Schizophrenia Bulletin vol. 38 no. 3 pp. 592–598, 2012
doi:10.1093/schbul/sbq137
Advance Access publication on November 26, 2010

Risk Factors for Ileus in Patients with Schizophrenia

Jimmi Nielsen[1,2,*] and Jonathan M. Meyer[3]

[1]Unit for Psychiatric Research, Aalborg Psychiatric Hospital, Aarhus University Hospital, Mølleparkvej 10, PO Box 210, DK-9100 Aalborg, Denmark; [2]Maximum Security Unit, Forensic Psychiatric Department, Nykøbing Sjælland, Region Sjælland, Denmark; [3]Department of Psychiatry, University of California, San Diego, CA

*To whom correspondence should be addressed; tel: +4525779926, fax: +4572137235, e-mail: jin@rn.dk

Constipation is a known side effect of psychotropics that possess high affinity for muscarinic cholinergic receptors. In severe cases, constipation progresses to ileus and bowel ischemia, with multiple fatalities related to sepsis and perforation described in the literature, primarily among patients with schizophrenia. A historical prospective database study was performed using registry data from psychiatric and somatic hospitals, combined with the prescription database to examine associations between medications and ileus. Only cases with an ICD-10 diagnosis of schizophrenia (F20) and a concurrent diagnosis of ileus in the years 1996–2007 were included in the study. A total of 26 720 patients with schizophrenia were identified with 123 cases of ileus noted in the study period. Increasing age (OR: 1.03 CI: 1.01–1.04) and female sex (OR: 1.60 CI: 1.10–2.31) were associated with an increased risk of ileus. Treatment with clozapine (OR: 1.99 CI: 1.21–3.29), high-potency first-generation antipsychotics (OR: 1.81 CI: 1.01–3.23), tricyclic antidepressants (OR: 2.29 CI: 1.29–4.09), anticholinergics (OR: 1.48 CI: 1.00–2.19), and opioids (OR: 2.14 CI: 1.36–3.36) were associated with an increased risk of ileus. The onset of ileus occurred on average more than 3 years after the first prescription of the offending drug. Aripiprazole and amisulpride were not associated with ileus. Nine of the ileus cases (7.3%) had a fatal course. Treatment with clozapine (OR: 6.73 CI: 1.55–29.17) or anticholinergics (OR: 5.88 CI: 1.47–23.58) were associated with increased risk of fatal ileus. Patients receiving psychotropics associated with significant anticholinergic properties should undergo proper monitoring and interventions in order to minimize the burden of constipation and the risk of ileus.

Key words: schizophrenia/clozapine/anticholinergic/TCA/antipsychotics/constipation

Introduction

Aside from recent surgery, several risk factors for ileus have been identified, such as inactivity, bowel disorders, colorectal cancer, low fiber diet and medications such as opioids,[1] antihistamines,[1] tricyclic antidepressants (TCAs),[2,3] and antipsychotics.[4,5] Patients with schizophrenia might be at higher risk due to the common use of antipsychotics[5] and anticholinergics,[4] and the fact that many patients with schizophrenia have a sedentary lifestyle and have low fiber diets.[6,7] Moreover, the relative pain insensitivity reported among schizophrenia patients may decrease awareness of somatic symptoms, such as those arising from severe constipation.[8,9]

Although constipation is a well-known side effect of antipsychotic treatment, this issue has received only limited coverage, with the peer reviewed literature comprised almost exclusively of case reports[4,10–30] and subsequent reviews of this case literature.[5,31] In severe cases, constipation progresses to ileus and bowel ischemia, with multiple fatalities related to sepsis and perforation described in the literature.[15,17,25,30] Clozapine is involved in most published cases of antipsychotic-induced ileus, with a risk that appears to be dose dependent.[31] Up to 60% of patients treated with clozapine experience constipation[13] and one Chinese study found that 1.3% of clozapine-treated patients developed ileus.[10] Furthermore, clozapine has been associated with an increased risk of infection[32] which could be due to constipation and consequently aspiration pneumonia.

