Comorbidity

Schizophrenia
The comorbidities of schizophrenia

- The life expectancy of patients with schizophrenia is shorter than the general population, by an estimated 14.5 years.\(^1\) This is only partly explained by higher suicide rates; the presence of comorbidities also plays a part\(^2-4\).

- **Psychiatric comorbidities** are common in patients with schizophrenia, including depression, anxiety, and substance use disorders\(^4,5\).

- Moreover, there is a multitude of **somatic comorbidities** that have a higher incidence in patients with schizophrenia than in the general population, including cardiovascular diseases, and diabetes\(^2,3\).

- Studies using registry data have shown that schizophrenia is associated with **elevated mortality**, and that lack of antipsychotic medication is associated with elevated mortality\(^6,7\).

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Swedish national cohort study of schizophrenia comorbidities

- A large-scale study used the Swedish national health care registries to follow >6,000,000 Swedish adults, including >8,000 patients with schizophrenia, over seven years\(^1\)
- Patients with schizophrenia had more than twice as many outpatient clinic visits per year, and hospital admissions per year, than the control population\(^1\)
- As is shown in the table, the mortality rate of various conditions was higher among patients with schizophrenia\(^1\)
- These findings have been replicated using Danish registry data, which demonstrated a pervasive and bidirectional comorbidity among the >42,000 patients with schizophrenia studied\(^2\)


COPD=chronic obstructive pulmonary disease
Psychiatric comorbidities
Cognitive dysfunction

- Cognitive deficits in schizophrenia are common, and are linked to vocational and functional impairments.

- To study the cognitive dysfunction of schizophrenia, a comprehensive neuropsychological test battery was performed in 53 patients with schizophrenia and 50 control individuals.

- Patients with schizophrenia showed deficits in all four higher order neurocognitive domains—executive function, working memory, visual memory, and verbal memory.

- A meta-analysis examined cognitive deficits from >18,000 cases over 247 publications, and concluded that there is a general impairment of cognitive functions in patients with schizophrenia.

MDD=major depressive disorder

Depressive disorders

- Depressive disorders commonly feature sad, empty, or irritable mood, accompanied by somatic or cognitive changes that affect the patients ability to function\(^1\)

- Patients with schizophrenia are prone to depression, with a modal frequency from one literature review of about 25\%,\(^2\) compared with 4.4\% in the global population\(^3\)
  - patients with schizophrenia had over four times greater frequency of depression

- However, other figures have been reported, ranging as high as 60\% of patients with schizophrenia experiencing depressive syndromes over the course of their illness\(^4,5\)

- Depression is comorbid with many conditions, and is sometimes described as ‘the common cold’ of psychiatry\(^1,2,6\)

- Longitudinal depression scores have been shown to correlate with schizophrenia symptom scores over time,\(^7\) however, care has to be taken in research of this nature because depression can present with psychotic features\(^1\)

- Some of the diagnostic criteria for depression overlap with those of schizophrenia, for example, anhedonia, amotivational and avolitional states, and social withdrawal,\(^1\) leading to the argument that depression should be considered part of schizophrenia rather than a comorbidity\(^7\)

Bipolar disorder

- Bipolar disorders bridge the diagnoses of schizophrenia and depression, and are characterised by periods of mania and periods of depression\(^1\)

- In a nationally representative sample of the US population, the lifetime prevalence of co-morbid bipolar disorder in patients with schizophrenia and other nonaffective psychoses was 21%, compared with 4% in the general population – patients with schizophrenia had four times greater frequency of bipolar disorder\(^2,3\)

- There is some evidence for a genetic relationship between schizophrenia and bipolar disorder, with a large overlap between the genetic loci that predispose individuals to either condition\(^4\)

- The correlation for genetic influences on schizophrenia and bipolar disorder is estimated to be 0.6, suggesting shared genetic risks\(^4\)

- As genome-wide association studies become more powerful, with larger and more demographically varied samples, polygeneic risk scores may become more powerful, and the relationship between schizophrenia and bipolar disorder may become more clear\(^4\)

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Sleep disorders

• Disturbed sleep patterns is an associated feature of many major psychiatric disorders, including schizophrenia, with some individuals displaying daytime sleepiness and night-time activity\textsuperscript{1,2}

• Sleep actigraphy has demonstrated that patients with schizophrenia have less overall sleep, and more interrupted sleep, than published community norms\textsuperscript{3}

• The quality of sleep in patients with schizophrenia is associated with impaired patient quality of life – in one study, quality of life, as assessed by the QLS scale, and sleep quality, as assessed by the PSI, were correlated\textsuperscript{3}

• In a patient survey study, patients vividly described the inability to “get a good night’s sleep”, the feelings of anxiety this created, the reticence to use hypnotics, and the effect that this lack of good sleep had, leading to poorer daytime functioning\textsuperscript{4}

