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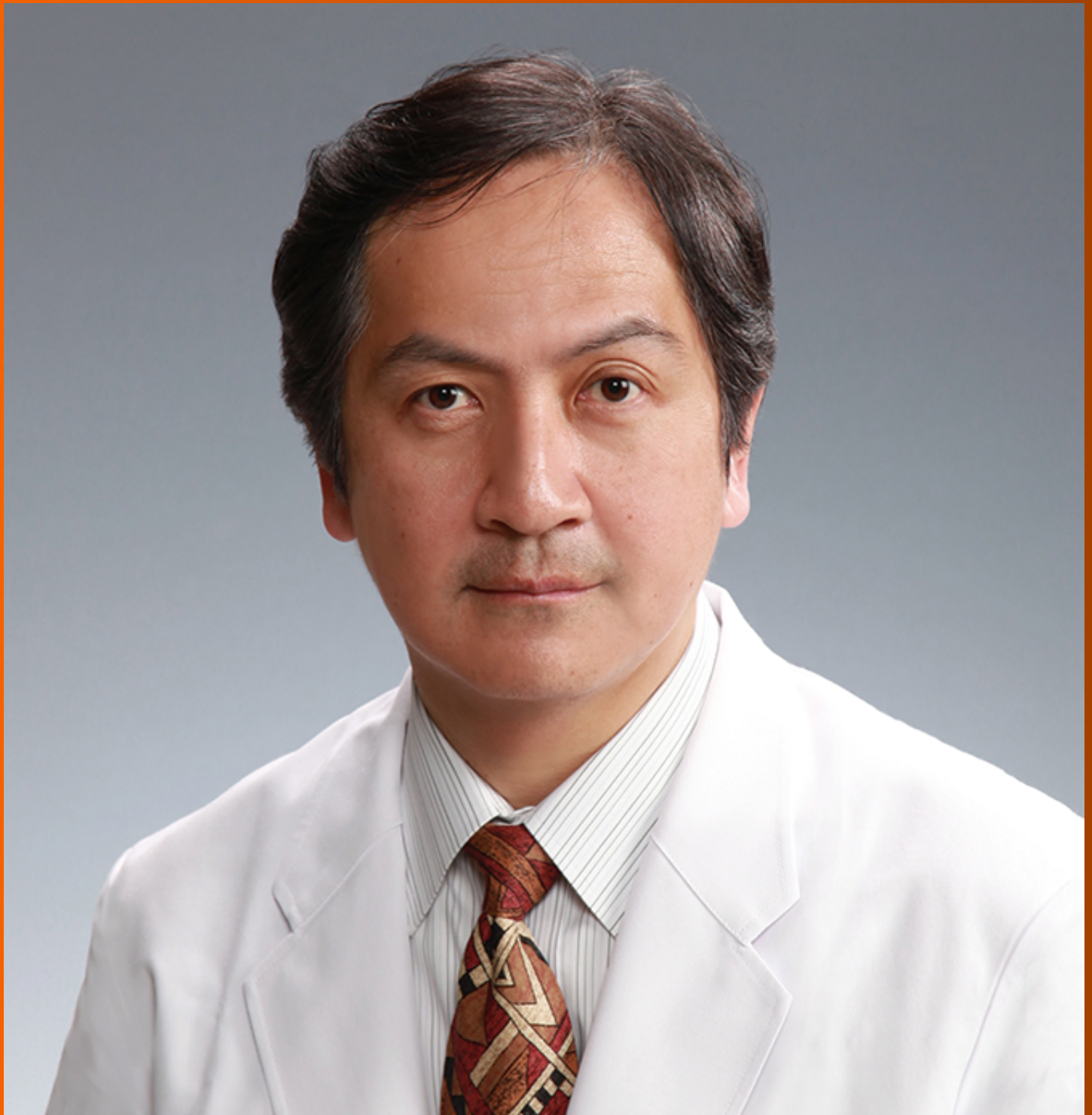
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## Gastrointestinal and liver disease in patients with schizophrenia: A narrative review

Rebecca K Grant, William M Brindle, Mhairi C Donnelly, Pauline M McConville, Thomas G Stroud, Lorenzo Bandieri, John N Plevris

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### Abstract

Schizophrenia is a severe mental illness which can have a devastating impact on an individual's quality of life. Comorbidities are high amongst patients and life expectancy is approximately 15 years less than the general population. Despite the well-known increased mortality, little is known about the impact of gastrointestinal and liver disease on patients with schizophrenia. We aimed to review the literature and to make recommendations regarding future care. Literature searches were performed on PubMed to identify studies related to gastrointestinal and liver disease in patients with schizophrenia. High rates of chronic liver disease were reported, with Non-Alcoholic Fatty Liver Disease being of particular concern; antipsychotics and metabolic syndrome were contributing factors. Rates of acute liver failure were low but have been associated with antipsychotic use and paracetamol overdose. Coeliac disease has historically been linked to schizophrenia; however, recent research suggests that a causal link is yet to be proven. Evidence is emerging regarding the relationships between schizophrenia and peptic ulcer disease, inflammatory bowel disease and irritable bowel syndrome; clinical vigilance regarding these conditions should be high. Patients with schizophrenia poorly engage with bowel cancer screening programmes, leading to late diagnosis and increased mortality. Clozapine induced constipation is a significant issue for many patients and requires close monitoring. There is a significant burden of gastrointestinal and liver disease amongst patients with schizophrenia. Better levels of support from all members of the medical team are essential to ensure that appropriate, timely care is provided.

