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Clozapine-induced gastrointestinal hypomotility: presenting features and outcomes, UK pharmacovigilance reports, 1992–2017

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Background

Clozapine-induced gastrointestinal hypomotility (CIGH) affects some 75% of patients treated with clozapine.

Aims

To document the incidence of potentially harmful CIGH in the UK.

Method

We studied spontaneous UK pharmacovigilance reports recorded as clozapine-related gastrointestinal adverse drug reactions, 1992–2017.

Results

There were 527 patients reported with potentially harmful CIGH; 33% ($n = 172$) died. Deaths averaged 1 per year 1992–1999, 5 per year 2000–2009 and 15 per year 2010–2017. Those who died were older (median 52 years *v.* 49 years) and had been prescribed clozapine for longer than those who recovered (median 11.3 years *v.* 4.8 years), but there was no difference in prescribed dose. Within the first 4 years of clozapine treatment, there were 169 reports of CIGH, of which 3% ($n = 5$) were fatal. At 10–14 years there were 63 reports of CIGH, of which 25% ($n = 16$) were fatal. Among the deaths, males were younger (median 51, range 22–89 *v.* median 57, range 24–89 years) with higher clozapine doses (median 450, range 100–900 *v.* median 300, range 12.5–800 mg/d) than females. In non-fatal CIGH, surgery was the most frequent outcome ($n = 92$). The procedures included appendectomy, ileostomy, total/partial colectomy, colostomy/stoma and proctosigmoidectomy. Clozapine dosage was reduced in 6 patients, stopped and restarted in 23, 'continued' in 6 and discontinued permanently in at least 76 patients.

Conclusions

The risk of serious morbidity/mortality from CIGH is substantial. The need to actively monitor bowel function and give laxatives to patients treated with clozapine is clear.

Keywords

Clozapine; gastrointestinal hypomotility; constipation; adverse drug reactions; pharmacovigilance.

Background

In the UK and in many other parts of the world, clozapine is licenced to treat treatment-resistant schizophrenia (treatment-refractory schizophrenia) in patients aged 18 years and older and Parkinson's disease psychosis (PDP). The dose for PDP is five- to ten-fold lower than in treatment-resistant schizophrenia. Off-label uses of clozapine include treatment of schizophrenia in patients younger than 18 years, bipolar disorder, depressive disorders, borderline personality disorder, substance misuse disorders, suicidality, aggression, tardive dyskinesia and tardive dystonia.

The benefits of clozapine

Clozapine is the only drug with proven efficacy in schizophrenia that has not responded to other antipsychotics.[1,2] In addition, clozapine acts to reduce suicidal behaviour in schizophrenia or schizoaffective disorder and is also indicated in patients with schizophrenia who show severe, untreatable adverse neurological reactions to other antipsychotics, including second-generation antipsychotics.

Adverse drug reactions

There is a recognised risk of blood dyscrasias especially in the first 3 months of clozapine treatment.[1] Current mandatory monitoring protocols focus on the known risk of agranulocytosis and have been very successful in minimising associated mortality. However, although clozapine has limited extrapyramidal effects, other adverse drug reactions (ADRs) limit its widespread use and pose special problems in the safe use of the drug.[2–5] Sialorrhea and dysphagia with clozapine may result in choking and aspiration pneumonia.[6] Clozapine-induced gastrointestinal hypomotility (CIGH) may cause constipation, ileus, bowel obstruction, aspiration pneumonia, peritonitis, life-changing surgery and even death.[7] Various forms of colitis in patients taking clozapine, apparently without constipation, have also been reported.[8]

Constipation is a common adverse effect of clozapine, occurring three times more frequently than with other antipsychotics.[9,10] The case-fatality rate for potentially harmful CIGH may be as high as 15.0–27.5%,[11,12] but depends on many factors, including the speed and efficacy of interventions. Training in the recognition of potentially harmful CIGH among those involved in the care of patients taking the drug varies greatly, in part because the clinical presentation is also so variable.[13,14] The significance of CIGH may not be considered following a sudden unexpected death of a patient taking clozapine unless the full clinical history is available for informed consideration by pathologists and coroners.[15]

Aims

In the UK, some ADR data are obtained through spontaneous reporting to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) Yellow Card scheme (https://yellowcard.mhra.gov.uk/) by health professionals and the public, including patients, carers and parents. All details are recorded, and clinical events are assessed and coded by medical assessors. This paper aims to describe the presenting features and post-mortem findings in patients reported to this scheme where a gastrointestinal ADR was reported and clozapine was mentioned.

Method

We studied reports to the MHRA Yellow Card scheme recorded as gastrointestinal disorders as per the Medical Dictionary for

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Regulatory Activities[16] and where clozapine was recorded as being either prescribed, or thought to be involved, 1992–2017 inclusive. Pharmacovigilance data were extracted using a pre-specified data-extraction form. We obtained the report identification number; reported date; patient demographics including age, gender; ADR event characteristics such as date of onset, severity and outcome; clozapine start date; clozapine dosage at ADR onset; concomitant gastrointestinal ADR terms; clinical investigations; other medications; treatment; and any additional documented commentary.

A subset of reports was created where any of the following ADRs were noted: intestinal obstruction, paralytic ileus, small intestinal obstruction, intestinal perforation, intestinal ischaemia, intestinal pseudo-obstruction, ischaemic colitis, large intestinal obstruction, megacolon, ileus, large intestine perforation, gastrointestinal obstruction, intestinal infarction, colitis ischaemic, faecal vomiting, gastrointestinal necrosis, necrotising colitis, gastrointestinal perforation, gastric perforation, gastrointestinal ischaemia, gastrointestinal mucosal necrosis or ileal perforation. We also included reports where the following ADRs were recorded, but only when the outcome resulted in hospital admission, surgery or was recorded as serious/life-threatening or fatal: constipation, faecaloma, oesophageal hypomotility, gastrointestinal hypomotility, functional gastrointestinal disorder, infrequent bowel movements, bowel movement irregularity, change of bowel habit, faecalith, faeces hard, gastrointestinal motility disorder, gastric hypomotility or impaired gastric emptying.