The treatment of patients with schizophrenia should take sleep problems into account, and the effect that any medication may have on those problems, including the sedating effects of some antipsychotics\textsuperscript{4}

\textsuperscript{PSI=Pittsburgh Sleep Quality Index; QLS=Quality of Life Scale}
Anxiety disorders

- Anxiety disorders share features that include excessive fear and anxiety, and the behavioural disturbances that are related to them\(^1\)

- The prevalence of anxiety disorders has been shown to be higher in patients with schizophrenia relative to control individuals, including panic disorder and obsessive–compulsive disorder\(^2,3\)

- In one study, anxiety disorder was significantly higher in patients with schizophrenia (45%) compared with controls (16%) – **patients with schizophrenia had three times greater frequency of anxiety disorders**\(^4\)

- In a meta-analysis examining the co-occurrence of anxiety disorders in schizophrenia, the following prevalence rates were reported:\(^5\)
  - **Obsessive–compulsive disorders**: 12.1% (95% CI: 7.0–17.1%)
  - **Social phobia**: 14.9% (95% CI: 8.1–21.8%)
  - **Generalised anxiety disorders**: 10.9% (95% CI: 2.9–18.8%)
  - **Panic disorders**: 9.8% (95% CI: 4.3–15.4%)
  - **Post-traumatic stress disorders**: 12.4% (95% CI: 4.0–20.8%)

CI=confidence interval

Panic disorder

• Panic disorder (whereby an individual suffers from unexpected attacks of panic symptoms) is a condition that is commonly comorbid with schizophrenia, but may still be overlooked\(^1\)–\(^3\)

• There are ranges of prevalence values reported in the literature, but panic attacks have been shown to occur in up to 63% of patients with schizophrenia,\(^1\) compared with 2–3% in the general population\(^3\) – **patients with schizophrenia had 20 times greater frequency of panic disorder**

• One study administered the SCID to 49 patients with schizophrenia\(^a\) to explore the prevalence of panic attacks/disorder\(^2\)

• Of the patients with schizophrenia, 43% experienced panic attacks, and 33% had a current or past diagnosis of panic disorder\(^2\)

Is schizophrenia with panic disorder a separate subgroup of schizophrenia?

• In a study of 255 inpatients with schizophrenia:\(^4\)
  • 165 with schizophrenia\(^a\) only
  • 39 with comorbid panic disorder
  • 51 with a non-panic anxiety disorder

• There were significant differences between the groups on cognitive measures, problem-solving tasks, and on measures of symptomatology\(^4\)

• This has led to the argument that psychosis with panic disorder may constitute a separate subgroup of schizophrenia, and should be treated as such\(^4\)

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\(^a\)Schizophrenia or schizoaffective disorder; SCID=Structured Clinical Interview for DSM-IV

Obsessive–compulsive disorder

- Obsessive–compulsive disorder (OCD) is typified by recurrent and persistent thoughts, urges, or images, and repetitive behaviours that an individual feels driven to perform in response to the obsessions\(^1\)

- The prevalence of obsessive–compulsive symptoms/OCD in patients with schizophrenia has been crudely estimated to be roughly 25%\(^2,3\) compared with a twelve-month prevalence of 1.2% in the general population\(^1\) – patients with schizophrenia had 20 times greater frequency of OCD

- Furthermore, schizophrenia with OCD has been linked to greater suicidality than schizophrenia alone\(^4\)

- A recent study has attempted to interrogate the distinction between OCD and schizophrenia\(^5\)

- The form of obsessions and compulsions was similar in the two groups, and no differences were found in severity\(^5\)

- However, differences were found in the content of the obsessions – patients with schizophrenia showed lower instances of:
  - Aggressive obsession
  - Contamination obsession
  - Sexual obsession
  - Somatic obsession

- The authors hypothesise that the similarity in neurology underlying the two conditions leads to similarities in the symptoms experienced\(^5\)

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OCD=obsessive–compulsive disorder

Substance use disorder and schizophrenia

- The rate of substance-related disorders in patients with schizophrenia is high – the ‘Epidemiologic Catchment Area Study’, one of the largest of its kind, found that 47% of patients with schizophrenia had a lifetime diagnosis of substance-use disorder\(^1,2\)

- The Epidemiologic Catchment Area (ECA) study showed that people with schizophrenia in the community had a >3 times greater rate of alcohol use disorders and a >6 times greater rate of other drug use disorders than the general population\(^2\)

- There is growing appreciation of the shared pathology between schizophrenia and addiction, given the importance of dopamine circuitry in reward pathways implicated in addiction, and the role of dopamine in the pathology of schizophrenia\(^1\)

Smoking

• Smoking is common in schizophrenia – **over half of individuals with schizophrenia have tobacco-use disorder and smoke cigarettes regularly**¹