**Key Words:** Schizophrenia; Gastrointestinal disease; Liver disease; Mental health



**Core Tip:** We report significant rates of liver disease, particularly Non-alcoholic Fatty Liver Disease, in patients with schizophrenia, in addition to emerging evidence regarding the prevalence of lower gastrointestinal disease and peptic ulcer disease. We have clearly demonstrated the importance of a multidisciplinary approach to management and propose recommendations to ameliorate future care of this vulnerable group of patients.

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## INTRODUCTION

Schizophrenia is a complex and frequently devastating illness, worldwide prevalence of which is estimated to be at 0.32%[1]. It is well established that patients with schizophrenia often suffer from a large number of comorbidities, with high rates of alcohol and substance misuse[2]. Life expectancy amongst patients has also been demonstrated to be approximately 15 years shorter than that of the general population[3].

Although the general rate of comorbidities is acknowledged to be high, no comprehensive review currently exists regarding the burden and distribution of gastrointestinal and liver disease amongst this cohort. This is particularly relevant in light of the coronavirus disease 2019 pandemic, as already marginalised patients may have become more isolated from services and only present when seriously unwell. This subject is of importance to gastroenterologists and hepatologists, in addition to general medical physicians, in order to better understand the particular risks associated with these patients and to help ensure that optimal inpatient and outpatient care is provided. It is also relevant to community and inpatient psychiatric teams to highlight when prompt referrals to specialists may be required.

In this review we summarise the available evidence regarding different aspects of gastrointestinal and liver disease in patients with schizophrenia (Figure 1) in a clear and systematic manner, highlighting key findings, and suggesting recommendations (Table 1) regarding the management of each illness to better inform the future care of this vulnerable group of patients. All articles referenced in this review were identified following a PubMed search for literature specifically considering both gastrointestinal and/or liver disease in patients who had a diagnosis of schizophrenia.

## CHRONIC LIVER DISEASE

Chronic liver disease (CLD) has consistently been demonstrated to have a higher prevalence amongst those with schizophrenia than amongst the general population. Carney *et al*[2] reported that people with schizophrenia were 4.42 times more likely than healthy controls to have a diagnosis of CLD; amongst a population of veterans, Fuller *et al*[4] reported an eightfold (8.73) increased likelihood of CLD, and Hsu *et al*[5] have also noted a significantly higher prevalence and incidence of CLD than in the general population. Furthermore, mild and severe liver disease were reported in a Danish study[6] (along with dementia) to have the highest incidence rate ratio amongst nineteen somatic chronic diseases in a cohort of 16,079 patients with schizophrenia who were hospitalised between 1995-2007. Only one study[7] has recorded no elevated risk of liver disease, however the results were adjusted for substance use disorders, which undoubtedly will have had a significant effect on results.

Given such findings, it is essential to reflect on the potential aetiology of the reported results. CLD primarily comprises non-alcoholic fatty liver disease (NAFLD), chronic viral hepatitis and alcohol related liver disease; each will presently be considered and their individual relevance to patients with schizophrenia reviewed.

### **Non-alcoholic fatty liver disease**

**Metabolic syndrome:** Prior to focusing specifically on NAFLD, the importance of the broader role of metabolic syndrome must be acknowledged. Metabolic syndrome is defined as insulin resistance, impaired glucose tolerance, abdominal obesity, reduced high-density lipoprotein cholesterol levels, elevated triglycerides, and hypertension[8]. A significant association has been widely reported[9,10]

Table 1 Key recommendations

Gastrointestinal/liver disease	Recommendations
NAFLD	Regular monitoring of body mass index and triglycerides Encouragement of lifestyle modification Liver function tests performed and Fibrosis-4 scores calculated in all psychiatric inpatients and outpatients
Viral hepatitis	Routine screening for viral hepatitis during contact with mental health services Integrated approach between mental health, sexual health, substance misuse and specialist hepatology services
ALD	Integrated approach between mental health, substance misuse and hepatology Long term studies prospective studies required to fully comprehend burden of ALD
ALF	Clinicians prescribing clozapine should be aware of the potential risk of ALF and have a low threshold for checking liver enzymes and prothrombin time Psychiatric review of all patients presenting with POD For patients presenting with POD who have a pre-existing psychiatric diagnosis prompt communication must be made with community mental health teams, and appropriate follow-up arranged for those with a new diagnosis Decisions regarding liver transplant in patients with schizophrenia must involve the multidisciplinary team and be made on a patient-by-patient basis
PUD	Encouragement of lifestyle modification, particular smoking cessation and alcohol reduction Physicians to have a high suspicion for <i>Helicobacter pylori</i> infection
Coeliac disease	Large-scale studies amongst diverse population required Diagnosis to be considered in patients with schizophrenia presenting with malabsorption
Colorectal cancer	Supporting patients to participate in screening programmes and to attend follow-up appointments is key
IBD	Increased vigilance amongst clinicians regarding a potential diagnosis of IBD is central in enabling prompt diagnosis and maintenance of remission
IBS	Patients should be directly questioned concerning IBS symptoms when undergoing physical health review as many cases may go unrecognised
Clozapine induced constipation	Lifestyle advice to reduce risk Regular screening and escalation to GP/secondary care as appropriate Physicians to be aware of clozapine as potential cause of constipation and to discuss with psychiatry if considering dose adjustment/cessation

NAFLD: Non-alcoholic fatty liver disease; ALD: Alcohol related liver disease; ALF: Acute liver failure; POD: Paracetamol overdose; PUD: Peptic ulcer disease; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; GP: General practitioner.