Each case was reviewed independently by two authors (S.A.H., S.E.-P.) to assess eligibility for inclusion. Reports where there were confounding comorbid conditions such as bowel cancer or inflammatory bowel disease that may have either caused, or contributed to the gastrointestinal pathology were excluded. In the case of disagreement or uncertainty about eligibility, a third opinion was sought (R.J.F.) and consensus was reached between authors. Published case reports[15,17] that had not been submitted as yellow card repots were excluded.

Data were extracted and imported into SPSS version 28 (SPSS Inc, Chicago, USA) for analysis. The data were analysed by age; gender; clozapine dose at onset of symptoms; duration of clozapine treatment prior to onset of CIGH; symptom onset date; clinical details of presentation; outcome and treatment; and other medications.

Demographic and clinical covariates were compared between those who were confirmed as having a fatal outcome and those who either recovered, or had an unknown outcome. Continuous variables such as duration of treatment were compared using Mann–Whitney *U*-tests. Differences were considered statistically significant when $P < 0.05$.

Ethics approval

MHRA Study Number AYCD044. To preserve anonymity, identifying demographic data were removed from the MHRA data and date-of-birth information has been translated into age ranges.

Results

There were 4426 clozapine-related yellow card ADR reports within the gastrointestinal disorders class (Table 1). There were 6980 individual ADRs recorded. Vomiting ($n = 1018$ reports), constipation ($n = 807$), salivary hypersecretion ($n = 698$), diarrhoea ($n = 585$), nausea ($n = 363$), abdominal pain ($n = 292$), intestinal obstruction ($n = 292$), and dysphagia ($n = 230$) were the features recorded most frequently, accounting for 62% of all reports. There were 704 unique reports ($n = 278$ fatalities) that met the CIGH inclusion criteria initially.

Excluded reports

Of the 704 unique reports, 175 ($n = 104$ fatal) were excluded on further review because of the presence of confounding pathology, and a further 2 deaths were excluded because they were literature reports (Supplementary Table 1 available at https://doi.org/10.1192/bjp.2022.24). Of the non-fatal excluded cases, comorbidities such as cancer or intestinal adhesions were recorded in 11 reports. A further 28 reports were excluded because constipation was noted without hospital admission, surgery or the event was recorded as not being potentially harmful. The remaining reports were excluded following individual review by two authors because insufficient information was provided to confirm the presence of potentially harmful CIGH. Of the deaths, 12 had features that were suggestive of CIGH, but again insufficient information was provided to confirm this with certainty. Overall, there were 222 gastrointestinal ADRs reported in the excluded reported (28 specific ADR terms; Supplementary Table 2). Constipation, intestinal obstruction and paralytic ileus were most frequently reported in non-fatal cases and in deaths. Intestinal dilation was reported in ten deaths, but was not remarked upon in someone who did not die.

Potentially harmful CIGH

There were 527 unique reports of potentially harmful CIGH ($n = 172$ fatal). Deaths averaged 1 per year 1992–1999, 5 per year 2000–2009, and 15 per year 2010–2017 (Table 1).

Among the deaths, men were significantly younger ($P < 0.05$) and were prescribed a higher dose of clozapine ($P < 0.02$) than women (Table 2).

Patients who died were older (median 52 years *v.* 49 years, $P < 0.005$) and had been prescribed clozapine for longer than those who recovered (median 11.3 years *v.* 4.8 years, $P < 0.001$), but there was no difference in prescribed dose (Table 3).

Clozapine concentrations of 1.69 and 1.29 mg/L, respectively, were reported in two non-fatal incidents (no other details provided). In two deaths, clozapine and *N*-desmethylclozapine (norclozapine) concentrations (sample type not given) were provided for samples taken in the month before death. In the first, clozapine and norclozapine concentrations of 0.56 and 0.43 mg/L, respectively, were reported and in the second, clozapine and norclozapine concentrations from three samples were 0.10 or less for both clozapine and norclozapine. Clozapine and norclozapine concentrations of 2.38 and 1.62 mg/L, and 1.12 mg/L and 0.68 mg/L, respectively, were reported in two deaths (details of sample type and timing not provided).

The duration of clozapine treatment until potentially harmful CIGH developed was provided in 316 (89%) and 37 (22%) of non-fatal and fatal reports, respectively (Fig. 1). Some 83 episodes occurred within the first year of treatment, but only 1 death was reported in this period. Within the first 4 years of clozapine treatment there were 169 reports, of which 3% ($n = 5$) were fatal. At 10–14 years of clozapine treatment, there were 63 reports of CIGH, of which 25% ($n = 16$) were fatal (Fig. 1).

In the 355 non-fatal reports, there were 110 mentions of the use of laxatives in 72 (20%) patients prior to the onset of potentially harmful CIGH (some reports had laxatives mentioned more than once). Specifically, osmotic, stimulant, bulk, and stool softening laxatives were mentioned in 56, 30, 13 and 11 instances, respectively. Regarding drugs known to cause constipation, opioids, tricyclic antidepressants and other anticholinergic drugs (principally ipratropium) were mentioned on 19, 13 and 13 instances, respectively. There were 93, 37 and 11 mentions of use of antipsychotics in addition to clozapine, antacids (omeprazole, 29 mentions), and antibiotics in 83 (23%), 29 (8%) and 8 (2%) reports, respectively.

