0.000	-	0.991
	Sleeping disorder	0.000	-	0.998
	Aggression, suicide ideation	-	-	-
	Convulsions	-	-	-
	Encephalitis	-	-	-
	Ataxia, dizziness and giddiness, and vertigo	-	-	-
14	Overall	1.085	0.862–1.238	0.502
	Confusion	0.000	-	0.996
	Hallucinations, paranoia	0.000	-	0.983
	Psychosis, schizophrenia	0.000	-	0.986
	Anxiety, restlessness, and nervousness	1.842	0.457–2.045	0.371
	Mood disorder	1.572	0.336–2.010	0.678
	Stress symptoms	0.000	-	0.999
	Sleeping disorder	1.116	0.901–1.700	0.101
	Aggression, suicide ideation	-	-	-
	Convulsions	-	-	-
	Encephalitis	-	-	-
	Ataxia, dizziness and giddiness, and vertigo	1.160	0.576–1.833	0.456
28	Overall	1.077	0.838–1.236	0.536
	Confusion	0.706	0.383–1.130	0.617
	Hallucinations, paranoia	0.781	0.281–1.203	0.723
	Psychosis, schizophrenia	0.856	0.779–1.225	0.281
	Anxiety, restlessness, and nervousness	1.280	0.904–1.896	0.099
	Mood disorder	1.198	0.568–1.688	0.482
	Stress symptoms	1.011	0.405–1.240	0.515
	Sleeping disorder	1.125	0.920–1.463	0.087
	Aggression, suicide ideation	-	-	-
	Convulsions	-	-	-
	Encephalitis	-	-	-
	Ataxia, dizziness and giddiness, and vertigo	1.017	0.832–1.319	0.121
56	Overall	1.066	0.819–1.224	0.599
	Confusion	0.569	0.276–1.107	0.783
	Hallucinations, paranoia	0.650	0.186–1.197	0.812
	Psychosis, schizophrenia	0.803	0.306–1.181	0.662

Contd...

Table 2: Contd...

Tracking (days)	Oseltamivir/zanamivir NAPEs subgroups	With versus without		
		Adjusted HR	95% CI	*P*
	Anxiety, restlessness, and nervousness	1.334	0.951–1.924	0.074
	Mood disorder	1.313	0.895–1.749	0.103
	Stress symptoms	1.024	0.779–1.224	0.271
	Sleeping disorder	1.148	0.838–1.306	0.184
	Aggression, suicide ideation	-	-	-
	Convulsions	-	-	-
	Encephalitis	-	-	-
	Ataxia, dizziness and giddiness, and vertigo	0.984	0.511–1.261	0.462

HR=Hazard ratio; CI=Confidence interval; NAPEs=Neuropsychiatric adverse events

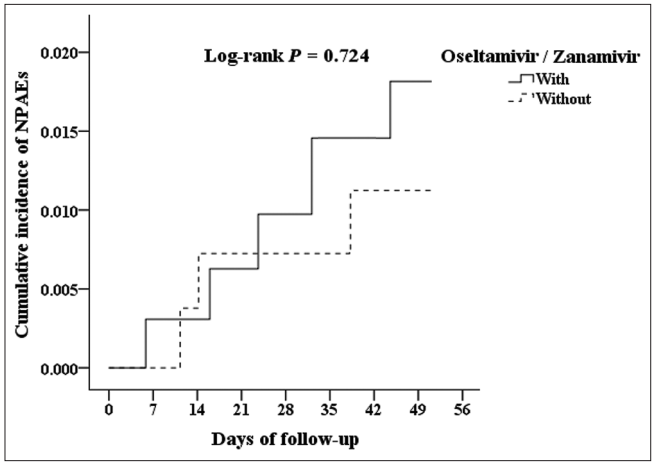

Figure 2: Kaplan–Meier for cumulative incidences of neuropsychiatric adverse events aged 13–19 stratified by oseltamivir/zanamivir with log-rank test. NPAEs: Neuropsychiatric adverse events

differences in the number of follow-up days. Among the NIs, the cumulative incidence of NPAEs was higher for oseltamivir than for zanamivir. The cumulative incidences of NPAEs are higher in the oseltamivir group in 56-day follow-up, but there is no statistical significance (log-rank test $P = 0.724$) [Figure 2]. A previous cohort study showed a 1.21-fold increase in the risk of psychiatric events associated with the use of oseltamivir and a 1.5-fold increase in the risk among aged 10–19 years patients but no statistical significance. In latent class analysis, the likelihood ratio of abnormal behavior was higher in juvenile boys, and signal detection of adverse drug events, abnormal behavior, hallucinations, agitation, and restlessness were the most common.[12]