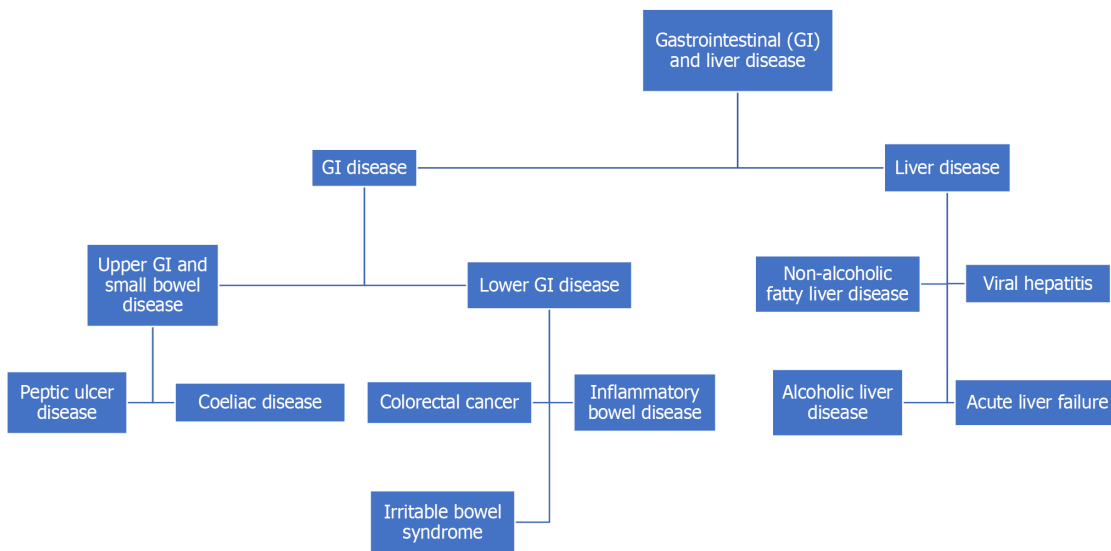
between major psychiatric disorders and metabolic syndrome; a prevalence of 32.5% was recorded in a 2013 meta-analysis[11] of patients with schizophrenia and related disorders. An unhealthy lifestyle[12] and use of antipsychotics[13] have been cited as contributing factors to its development in this group.

**Definition:** The development of NAFLD is associated with obesity, insulin resistance, and type 2 diabetes mellitus and it therefore may be viewed as the hepatic manifestation of metabolic syndrome. NAFLD is characterised by excessive hepatic fat accumulation, which is defined as the presence of steatosis in > 5% of hepatocytes[9]. For a diagnosis of NAFLD to be made, steatosis secondary to factors including hepatitis C, alcohol use, genetics, medications and toxins must first be excluded. NAFLD is reported to have a prevalence amongst the general population of 20% to 30%[14].

**Role of antipsychotic medications:** The metabolic side effects of antipsychotic medications are well-established, with clozapine and olanzapine in particular being related to weight gain, hyperglycaemia and dyslipidaemia[15]. Understandably, therefore, much of the research into NAFLD and schizophrenia has focused on the potential role of these medications in its development.

A 2016 prospective Spanish study[16] involving 191 patients with a first episode of schizophrenia (94.2% of which were antipsychotic naïve), reported that 25.1% (48/191) of patients demonstrated a fatty liver index (FLI) result suggestive of the presence of steatosis after three years of antipsychotic treatment; none of the included patients had steatosis at index abdominal ultrasound scan (AUSS). The patients in the study were randomised to aripiprazole, risperidone, quetiapine and ziprasidone; the





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**Figure 1** Summary of gastrointestinal and liver disease in patients with schizophrenia. GI: Gastrointestinal.

dose and type of antipsychotic changed throughout the follow-up period and results were not stratified according to medications. There was no control group. This study is unique in that it prospectively demonstrated the development of NAFLD following the initiation of antipsychotics; the other studies considered hereafter have focused on NAFLD in patients already established on treatment regimes.

In a cohort of 253 patients with schizophrenia, Koreki *et al*[17] reported that 42.7% (108/253) were found to have steatosis on AUSS. All patients included in this study were on at least one antipsychotic treatment (duration was not specified); on univariate analysis total antipsychotic dose (all daily doses were calculated based on chlorpromazine equivalents) was noted to be significantly associated with the presence of steatosis ( $P = 0.009$ ). On regression analysis, doses of antipsychotic medications recognised as carrying an increased risk of metabolic syndrome and hyperprolactinaemia were significantly associated with NAFLD ( $P = 0.049$  and  $P = 0.041$  respectively). A comparably high prevalence of NAFLD was also reported in a 2017 Chinese study[18] which compared 202 male patients aged 18-35 with schizophrenia and on antipsychotics for at least one month to 149 controls. 49.5% (100/202) of the schizophrenia group had steatosis on AUSS, compared with 20.1% (30/149) of the control group. Although NAFLD prevalence amongst inpatients with schizophrenia was not as high (22.44%) as in the aforementioned studies, in another 2021 Chinese study[19] comprising 66,273 patients with “mental disorders”, it was still higher than amongst those with bipolar affective disorder (17.89%), depressive disorder (12.62%) and other mental disorders (12.99%) and was demonstrated to be associated with antipsychotic treatment.

The highest reported prevalence of NAFLD was recorded in a 2021 Taiwanese study[20] which considered 182 patients with schizophrenia who had been hospitalised for at least two years and been on antipsychotic treatment for at least one year. 70.8% (129/182) were diagnosed with steatosis on AUSS; results were stratified according to antipsychotic generation and cumulative dose (using chlorpromazine equivalents), however no significant association between these and NAFLD were demonstrated. Given the reported increased association of NAFLD with second generation antipsychotics[15], the authors attribute the disparity in their results to population demographics and sample size. Interestingly, antipsychotic treatment duration, potentially the biggest contributor to the reported results in this cohort, was not reported in the results.