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Table 1 UK clozapine-related adverse drug reactions (ADR) reports submitted to the Medicines and Healthcare Products Regulatory Agency (MHRA) via the Yellow Card System, 1992–2017; data are number of reports[a]

	All reports, *n* (% male)		Gastrointestinal disorders, *n* (% male)		Potentially harmful CIGH, *n* (% male) (see Tables 2 and 3)	
Year received	Non-fatal	Fatal	Non-fatal	Fatal	Non-fatal	Fatal
1992	211 (62)	12 (58)	27 (74)	0 (–)	0 (–)	0 (–)
1993	227 (62)	30 (67)	27 (52)	3 (67)	0 (–)	1 (0)
1994	159 (66)	25 (64)	14 (71)	0 (–)	0 (–)	0 (–)
1995	150 (59)	35 (74)	9 (33)	2 (100)	0 (–)	0 (–)
1996	164 (67)	18 (83)	11 (82)	0 (–)	1 (100)	0 (–)
1997	142 (57)	11 (36)	15 (73)	3 (33)	2 (100)	3 (33)
1998	207 (70)	27 (63)	16 (56)	7 (43)	2 (100)	1 (–)
1999	396 (65)	38 (68)	47 (62)	11 (64)	10 (50)	2 (50)
2000	480 (62)	37 (70)	72 (57)	11 (73)	8 (50)	4 (75)
2001	585 (66)	37 (73)	77 (69)	10 (80)	12 (67)	4 (100)
2002	779 (63)	44 (70)	105 (70)	11 (64)	7 (71)	6 (83)
2003	1015 (67)	50 (64)	191 (68)	10 (70)	13 (85)	4 (50)
2004	1191 (67)	61 (87)	183 (62)	11 (91)	15 (80)	3 (100)
2005	1588 (68)	74 (72)	149 (64)	9 (78)	10 (80)	4 (50)
2006	871 (65)	83 (60)	116 (66)	10 (70)	10 (80)	4 (50)
2007	1156 (68)	137 (67)	174 (61)	17 (71)	14 (86)	4 (100)
2008	1343 (68)	209 (67)	217 (72)	32 (72)	13 (77)	8 (63)
2009	1586 (64)	262 (66)	208 (63)	39 (67)	14 (57)	7 (29)
2010	2027 (65)	391 (69)	279 (64)	68 (71)	16 (81)	17 (71)
2011	3173 (62)	629 (70)	458 (62)	95 (69)	23 (61)	18 (61)
2012	2188 (66)	348 (72)	299 (64)	68 (72)	21 (57)	10 (90)
2013	2037 (66)	344 (71)	248 (65)	59 (66)	32 (84)	16 (50)
2014	1678 (66)	362 (69)	191 (70)	65 (69)	27 (70)	13 (62)
2015	1603 (63)	397 (68)	181 (61)	50 (72)	31 (81)	11 (73)
2016	2037 (66)	456 (67)	187 (66)	68 (66)	25 (72)	20 (65)
2017	2468 (67)	430 (71)	207 (62)	59 (73)	49 (65)	12 (75)
Totals	29 461 (65)	4547 (69)	3708 (64)	718 (70)	355 (72)	172 (65)

CIGH, clozapine-induced gastrointestinal hypomotility.
a. All ADR reports include ADRs from all system organ classes. All ADR reports and gastrointestinal disorders data obtained directly from the MHRA interactive drug analysis profile (MHRA Yellow Card Data; https://yellowcard.mhra.gov.uk/)

In the 172 deaths, there were 94 mentions of the use of laxatives in 59 (34%) patients prior to the onset of potentially harmful CIGH. Specifically, use of osmotic, stimulant, bulk and stool softening laxatives were mentioned in 51, 19, 14 and 10 instances, respectively. Agents known to increase the risk of constipation such as tricyclic antidepressants, opioids and other anticholinergics had been recorded in 15, 6 and 4 instances, respectively. There were 78, 35 and 10 mentions of prior use of other antipsychotics together with clozapine, antacids (omeprazole, 22 mentions) and antibiotics in 9 (5%), 29 (17%), and 9 (5%) reports, respectively.

Treatment of established CIGH

In eight non-fatal reports treatment location was not provided; in four laxatives were given, and in the remaining four an enema was undertaken. A further 220 patients recovered after hospital treatment. Ten such patients were given oral laxatives, seven received an enema, and in six 'conservative management' was recorded. However, surgery was the outcome mentioned most frequently ($n = 92$). No further details were provided in 37 of these latter reports, but laparotomy ($n = 22$), appendectomy ($n = 7$), ileostomy ($n = 9$), total colectomy ($n = 7$), partial colectomy ($n = 11$), colostomy ($n = 5$), stoma ($n = 7$), hemicolectomy ($n = 2$), and proctosigmoidectomy ($n = 2$) were recorded. The clozapine dose was reduced in 6 instances, stopped and restarted in 23, and 'continued' in 6. Clozapine was discontinued permanently in at least 76 patients.

