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GPs are central to improving care of schizophrenia patients

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What are the risk factors for schizophrenia?

How should diagnosis be confirmed?

How should GPs monitor mental and physical health?

SCHIZOPHRENIA IS A NEUROPSYCHIATRIC DISORDER WITH A PREVALENCE OF AROUND 0.7% in England.[1] Though the prognosis is highly variable, it often runs a chronic course, associated with considerable morbidity and mortality.

While psychotic symptoms are the most obvious manifestations of the condition, negative symptoms (e.g. apathy and withdrawal) and cognitive symptoms (especially deficits in executive function) are often more disabling.[2]

Since the 1980s, the care of people with schizophrenia has shifted from hospital to the community. Commensurate with this, the role of GPs in delivering this care has expanded, a fact reflected by the emphasis placed on primary care involvement in the NICE guidelines on schizophrenia.[3] In the UK, on average, GPs will have 7-12 patients with schizophrenia on their list,[4] and 31% of these patients are managed solely in primary care.[5]

RISK FACTORS

Schizophrenia is a brain disorder that probably comprises multiple aetiologies. It affects both sexes, all races and every socioeconomic class. It typically presents in late adolescence or early adulthood, age of onset is a few years later in women than men.

Aetiology is conceptualised within the vulnerability-stress model, manifesting from interactions between biopsychosocial predisposition and environmental stress. Although in recent decades there have been great advances in our understanding of the neurobiology of the condition (see box 1, p16), these have not yet translated into major diagnostic or treatment advances. The following groups are at particular risk of developing schizophrenia:

- People who have a first-degree relative with schizophrenia - the risk is 10% if an individual has an affected parent[6]
- Immigrants from developing to developed countries (and their children) - for example, diagnosis is more common in African-Caribbean people living in the UK
- Adolescents and young adults; the vast majority of first episodes of psychosis occur between the ages of 16 and 30
- People with cognitive impairment or a vulnerable personality - e.g. learning disability, eccentricities of behaviour, propensity to perceptual distortions, poor social adjustment
- Drug users - a particular association with cannabis use is recognised

DETECTION

Schizophrenia typically develops insidiously, potentially over several »

Box 1

The neurobiology of schizophrenia

Genetic studies
Heritability of 80%. Risk conferred by common genes of small effect (identified through genome-wide association studies) and rare genes of large effect (e.g. copy number variants such as DiGeorge syndrome, 12q11 deletion)

Structural imaging
Reduced volume of temporal and prefrontal lobes, loss of volume in the latter being associated with transition from at-risk state to psychosis

Functional imaging
Abnormalities of limbic system activation on exposure to emotional stimuli and in the dorsolateral prefrontal cortex during executive tasks

Neurotransmitters
Abnormalities in dopamine signalling, but other neurotransmitters such as glutamate and GABA seem important too

Immunology
Increased cytokines and other evidence of immune system activation. Oxidative stress may be elevated

Box 3

Useful questions to elicit psychotic symptoms

Delusions
- Have you been concerned about anything unusual recently, or thought strange things were happening around you, or to you?
- Have you been feeling as if something bad is happening to you, or that people have turned against you in some way?

Hallucinations
- Have you experienced any strange or unpleasant experiences recently, for example hearing things that others could not?

Thought insertion/broadcast or withdrawal
- Have you had the experience of someone interfering with your thoughts? Maybe putting thoughts in your mind that are not your own (thought insertion), or others having access to your thoughts (thought broadcast or withdrawal)

Table 1

ICD-10 diagnosis of schizophrenia

At least one of the following present most of the time for a month:
- Thought echo, insertion or withdrawal, or thought broadcast
- Delusions of control referred to body parts, actions, or sensations
- Delusional perception
- Persistent bizarre or culturally inappropriate delusions

Or at least two present most of the time for a month:
- Persistent daily hallucinations accompanied by delusions
- Incoherent or irrelevant speech
- Catatonic behaviour such as stupor or posturing
- Negative symptoms such as marked apathy, blunted or incongruous mood

None of these symptoms are pathognomonic for schizophrenia and all can occur in other psychiatric or medical conditions

Box 2

Prodromal symptoms

- Changes in mood - anxiety, irritability, depression
- Changes in cognition – difficulties with concentration or memory
- Changes in thought content - preoccupation with new ideas often of an unusual nature
- Physical changes - sleep disturbance, loss of energy
- Social withdrawal and deterioration in work/social functioning
- Delusional atmosphere – a feeling that the world has changed in an indefinable way

years. This period is characterised by subtle symptoms and social decline (see box 2, above), and when concerns are raised it is generally by friends or family.