The mechanism behind medication-induced gastrointestinal (GI) hypomotility is primarily mediated by antagonism of muscarinic anticholinergic activity.[1,19] Anticholinergic potency differs markedly among antipsychotics, with high-potency typical agents and atypical agents released since 2000 (ziprasidone, aripiprazole, paliperidone, asenapine, and iloperidone) having limited affinities.[33–36] Clozapine has the highest anticholinergic activity at most receptor sites,[33,37] although it is an agonist at muscarinic M_1 and M_4 receptors.[38,39] Besides the

anticholinergic load from antipsychotic drugs, many schizophrenia patients also receive anticholinergic medications for the treatment of extrapyramidal side effects (EPS).[38] Another possible contributing factor is sedation due to histamine H_1 receptor antagonism and resulting inactivity, with clozapine again showing higher affinity than other antipsychotics.[40] Serotonin (5HT) receptors are involved in GI motility, with $5HT_3$ antagonists and $5HT_4$ agonists showing promise as therapeutic targets for the treatment of dysmotility syndromes,[41–43] whereas the impact of $5HT_{2B}$ and $5HT_7$ receptors remains to be explored. Antipsychotics have multiple actions at various 5HT receptor subtypes, and this may be another mechanism for interference with normal GI functioning. Though not implicated in antipsychotic-induced constipation, opioid treatment is commonly associated with risk of constipation via stimulation of enteric μ-opioid receptors, thereby decreasing peristalsis and intestinal fluid secretion.[1]

Despite the number of case reports related to psychotropic exposure and bowel dysfunction, there is no data on relative risk for various agents in schizophrenia patients, only prevalence estimates[5,10] and descriptive data on associated risks.[31] To clarify the exposure-related risk in schizophrenia patients, we investigated the relative risk of ileus for various psychotropics in this patient population using the Danish National Registers. These national registers provide extensive data on somatic and psychiatric diagnoses, along with all outpatient pharmaceutical prescriptions, thus permitting identification of ileus cases along with the associated psychiatric diagnoses and pharmacological risks. The underlying hypothesis is that antipsychotics and other psychotropics with greater affinity for the muscarinic receptors would be associated with an increased risk of ileus.

Methods and Materials

Sample

The Danish Data Protection Agency, National Board of Health and Statistics Denmark approved use of data for this study. Subjects for the analyses were identified by having an ICD-10 F20 schizophrenia diagnosis in the Danish Central Psychiatric Research Registry[44] in the period from January 01, 1996 until December 31, 2007. The register has a high validity and has contributed significantly to epidemiological research.[44–49] Prescription data for the included subjects were obtained from the national prescription database from January 01, 1996 through December 31, 2007. The prescription database contains information about number of sold daily defined doses (DDDs), which are assigned and reviewed by researchers of the World Health Organization Collaborating Centre of Drug Statistics Methodology.[50]

Medication status was based on prescriptions picked up from the pharmacy within the last 3 months before index date (ie, diagnosis of ileus, death or end of registry on December 31, 2007). Patients were considered under treatment with the drug if they picked up at least one prescription within the last 3 months. Antipsychotics were divided into first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA), also called atypical antipsychotics. FGAs were subdivided in low-, mid-, and high-potency FGAs. The low-potency FGA group consisted of chlorpromazine, levomepromazine, chlorprothixene, and pipamperone. The midpotency FGA group consisted of zuclopenthixol, periciazine, prochlorperazine, and perphenazine. The high-potency FGA group consisted of haloperidol, pimozide, flupenthixol, and fluphenazine. The SGA group consisted of olanzapine, quetiapine, sertindole, amisulpride, aripiprazole, risperidone, ziprasidone, sulpiride, and clozapine. The anticholinergic group consisted of atropine, benztropine, biperiden, orphenadrine, and procyclidine. The group of TCAs consisted of amitriptyline, clomipramine, doxepin, imipramine, and nortriptyline.

In Denmark, only one somatic hospital system exists and all admissions and outpatient contacts are recorded in the National Patient Registry. Only ileus cases with onset in the period from March 01, 1996 to December 31, 2007 were used for the analysis, to ensure at least 3 months of pharmacy history. Fatal cases were identified by linkage to the Danish Cause of Death registry.

Statistical Analyses

Statistical analyses were performed with STATA 11, residing on the Statistics Denmark server, via remote access. Furthermore, 2 variables were created as a proxy measure of psychiatric illness severity: living in an institution and average chlorpromazine equivalents during the last 3 months. Chlorpromazine equivalents were derived from the literature.[51,52] Days with inpatient status were excluded from the calculation of average DDD and chlorpromazine equivalents because medications dispensed during hospitalization are not included in the national prescription database. All prescriptions of psychotropics within the 3 months window were attributed to the respective drugs not accounting for the fact that some patients may have received, eg, 2 antipsychotics at the same time. However, we used a multiple regression model adjusting for this.