In the deaths, details of treatment immediately prior to death were provided in 22 (13%) instances. Laxative administration was recorded in four reports, enemas in eight and manual evacuation of faeces was performed in two instances. Surgery (no details of procedure provided) was recorded in five reports, laparotomy in two and colectomy, colostomy and partial colectomy in three separate

Table 2 Summary data: male versus female – potentially harmful clozapine-induced gastrointestinal hypomotility, UK pharmacovigilance reports, 1992–2017

	Male		Female				
Variable	*n*	Median (range)	*n*	Median (range)	*P*	*U*-statistic	*Z*-score
Non-fatal	256		99				
Age, years	248	48 (17–80)	95	50 (19–81)	0.17	10 649	−1.38
Dose, mg/d	77	400 (75–825)	29	350 (12.5–1000)	0.93	1170	−0.09
Duration of treatment, days	228	1925 (3–9643)	88	781 (6–9141)	0.73	9425	−0.34
Fatal	112		60				
Age, years	106	51 (22–89)	55	57 (24–89)	<0.05	2361	−1.98
Dose, mg/d	72	450 (100–900)	29	300 (12.5–800)	<0.02	706.5	−2.54
Duration of treatment, days	23	4280 (3–8439)	14	3944 (1411–8291)	0.80	146.0	−0.26

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Table 3 Summary data: non-fatal versus fatal – potentially harmful clozapine-induced gastrointestinal hypomotility, UK pharmacovigilance reports, 1992–2017

	Non-fatal (n = 355)		Fatal (n = 172)				
Variable	n	Median (range)	n	Median (range)	P	U-statistic	Z-score
Age, years	343	49 (17–81)	161	52 (22–89)	<0.005	23 108	−2.96
Dose, mg/d	106	400 (12.5–1000)	101	400 (12.5–900)	0.81	5248	−0.24
Duration of treatment, days	316	1745 (3–9643)	36	4129 (3–8439)	<0.001	2567	−5.20

reports. One patient died awaiting surgery. The location of treatment was only provided in 13 instances; all were within a hospital (surgery n = 10, manual evacuation n = 2, enema n = 2).

Pathology of CIGH

Of the 527 reports included in the study, 1218 gastrointestinal ADRs were recorded (96 specific ADR terms; Table 4). Intestinal obstruction and constipation were most commonly reported. Of the non-fatal reports, 57% had more than one ADR recorded (eight reports, six or more). In the deaths, two had eight ADRs recorded, one had nine reported, and a single patient had 10 reported (abdominal distension, abdominal pain upper, diarrhoea, faecaloma, gastrointestinal motility disorder, paralytic ileus, intestinal dilatation, intestinal infarction, large intestinal obstruction and vomiting).

The presenting clinical features were not always reported. In those who died, the clinical features recorded immediately prior to death included constipation (n = 12), abdominal pain (n = 11), vomiting (n = 10), diarrhoea (n = 4), shortness of breath (n = 3) and abdominal distension (n = 3). In two instances where patients died from intestinal obstruction secondary to faecal impaction, it was noted specifically that they had not complained of any gastrointestinal symptoms beforehand. Often, minor or non-specific symptoms seemed to belie potentially harmful pathology. For example, one patient died after one day of nausea, vomiting and abdominal pain. At the post-mortem toxic megacolon with bowel ischaemia and infarction were recorded. Another patient who experienced abdominal pain only 3 days after initiation of clozapine had a bowel resection, but died of septicaemia secondary to intestinal ischaemia. Two patients presented to hospital following a week of abdominal pain and vomiting, eventually dying of intestinal obstruction. The reports summarised in Supplementary Table 3 were selected to illustrate how critically ill many people became even if they recovered.

In some of the reports studied, gastrointestinal hypomotility events were not attributed to clozapine by clinicians reporting the ADRs. Examples include a woman aged 50–59 years who had been prescribed clozapine for over 5 years (final dose 400 mg/d). She survived a major operation for bowel obstruction and clozapine was stopped. The reporter thought that the cause of the bowel obstruction was simply that the patient did not drink enough fluids.

Another example is of a man aged 50–59 years who was prescribed clozapine who presented with abdominal pain. It was thought that he may have aspirated gastric contents. He developed respiratory failure and was intubated and ventilated. Peritonitis owing to perforation of the sigmoid colon was diagnosed. The distal descending colon and proximal sigmoid colon were resected leaving double-barrelled ileostomy, but he developed renal and cardiac failure and died. It was suggested that severe constipation had been caused simply by a diet lacking in fibre. We cannot locate any published reports of reduced fluid intake or a diet relatively lacking in fibre causing fatal bowel obstruction/perforation.

Finally, a 40–49 year old woman had been prescribed 300 mg/d clozapine. She had complained of constipation for several months and had accepted treatment for this occasionally, but died after aspirating faeculent vomit. Death was attributed to paralytic ileus, megacolon and faecal impaction. It was thought that the most likely cause of the bowel spasticity was the use of benztropine. Benztropine is a possible exacerbating factor for CIGH, but benztropine use has only been reported as a causal factor in fatal gastrointestinal hypomotility in combination with antipsychotics, particularly clozapine.

Discussion

The fact that treatment with clozapine can cause life-threatening constipation unless managed appropriately has been known since at least 1991, yet it only become apparent that CIGH is such a

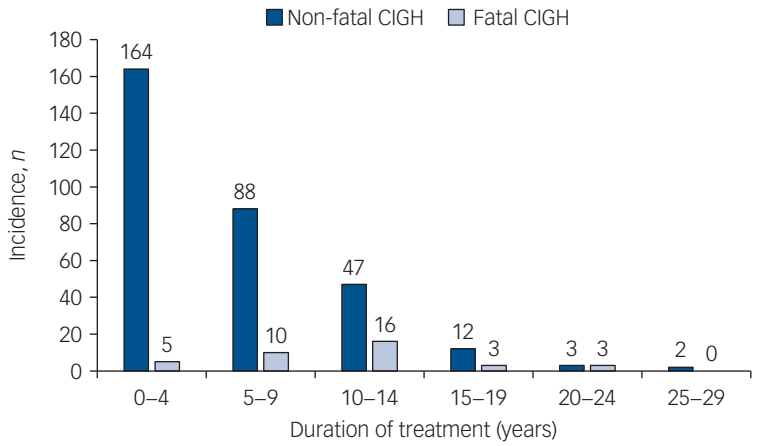

Fig. 1 Duration of clozapine treatment until development of life-threatening clozapine-induced gastrointestinal hypomotility (CIGH) in 316 non-fatal and 37 fatal reports.