Recognition of the importance of prompt initiation of treatment for schizophrenia has resulted in considerable focus on early detection. It is hoped that this will impact on prognosis, but achieving it depends on GPs having the necessary index of suspicion. This is hampered by the fact that prodromal symptoms are vague, and only around a third of clinically high-risk patients will actually transition to psychosis within three years.[7]

The GP is ideally placed to respond to family concerns, identify prodromal symptoms, screen for psychotic symptoms (see box 3, left) and initiate either a mental health review or active monitoring in primary care. Given that suspiciousness is a central feature of psychosis, the patient may be reluctant to attend the practice.

While keeping personal safety paramount, if the history is suggestive of psychosis every effort should be made to assess the patient.

NICE recommends immediate referral to a mental health service if a patient is distressed, exhibits a decline in social functioning and has:
- Transient or attenuated psychotic symptoms or
- Other experiences or behaviour suggestive of possible psychosis or
- A first-degree relative with psychosis or schizophrenia

There is no test for schizophrenia, diagnosis is based on symptomatology (see table 1, left) and exclusion of other diagnostic possibilities. The differential diagnosis is broad, including drug intoxication and withdrawal, other psychiatric conditions and

medical/neurological diagnoses. Diagnosis should be confirmed by a psychiatrist, and centres on clarification of psychopathology and investigations to exclude other causes (see below).

INVESTIGATIONS IN FIRST EPISODE PSYCHOSIS

Indicated in all cases

- Full physical, including neurological, examination*
- FBC, U&Es, calcium, LFTs, TFTs, glucose, ESR or CRP*
- Urinary drug screen*
- Brain imaging (increasingly MRI)

** If feasible, it is helpful if these form part of the GP's baseline assessment*

Additional investigations that may be indicated (e.g. if atypical presentation, neurological signs)

- MRI head
- B_{12} and folate
- HIV and syphilis serology
- Antinuclear antibody
- Serology for antibodies to NMDA, VGKC (LGI1 and CASPR2), GABAB and AMPA receptors (limbic encephalitis)
- Serum ceruloplasmin (Wilson's disease)
- EEG
- LP and CSF analysis (including autoantibodies)

Potential pointers to a non-psychiatric diagnosis are summarised in table 2, below. In recent years there has been increasing recognition that limbic encephalitis (particularly NMDA-receptor antibody encephalitis) can initially present as a psychotic disorder. If features such as delirium, seizures or a movement disorder are prominent then initial assessment by a medical/neurological team is mandatory.

Even when it seems clear that the cause of symptoms is psychiatric, early diagnostic uncertainty is common (potential psychiatric differentials being, for example, bipolar affective disorder or psychotic depression). This, together with the stigma and negative prognostic associations of the disorder, means patients are often initially diagnosed with a 'first episode psychosis'. In time the diagnosis of schizophrenia generally becomes clear.

The GP plays a central role in providing a basic assessment, evaluating risk, identifying the most appropriate mental health resource, and may on occasion be required to use the Mental Health Act. The structure of mental health services varies with region, but all will have resources in place for psychiatric emergencies.

If risk to self or others is considered significant, then urgent referral to this team is mandatory. This will generally involve direct discussion with the clinicians.

INITIATION OF TREATMENT

Antipsychotic medication is the cornerstone of treatment. The original NICE guidelines recommended second-generation antipsychotics (previously called atypicals) as first-line treatment, but this was dropped in subsequent revisions. This reflects acknowledgement that:

1 All antipsychotics (with the possible exception of clozapine) are of similar efficacy, and

2 Though second-generation antipsychotics have a lower propensity to cause extrapyramidal side effects at therapeutic doses, some (especially clozapine and olanzapine) have a greater propensity to cause metabolic syndrome (see below).

The importance of patient involvement in antipsychotic choice is emphasised, requiring discussion of the relative benefits and side effects of the different preparations (see table 3, p18). Depot preparations can be invaluable when compliance is an issue, though their administration in patients refusing treatment may necessitate use of the Mental Health Act.