In order to identify a dose-effect relationship, dosages of psychotropics associated with an increased risk of ileus were also calculated. The dose used for these calculations was the average daily dose during the last 3 months before the index date and was derived by calculating the total amount of dispensed drug (in milligrams) divided by (91 – [number of bed-days]). For individual drug classes (eg, TCA, anticholinergics, antipsychotic classes), average DDDs were also calculated. The dose-effect relationship was tested in a logistic regression model adjusted for sex and age. Furthermore, time from first prescription of the offending drug until onset of ileus was also calculated. Because the drug could have been initiated during an inpatient admission where medication status is not

accessible, the value of this number is conservative and could be an underestimate.

Comparisons with normally distributed data were performed with Student's *t*-test. For ordinal data (eg, number of bed-days), a negative binomial regression model was used due to the distribution of the data (skewed distribution with long tail). Data that were not normally distributed without the possibility of transformation were displayed as median values (with interquartile range) and analyzed with the nonparametric Wilcoxon rank sum test. Dichotomous variables were compared using a chi-square test.

In the multivariate models, the following continuous variables were treated as discrete variables: age (years), percent time hospitalized (percentage points), clozapine dosage (1 mg increments), and DDDs. This was done to calculate (ORs) in 1 year age increments, by percent of time hospitalized in one percent increments (eg, 2%–3%, etc) and in DDD by whole number intervals (ie, 1 vs 2 DDD, etc).

Results

A total of 28 493 schizophrenia patients were identified in the study period, of whom 188 (0.66%) had an episode of ileus. Of these, 1735 patients (with a total of 30 ileus cases) were excluded from further analyses because they were admitted at the time of the index episode. Of the remaining sample of 158 ileus cases, 10 were associated with a diagnosis of GI cancer, and 38 cases had been admitted within the last 14 days due to various GI issues. All 48 of these cases were excluded from further analysis. The remaining cohort comprised 26 720 patients (58.3% male), with 123 identified cases of ileus (41.5% males; 58.5% females). Table 1 displays patient demographics and treatment variables.

Factors Associated With Risk of Ileus

Treatment with clozapine, TCAs, high-potency FGAs, opioids, and anticholinergics were associated with an increased risk of ileus as shown in table 2. The demographic variables of female sex and increasing age were also associated with an increased risk. In contrast, aripiprazole and amisulpride were not associated with ileus and only one case was found during treatment with ziprasidone. A dose-effect relationship was found for anticholinergics (OR: 1.19/DDD CI: 1.02–1.39, $P < .025$), TCA (OR: 1.79/DDD

Table 1. Demographics and Treatment Variables

	Controls (n = 26 597)	Ileus (n = 123)	Total (n = 26 720)	P
Male sex	15 525 (58.4%)	51 (41.5%)	15 576 (58.3%)	.0001
Mean age	47.3 (47.1–47.5)	56.2 (53.3–59.2)	47.4 (47.2–47.5)	.0001
Mean CPZ equivalent dose last 3 months (mg)	562.2 (554.5–569.9)	708.3 (574.9–872.7)	562.9 (555.2–570.7)	.019
Living institution (%)	2070 (7.8%)	22 (17.9%)	2092 (7.8%)	.0001
Living alone (%)	17 845 (67.1%)	83 (67.5%)	17 928 (67.1%)	.93
Early retirement pension (%)	15 583 (58.6%)	80 (65.0%)	15 663 (58.6%)	.15
Treatment variables				
Antipsychotics	18 329 (68.9%)	94 (76.4%)	18.423 (69.0%)	.07
Antipsychotic polypharmacy	7129 (26.8%)	34 (27.6%)	7163 (26.8%)	.83
Amisulpride	227 (0.9%)	0 (0%)	227 (0.9%)	.3
Aripiprazole	2158 (8.1%)	0 (0%)	2158 (8.1%)	.001
Clozapine	2488 (9.4%)	20 (16.4%)	2508 (9.4%)	.009
Olanzapine	4836 (18.2%)	20 (16.3%)	4856 (18.2%)	.64
Quetiapine	2432 (9.1%)	7 (5.7%)	2439 (9.1%)	.21
Risperidone	3855 (14.5%)	13 (10.6%)	3868 (14.5%)	.3
Ziprasidone	970 (3.7%)	1 (0.9%)	971 (3.6%)	.14
First-generation antipsychotics (FGA)				
Low potency	4414 (16.6%)	30 (24.4%)	4444 (16.6%)	.02
Mid potency	4319 (16.2%)	28 (22.8%)	4347 (16.3%)	.05
High potency	1192 (4.5%)	14 (11.4%)	1206 (4.5%)	.001
Antidepressants	7367 (27.7%)	38 (30.9%)	7405 (27.7%)	.43
Tricyclic antidepressants (TCA)	990 (3.7%)	14 (11.4%)	1004 (3.8%)	.0001
Anticholinergics	5179 (19.5%)	41 (33.3%)	5220 (19.5%)	.0001
Opioids	2085 (7.8%)	27 (22.0%)	2112 (7.9%)	.0001
Dosages				
Mean clozapine dose (mg)	385.5 (372.3–399.21)	589.5 (431.1–805.8)	387.2 (374.1–400.8)	.008
Mean DDD anticholinergics	0.64 (0.62–0.66)	1.03 (0.76–1.39)	0.64 (0.62–0.67)	.002
Mean DDD TCA	1.02 (0.96–1.08)	1.67 (1.05–2.64)	1.03 (0.97–1.10)	.019
Mean DDD high-potency FGA	2.20 (2.07–2.33)	2.38 (1.46–3.87)	2.20 (2.08–2.35)	.76
Median DDD opioids	0.36 (0.15–0.88)	0.48 (0.07–1.10)	0.36 (0.15–0.88)	.049