Rates of NAFLD have also been reported in studies not specifically considering antipsychotic therapies. In a population of veterans in the United States[4], those with a diagnosis of schizophrenia were significantly more likely to be diagnosed with NAFLD ( $P \leq 0.001$ ) and in a cross-sectional Danish study[21] 21.4% (31/145) were diagnosed with moderate-severe steatosis on non-enhanced CT. In these studies, significant associations were however demonstrated with metabolic syndrome, suggesting (although not confirming due to lack of data) that antipsychotics may also be potentially playing a role in these reported results.

**Lifestyle and negative symptoms:** While research has predominantly focused on the close links between antipsychotics and NAFLD, it is also important to briefly consider potential alternative aetiologies that have been proposed.

Patients with schizophrenia are acknowledged as being at higher risk of an unhealthy lifestyle compared to the general population[17]. They may have an unbalanced diet, poor self-care, avoid certain foods due to paranoid delusions or hallucinations, and withdraw from physical and social

activities, leading to a lack of exercise[22]. Yan *et al*[18] in their 2017 study emphasised the role of negative symptoms in young men with schizophrenia and NAFLD; a negative factor score in the Positive and Negative Syndrome Scale (PANSS) was significantly associated with a NAFLD diagnosis ( $P = 0.025$ ). It is not challenging to understand how the negative symptoms of anhedonia, poor attention, low motivation, apathy and social withdrawal may lead to obesity and the associated sequelae of metabolic syndrome.

**Recommendations:** It is evident that a diagnosis of schizophrenia carries with it a significant risk of developing NAFLD, both due to treatment with antipsychotics and also due to the intrinsic nature of the illness itself. In order to prevent progression to cirrhosis and its associated complications it is necessary to increase awareness of this risk and consider how it may be ameliorated. At the very least, body mass index (BMI) and triglycerides should be monitored regularly in all patients with schizophrenia and psychiatrists and general medical physicians should make every effort to support patients in modifying their lifestyles. Furthermore, all patients admitted to psychiatric hospitals and attending outpatient psychiatry appointments ought to have liver function tests performed and Fibrosis-4 (Fib-4) scores calculated to determine if a referral to hepatology is necessary.

### **Chronic viral hepatitis-hepatitis B and hepatitis C**

People with serious mental illness (including schizophrenia) have been shown to be at increased risk of blood borne viruses (BBVs)[23]. A significant minority of patients with schizophrenia engage in risky behaviour (unprotected sex with multiple partners, sex work, and intravenous drug use) putting them at risk of infection; they are also more likely to live in shared accommodation and may share personal equipment such as razors and toothbrushes, carrying a potential increased risk of hepatitis B and C transmission[23]. Patients with hepatitis B and C have an increased risk of developing hepatocellular carcinoma[24], therefore adequate treatment and monitoring of the conditions is vital.

In 2017 a Swedish study[25] considered the prevalence and risk factors for BBVs amongst people with severe mental illness; when compared with healthy controls, those with schizophrenia were significantly more likely to have either a diagnosis of hepatitis B ( $P \leq 0.001$ ) or hepatitis C ( $P \leq 0.001$ ). A history of substance misuse was noted as having contributed the most to the risk of developing a BBV ( $P \leq 0.001$ ). Increased prevalence of hepatitis C was also shown in a study of veterans[4] diagnosed with schizophrenia when compared to controls ( $P \leq 0.001$ ). Substance use disorder and alcohol use disorder were identified as significant risk factors for development of schizophrenia ( $P \leq 0.001$  and  $P \leq 0.001$  respectively). A small study performed in Boston[26] identified eight patients with hepatitis C out of a total cohort of 98 patients (8.2%) treated with clozapine; one was a confirmed intravenous drug user, three had a history of polysubstance misuse and in the remaining four patients no risk factors were identified. A further small Canadian study[27] reported a hepatitis C rate of 2.7% (3/110) of clozapine-treated patients. Two of the three patients diagnosed with hepatitis C had a history of intravenous drug use.

Outcomes in patients with schizophrenia diagnosed with hepatitis C and hepatitis B were considered in a 2021 Chinese study[24]. From a total cohort of 15,914 patients with newly diagnosed schizophrenia between 2007 and 2013, 614 patients were identified with viral hepatitis and were matched with 1228 controls. The primary outcome measure was the incidence and risk of “severe hepatic outcomes” (SHOs), including liver cancer, failure and decompensation. The viral hepatitis group were significantly more likely to develop SHOs ( $P \leq 0.001$ ) than the control group; a total of 26 patients with viral hepatitis developed SHOs (20/26 Liver decompensation, 3/26 Liver failure, and 3/26 Liver cancer).

**Recommendations:** While the risk of viral hepatitis amongst people with schizophrenia cannot be disputed, optimal management of it is challenging. Routine screening for viral hepatitis during contact with mental health services would allow an opportunity for discussion about safe sex and drug use, it may also prompt consent to other tests (such as HIV), leading to the discovery of potentially treatable illnesses, and, crucially, a positive result may allow prevention of further liver damage[26]. If diagnosed, encouragement of treatment adherence in this population may be difficult, therefore an integrated approach between mental health, sexual health, substance misuse[25] and specialist hepatology services would be required to aid optimal patient outcomes.

### **Alcohol related liver disease**

A high prevalence of alcohol use disorder (AUD) has been demonstrated in patients with schizophrenia, with a recent meta-analysis reporting a lifetime prevalence of AUD of 24.3%[28]. A number of hypotheses have been put forward to explain this association, including genetic polymorphisms, poor cognitive development, poor social functioning, the effects of poverty, poor social environments and “self-medication” to gain relief from distressing symptoms[29].