NICE is clear that antipsychotic »

Table 2

Red flags indicating that a non-psychiatric cause for symptoms should be considered

Feature	Explanation
Acute onset	Consider intoxication/drug-induced psychosis, alcohol or benzodiazepine withdrawal or delirium/encephalopathy
Atypical age	Though there is a second peak of schizophrenia post menopause, onset before the age of 35 is typical. If first episode of psychosis is in an older patient suspect psychosis as part of a neurodegenerative process (e.g. frontotemporal dementia)
Cognitive impairment prominent	Cognitive impairment in schizophrenia is predominantly executive and relatively subtle. Features such is amnesia, disorientation or gross attentional impairment suggest another pathology
Highly changeable and/or fluctuating presentation	Delusions in schizophrenia are generally fixed and fairly sophisticated. Simple, fleeting delusions are more typical of organic psychoses
Movement disorder at onset	If acute/subacute onset suspect limbic encephalitis. If more insidious suspect Huntington's disease, Parkinsonian/Lewy body syndrome, or (rarely) Wilson's disease
Unexpected neurological features	Features such as dysarthria, altered gait, visual field defects, seizures etc indicate more generalised brain dysfunction and clearly necessitate a neurological work up
Visual hallucinations prominent	These can occur in schizophrenia but should prompt consideration of an alternative diagnosis. Consider delirium/encephalopathy, or in older people Lewy body dementia

medication should only be initiated in a first presentation of psychosis (not in an at-risk mental state) by, or following discussion with, a psychiatrist.[2]

If immediate initiation is felt to be necessary and this discussion is not possible, the chosen drug should be initiated at the lower end of the therapeutic range e.g. risperidone 1 mg, increasing to 2 mg following review. The introduction of antipsychotics is a therapeutic trial, and as such response to treatment and side effects should be carefully documented.

ONGOING TREATMENT

Following their first episode of psychosis 20% of patients will have no further episodes, 20% will have a completely treatment resistant psychosis and the rest will have significant recovery but further episodes.[8] To minimise the chance of relapse antipsychotics are continued for a minimum of 18 months and discontinued gradually.

A second episode will often necessitate prolonged and possibly lifelong treatment, though it is recognised that many patients are likely maintained on higher doses of antipsychotics than are necessary. The wide range of potential adverse effects of antipsychotic treatment necessitates active monitoring.

GP MONITORING OF PATIENTS TREATED WITH ANTIPSYCHOTICS

History and examination

- Extrapyramidal side effects: acute dystonia, parkinsonism, akathisia, tardive dyskinesia
- Lethargy/sedation
- Anticholinergic effects: dry mouth,

Table 3

Common antipsychotic drugs: dosages and side effects

Type	Usual starting dose	Usual clinical dose	Notes/notable side effects
First generation			
Chlorpromazine	25-100 mg/day	300-600 mg/day	Sedation, hypotension, anticholinergic, photosensitivity
Haloperidol	5 mg as required	Generally used for inpatient acute tranquilisation	Extrapyramidal side effects, poorly tolerated and rarely used for long-term treatment. Association with QTc prolongation
Sulpiride	400 mg/day	800-1,600 mg/day	Lower propensity to cause sedation and extrapyramidal side effects
Second generation			
Risperidone	1-2 mg a day	2-6 mg a day	Hypotension on initiation, extrapyramidal side effects at higher doses. Lower propensity for metabolic syndrome than olanzapine and quetiapine
Olanzapine	5 mg/day	10-20 mg/day	Sedation, weight gain, impaired glucose tolerance
Quetiapine	300 mg/day (only if modified release)	300-750 mg/day	Hypotension on initiation, sedation, low propensity to cause extrapyramidal side effects
Aripiprazole	10-15 mg/day	15-30 mg/day	Low propensity to weight gain/metabolic syndrome. Extrapyramidal side effects may occur and anxiety on initiation
Clozapine	Only initiated by psychiatrists	200-500 mg/day	Agranulocytosis (FBC monitoring mandatory), sedation, weight gain, glucose intolerance
Depot/long-acting injections			
Zuclopenthixol decanoate	100 mg test dose	200 mg four weekly to 400 mg fortnightly	Extrapyramidal side effects
Paliperidone long-acting injection	150 mg on day 1, then 100 mg on day 8	25-100 mg monthly	Extrapyramidal side effects
Aripiprazole long-acting injection	400 mg	400 mg monthly	Continue oral aripiprazole for first 14 days. Dose reduced to 300 mg monthly in CYP2D6 poor metabolisers

key points

SELECTED BY

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Schizophrenia often runs a chronic course and is associated with considerable morbidity and mortality. While psychotic symptoms are the most obvious manifestations of the condition, negative symptoms (e.g. apathy and withdrawal) and cognitive symptoms (especially deficits in executive function) are often more disabling. It generally presents in late adolescence or early adulthood. Schizophrenia typically develops insidiously, potentially over several years. This period is characterised by subtle symptoms and social decline, and when concerns are raised it is generally by friends or family.

