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## Risk of gastrointestinal Hypomotility in schizophrenia and schizoaffective disorder treated with antipsychotics: A retrospective cohort study

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### ABSTRACT

**Objective:** **The risk of gastrointestinal hypomotility (GIHM) with the use of antipsychotic medications in patients with schizophrenia remains inadequately recognized.** The aim of this study was to explore the incidence of GIHM and its risks in patients with schizophrenia treated with antipsychotics.

**Methods:** We conducted a retrospective cohort **study** using the National Health Insurance Research Database. We identified adult ( $\geq 20$  years **of age**) patients with a first-time diagnosis of schizophrenia or schizoaffective disorder in the Registry for Catastrophic Illness Patients **during** the period from 2001 to 2011. **Each subject in the cohort was followed until their corresponding diagnosis of GIHM was made, until the time of death, or to December 31, 2012.** The incidence rates of each outcome were calculated. Cox proportional hazards regression with time-dependent covariates for antipsychotics use was employed to evaluate the associations between different types of antipsychotics and the risk of GIHM.

**Results:** Our study **found** that the incidence densities of constipation, ileus, and ischemic bowel disease were 42.5, **4.4**, and 0.1 per 1000 person-years. In terms of **the risk of hypomotility with the use of** antipsychotics, clozapine and quetiapine were significant in developing constipation, with a hazard ratio of 2.15 and 1.34, **respectively**. High-potency first-generation antipsychotics and clozapine were also significant in the occurrence of ileus, with a hazard ratio of **1.30 and 1.95, respectively**. Similar associations were found in an anticholinergic agent subgroup analysis.

**Conclusion:** Patients receiving antipsychotics such as high-potency first-generation antipsychotics, clozapine, or quetiapine should undergo proper evaluation and intervention to minimize the disease burden and life-threatening outcomes of treatment.

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### 1. Introduction

**Patients with schizophrenia are more likely than the general population to have poor physical health and shorter life expectancy (Casey Crump et al. 2013; Correll et al. 2017; Nordentoft et al. 2013; Vancampfort et al. 2016; Vancampfort et al. 2015). Among various poor health effects, gastrointestinal hypomotility (GIHM) is a very common but under-recognized condition. GIHM consisting of constipation, ileus, and ischemic bowel disease refers to a state of decreased gastrointestinal tract muscle contractions or slower bowel transit, caused by the pharmacologic properties of antipsychotics (Every-Palmer and Ellis 2017).** Constipation may cause serious

conditions such as ileus, ischemic bowel disease, sepsis, **and** death without proper intervention (De Hert et al. 2011; Palmer et al. 2008). Therefore, early identification and intervention **are** vital for reducing morbidity and mortality associated with constipation from a public health perspective.

**The prevalence of antipsychotic related constipation** in schizophrenia is **approximately** one-third (De Hert et al. 2011; Koizumi et al. 2013) with the highest rate reaching 60% of a population (Hayes and Gibler 1995). **There are conclusive evidences on the existence of clozapine-induced GIHM (Baptista et al. 2015; Every-Palmer et al. 2016; Shirazi et al. 2016).** For example, radiopaque marker studies show that clozapine-treated patients have significant GIHM (Baptista et al. 2015). **In addition, the median colonic transit time of patients taking clozapine is four times longer than those on other antipsychotics or normative medications and 80% of patients receiving clozapine had colonic hypomotility, but none of the**

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other antipsychotics have the same effects (Every-Palmer et al. 2016). Furthermore, a recent systematic review (Shirazi et al. 2016) found that the overall prevalence of constipation associated with clozapine is 31.2%. In that study, patients taking clozapine were significantly more likely to have constipation compared with other antipsychotics. In addition, the rates of constipation are significantly higher in those treated as inpatients than as outpatients or in mixed settings. Finally, a cross-sectional study (Bailey et al. 2015) investigating 202 outpatients taking clozapine reported that the prevalence of constipation was 35%. The mechanisms of antipsychotic-induced constipation are the effects of using an antipsychotic and an anticholinergic medication concomitantly (Giordano et al. 1975; Stanniland and Taylor 2000; Suzuki et al. 2007); the intrinsic anticholinergic effects of antipsychotics (Hibbard et al. 2009); and the effects of serotonin receptor antagonism (Palmer et al. 2008). However, the anticholinergic and anti-serotonergic properties of antipsychotics may vary among antipsychotics due to their diverse affinities (Lieberman et al. 2005; Stroup et al. 2009).

The prevalence of ileus and ischemic bowel disease are far lower than that of constipation. A recent pharmaco-epidemiologic study (Every-Palmer and Ellis 2017) including a sample of 43,132 Australian and New Zealander patients taking clozapine showed that 160 (37/10,000) had serious or lifethreatening GIHM such as ileus and ischemic bowel disease.

A large database study (Nielsen and Meyer 2012) showed the cumulative incidence of ileus is 0.46%. In that study, patients treated with clozapine, high-potency first-generation antipsychotics (FGAs), tricyclic antidepressants, anticholinergics, and opioids were associated with an increased risk of ileus. In addition, 9 of the 123 cases of ileus (7.3%) were fatal. High case fatality rates (27.5%) of ileus were also found in a case series study by Palmer et al. (2008). In addition, a study (Peyriere et al. 2009) analyzing 38 cases of ischemic colitis and gastrointestinal necrosis associated with antipsychotics showed that 14 patients had a fatal course, with a mortality rate of 39.5%. Other studies are primarily case reports of ileus (Dome et al. 2007; Kwiatkowski et al. 2011; Suzuki et al. 2007) or ischemic bowel disease (Prieto Peraita et al. 2012; Yu et al. 2013).