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Table 4 Adverse drug reactions ($n = 1218$) reported in patients with potentially harmful clozapine-induced gastrointestinal hypomotility (CIGH) ($n = 527$)

Adverse drug reaction	Non-fatal, *n*	Fatal, *n*
Abdominal adhesions	4	2
Abdominal discomfort	5	5
Abdominal distension	25	17
Abdominal mass	1	1
Abdominal pain	41	21
Abdominal pain lower	2	1
Abdominal pain upper	3	3
Abdominal rigidity	2	0
Abdominal symptom	1	0
Abdominal tenderness	3	0
Abnormal faeces	1	0
Acute abdomen	2	0
Anal incontinence	2	1
Bowel movement irregularity	1	0
Breath odour	1	0
Colitis	3	0
Colitis ischaemic	5	6
Constipation	123	72
Diarrhoea	22	7
Diverticular perforation	0	2
Diverticulum	0	2
Dry mouth	1	0
Dyschezia	1	0
Dyspepsia	2	0
Dysphagia	4	2
Enteritis	1	0
Eructation	1	0
Faecal vomiting	7	2
Faecalith	0	2
Faecaloma	26	37
Faeces discoloured	1	0
Faeces hard	3	0
Flatulence	2	1
Functional gastrointestinal disorder	7	1
Gastric dilatation	1	1
Gastric disorder	3	3
Gastric hypermotility	1	0
Gastric ulcer	0	2
Gastritis	1	1
Gastritis erosive	0	1
Gastrointestinal disorder	1	1
Gastrointestinal haemorrhage	0	3
Gastrointestinal hypomotility	3	5
Gastrointestinal motility disorder	1	3
Gastrointestinal necrosis	2	2
Gastrointestinal obstruction	16	3
Gastrointestinal oedema	1	0
Gastrointestinal perforation	1	0
Gastrointestinal sounds abnormal	3	2
Haematemesis	3	5
Ileus	17	1
Ileus paralytic	50	4
Ileus spastic	0	1
Impaired gastric emptying	0	1
Inflammatory bowel disease	1	0
Infrequent bowel movements	2	1
Intestinal congestion	0	1
Intestinal diaphragm disease	1	0
Intestinal dilatation	14	13
Intestinal haemorrhage	0	1
Intestinal infarction	2	10
Intestinal ischaemia	12	12
Intestinal obstruction	171	55
Intestinal perforation	16	13
Intestinal prolapse	0	1
Intestinal pseudo-obstruction	19	9
Intestinal stenosis	1	1
Intestinal ulcer	1	1
Intra-abdominal fluid collection	1	0
Irritable bowel syndrome	1	0
Large intestinal obstruction	8	15
Large intestinal ulcer	0	1
Large intestine perforation	8	9
Megacolon	8	10
Melaena	1	0
Mesenteric arteriosclerosis	0	1
Mesenteric artery thrombosis	0	2
Nausea	8	1
Necrotising colitis	1	0
Oesophagitis	1	0
Pancreatic disorder	0	1
Pancreatic steatosis	1	0
Pancreatitis	1	1
Pancreatitis necrotising	0	1
Peritoneal adhesions	0	2
Rectal haemorrhage	1	0
Retching	1	0
Salivary hypersecretion	1	5
Small intestinal obstruction	24	5
Stomach mass	0	1
Thrombosis mesenteric vessel	1	0
Upper gastrointestinal haemorrhage	0	1
Vasculitis gastrointestinal	1	0
Volvulus	8	15
Volvulus of small bowel	1	0
Vomiting	53	28

serious problem in clinical practice some 15–20 years later.[7,15,18] Why, when pharmacovigilance mechanisms detected the risk of clozapine-induced agranulocytosis so rapidly, were they so much less effective in detecting CIGH? The explanation for this fact is likely several fold.

First, agranulocytosis is a discrete condition, with a low base rate in the general population. It is easily diagnosed by a blood test and is always considered pathological. It is attributed to an ADR in 70% of cases, the case-fatality rate is high if untreated, and it is considered a medical emergency requiring immediate action. In contrast, gastrointestinal hypomotility is non-specific. There is no simple, accurate diagnostic test. In the general population constipation is common, yet people do not normally die from it. Clinicians continue to be influenced by this and view CIGH as a vexatious, yet relatively benign, adverse effect, one that should go away if only their patients were to eat better and exercise more. To create a pharmacovigilance signal, CIGH needed to be recognised and reported as an ADR by clinicians, but this often does not occur because CIGH is misattributed to either diet or lifestyle factors. When CIGH was reported as an ADR, it is possible that the myriad of possible synonyms diluted the signal.

Although constipation is the most commonly reported problem, CIGH can also result in dysphagia, gastroparesis, ileus, bowel obstruction, faecal aspiration, colon perforation, toxic megacolon, 'acute abdomen' and death (Supplementary Tables 3–5). Dysphagia on clozapine can lead to choking and in some cases vomiting and/or inhalation of food particles, which in turn may precipitate and be reported as pneumonia.[19] It may be that for many years CIGH was simply not as apparent as other adverse effects such as agranulocytosis that have one commonly recognised term. In addition, it is possible that the dramatic cluster of agranulocytosis deaths reported in Finland galvanised action on haematological adverse effects, whereas the insidious accumulation of deaths owing to CIGH meant that for many years it remained both poorly recognised and below the threshold for action by regulators. It was not until 2007 that warnings about CIGH began to be issued by pharmacovigilance agencies.