The timing of influenza onset and exposure to NIs remains unclear. Children may manifest abnormal behaviors, which usually occur in the early stages of the illness. Hence, it has been suggested that children with influenza should be aware of the disease within 48 h of disease onset.[13,14] In our study, we focused on teenagers (13–19 years old) with NPAEs because the diagnosis of NPAEs in younger children is relatively difficult to define. While reviewing teenagers using NIs, psychosis manifestations such as confusion, hallucinations, paranoia, psychosis, and schizophrenia were not observed during the 7-day and 14-day track periods. Neurotic manifestations such as mood disorders, anxiety, restlessness, nervousness, and sleeping disorders were relatively remarkable. During 28-day and 56-day track periods, the manifestation of neurosis was higher than that of psychosis. However, teenagers are relatively mood unstable during the development. In addition, the adjusted HR for mood and anxiety disorders was relatively higher when using NIs, which might be an issue in teenage patient care during influenza disease [Table 2]. However, the adjusted HR of NPAE associated with NIs use decreased in the long-term follow-up interval [Table 1].

Although the mechanism of NPAEs in patients with NI use was still considered to be influenza-related encephalopathy, some Japanese studies postulated possible mechanisms of NPAEs caused by oseltamivir. Oseltamivir use was correlated with a higher concentration of dopamine. Thus, oseltamivir may act as a dopamine reuptake inhibitor. In addition, another study indicated that the hypothermic effect of oseltamivir was caused by dopamine receptor blockade; it was considered that oseltamivir activated the D2 receptor.[15] Another possible pathway involves dopamine release. Blocking nicotinic acetylcholine receptor channels leads to the activation of the dopaminergic system.[16] These mechanisms might result in adverse neuropsychiatric reactions, such as abnormal behavior, delusions, and hallucinations. In animal studies, analysis of neurotransmitter changes, such as dopamine and serotonin metabolism, after the systemic administration of oseltamivir revealed that neurotransmitters affect the medial prefrontal cortex.[17] The concentration of extracellular dopamine in the medial prefrontal cortex of rats is significantly higher and induces psychostimulants, including phencyclidine and methamphetamine, in correlation with abnormal behavioral

Table 3: Characteristics of study in the baseline

Variables	Total	Oseltamivir/zanamivir		*P*
		With	Without	
Total	11,435	2287 (20.00)	9148 (80.00)	
Gender				
Male	5945 (51.99)	1189 (51.99)	4756 (51.99)	0.999
Female	5490 (48.01)	1098 (48.01)	4392 (48.01)	
Age (years)	15.91±6.90	15.78±6.85	15.94±6.91	0.321
Asthma/chronic obstructive pulmonary disease				
Without	10,476 (91.61)	2090 (91.39)	8386 (91.67)	0.661
With	959 (8.39)	197 (8.61)	762 (8.33)	
Ischemic heart disease				
Without	11,422 (99.89)	2284 (99.87)	9138 (99.89)	0.732
With	13 (0.11)	3 (0.13)	10 (0.11)	
Other forms of heart disease				
Without	11,421 (99.88)	2284 (99.87)	9137 (99.88)	0.999
With	14 (0.12)	3 (0.13)	11 (0.12)	
Diabetes mellitus				
Without	11,286 (98.70)	2259 (98.78)	9027 (98.68)	0.758
With	149 (1.30)	28 (1.22)	121 (1.32)	
Metabolic disorder/immunosuppressive disorder				
Without	11,290 (98.73)	2261 (98.86)	9029 (98.70)	0.602
With	145 (1.27)	26 (1.14)	119 (1.30)	
Renal disease				
Without	11,433 (99.98)	2286 (99.96)	9147 (99.99)	0.360
With	2 (0.02)	1 (0.04)	1 (0.01)	
Hemoglobinopathy				
Without	11,247 (98.36)	2256 (98.64)	8991 (98.28)	0.269
With	188 (1.64)	31 (1.36)	157 (1.72)	
Cancer				
Without	11,392 (99.62)	2279 (99.65)	9113 (99.62)	0.939
With	43 (0.38)	8 (0.35)	35 (0.38)	
Neurologic/neurodevelopment conditions				
Without	11,384 (99.55)	2278 (99.61)	9106 (99.54)	0.861
With	51 (0.45)	9 (0.39)	42 (0.46)	

P: Chi-square/Fisher's exact test on category variables and *t*-test on continuous variables

changes. Alterations in the dopaminergic system have also been observed with zanamivir treatment.[18] However, there is no further research to explore the detail mechanism of oseltamivir and zanamivir by conducting *in vitro* study.