Note: DDD, daily defined dose.

Table 2. Risk Factors for Ileus

	OR	z	*P*	95% CI
Age (years)[a]	1.03	4.41	.0001	1.01–1.04
Anticholinergics	1.48	1.97	.049	1.00–2.19
Female sex	1.60	2.47	.014	1.10–2.31
High potency first-generation antipsychotics	1.81	2.00	.045	1.01–3.23
Clozapine	1.99	2.69	.007	1.21–3.29
Opioids	2.14	3.31	.001	1.36–3.36
Tricyclic antidepressants	2.29	2.81	.005	1.29–4.09

[a]Age used as discrete variable including integer numbers (eg, OR for 52–55 is 3 times the listed value).

CI: 1.18–2.70, $P < .006$), and clozapine (OR: 1.33/100 mg CI: 1.15–1.54, $P < .0001$). No dose-effect relationship was found for opioids or high-potency FGAs. All odds ratios were adjusted for age and sex. For those drugs associated with ileus, the median time from first outpatient prescription of the offending agent until onset of ileus ranged from 1528 to 2077 days, as displayed in table 3.

The significant relationship between high-potency FGA use and ileus (OR = 1.81) and the role of concurrent anticholinergic use were further tested in a regression model that adjusted for dosages of anticholinergics and high-potency FGAs. Only increasing doses of anticholinergics (OR: 2.20/DDD CI: 1.59–5.36, $P < .001$) were associated with the development of ileus and a much greater risk than that noted previously for all users of anticholinergics (OR: 1.19/DDD CI: 1.02–1.39, $P < .025$). In general, patients treated with high-potency FGAs received higher dosages of anticholinergics (DDD 0.69 CI: 0.66–0.73 vs DDD 0.64 CI: 0.62–0.65 than nonusers of high-potency FGAs, $P < .03$).

Factors Associated With Fatal Ileus

Nine of the ileus cases (7.3%) were fatal; 4 of them were males (44.4%). Treatment with clozapine (OR: 6.73 CI: 1.55–29.17) or anticholinergics (OR: 5.88 CI: 1.47–23.58) were associated with increased risk of fatal ileus as shown in table 4. Five of the 9 cases were treated with antipsychotic polypharmacy (55.6%). The fatal cases were on the following medications (the total number is higher than 9 due to antipsychotic polypharmacy): risperidone-1, high-potency FGA-3, midpotency FGA-2, low-potency FGA-2, clozapine-3, olanzapine-2. Five patients were receiving anticholinergics and one patient was treated with a TCA. Table 3 displays a multiple logistic regression of factors associated with fatal ileus. Increasing age and treatment with clozapine and anticholinergics were associated with an increased risk of fatal ileus.

Table 3. Median Time from First Prescription Until Onset of Ileus (Interquartile Range)

Time from First Prescription Until Ileus	Days
Clozapine	1528 (1145–2039)
High-potency first-generation antipsychotics	1552 (1252–1925)
Tricyclic antidepressants	2077 (1608–2683)
Anticholinergics	1866 (1587–2194)

Table 4. Risk Factors for Fatal Ileus

	OR	*z*	*P*	95% CI
Age (years)[a]	1.07	2.82	.005	1.02–1.12
Anticholinergics	5.88	2.50	.012	1.47–23.58
Clozapine	6.73	2.55	.011	1.55–29.17

[a]Age used as discrete variable including integer numbers (eg, OR for 52–55 is 3 times the listed value).