Despite such a high prevalence of AUD in patients with schizophrenia, research into alcohol related liver disease (ALD) in this cohort is relatively limited with variable results. The most common manifestations of ALD are alcoholic fatty liver, acute alcoholic hepatitis and alcohol related cirrhosis of the liver. In 2014 Hsu *et al*[5] reported an increased risk of alcohol related fatty liver in patients with schizophrenia when compared with the general population ( $P = 0.007$ ); risk of alcoholic hepatitis and cirrhosis

did not vary significantly between the two cohorts. In a 2022 Scottish study[30] of patients with schizophrenia admitted to a general hospital under the care of gastroenterology, 42.5% (17/40) of patients had a background of cirrhosis (88.2% of which had a background of alcohol excess) and 60.0% (24/40) of all patients had a history of alcohol excess. Interestingly, Fuller *et al*[4], in their 2011 study, reported schizophrenia being a protective factor (odds ratio = 0.53) in the diagnosis of alcohol related cirrhosis when a group of veterans with schizophrenia were compared to those without.

**Recommendations:** In common with viral hepatitis, an integrated approach between mental health, substance misuse services and specialist hepatology services is key in supporting patients with schizophrenia and alcohol use disorder. Further research, including long term prospective studies, is also required to better comprehend the burden of ALD amongst patients with schizophrenia.

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## ACUTE LIVER FAILURE

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Acute liver failure (ALF) is a rare clinical syndrome in which the onset of liver injury, with coagulopathy and hepatic encephalopathy, occurs in a patient with no underlying CLD and previously normal liver function. The associations between ALF and schizophrenia can be considered under the following categories: ALF arising as a result of pharmacological treatment for schizophrenia, ALF arising as a consequence of mental state alteration in patients with schizophrenia and finally the implications of a diagnosis of schizophrenia on decision making around emergency liver transplantation for ALF.

### Pharmacological treatments

In patients with treatment resistant schizophrenia (*i.e.*, following the failure of at least two antipsychotics, including a second-generation antipsychotic) prompt initiation of clozapine, the only remaining evidence-based treatment, is required to reduce symptoms and risk of relapse[31,32]. Clozapine acts as a dopamine and serotonin receptor antagonist. The most recognised and feared side effect of clozapine is agranulocytosis, however there are now case reports of clozapine induced ALF[33, 34]. The mechanism of liver injury in this scenario is unclear, but it is idiosyncratic. A modest elevation in liver enzymes occurs in up to two thirds of patients treated with clozapine, and often resolves spontaneously[35]. Clinically apparent liver injury (with jaundice) occurs in approximately 1 in 2000 patients treated with clozapine[35] and progression to ALF (and death, or the need for emergency liver transplant) is now reported. ALF secondary to clozapine is extremely rare however, with less than five reported cases in the literature[33,34,36]. ALF has also been reported as a rare side effect of quetiapine therapy[37]; no cases of ALF have been reported with olanzapine or risperidone. Most treatment guidelines do not give clear recommendations on monitoring liver function tests in patients on clozapine and other antipsychotics, in part due to the fact that the vast majority of liver enzyme abnormalities secondary to these drugs do resolve spontaneously. Clinicians prescribing clozapine should be aware of the risk of ALF and could consider checking liver enzymes and prothrombin time when performing blood work monitoring for agranulocytosis.

### Paracetamol overdose

Schizophrenia is associated with suicidal ideation[38]. In the United Kingdom, intentional paracetamol overdose is the most frequent cause of ALF. There is no clear evidence that schizophrenia is associated with an increased risk of paracetamol overdose resulting in ALF compared with the general population or patients with other psychiatric diagnoses. Scottish data have shown that of 472 patients with paracetamol overdose requiring admission to the Scottish Liver Transplant Unit who underwent formal inpatient assessment by psychiatry, schizophrenia was diagnosed or recorded in 2.8% of patients [Personal communication: Dr Roger Smyth, Consultant Liaison Psychiatrist, Royal Infirmary of Edinburgh]. In comparison, affective disorders were recorded in 16.1% and personality disorders in 6.9% of patients. One Danish study assessed the association between paracetamol (and other weak analgesic) poisoning and the subsequent diagnosis of a psychiatric disorder[39]. The risk of an admission with schizophrenia increased 3.9-fold after paracetamol poisoning and 2-fold after non-paracetamol poisoning compared with matched population controls. Patients with a previous psychiatric admission were excluded, but it is possible that patients with schizophrenia who had not required prior hospitalisation (*i.e.*, but who already had an established diagnosis) were included in the study. Furthermore, the admission with poisoning is likely to have prompted a psychiatric review and subsequent diagnosis. These data suggest that poisoning is a risk marker for a psychiatric disorder, rather than there being a causative association. Clinicians assessing patients presenting with paracetamol overdose should be aware of the risk of underlying psychiatric disorder and ensure appropriate assessments are arranged.

Interestingly, in addition to its role in treatment of paracetamol overdose, there is ongoing research into the reduction of negative symptoms and anti-suicidal properties of N-acetyl cysteine (NAC) in the treatment of schizophrenia. Chen *et al*[40] identified two placebo-controlled, double-blind, randomised

clinical trials of NAC in schizophrenia and reported that NAC may be efficacious in reducing the negative and general symptoms of schizophrenia. A meta-analysis by Zheng *et al*[41], which included three randomized control trials with 307 (N-acetylcysteine: 153, placebo: 154) participants, showed that NAC significantly improved total symptom scores in schizophrenia. Other related systematic reviews, including a Cochrane review on antioxidant treatment for schizophrenia, have also found NAC to be a promising add-on treatment for schizophrenia[42].