• Abnormalities in nicotine receptors are associated with schizophrenia, and it is thought that smoking may be a form of self-medication that alleviates some of the symptoms that patients experience²,³

• In a study of 78 patients with schizophrenia, smokers were compared with non-smokers:⁴
  • Due to changes in antipsychotic metabolism, smokers received higher doses of antipsychotic medication than non-smokers
  • It is thought that smoking reduces the level of antipsychotic in the blood, and patients therefore smoke to reduce potential side effects of treatment
  • Smoking status should therefore be taken into account when considering patient treatment

Cannabis use

- Although now also thought to be a causative factor for the development of schizophrenia in some cases, cannabis use is frequent in patients with schizophrenia[1,2]
- A literature review, which identified 35 studies spread across the world, found:[2]
  - An estimated median lifetime rate of cannabis-use disorder of 27% among patients with schizophrenia
  - A higher incidence of cannabis-use disorder among patients with first-episode schizophrenia
  - Cannabis-use disorder was more common among male patients, and the young
- Cannabis use has been associated with failure of antipsychotic treatment, and the development therefore of treatment resistance[3]

Cannabis-use disorder is common in patients with schizophrenia, and is more prevalent among males, the young, and first-episode patients[2]

The consequences of substance use disorder in schizophrenia

• It has been noted that cannabis use can contribute to the onset of psychosis, but it can also exacerbate the symptoms, and adversely affect the treatment, of schizophrenia


Consequences of comorbid substance use in patients with schizophrenia

- Heightened risk of suicide
- More positive symptoms
- Heightened risk of violence
- More medical comorbidities
- Legal complications, including heightened risk of incarceration
- Relapse of psychosis
- Greater propensity for antipsychotic-related adverse effects
Physical comorbidities
Cardiovascular disease (CVD)

Risk factors for CVD

Dyslipidaemia
 Patients with schizophrenia often have higher levels of cholesterol than individuals without schizophrenia\(^1\)

Metabolic syndrome
 The prevalence rate of metabolic syndrome in schizophrenia is 37–63%: 2–3 times higher than in general population\(^3\)

Smoking
 Approximately 75% of patients with schizophrenia smoke cigarettes\(^1\)

Diabetes
 The estimated prevalence of diabetes mellitus in schizophrenia is 10–15%: at least twice that of the general population\(^2,3\)

Obesity
 Obesity is approximately twice as prevalent in patients with severe mental illness, such as schizophrenia, as it is in the general population\(^4\)

Costs of cardiovascular comorbidities

- In a retrospective database analysis, patients with schizophrenia were stratified based on the number of ICD-9-CM cardiometabolic comorbidities they had, and their healthcare-use data was analysed.

- Of more than 50,000 patients with schizophrenia:
  - 66% had at least one cardiometabolic comorbidity
  - 39% had two or more cardiometabolic comorbidities

- Greater cardiometabolic burden was associated with increased likelihood of readmission to hospital, and higher costs.

ICD-9-CM=International Classification of Diseases 9th revision – Clinical Modification

Metabolic syndrome

- Risk factors for cardiovascular disease frequently occur together, in a cluster, known as metabolic syndrome, including:
  - Dyslipidaemia – elevated concentrations of triglycerides and small LDL particles, and low concentrations of HDL
  - Elevated blood pressure
  - Elevated plasma glucose
  - Prothrombotic state
  - Proinflammatory state
- Metabolic syndrome directly increases the risk for cardiovascular disease and mortality, to a greater extent than any of its individual risk factors alone.\(^1\)–\(^4\)
- Metabolic syndrome has a prevalence rate in schizophrenia of 37–63% and, compared with the general population, is 2–3 times more likely to occur in patients with schizophrenia\(^5\).
- In a systematic review and meta-analysis, the results of 77 publications were combined to show that 1 in 3 patients with schizophrenia suffer from metabolic syndrome\(^6\).
- It is difficult to know how factors other than antipsychotic use contribute to the risk of metabolic syndrome in patients with schizophrenia, because there are only limited data in drug-naïve patients with schizophrenia\(^7\).

LDL=low-density lipoprotein; HDL=high-density lipoprotein

Lipid profiles

- Dyslipidaemia has a prevalence rate in schizophrenia of 25–69% and, compared with the general population, is **up to 5 times more likely** to occur in patients with schizophrenia\(^1\)
- In a long-term study, following patients with schizophrenia over the course of five years, lipid disturbances were observed relative to healthy controls:\(^2\)
  - Total serum triglyceride levels were elevated in patients with schizophrenia
  - Membrane lipid levels (e.g., omega-3 and omega-6 polyunsaturated fatty acids) were lower during acute schizophrenia
  - During the chronic phase of schizophrenia, the profile of serum and membrane lipid levels was associated with symptoms, and functioning, of patients with schizophrenia