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Finally, the move to non-smoking hospitals may have added to the problem, clozapine dose requirement being markedly reduced if the patient stops smoking. Indeed, giving up smoking is itself associated with constipation in 1 in 6 smokers not taking clozapine, and that for about 1 in 11 the problem can be severe.[20] One patient who stopped smoking had been prescribed 550 mg/d clozapine (plasma clozapine and norclozapine 1.15 and 0.88 mg/L, respectively). The dose was reduced to 500 mg/d, but the patient became severely constipated and died (Supplementary Table 5). Clozapine was stopped on admission to an acute hospital, but the plasma clozapine and norclozapine were 2.84 and 1.60 mg/L, respectively, 4 days post-admission.

Pathologists have little specialist knowledge of clozapine. These difficulties plus the fact that yellow card reports are voluntary except for manufacturers if they are informed of a suspected ADR in a patient prescribed one of their products makes it unlikely that the data presented here are a complete picture of the burden of CIGH in the UK over the period studied. This is emphasised by the fact that one of us (R.J.F.) gave evidence at nine inquests or procurator fiscal enquiries in the UK where CIGH was the likely underlying cause of death in the period under study, none of which were notified to the MHRA via the yellow card scheme as gastrointestinal related and are thus not included in our survey (Supplementary Table 5).

Bowel motility studies suggest CIGH occurs in at least 75% of patients given clozapine.[14] Potentially harmful CIGH can develop at any time in treatment (Tables 2 and 3) and is often difficult to diagnose, with many patients not complaining of symptoms until serious pathology has developed, if indeed they complain at all (Supplementary Tables 3–5). Although many patients were reported as having massive faecal impaction at autopsy, constipation had often not been reported beforehand. In the non-fatal cases and in those who died the prior use of laxatives was recorded in only 20% and 34% of people, respectively. This suggests constipation is not being recognised and treated seriously despite the sometimes fatal consequences.

Patients treated with clozapine may not recognise or experience constipation in the same way as others owing to changes in pain sensitivity or habituation, and thus may be less likely to complain.[14] This decreased sensitivity places the responsibility for actively monitoring and treating CIGH on health professionals; yet the potential severity of CIGH remains poorly recognised among mental health staff.[13,14]

Limitations of the study

Retrospective pharmacoepidemiological studies are subject to several limitations. Firstly, ADR reporting in the UK is voluntary except for industry reporting. Spontaneous reporting is beleaguered by underreporting, with only some 5% of ADRs reported to pharmacovigilance centres. Although clozapine ADR reporting rates are said to be high owing to clozapine monitoring systems, reporting is unlikely to be complete. Spontaneous reporting is also vulnerable to selection bias, with serious (and fatal) ADRs reported more often. These factors mean that case-fatality rates calculated from such data can be overestimates, whereas the true incidence is underestimated. Finally, the complex nature of many presentations and the lack of recognition of CIGH as the underlying cause inevitably meant that data of interest such as plasma clozapine concentration at the time of onset of potentially harmful CIGH, information on (changes in) smoking habit and total anticholinergic load were missing in almost all instances.

Overall, the incidence of the potentially dangerous complications of CIGH has been estimated as 4–8 per 1000 patients treated with clozapine in a 1-year period and the case-fatality rate at 15–27.5%.[11] In the UK in November 2019 there were 37 301 patients under treatment with clozapine.[21] In 2017 there were 61 ADR reports of potentially harmful CIGH with a case-fatality rate of 20% (Table 1). Taking the 2019 figure of patients prescribed clozapine this gives an incidence of potentially dangerous CIGH of 1.6 per 1000 suggesting incomplete reporting of non-fatal cases. Overall, the case-fatality rate was 33%, again suggesting incomplete reporting of non-fatal CIGH (Table 1). Study of non-fatal occurrences is important because often treatment is profound and the outcome life-changing (Supplementary Tables 3–5).

The EudraVigilance database (https://dap.ema.europa.eu/analytics/saw.dll?PortalPages) listed 79 390 individual cases for clozapine, of which 41 330 (73%) reports from the European Economic Area (EEA, population some 520 million) were received from the UK (population some 67 million). The reason for this anomaly may lie in different rates of adverse event reporting between the UK and the rest of the EEA, especially since clozapine is thought to be underutilised in the UK as compared with the rest of Europe.[22] The corollary is of course that other European countries may experience relative underreporting of clozapine ADRs as compared with the UK.

A report using the EudraVigilance database cited 1472 CIGH cases from the study period (2011–2020) with a mortality rate of 10%.[23] Clearly there may be overlap with the data presented here (Table 1) and also with some of the pharmacovigilance reports studied by De Leon et al.,[24] which gave a global estimate of CIGH-related mortality data (2842 cases, mortality rate 12%).

Be this as it may, it should be remembered that the data presented in Tables 1, 2 and 3 are incomplete as regards UK CIGH-related deaths 1992–2017 (Supplementary Table 5). Some of the excluded reports (Supplementary Table 1) may have been CIGH related, at least in part. The full extent of the morbidity and mortality from CIGH in the UK in the period studied thus remains unknown.

Mechanism of CIGH

There appear to be four main mechanisms whereby CIGH can progress to life-threatening conditions. All involve the accumulation of faeces within the bowel leading to distension, ischaemia, infection and/or aspiration. The first mechanism, distension, seems to be the most common and often precedes the others. There may also be a positive feedback loop: gastrointestinal hypomotility causes inflammation, which may impede clozapine metabolism resulting in increased clozapine plasma concentrations at constant dose,[25] which in turn could lead to greater gastrointestinal hypomotility.