### **Emergency liver transplantation**

Emergency liver transplantation may be required in patients with ALF if spontaneous recovery of sufficient liver function is deemed unlikely. Psychiatric disorders can be relative or absolute contraindications to liver transplantation, particularly if the disorder is deemed “untreatable” and may be graft threatening. A diagnosis of a psychiatric condition such as schizophrenia is relevant if it affects the prospect of survival post-transplant or affects compliance with medication and clinic follow-up. In a Scottish cohort of patients with ALF secondary to paracetamol overdose, 56.6% of patients who were rejected for listing for liver transplantation were rejected on the basis of psychiatric contraindications [43]. As described above, schizophrenia is associated with an increased risk of suicide, and this must be taken into account when considering the role of transplantation in an illness potentially arising from self-harm or parasuicide such as paracetamol overdose; the consequences of further suicidal intent must be reviewed. Specific to severe psychiatric disorders such as schizophrenia, absolute contraindications to liver transplantation include chronic, severe illness with a poor prognosis, especially if refractory to appropriate treatment. The potential impact of a diagnosis of schizophrenia on substance misuse, compliance with immunosuppression and clinic follow-up must be considered. Therefore, patients with schizophrenia being considered for emergency liver transplantation for ALF should be assessed by the wider multi-disciplinary team and decisions made on a highly individualised basis.

**Recommendations:** While cases of ALF are rare in patients treated with clozapine, prescribing clinicians should be aware of the potential risk and have a low threshold for checking liver enzymes and prothrombin time, particularly in patients presenting with possible symptoms of liver dysfunction such as nausea, vomiting and/or anorexia[44].

Regarding paracetamol overdose, it is essential that treating physicians are aware of the risk of a diagnosis of a psychiatric disorder and ensure patients are reviewed by psychiatric teams during their admission. For patients who have a pre-existing diagnosis prompt communication must be made with community mental health teams (CMHT), and appropriate follow-up arranged for those with a new diagnosis. The use of NAC in the treatment of schizophrenia is an emerging area of research and further evidence is required regarding its potential.

The assessment of patients with schizophrenia for liver transplant is complex. Decisions must involve the multidisciplinary team (MDT) and be made on a patient-by-patient basis.

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## **UPPER GASTROINTESTINAL AND SMALL BOWEL DISEASE**

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### **Peptic ulcer disease and upper gastrointestinal bleeding**

Upper gastrointestinal bleeding (UGIB) is the consequence of often readily treatable digestive conditions such as gastroduodenal ulcers and reflux oesophagitis progressing to a potentially fatal event; in patients with schizophrenia the risk may be heightened due to high rates of alcohol misuse, smoking and non-steroidal anti-inflammatory drug use, in addition to reluctance to present to medical services. There are relatively limited studies which have considered incidence of peptic ulcer disease (PUD) and UGI bleeds in this cohort, with evidence being inconclusive, and, at times, contradictory.

*Helicobacter pylori* (*H. pylori*) infection is recognised[45] as a major contributor to PUD and consequently UGIBs. Following a 1997 study by De Hert *et al*[46] and a 2005 study by Yilmaz *et al*[47] (both of which reported high rates of *H. pylori* infection in patients with schizophrenia), a Turkish group [47] discussed the role of *H. pylori* as a possible environmental contributor to the pathogenesis of schizophrenia in genetically predisposed individuals. The authors identified four mechanisms to support this theory: (1) Dopaminergic dysfunction; (2) inflammation; (3) polyunsaturated fatty acids; and (4) hyperhomocysteinaemia. With regard to dopaminergic dysfunction specifically, the authors propose that dopamine antagonists (such as commonly used antipsychotics) promote ulcer formation favouring the growth of *H. pylori*; this is a theory which is supported by Ozdemir[48] in their 2007 paper in which they propose that the lesser prevalence of PUD in their cohort of patients with schizophrenia was due to the over expression (and subsequent protective effect) of dopamine.

The reduced prevalence of PUD in patients with schizophrenia reported by Ozdemir *et al*[48] is in contrast to results reported in other studies. In 1968 Hussar[49] proposed that the incidence of PUD was at least as high amongst long term institutionalised patients with schizophrenia compared with the general population and, more recently, in 2014, Liao *et al*[50] reported an incidence of PUD that was 1.27 times higher in patients with schizophrenia than in the general population. An American study in 2014 [51] of 224,361 patients with schizophrenia, reported an incidence of bleeding ulcers amongst this cohort



as being 1.4 per 1000 person years, compared to 1.2 per 1000 person years in those without schizophrenia. Similarly increased risk of UGIB was also noted in a 2018 Danish study[52] of 39,998 patients with schizophrenia; the authors acknowledge the role that increased rates of *H. pylori* infectivity amongst patients with schizophrenia may have played in the observed results.

**Recommendations:** It is challenging to draw definitive conclusions regarding biological links between the aetiology of PUD and schizophrenia and more research is required before such links are established. However, it is important to acknowledge the increased risk of PUD those patients with schizophrenia has due to lifestyle factors, and, as a result, ensures that help is given to aid modification. Suspicion regarding the presence of *H. pylori* should also be high, particularly as it may have the potential to contribute to mortality through a catastrophic UGIB or the development of gastric cancer[53].

### **Coeliac disease**

Coeliac disease is an autoimmune disease which is triggered by gluten peptides in wheat, rye, barley and other grains. Histologically it is characterised by villous atrophy, hypertrophy of intestinal crypts and increased lymphocytes in the epithelium and lamina propria[54]. This results in malabsorption and the associated bloating, pain and diarrhoea in sufferers. Current prevalence of coeliac disease is estimated at 1% of the general population[54].

**Historical perspective:** A potential association between coeliac disease (or gluten intolerance) and schizophrenia is one which has long since interested researchers[55], with Bender[56] first reporting in 1953 that children with schizophrenia were more likely to have coeliac disease. This was then followed by the publication of a case series on five patients with schizophrenia with coeliac disease who were admitted to a psychiatric hospital during the same year[57]. Dohan was particularly prolific in the publication of papers regarding coeliac disease and schizophrenia, with results variably showing reduced prevalence of schizophrenia in areas of low grain consumption and an improvement in the symptoms of schizophrenia following the initiation of a gluten free diet[58-62].