Discussion

This is the largest study investigating risk factors of ileus in patients with schizophrenia and the first to provide ORs for various ileus risk factors, including specific drug classes. Demographically, both older age and female sex were associated with an increased risk of ileus. Although the former is well known, the significant effect of gender was less obvious from the earlier case literature and provides an important clinical point that was not highlighted previously. However, one study found that female patients with schizophrenia more often had antipsychotic-induced constipation.[53] Overall, the schizophrenia patients who developed ileus were more chronic, as illustrated by a greater proportion living in institutions and receiving higher antipsychotic dosages.

That certain medications were associated with an increased risk of ileus is not surprising, given their known antimuscarinic properties (eg, clozapine, TCAs) or known effects on GI motility (eg, opioids). Previous reviews[27,31] have highlighted the risk of ileus related to clozapine, but we now have an exact odds estimate: treatment with clozapine doubles the risk for ileus and is associated with a 6-fold increased risk for fatal ileus in patients with schizophrenia. Because clozapine is reserved for treatment-resistant schizophrenia, and many psychiatrists are reluctant to prescribe clozapine,[54] the impact of clozapine on ileus risk seen in this study might be an overestimate due to confounding by indication, namely the fact that clozapine patients represent an extremely ill cohort suffering from the effects of greater symptoms. This greater degree of impairment may result in a more sedentary lifestyle due to profound negative symptoms or the sedating effects of clozapine and possibly greater pain insensitivity.[9] In contrast, many patients treated with clozapine receive laxatives that may reduce the incidence of clozapine-induced ileus.[55] Unfortunately, we did not have access to laxatives use. Nonetheless, these

data reinforce the fact that attention to bowel regimens must be part of clozapine treatment in the manner that routine metabolic monitoring is considered the standard of care. The time from first prescription of clozapine to onset of ileus was more than 4 years suggesting that this side effect is more associated with the maintenance phase rather than the acute phase of clozapine treatment, implying that ongoing vigilance around the issue of constipation is necessary. Furthermore, psychiatrists should ensure that patients treated with clozapine are compliant with their laxatives. Importantly, despite all the side effects of clozapine, it still remains the choice of drug for treatment-resistant schizophrenia and the overall mortality is low.[56]

Olanzapine was in contrast to clozapine not associated with an increased risk of ileus despite potent anticholinergic activity. As already mentioned, this could be due confounding by indication that clozapine are reserved for treatment-resistant patients or the fact that olanzapine only possesses around one-fifth of anticholinergic affinity compared with clozapine.[14] Furthermore, clozapine patients may be more likely to assess health care increasing the detection of ileus.[57]

TCA use has declined significantly since the advent of selective serotonin reuptake inhibitors in part due to tolerability concerns related to anticholinergic side effects, such as dry mouth and constipation. A meta-analysis[3] investigating 84 randomized clinical trials found a 22% rate of constipation, including cases of ileus.[2] Nonetheless, TCAs have important uses for mood and pain disorders, so the data generated here should reinforce the fact that TCA-treated schizophrenia patients are at 2-fold greater risk for ileus.

The significant risk associated with high-potency FGAs is less obvious, as high-potency FGAs, such as haloperidol, possess little affinity for muscarinic receptors.[33] The increased risk of ileus with this group of antipsychotics could be due to 2 possible reasons. The first is confounding by indication—in the 21st century, prescriptions for high-potency FGAs may be reserved for patients with more chronic and severe forms schizophrenia. As noted previously, it is plausible that a patient cohort comprised of individuals with greater overall illness severity might have greater negative symptoms and a more sedentary lifestyle. Supporting this hypothesis is the fact that patients treated with high-potency FGAs were receiving on average with more than double the defined daily dosages of these agents. Moreover, the OR for development of ileus based on anticholinergic DDD was nearly 2-fold greater within patients receiving high-potency FGAs than that seen for all users of anticholinergics (2.20 vs 1.19), indicating an interaction between the presence of high dose, high-potency FGA therapy and a higher ileus risk at any anticholinergic dose. Secondly, the use of high-defined daily dosages of high-potency FGA agents may necessitate the use of higher anticholinergic dosages to mitigate EPSs, resulting in an overall increased ileus risk. This is supported by the fact that treatment with anticholinergics was also associated with an increased risk of ileus for all patients, and the significantly greater anticholinergic DDD among those on high-potency FGAs compared with those on mid- or low-potency FGAs. Despite the widespread use of atypical antipsychotics, which, as a class, have lower extrapyramidal symptom risk than FGAs, nearly 20% of the patients with schizophrenia were using anticholinergics.