The risk of GIHM with antipsychotic treatment remains inconclusive, and the aforementioned studies have methodological issues. For example, some are primarily case reports or case series (Palmer et al. 2008; Peyriere et al. 2009), cross-sectional studies (De Hert et al. 2011; Koizumi et al. 2013), or case control studies (Nielsen and Meyer 2012), which may have limited evidence when it comes to the causal relationship between risk factors and disease outcomes. In addition, we could not directly compare three outcomes of GIHM because the samples of the previous studies were collected from different populations. Thus, we conducted a nationwide cohort study of schizophrenia. The aim of this study was to explore the incidence of GIHM and its risks in patients with schizophrenia treated with antipsychotics.

## 2. Methods and materials

### 2.1. Data source

The National Health Insurance Research Database (NHIRD) is provided by Taiwan's National Health Insurance program, which covered 98% of the Taiwanese population since 1997 (Lu and Hsiao 2003). The database, consisting of comprehensive medical claim files (disease diagnoses, hospital admissions, outpatient visits, and prescription medications), represents the entire population of Taiwan, making it one of the largest and the most complete population-based database worldwide (Chang et al. 2017). The diagnoses of schizophrenia in the database were made by board-certified psychiatrists. To verify the accuracy of the diagnoses, 1 of 100 ambulatory cases and 20 inpatient cases form patient charts are randomly checked, and then the patients are interviewed (Chang et al. 2012). There have been high accuracy and validity of the diagnoses in

previous studies using the NHIRD (Cheng et al. 2011; Chien et al. 2004; Hsieh et al. 2015).

Data for this study were obtained from the Registry for Catastrophic Illness Patient Database (RCIPD), which is a subset of the Taiwan NHIRD that contains the complete medical records of all schizophrenia and schizoaffective disorder patients. In Taiwan, patients diagnosed with a "catastrophic illness" such as schizophrenia, schizoaffective disorder, dementia, or cancer usually apply for a catastrophic illness card that excuses them from cost sharing. The application is formally reviewed by experts, which could indirectly increase the validity of disease diagnoses in our analysis. We included data from all individuals who were enrolled between January 1, 2001 and December 31, 2012. This study was approved by the Institutional Review Board of Hualien Tzu Chi Hospital, Taiwan.

### 2.2. Study population

This study had a retrospective cohort design. We first identified adult ( $\geq 20$  years of age) patients with a first-time diagnosis of schizophrenia or schizoaffective disorder (ICD-9-CM 295) in the Registry for Catastrophic Illness Patients (HV) during 2001–2011 ( $N = 41,113$ ), so that we would have at least a full 1-year observation period. The index date was defined as the date when the subject being treated for schizophrenia or schizoaffective disorder was first receiving antipsychotic medication. The following groups of patients were excluded: those with a history of constipation, ileus (paralytic ileus, intestinal pseudo-obstruction, bowel obstruction, fecal impaction), ischemic bowel disease, cancer, or irritable bowel disease; and those who received abdominal surgery or antipsychotic treatment before the index date. After these exclusions, we further disqualified patients who had never had prescriptions for antipsychotics. Outcome variables included constipation (ICD-9-CM 564.0); ileus consisting of paralytic ileus (ICD-9-CM 560.1), intestinal pseudo-obstruction (564.89), bowel obstruction (860.9), fecal impaction (560.32); and ischemic bowel disease (ICD-9-CM 557). Each subject of the cohort was followed up until their corresponding diagnosis of GIHM was made, until death, or to December 31, 2012. Fig. 1 presents a flowchart of the patient selection procedure.

### 2.3. Measurement of exposure

We obtained data on antipsychotic drug use from inpatient and outpatient medical records and calculated the duration of treatment for each patient. We classified antipsychotics into 6 categories according to their anticholinergic activity. We initially divided FGAs into 2 groups containing high-potency and low-potency FGAs. We then split the second-generation antipsychotics into 4 groups including clozapine, olanzapine, quetiapine, and others (amisulpride, risperidone, zotepine, aripiprazole, paliperidone, and ziprasidone). Because the effects of antipsychotic drugs may change over time and their impact on the risk of GIHM may be different, we defined the term "user" as a patient with use of a single antipsychotic drug if the prescription length covered any duration of the study interval; we used the term "non-user" if the use did not cover any duration of the study interval.

### 2.4. Covariate assessment

Covariates for adjustment included age, gender, socioeconomic status, geographic area, psychiatric illness severity, medical comorbidities, and medications. The monthly income served as a proxy indicator of socioeconomic status. In addition, we used admission to psychiatric acute wards within 12 months before the outcome development or censoring as a proxy measure of psychiatric illness severity, which has been used in previous research (Nielsen and Meyer 2012). Furthermore, we assessed medical comorbidity within 12 months before the index date using the Charlson comorbidity index (Charlson et al. 1987), which is

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