**Current status:** More recent research has focused on the risk of patients with coeliac disease developing schizophrenia as opposed to prevalence of coeliac disease amongst those with schizophrenia; nevertheless, the strength of an association between the two conditions may be extrapolated from the available evidence. A 2018 meta-analysis[63] of the four most recent epidemiological studies[64-67] reported a significantly higher risk (two-fold) of schizophrenia in those with coeliac disease when compared with controls. Of the four studies, three[64,66,67] reported a significant association and one [65] did not (in common with an earlier British study[68]). The authors of the meta-analysis acknowledge that the mechanism underlying this association is unclear, however propose the following potential explanations: (1) There is high prevalence of folate deficiency in individuals with coeliac disease, given the important role of folate in DNA methylation, aberrant methylation may contribute to the development of schizophrenia; (2) schizophrenia may share a genetic diathesis with coeliac disease; and (3) diagnoses of schizophrenia in patients with coeliac disease may be resulting from surveillance bias as those with coeliac will present more often to physicians due to their chronic illness requiring regular follow-up. Since the publication of the meta-analysis, a small study[69] of 16 patients with IgG antigliadin antibodies (raised in coeliac disease) has also demonstrated an improvement in psychiatric patients with schizophrenia or schizoaffective disorder with a gluten free diet; a larger scale clinical trial is planned.

**Recommendations:** While research into a possible link between coeliac disease and schizophrenia has previously relied on relatively small case reports and series, more recently trial evidence has emerged to strengthen the association. Proof of a causal relationship between the two remains unclear and further large-scale studies, amongst more diverse populations, are required. Nevertheless, current evidence does serve to increase awareness of the likelihood of a diagnosis of coeliac disease amongst patients with schizophrenia presenting with symptoms of malabsorption.

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## **LOWER GASTROINTESTINAL DISEASE**

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### **Colorectal cancer**

Evidence regarding rates of cancer mortality in patients with schizophrenia has historically been contradictory, with some studies reporting lower or similar risk of cancer mortality compared to the general population[70-72], while others have reported higher rates[73-75]. Regarding colorectal cancer, however, a recent systematic review and meta-analysis[76] found that patients with schizophrenia had a significantly higher risk of mortality, with male patients having a relative risk of 1.90 and female patients 2.42. Increased risk of colorectal cancer[77] was also reported in a 2007 study. As in the general population, screening is vital in promoting earlier diagnosis and reducing mortality; a 2018 Japanese study[78] reported a rate of participation in colorectal cancer screening of 13.4% in patients with schizophrenia (in contrast to 47.8% of men and 40.9% of women in the general population[79]). The benefit of

case management interventions, in the form of three counselling sessions to support adherence to screening, was demonstrated in a 2021 Japanese study[79], which showed a 35.3% increase in participation amongst the case management group.

**Recommendations:** As reported in the 2021 study[79], participation in screening programmes is key to reducing mortality from colorectal cancer amongst patients with schizophrenia to be in line with the general population. Supporting patients to participate in screening and attend potential follow-up procedures is essential to address the disparity between colorectal cancer mortality in this cohort when compared to the general population.

### **Inflammatory bowel disease**

Crohn's disease (CD) and ulcerative colitis (UC) are the two main types of inflammatory bowel disease (IBD) and are characterised by chronic inflammation - in the case of UC it is limited to the mucosa of colon and rectum, and, in CD, it is transmural and extends potentially to the whole GI tract. Symptoms of both conditions include diarrhoea, abdominal pain and extreme fatigue. Prevalence of IBD is increasing and is projected to reach 1% by 2028[80].

The relationship between IBD and schizophrenia has been explored in a small number of studies, with variable results. Bernstein *et al*[81] reported an increased incidence of schizophrenia amongst patients with CD but not with UC, whereas no increased risk in either form of IBD was demonstrated by West *et al*[68]; a Swedish study actually noted a diminished risk of schizophrenia in those with IBD[82].

In contrast to earlier studies which focused on risk of schizophrenia in IBD patients, a recent study from Taiwan[83] considered risk of a new IBD diagnosis amongst patients with a diagnosis of schizophrenia. It included 116,164 patients with schizophrenia and 464,656 matched controls and concluded that overall incidence of IBD was significantly higher amongst the schizophrenia cohort (1.14% *vs* 0.25%); risk was also higher amongst those with more severe schizophrenia. These findings are potentially supportive of research suggestive of shared genetic susceptibility between the two conditions[84,85], although the role of diet and microbiota remain important confounding factors.

**Recommendations:** CD and UC are challenging conditions to manage, this risk is heightened in vulnerable patients with schizophrenia as engagement with health services is essential for positive outcomes. As recommended by the authors of the recent Taiwanese study[83], increased vigilance amongst clinicians and other members of the MDT regarding potential cases of IBD may prove vital in enabling prompt diagnoses and maintenance of remission.

### **Irritable bowel syndrome**

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterised by abdominal pain, bloating and a change in bowel habit [either constipation (IBS-C), or, more commonly, diarrhoea (IBS-D)]; diagnosis is made based on the Rome IV criteria. Current prevalence of IBS in the United Kingdom is estimated to be at 14%[86].

The first study to consider IBS in patients with schizophrenia was published in 1997[87]. The authors reported that 19% of the patients with schizophrenia met the diagnostic criteria for IBS, compared with 2.5% of those in the control group. It must however be acknowledged that the study only included 87 patients in total. Interestingly, it was noted that the patients with schizophrenia did not complain of symptoms of IBS, unlike when the authors considered a group of patients with anxiety and depressive disorder; the authors attributed this to a preoccupation with delusions and hallucinations or being due to apathy resulting from negative symptoms.