Recognition of the importance of prompt initiation of treatment for schizophrenia has resulted in considerable focus on early detection. The GP is ideally placed to respond to family concerns, identify prodromal symptoms, screen for psychotic symptoms and initiate either a mental health review or active monitoring in primary care. NICE recommends immediate referral to a mental health service if a patient is distressed, exhibits a decline in social functioning and has: transient or attenuated psychotic symptoms or other experiences or behaviour suggestive of possible psychosis or a first-degree relative with psychosis or schizophrenia.

Diagnosis of schizophrenia is based on symptomatology and exclusion of other diagnoses. The differential diagnosis is broad, including drug intoxication and withdrawal, other psychiatric conditions and medical/neurological diagnoses. Diagnosis should be confirmed by a psychiatrist, and centres on clarification of psychopathology and investigations to exclude other causes.

Antipsychotic medication is the cornerstone of treatment. NICE states that antipsychotic medication should only be initiated in a first presentation of psychosis (not in an at-risk mental state) by, or following discussion with, a psychiatrist. The introduction of antipsychotics is a therapeutic trial, and as such response to treatment and side effects should be carefully documented.

Following a first episode of psychosis 20% of patients will have no further episodes, 20% will have treatment resistant psychosis and the rest will have significant recovery but further episodes. To minimise the chance of relapse antipsychotics are continued for a minimum of 18 months and discontinued gradually. A second episode will often necessitate prolonged and possibly lifelong treatment. Patients with schizophrenia should also be offered CBT and family therapy. GPs are able to place a psychotic episode within the context of what is 'normal' for that person.

People with schizophrenia die up to 20 years prematurely, the most common cause of death being cardiovascular disease. They often have manifold risk factors, including smoking, alcohol and drug use, poor nutrition, obesity and a sedentary lifestyle. A key role of the primary healthcare team is provision of physical healthcare and screening. Health promotion and smoking cessation are also important.

blurred vision, constipation, urinary retention
- Sexual dysfunction
- Amenorrhoea (raised prolactin)
- Postural hypotension

Routine baseline and generally at least annual physical checks*
- Weight and waist circumference
- BP and pulse
- U&Es, LFTs
- HbA_{1c}, lipid profile
- Prolactin
- General health promotion: smoking cessation, exercise, good diet
- For patients with a cardiac history or on high doses/combinations of psychotropics an ECG is necessary

* *Metabolic syndrome is associated with most antipsychotics, and is a particular problem with clozapine and olanzapine. If patients are on these drugs this monitoring is especially important*

Practitioners should be particularly alert to extrapyramidal side effects (such as parkinsonism and akathisia), risk of QTc prolongation (particularly if drugs with this propensity are combined or there is a cardiac history) and metabolic syndrome. Parkinsonism (best detected by the presence of cogwheel rigidity) responds to dose reduction, a change to a second-generation preparation or addition of an anticholinergic such as procyclidine; akathisia may be helped by addition of a benzodiazepine or propranolol, but its highly unpleasant nature and strong association with suicide necessitates discussion with a psychiatrist.

NICE guidelines place particular emphasis on psychosocial interventions, recommending that all patients with schizophrenia should be offered CBT (for persistent positive symptoms and to prevent relapse) and family therapy (to help families cope more effectively with the patient's problems and prevent relapse) and arts therapy should also be considered (for negative symptoms; unfortunately more recent research suggests little benefit, however). While these interventions are certainly desirable, the reality is that implementation is hampered by resource limitations; despite CBT and family therapy being recommended in the original NICE guidelines, only half of eligible patients were offered these interventions.[9]

Tragically, 5% of patients with schizophrenia die by suicide,[10] this is generally in the first few years following diagnosis. Hence vigilance for depressive symptoms is vital.