Despite the increased use of atypical antipsychotics, anticholinergics are still widely prescribed,[58] and this study emphasizes that anticholinergic is associated with a significant risk of ileus, and the continuous use of these drugs should be reevaluated.

Aside from the unique association found here between use of high-potency FGAs and ileus, other antipsychotics with little muscarinic affinity generally have limited risk for constipation and ileus. Registrational trial data filed with the United States Food and Drug Administration previously showed that aripiprazole and ziprasidone, agents with no significant anticholinergic properties, were associated with lower risk for constipation compared with other atypical antipsychotics, whereas clozapine-exposed patients experienced the highest risk.[5] Our findings replicate this data, with no ileus cases found associated with aripiprazole treatment and only one during treatment with ziprasidone.

This study should be interpreted within its limitations. These include the observational study design, lack of randomized treatment assignment, lack of a healthy control group, and potential influence of unmeasured and unknown confounding factors that cannot be controlled for, such as severity of psychiatric illness, inactivity, and diet. Furthermore, as already mentioned, confounding by indication might have biased the results for certain agents. Because we did not have access to the medical records, the increased risk of ileus related to any medication treatment represents a statistical association and not definite proof of causality. However, the exclusion from analysis of patients admitted within the last 14 days for any gastric complication and those cases with concomitant GI cancer increases the likelihood that antipsychotic usage or other psychotropic exposure played a role in the development of ileus. Some of the excluded ileus cases may have been related to the medication but we find it most correct to be conservative even though underreporting may occur. Although, excluding these patients may cause bias. Furthermore, another underreporting may have occurred; the fatal cases was derived from death certificates and not all physicians/pathologists might not be aware of clozapine effects on the GI systems.[59] Number of fatal cases was low, illustrated by the CIs of the ORs. Finally, over the counter medications, such as antihistamines and laxatives, which we were not able to control for, may have influenced the rate of ileus.

In conclusion, ileus is an important but little discussed side effect related to antipsychotic treatment, with potentially fatal consequences. This analysis should emphasize to psychiatrists the need for routine prophylaxis and ongoing monitoring for this side effect when prescribing certain antipsychotics and other psychotropics with anticholinergic activity. New guidelines for antipsychotic treatment should include recommendations about monitoring and interventions to avoid ileus among patients with schizophrenia, emphasizing the demographic parameters associated with increased ileus risk identified in this analysis, those antipsychotic agents associated with higher risk, and the role of concurrent exposure to other psychotropics with anticholinergic affinity.

Funding

Aalborg Psychiatric Hospital.