A further study[88] comprising 134 patients with schizophrenia reported IBS in 48.8%; the study also reported higher rates of IBS-D in patients presenting with positive symptoms of schizophrenia, IBS-C and alternating IBS-D/C were more common in those with negative symptoms. The group was not compared to a control, which makes conclusions limited.

**Recommendations:** Research suggests that there may be an under-reporting of IBS symptoms amongst patients with schizophrenia. Consideration should therefore be given to IBS symptomatology in patients with schizophrenia undergoing physical health review as many cases may go unrecognized unless patients are directly questioned. Addressing diet and lifestyle factors are also important in improving the quality of life in patients with schizophrenia and IBS symptoms.

### **Clozapine induced constipation**

Whilst recognising it as a side effect of clozapine treatment as opposed to a disease in itself, it is necessary to acknowledge the risk of clozapine induced constipation in patients with schizophrenia. Risk of constipation is greatest in the first four months following treatment initiation, however may occur at any time[89]. A 2016 systematic review and meta-analysis[90] of 11 studies reported a prevalence of clozapine induced constipation of 31.2%. The authors attribute increased risk of constipation to the anti-muscarinic and anti-histaminergic effects of the drug, as well as to a sedentary lifestyle, dehydration, obesity and a diet which is low in fibre. Complications of constipation such as bowel obstruction, ileus (a Danish study[91] reported a 0.8% incidence of ileus in clozapine treated



patients) and toxic megacolon may be life threatening; in severe constipation the case fatality rate has been documented at approximately 20%-30% [89]. Following the aforementioned systematic review and meta-analysis [90], subsequent studies and case reports [92-96] have also reported similarly high incidence of clozapine induced constipation and gastrointestinal hypomotility, highlighting the ongoing significance of this issue.

**Recommendations:** Given the high prevalence of clozapine-induced constipation, all patients on clozapine should be given lifestyle advice to help prevent the development of constipation. It is crucial to screen for its presence during CMHT review (regular attendance at clozapine blood monitoring may help to facilitate this) and it is particularly important to ask directly about it as incidence may be underreported by patients. Patients may be referred to their general practitioner (GP) for prescription of laxatives and ongoing monitoring if constipation is present, in addition to plasma clozapine levels being reviewed by the CMHT; if there are features concerning for obstruction prompt referral to secondary care is required.

Caution should be exercised in the prescription of anti-cholinergics for hypersalivation (a known side effect of clozapine) due to their potential to contribute to constipation; other regular medications with constipating side effects should also be kept under close review. For secondary care physicians it is important to be aware of clozapine as a potential cause of constipation and essential to seek advice from colleagues in psychiatry if dose adjustment or treatment cessation is being considered.

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## GUT MICROBIOME AND SCHIZOPHRENIA

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In consideration of gastrointestinal disease in schizophrenia it is important lastly to acknowledge an emerging area of active research - the gut microbiome. The gut microbiome in humans comprises a diverse population of microbes, the most numerous of which are reported to be Bacteroidetes and Firmicutes [97]. Factors such as diet, smoking and social circumstances have been suggested to influence the composition of an individual's developing microbiome. While each microbiome is unique, when the microbial composition differs significantly from controls, it is referred to as dysbiosis. Alterations in gut microbiota have been demonstrated to be implicated in several psychiatric illnesses, including depression, addiction and eating disorders. Evidence is now emerging regarding the potential role of gut dysbiosis in the aetiology of schizophrenia and the use of pre and probiotics in treatment pathways is also being explored.

In 2020 Szeligowski *et al* [98] performed a narrative review of research considering the differences in microbiome between healthy controls and patients with schizophrenia; six studies were identified. The authors reported only one consistent finding between the studies-that patients with schizophrenia had significantly elevated Lactobacilli, which also correlated with symptom severity. As Lactobacilli are typically thought to be beneficial for gut health, this finding was attributed to the existence of different subtypes. The authors conclude that different exclusion criteria, stage of illness and treatments make definitive conclusions regarding the role of dysbiosis in schizophrenia challenging and further larger scale prospective studies are required.

Pre and probiotics are also being investigated for their ability to reduce the effect of antipsychotic medications on the microbiome which can lead to potentially life- threatening constipation and significant weight gain. Results of small studies which have been reported in reviews of the literature [98-101] are encouraging, for example co-administration of prebiotics to olanzapine treated rats led to attenuation of weight gain [102]. As with the role of dysbiosis in the aetiology of schizophrenia, more detailed studies in human subjects are of course needed but early results do suggest this may be a promising area for future treatment.

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## CONCLUSION

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Gastrointestinal and liver disease have been shown to have a profound impact on patients with schizophrenia. The scale of liver disease, and metabolic syndrome in particular, in this population, is perhaps the most significant finding upon review of the literature. Optimal management of these conditions deserves close consideration from psychiatrists, hepatologists and all members of the MDT involved in the care of patients with schizophrenia. A recurring theme from consideration of all gastrointestinal and liver diseases is that patients with schizophrenia need appropriate additional levels of support from care providers to ensure that their physical health receives the attention it requires and which they, as individuals, deserve.

## FOOTNOTES

**Author contributions:** Grant RK and Brindle WM conceived the study; Grant RK performed the literature review and drafted all sections of the manuscript except for the section on acute liver failure; Donnelly MC performed the literature review and drafted the section on acute liver failure; Brindle WM, Donnelly MC, McConville PM, Stroud TG, and Bandieri L critically revised the manuscript; Plevris JN was senior author and critically revised the manuscript for important intellectual content.

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