Usual markers of suicide risk (male, isolated, unemployed etc) contribute, though the educated, insightful young man painfully aware that his ambitions are unlikely to be fulfilled should raise particular concern.[11] Substance misuse can be a major issue, increasing suicide risk, compounding social decline, and precipitating relapse. It should be actively screened for and particularly suspected in cases of poor treatment response.

KEY ROLES OF THE PRIMARY CARE TEAM

People with schizophrenia die up to 20 years prematurely, the most common cause of death being cardiovascular disease.[12]

One of the most fundamental roles of the primary healthcare team is provision of physical healthcare. Patients with schizophrenia frequently have manifold risk factors for poor physical health, including smoking, alcohol and drug use, poor nutrition and hygiene, obesity, a sedentary lifestyle and poverty. When the weight gain, impaired glucose tolerance and dyslipidaemia (metabolic syndrome) associated with antipsychotic treatment is also taken into account, cardiovascular mortality in this population is roughly doubled.[13]

Despite this acknowledged excess morbidity and mortality however, it has been reported that schizophrenia patients are half as likely as asthma patients to have risk factors such as blood pressure and cholesterol recorded.[14] They are also less likely to undergo routine cancer screening,[15] though people with schizophrenia who develop cancer are less likely to survive than the general population.[16]

Recognition of unmet physical health needs has led to much focus on monitoring risk factors for physical morbidity, primary and secondary prevention, and encouragement of the use of general practice case registers to ensure these needs are addressed. While NICE recommends that physical health monitoring in the first year of treatment is undertaken by secondary care, it is generally expected that it subsequently becomes the responsibility of primary care. The QOF indicators for mental health are shown in table 4, p20.

Of course, screening is only useful if it leads to interventions. The British Association for Psychopharmacology recommends that if significant weight gain occurs, lifestyle interventions and consideration of switching antipsychotic (to one less associated with weight gain) should be first line.[17] Adjunctive »

Table 4

Quality and Outcomes Framework: Mental health indicators (2019/20)

Records
MH001 The contractor establishes and maintains a register of patients with schizophrenia, bipolar affective disorder and other psychoses and other patients on lithium therapy. **4 points**

Ongoing management
MH002 The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a comprehensive care plan documented in the record, in the preceding 12 months, agreed between individuals, their family and/or carers as appropriate. **6 points**

MH003 The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a record of blood pressure in the preceding 12 months. **4 points**

MH006 The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a record of BMI in the preceding 12 months. **4 points**

aripiprazole may be helpful with weight gain associated with clozapine and olanzapine. If lifestyle interventions are ineffective, and the GP is in agreement, metformin can be trialled with appropriate monitoring (renal function and vitamin B_{12}).

Achieving smoking cessation is important but challenging. A recent trial suggested engagement of people with severe mental illness can be improved with bespoke interventions, albeit rates of quitting at 12 months were not significantly different from those receiving standard smoking cessation input (15% in the former group vs 10% in the latter).[18]

With the increased emphasis on a 'recovery' approach to schizophrenia, and the aspiration that patients are stabilised and discharged to primary care, the number of patients discharged from psychiatric services is likely to increase.

The GP has a central role in the holistic care of all patients however, even those with regular mental health input. These can be summarised as:

- Early identification of psychosis/prodromal state and ensuring prompt psychiatric review
- Attending to patient and family distress arising from diagnosis and providing information about the condition
- Building a relationship with family/carers and contributing to work on relapse prevention/recognition of relapse signature
- Providing continuity of care and ensuring good communication between services. This has become even more crucial following the profusion of specialised mental health services and separation of inpatient and outpatient teams
- Physical health monitoring, health screening and attending to physical health needs
- Health promotion/smoking cessation
- Monitoring mental health and instituting secondary care review when indicated
- Identification of drug and alcohol problems
- Vigilance for social problems, child protection concerns etc

Additionally, having often been the only healthcare professional to have known an individual before the illness GPs have the invaluable ability to place a psychotic episode within the context of what is 'normal' for that person. This knowledge is crucial when making applications for use of the Mental Health Act, underlying the importance of the GP's report in these circumstances.

Competing interests: None

Further reading

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See also *Early intervention key in first episode psychosis,* p11

Useful information

Royal College of Psychiatrists
Patient information/leaflets
www.rcpsych.ac.uk/mental-health/problems-disorders/schizophrenia

MIND
www.mind.org.uk/media/990900/understanding-schizophrenia-2014-.pdf

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