Acknowledgments

J.N. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Disclosures: J.N. has received research grants from H. Lundbeck, Chempaq, and Pfizer for clinical trials and received speaking fees from Bristol-Myers Squibb, AstraZeneca, Janssen Pharmaceutica, and Eli-Lilly. J.M.M. reports having received research support from: National Institutes of Health (as General Clinical Research Center support), National Institute of Mental Health, Bristol-Myers Squibb, and Pfizer, Inc. He also reports having received speaking or advising fees from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Dainippon Sumitomo Pharmaceuticals, Inc. (now Sunovion), Janssen Pharmaceutica, Novartis Pharmaceuticals, Organon USA (now Merck), Pfizer, Inc., Schering-Plough (now Merck), Vanda Pharmaceuticals, and Wyeth Pharmaceuticals Inc. (now Pfizer, Inc.). These entities had no influence on data analysis and preparation of the manuscript. The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Talley NJ, Jones M, Nuyts G, Dubois D. Risk factors for chronic constipation based on a general practice sample. *Am J Gastroenterol*. 2003;98:1107–1111.
2. McMahon AJ. Amitriptyline overdose complicated by intestinal pseudo-obstruction and caecal perforation. *Postgrad Med J*. 1989;65:948–949.
3. Trindade E, Menon D, Topfer LA, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *CMAJ*. 1998;159: 1245–1252.
4. Peyriere H, Roux C, Ferard C, et al. Antipsychotics-induced ischaemic colitis and gastrointestinal necrosis: a review of the French pharmacovigilance database. *Pharmacoepidemiol Drug Saf*. 2009;18:948–955.
5. de Hert M, Hudyana H, Dockx L, et al. Second-generation antipsychotics and constipation: a review of the literature. [published online June 9, 2010]. *Eur Psychiatry*. doi:10.1016/j.eurpsy.2010.03.003.
6. Davidson S, Judd F, Jolley D, Hocking B, Thompson S, Hyland B. Cardiovascular risk factors for people with mental illness. *Aust N Z J Psychiatry*. 2001;35:196–202.
7. Bobes J, Arango C, Aranda P, et al. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS Study. *Schizophr Res*. 2007;90:162–173.
8. Dworkin RH. Pain insensitivity in schizophrenia: a neglected phenomenon and some implications. *Schizophr Bull*. 1994; 20:235–248.
9. Singh MK, Giles LL, Nasrallah HA. Pain insensitivity in schizophrenia: trait or state marker? *J Psychiatr Pract*. 2006;12(2):90–102.
10. Lu MK. [Clinical analysis in the main side effects of clozapine: enclosed 600 cases report]. *Chung-Hua Shen Ching Ching Shen Ko Tsa Chih [Chin J Neurol Psychiatry]*. 1991;24(2):71–74.
11. Schwartz BJ, Frisolone JA. A case report of clozapine-induced gastric outlet obstruction. *Am J Psychiatry*. 1993;150:1563.
12. Hayes G, Gibler B. Clozapine-induced constipation. *Am J Psychiatry*. 1995;152:298.
13. Young CR, Bowers MB, Jr., Mazure CM. Management of the adverse effects of clozapine. *Schizophr Bull*. 1998;24:381–390.
14. Chengappa KN, Pollock BG, Parepally H, et al. Anticholinergic differences among patients receiving standard clinical doses of olanzapine or clozapine. *J Clin Psychopharmacol*. 2000;20:311–316.
15. Freudenreich O, Goff DC. Colon perforation and peritonitis associated with clozapine. *J Clin Psychiatry*. 2000;61:950–951.
16. Levin TT, Barrett J, Mendelowitz A. Death from clozapine-induced constipation: case report and literature review. *Psychosomatics*. 2002;43(1):71–73.
17. Khaldi S, Gourevitch R, Matmar M, Llory A, Olie JP, Chauvelot-Moachon L. Necrotizing enterocolitis after antipsychotic treatment involving clozapine and review of severe digestive complications—a case report. *Pharmacopsychiatry*. 2005;38:220–221.
18. Townsend G, Curtis D. Case report: rapidly fatal bowel ischaemia on clozapine treatment. *BMC Psychiatry*. 2006;6:43.
19. Dome P, Teleki Z, Kotanyi R. Paralytic ileus associated with combined atypical antipsychotic therapy. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:557–560.
20. Pelizza L, De Luca P, La Pesa M, Borella D. Clozapine-induced intestinal occlusion: a serious side effect. *Acta Biomed*. 2007;78(2):144–148.
21. Raedler TJ, Reimer J, Wiedemann K. Dose-dependent constipation with higher doses of quetiapine: a case series. *Int Clin Psychopharmacol*. 2007;22:244–246.
22. Rondla S, Crane S. A case of clozapine-induced paralytic ileus. *Emerg Med J*. 2007;24(2):e12.
23. Anonymous.Clozapine: ileus. *Prescrire Int*. 2008;17(96):160.
24. Leung JSY, Lee CC, Lee WK, Kwong PPK. Rapidly fatal clozapine-induced intestinal obstruction without prior warning signs. *Aust N Z J Psychiatry*. 2008;42:1073–1074.
25. Rege S, Lafferty T. Life-threatening constipation associated with clozapine. *Australas Psychiatry*. 2008;16:216–219.
26. de Bruin GJ, Bac DJ, van Puijenbroek EP, van der Klooster JM. [Ogilvie Syndrome induced by clozapine]. *Ned Tijdschr Geneeskd*. 2009;153:B437.