Lipid levels in patients with schizophrenia constitute a disease trait, and could be used as a biomarker of disease\(^2\)

Diabetes

- The estimated prevalence of diabetes mellitus in patients with schizophrenia is 10–15%—i.e., twice that of the general population\(^1\)
- Impaired glucose tolerance is also seen in patients with schizophrenia\(^2,3\)
- Given the strength of the association, screening of patients with schizophrenia for the risk factors of diabetes is recommended\(^3\)
- Early detection of impaired glucose metabolism allows for timely interventions to prevent the development of diabetes, and may protect against long-term complications\(^3\)

Cancer

- The relationship between cancer and schizophrenia is complex\(^1,2\)
- Most of the evidence points to cancer being more common among patients with schizophrenia than in the general population\(^1\)
- Almost as many patients with schizophrenia die from cancer as from cardiovascular disease\(^1\)

Whilst more research is needed, screening programs should be used to monitor patients with schizophrenia for the development of cancer\(^1\)

Chronic obstructive pulmonary disease (COPD)

• The one-year prevalence of COPD in patients with schizophrenia has been reported to be 3.8%, compared with 2.9% in the general population – an odds ratio of 1.66\(^1\)

• The incidence of smoking is appreciably higher in patients with schizophrenia than in the general population; according to one study, as many as 75% of patients with schizophrenia smoke cigarettes\(^2\)

• Smoking is a major risk factor for COPD, and so the high smoking rate among patients with schizophrenia may contribute to the greater incidence of COPD in this patient group\(^1\)

• Interestingly, younger adults, and men, had a greater prevalence of COPD compared with the corresponding groups in the general population, with an odds ratio as high as 3.5, which is a result that warrants further study\(^1\)

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Liver disease

• There are some indications that the incidence of liver disease is greater among patients with schizophrenia than the general population\textsuperscript{1,2}

• One study found a prevalence rate of 7.0\% in patients with schizophrenia, compared with 6.1\% in the general population – i.e., \textbf{1.27 times greater}\textsuperscript{1}

• Younger patients with schizophrenia had a much higher risk of liver disease than the general population\textsuperscript{1}

• A key risk factor for the development of chronic liver disease was diabetes, highlighting the interrelatedness of the various comorbidities of schizophrenia, and how they appear to interact with one another\textsuperscript{1}

The impact of comorbidities on patients with schizophrenia
**Impact of the comorbidities of schizophrenia on patient quality of life**

- Depression and low mood can have a substantial impact on patient quality of life, and when occurring comorbidly, patients with depression experience greater physical illness than those who do not.

- In a study of patients with schizophrenia with comorbid depressive symptoms, depression was associated with significantly lower quality of life (as assessed by the mental component of the SF-12 scale).

- It is important for physicians to be mindful of the comorbidities of schizophrenia, because patients with schizophrenia tend to have poorer physical health but also decreased healthcare service utilisation.

- Testing the association between comorbid substance dependence and schizophrenia severity, a European study analysed >1,200 patients with schizophrenia:
  - Patients with schizophrenia who had comorbid dependence on drugs or alcohol:
    - Had higher PANSS general psychopathology scores
    - Had poorer quality of life
    - Experience more EPS
    - Scored lower (worse) on the GAF scale
    - But, had fewer negative symptoms

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**EPS=extrapyramidal symptoms; GAF=Global Assessment of Functioning; PANSS=Positive and Negative Syndrome Scale; SF-12=Medical Outcomes Study Short Form 12**

## Treating physical illness in patients with severe mental disorders

### Patient and illness-related factors
- Severity of mental illness (SMI patients have fewer medical visits, with the most severely ill patients making the fewest visits)
- Not seeking adequate physical care due to symptoms of the SMI (e.g., cognitive impairment, social isolation and suspicion)
- Less compliant with treatment

### Psychiatrist-related factors
- Unequipped or underfunded teams to handle behavioural and emotional problems of patients with SMI
- Tendency to focus on mental rather than physical health with infrequent baseline and subsequent physical examination of patients
- Poor communication with patient or primary care health workers

### Other physician-related factors
- Stigmatisation of people with mental disorders
- Complexity and time intensity of coordinating both medical and psychiatric medications

### Service-related factors
- Lack of clarity and consensus about who should be responsible for detecting and managing physical problems in patients with SMI
- Lack of access to health care

SMI=severe mental illness
De Hert et al. World Psychiatry 2011;10(2):138–151
Improved physical health outcomes in [patients with severe mental illness] will benefit both patients and societies. This benefit will come from improving functioning, and reducing suffering and physical health care costs that arise from poorly screened and managed patients with advanced physical illnesses compounded on the presence and effects of psychiatric conditions. Even small changes in the monitoring and management of physical disorders that do not have to be costly can make a positive change in this generally underserved and disadvantaged patient group.

De Hert et al. World Psychiatry 2011;10(2):138–151