Obstruction caused by impacted faeces (sometimes termed 'pseudo-obstruction') can produce increased intraluminal pressure proximal to the impaction. This distension may lead to perforation, especially if the resultant bowel diameter exceeds 12 cm. The mortality rate for pseudo-obstruction is estimated at 40% if perforation occurs. Increased intraluminal pressure may eventually lead to reduced local arterial circulation and ischaemia. Ischaemic phenomena may result in local inflammatory reactions and necrosis, leading to ulcers and the risk of perforation, known as ischaemic colitis, ulcers and stercoral perforation, respectively. Stercoral perforation is defined as a perforation secondary to a faecal bolus, with evidence of local pressure ulcer and acute inflammation, in the absence of another explanation for perforation. This complication occurs most frequently in the sigmoid and rectosigmoid colon for three reasons: the faeces become harder in these regions as water is absorbed prior to excretion, the diameter of the colon becomes smaller and the vascularisation on the antimesenteric border is poorer.

Toxic megacolon involves the processes of distension and ischaemia, being characterised by colonic distension exceeding 6 cm in the

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presence of colitis, with signs of systemic toxicity. Although usually associated with ulcerative and pseudomembranous colitis, toxic megacolon may evolve secondary to faecal impaction caused by increased intraluminal pressure.[26] Distension of the bowel because of CIGH and faecal stasis may also increase susceptibility to microbial pathogens such as *Clostridium perfringens*. Gastrointestinal stasis can promote the proliferation of intestinal flora causing bacterial migration across the bowel wall resulting in sepsis. The impacted stool may hinder the normal protective mechanism of diarrhoea with retained enterotoxins causing intestinal tissue damage. This could account for fatal outcomes in psychiatric patients treated with clozapine who have gastroenteritis whereas patients who are not treated with clozapine experience benign illnesses.

Aspiration may result either from inhalation of faeculent vomitus, or as a result of dysphagia. Faeculent vomiting occurs after gastrointestinal mass peristalses act against an impacted mass, causing retrograde movement of faecal matter through the pylorus and into the stomach. Aspiration of this material can cause a chemical pneumonitis, pneumonia or even asphyxiation. A cause of death simply recorded as 'bronchopneumonia' will likely miss an underlying connection to CIGH.[27]

Prevention of CIGH

CIGH is an anticholinergic and antiserotonergic effect,[9] hence other products with these effects should be used with caution in patients taking clozapine. There is a risk that anticholinergics such as hyoscine used to treat clozapine-induced hypersalivation may exacerbate CIGH. Prophylactic laxatives(s) such as senna (with or without docusate) and/or polyethylene glycol, for example macrogol, should be prescribed. Frequent bowel performance review is indicated. The risk of developing potentially harmful CIGH may be higher at higher plasma clozapine concentrations,[28] hence prompt dose adjustment if a patient stops smoking may help limit progression to CIGH.[29]

Patients, relatives and other carers must be informed of the factors inherent in the safe use of clozapine including the risks of dysphagia and constipation (Appendix). The risks inherent in altering smoking habit (and of passive smoking) without discussing the required alteration in clozapine dosage with their psychiatrist must be stressed. There may be an increasing risk of harm from CIGH with duration of clozapine therapy (Fig. 1). People tend to smoke less as they get older,[30] whereas the number of chronic conditions and thus of co-prescribed medication tends to increase. Adverse effect monitoring may become less assiduous with time. There may not be regular review of clozapine dose requirement.[31] In any event, there must be guidance as to what action to take once an issue possibly related to clozapine has been identified.

The most commonly reported presentations of potentially harmful CIGH are abdominal pain and abdominal distension (sometimes referred to as 'clozapine belly'), occurring in 73% and 55% of reports, respectively.[7] The significance of these signs is often missed. The patient's general practitioner must be informed that their patient has been prescribed clozapine and must be aware of the special issues surrounding the safe use of the drug.[4,6] The fact of prescription of clozapine should be recorded on the patient's electronic prescribing record, so that it appears in the patient's summary care records if they are admitted to hospital. Issues do arise because clozapine is prescribed in secondary care but treatment of some ADRs such as CIGH is delegated to primary care. General practitioners must not only recognise clozapine adverse effects such as CIGH but also report them to the prescriber. Laxative treatment once initiated must be continued. The mental health pharmacist also has an important role here. The suggestion that education and training in the use of clozapine must become a mandatory requirement of all psychiatry residence and continuing professional development programmes[32] would need to take into account the fact that prevention of CIGH requires a concerted effort from all those involved in the care of the patient, not just the prescribing psychiatrist.

Treatment of CIGH

Patients with potentially harmful CIGH should have bowel rest, intravenous fluids, correction of acidosis and antibiotics as appropriate. Nasogastric or colonoscopic decompression may be sufficient, but clinical instability or abdominal sepsis are indications for immediate surgery. First responders, accident and emergency, admission wards and intensive therapy unit staff need to have ready access to information on the various manifestations of CIGH such as constipation and choking. They also need to be aware of the special issues surrounding the prescription and dispensing of clozapine and the need to liaise with specialists (psychiatrists, mental health pharmacists) in order to maintain clozapine treatment unless contraindicated by other factors. For example, if someone taking clozapine is admitted to a medical or other non-smoking unit, their smoking status must be assessed promptly and their clozapine dose reduced as necessary. Because clozapine may not appear on a patient's GP summary care record any patient admitted with a significant mental health diagnosis such as schizophrenia but not on medication to treat it should be followed up in case they are taking clozapine and in case the underlying problem is related to CIGH.