27. Hibbard KR, Propst A, Frank DE, Wyse J. Fatalities associated with clozapine-related constipation and bowel obstruction: a literature review and two case reports. *Psychosomatics*. 2009;50:416–419.
28. Lavi E, Rivkin L, Carmon M, Reissman P. Clozapine-induced colonic obstruction requiring surgical treatment. *Isr Med Assoc J*. 2009;11:385–386.
29. Martinez Diaz-Caneja C, Gonzalez-Molinier M, Conejo Galindo J, Moreno Iniguez M. Severe bowel ischemia due to clozapine with complete remission after withdrawal. *J Clin Psychopharmacol*. 2010;30:463–465.
30. McKinnon ND, Azad A, Waters BM, Joshi KG. Clozapine-induced Bowel Infarction: a case report. *Psychiatry (Edgmont)*. 2009;6(3):30–35.
31. Palmer SE, McLean RM, Ellis PM, Harrison-Woolrych M. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. *J Clin Psychiatry*. 2008;69:759–768.
32. Nielsen J, Foldager L, Meyer JM. Increased use of antibiotics in patients treated with clozapine. *Eur Neuropsychopharmacol*. 2009;19:483–486.
33. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors: focus on newer generation compounds. *Life Sci*. 1992;68:29–39.
34. Shahid M, Walker GB, Zorn SH, Wong EHF. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol*. 2009;23:65–73.
35. Kalkman HO, Subramanian N, Hoyer D. Extended radioligand binding profile of iloperidone: a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist for the management of psychotic disorders. *Neuropsychopharmacology*. 2001;25:904–914.
36. de Leon J, Wynn G, Sandson NB. The pharmacokinetics of paliperidone versus risperidone. *Psychosomatics*. 2010;51:80–88.
37. de Leon J, Odom-White A, Josiassen RC, Diaz FJ, Cooper TB, Simpson GM. Serum antimuscarinic activity during clozapine treatment. *J Clin Psychopharmacol*. 2003;23:336–341.
38. Bolden C, Cusack B, Richelson E. Antagonism by antimuscarinic and neuroleptic compounds at five cloned human muscarinic cholinergic receptors in Chinese hamster ovary cells. *J Pharmacol Exp Ther*. 1992;260:576–580.
39. Weiner DM, Meltzer HY, Veinbergs I, et al. The role of M1 muscarinic receptor agonism of N-desmethylclozapine in the unique clinical effects of clozapine. *Psychopharmacology*. 2004;177:207–216.
40. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology*. 2003;28:519–526.
41. Gershon MD. Review article: serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther*. 2004;20(suppl 7):3–14.
42. Sanger GJ. 5-hydroxytryptamine and the gastrointestinal tract: where next? *Trends Pharmacol Sci*. 2008;29:465–471.
43. Camilleri M. Serotonin in the gastrointestinal tract. *Curr Opin Endocrinol Diabetes Obes*. 2009;16(1):53–59.
44. Munk-Jorgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull*. 1997;44(1):82–84.
45. Barr CE, Mednick SA, Munk-Jorgensen P. Exposure to influenza epidemics during gestation and adult schizophrenia. A 40-year study. *Arch Gen Psychiatry*. 1990;47:869–874.
46. Pedersen CB, Mortensen PB. Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. *Arch Gen Psychiatry*. 2001;58:1039–1046.
47. Laursen TM, Labouriau R, Licht RW, Bertelsen A, Munk-Olsen T, Mortensen PB. Family history of psychiatric illness as a risk factor for schizoaffective disorder: a Danish register-based cohort study. *Arch Gen Psychiatry*. 2005;62:841–848.
48. Qin P, Nordentoft M. Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. *Arch Gen Psychiatry*. 2005;62:427–432.
49. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health*. 2009;5:4.
50. World Health Organization Collaborating Centre for Drug Statistics Methodology.*Guidelines for ATC Classification and DDD Assignment. Oslo, Norway 2010.* http://www.whocc.no/atc_ddd_index/. Accessed November 11, 2010.
51. Atkins M, Burgess A, Bottomley C, Riccio M. Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. *Psychiatr Bull*. 1997;21:224–226.
52. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry*. 2003;64:663–667.
53. Barbui C, Nose M, Bindman J, et al. Sex differences in the subjective tolerability of antipsychotic drugs. *J Clin Psychopharmacol*. 2005;25:521–526.
54. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. *J Psychopharmacol*. 2010;24:965–971.
55. John JP, Chengappa KN, Baker RW, Gupta B, Mortimer MT. Assessment of changes in both weight and frequency of use of medications for the treatment of gastrointestinal symptoms among clozapine-treated patients. *Ann Clin Psychiatry*. 1995;7(3):119–125.
56. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374:620–627.
57. Nielsen J, Munk-Jorgensen P, Skadhede S, Correll CU. Determinants of poor dental care in patients with schizophrenia: a historical, prospective database study. [epub ahead of print June 15, 2010]. *J Clin Psychiatry*. doi:10.4088/JCP.09m05318yel.
58. Nielsen J, le Quach P, Emborg C, Foldager L, Correll CU. 10-year trends in the treatment and outcomes of patients with first-episode schizophrenia. *Acta Psychiatr Scand*. 2010;122:356–366.
59. Flanagan RJ, Ball RY. Gastrointestinal hypomotility: an under-recognised life-threatening adverse effect of clozapine. [published online August 18, 2010]. *Forensic Sci Int*. doi:10.1016/j.forsciint.2010.07.021.