In our study, we observed that NPAEs were not significantly positively correlated with NIs. Serious central nervous system complications, such as convulsions, encephalitis, ataxia, dizziness, giddiness, and vertigo, were not observed after oseltamivir treatment. In addition, bizarre behaviors, such as aggression and suicidal ideation, were not noted. Concerns regarding the safety of NIs are still well established for clinical applications.

Despite efforts to control for confounding factors, the present study has several limitations. First, the information obtained from the NHIRD regarding patient characteristics was lacking in terms of the severity of influenza, medication use compliance, and treatment modalities. Second, thorough information regarding the detailed medical records of patients with psychotic diagnoses was not disclosed to obtain additional information. Third, despite the review by

a specialist, there was a potential bias owing to complicated comorbidities that may be missed. Further prospective studies are required because of the retrospective nature of this observational study. Furthermore, conducting *in vitro* studies by collaborating with pharmacologists could be considered.

CONCLUSION

Our findings revealed that, compared with the control group, individuals who received NIs ("Oseltamivir" and "Zanamivir") were not associated with significantly increased NPAEs.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Abbreviation, International Classification of Diseases, Ninth Revision, Clinical Modification, National Health Insurance code and definition

	Abbreviation	ATC code/ICD-9-CM/NHI code/definition
Study population		
Zanamivir		B023336155
Oseltamivir		B023253100
Events: Neuropsychiatric adverse events	NPAEs	
Confusion		290.12, 290.20, 290.3, 293.0, 293.1, 294.0, 307.9, 310.1, 314.00, 780.01, 780.9, 781.8, 797, 799.8, V62.89
Hallucinations, paranoia		293.81, 293.82, 293.9, 294.8, 310.1, 310.2, 310.8, 310.9, 315.32, 368.16, 388.40–388.44
Psychosis, schizophrenia		293.89, 295.00–295.05, 295.41–295.45, 295.50–295.55, 295.80, 295.81, 295.90–295.95, 297.0–297.2, 297.8, 297.9, 298.3, 298.4, 298.8, 298.9, 310.9
Anxiety, restlessness, and nervousness		293.84, 300.00–300.02, 300.09, 300.20–300.23, 300.29, 300.9, 301.3, 307.9, 308.9, 799.2
Mood disorder		293.83, 296.00–296.06, 296.10–296.16, 296.20–296.25, 296.40–296.46, 296.50–296.56, 296.60–296.62, 296.8, 296.82, 296.90, 298.0, 311
Stress symptoms		209.29, 300.5, 300.6, 300.89, 300.9, 308.0–308.4, 308.9, 309.0, 309.1, 309.24, 309.28, 309.3, 309.4, 309.81–309.83, 309.89, 309.9, 310.8, V40.2, V40.9
Sleeping disorder		306.8, 307.40–307.48, 347, 729.82, 780.50–780.51
Aggression, suicide ideation		292.0, 292.11, 292.12, 292.2, 292.81, 300.9, 301.3, 799.2, E950–E959
Convulsions		345.01, 345.10–345.11, 345.2, 345.3, 345.40, 345.41, 345.50, 345.51, 345.60, 345.61, 345.70, 345.71, 345.80, 345.81, 345.90, 345.91, 780.31, 780.39
Encephalitis		322.9, 323.0, 323.4, 323.6–323.9, 344.1, 348.3, 349.82
Ataxia, dizziness and giddiness, and vertigo		334.0, 334.2–334.3, 780.4, 781.2–781.3
Comorbidities		
Asthma/chronic obstructive pulmonary disease	Asthma/COPD	490–496
Ischemic heart disease	IHD	410–414
Diabetes mellitus	DM	250
Metabolic disorder/immunosuppressive disorder		240–279
Renal disease		585
Hepatic disease		570–573
Hemoglobinopathy		280–289
Cancer		140–208
Neurologic/neurodevelopment conditions		290–319, 320–389 excluding NPAEs

ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; NHI=National Health Insurance; ATC=Anatomical Therapeutic Chemical (ATC) Classification System