Post-mortem diagnosis

It is important to collate information on people who die while taking clozapine in order to help prevent future deaths. Suspected ADRs need to be reported to pharmacovigilance agencies with detailed and accurate clinical data. Pathologists must be provided with as much information as to the sequence of events leading up to death as possible before undertaking post-mortem examinations. If this is not feasible then the information should be provided as soon as possible thereafter. Pathologists also need more education as to the protean manifestations of CIGH.

Research needs

More research is indicated in order to better understand factors that may increase the risk of harm from CIGH. Potentially important factors include age, gender, effective clozapine dose, concomitant medication, the duration of clozapine therapy, (changes in) smoking habit, adherence to and effectiveness of laxative treatment, and the relationship between plasma concentrations of clozapine and the risk of complications from CIGH.[33–35] Reports should include plasma clozapine and norclozapine data whenever possible.

Implications

Although the findings presented here as to the morbidity and mortality from the complications of CIGH in the UK in the period studied are incomplete, the data do emphasise the gravity and complexity of the problem. The continued trickle of case reports often repeating findings that are already well-known simply serves to give the problem a rarity value that is not borne out by studying national pharmacovigilance data.[12] Moreover, simply concentrating on the mortality from CIGH ignores the sometimes life-changing surgery and other interventions that may be necessary to ensure survival once CIGH has become established. Indeed, the longer-term outcome in those who undergo life-changing surgery such as colectomy as a result of CIGH remains unknown.

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The need to monitor bowel function actively in patients treated with clozapine is clear. This being said, neither the use of anticholinergics such as hyoscine to ameliorate clozapine-induced hypersalivation nor the optimal use of laxatives to prevent the onset of potentially harmful CIGH is clear-cut. More effort is needed especially in monitoring adherence to, and efficacy of, laxative treatment in order to minimise morbidity and mortality from CIGH.

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Supplementary material

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Data availability

The authors confirm that summaries of the data supporting the findings of this study are available within the article and its supplementary material. The primary data are not publicly available owing to reasons of patient confidentiality and could only be obtained by direct application to the MHRA.

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Author contributions

S.A.H. and S.E.-P. analysed the data and wrote an initial draft of the paper, A.I. extracted the data and R.J.F. initiated and planned the study, helped with data analysis and wrote the final draft of the paper.

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None.

Appendix

Recommendations for the prevention and identification of potentially harmful clozapine-induced gastrointestinal hypomotility (CIGH)

Appendix

Recommendations

Regulators

1. Review and update the information provided to prescribers and consumers on clozapine including:
   (a) a description of the CIGH spectrum;
   (b) updated information about prevalence.

   A warning regarding CIGH 'red flags' should be included, that is, either moderate-to-severe abdominal pain lasting over an hour; or any abdominal pain/discomfort lasting over an hour and any one or more of the following: abdominal distension; diarrhoea; vomiting; absent or high-pitched bowel sounds; metabolic acidosis; haemodynamic instability; leucocytosis; or other signs of sepsis. These signs and symptoms must be treated seriously and an urgent medical and/or surgical opinion must be sought, notifying the assessing clinician that the person is taking clozapine and consequently is at high risk for serious gastrointestinal complications.
2. Clozapine should remain a restricted medication, to be used under expert guidance and restricted to people who have conditions for which there is strong evidence of better outcomes with clozapine compared with other medications (for example treatment-resistant schizophrenia).

Prescribers

1. Recommend clozapine only for those for whom it will have clear benefits for (such as treatment-resistant schizophrenia where two other antipsychotics have been used unsuccessfully).
2. Use the lowest effective dose of clozapine. Monitor the plasma concentration if smoking habit changes or there is intercurrent illness and adjust the dose accordingly.
3. Avoid the co-prescription of other medications with known effects on bowel motility (such as opioids and anticholinergic medication) whenever possible.
4. If clozapine does not result in any improvements replace it with another treatment.
5. Educate everyone involved in the care of a person being treated with clozapine about the CIGH spectrum, especially the person and their family. Knowledge of the 'red flags' is particularly important so that medical attention can be sought early if these arise.
6. Ask regularly about constipation (using standard tools like the Bristol Stool Chart or Rome IV symptoms) and the 'red flags' described above. Be aware that some people will not be subjectively aware of symptoms, but regular enquiry may help to educate people about the importance of bowel function.
7. In the absence of of specific evidence for the pharmacological treatment of antipsychotic-related constipation, treatment for CIGH is pragmatic. Prophylactic treatment with stimulant laxatives and/or macrogol and a daily fluid intake of at least 2 L is recommended. Recommending lifestyle interventions (such as a healthy fibre-rich diet and adequate exercise) is sensible advice to give to patients (and likely to have general health co-benefits), but is likely to be inadequate to address the degree of slow transit found in people treated with clozapine.
8. Be aware that although CIGH is common, there has been little research on its treatment. Prescribers need to stay up to date with any new research that might fill the evidence gap regarding the most effective mitigation strategies for CIGH.
9 It is disappointing that to date, CIGH has not received more attention. Clinicians have a responsibility to encourage research in this area.

Recommendations for clozapine users and their family/carers

1. Be aware that although clozapine is likely to cause slow gut, overall it remains the best treatment for schizophrenia that has not responded well to other treatments.
2. Consider starting laxatives at the same time as starting clozapine.
3. Monitor bowel function. Talk to a health professional if there are any concerns.
4. Seek immediate medical advice if you have moderate-to-severe abdominal pain that lasts for more than an hour, or your abdomen is distended, or you have diarrhoea with blood in it, or vomiting or you feel very unwell. These could be signs of serious problems.

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