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# Treatment of the patient with long-term schizophrenia

Ann Mortimer

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At most, 15% of patients in Western countries remain free of relapse after their first episode of schizophrenia (Crow *et al*, 1986). Like many chronic illnesses, schizophrenia can be controlled by appropriate treatment, but there may be a gradual deterioration over time. This encompasses problems such as loss of self-care, communication and community skills; negative symptoms of poverty of affect and ideation; cognitive impairment; behaviour problems such as aggression; and poorly controlled positive symptoms.

Deterioration often appears consequent upon repeated relapse. Indeed, the prognosis of schizophrenia may have improved significantly following the introduction of neuroleptics (see McKenna, 1994) because of their marked prophylactic effect in preventing relapse. One analysis of 24 placebo-controlled studies of continuing antipsychotic treatment showed that patients relapsed more frequently on placebo than on active medication: active treatment over three years reduced the risk of relapse almost threefold (Davis, 1975).

Two issues are, therefore, germane to the long-term treatment of schizophrenia. The first is the prevention of relapses, most of which are caused by non-compliance (Davis *et al*, 1994), and the second is the management of unresolved symptoms and social deficits. Optimal management should include a spectrum of approaches from sophisticated use of medication to appropriate psychotherapy. Its rationale is essentially rehabilitative, comprising assessment of individual difficulties plus targeted interventions. If the patient cannot be returned to adequate function, ongoing support and care are necessary.

Continuous management of this nature is best facilitated by a multi-disciplinary framework,

currently exemplified by the Care Programme Approach (CPA).

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## Relapse prevention

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### *Relapse rates, neuroleptic prophylaxis and compliance*

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After an acute episode, 8–16% of patients per month relapse without medication (Davis *et al*, 1994). The figure is similar if medication is withdrawn after several years' successful maintenance. Intermittent treatment targeted at prodromal symptoms and 'drug holidays' is relatively unsuccessful and cannot be recommended (Anonymous, 1994; Christison *et al*, 1991).

Up to 60% of patients in the community are, at least episodically, non-compliant: relapse rates could possibly be halved if compliance were significantly improved (Kissling, 1994). The causes of non-compliance resemble those in non-psychiatric disorders: lack of information and understanding about illness, difficulty managing complex regimens of medication, denial, forgetfulness, inconvenience, expense, side-effects, lack of active symptoms, and fear of long-term harm or addiction. Schizophrenia adds to this list poor, or fluctuating, insight and stigma. These difficulties, however, suggest several approaches to improve compliance.

### *First or subsequent acute episodes*

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Information about illness and treatment should be imparted to and discussed with patients and carers

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as soon as possible (Anonymous, 1994). Learning objectives of this process of 'psychoeducation' include understanding the origins and significance of the episode; acceptance of vulnerability and dependence on psychotropic medication; recognition of links between stressful events and exacerbation of illness, and understanding the distinction between the patient's personality and their schizophrenia. The success of psychoeducation rests upon a constructive relationship between professionals and family.

For patients nearing discharge a process of gradually increasing responsibility for medication should occur, ideally with patients becoming fully self-medicating prior to discharge. Step-wise practice towards this goal begins with the patient asking for medication at the relevant time, and culminates in the patient taking complete responsibility, with regular or random checks of pill numbers. It is advisable to implement or change drug regimens gradually: many rapid alterations may be confusing for both patient and doctor.

### *After discharge*

Follow-up of patients should be assertive: non-attenders should be traced. The time to intensify follow-up is when the patient insists on non-compliance, because relapse may be anticipated within the next few months. For patients subject to supervised discharge or listed on the supervision register, there may be a lower threshold for attempting to return the patient to hospital.

Patients should be encouraged to participate in their own care. It is important to discuss medication with each patient, so that they feel involved in decision-making. One randomised controlled trial of 'compliance therapy' (motivational interviewing and cognitive therapy) found that the compliance therapy group improved significantly compared with a non-specific counselling group regarding insight, attitudes to medication and compliance six months after discharge: there was a trend towards improved social functioning (Kemp *et al*, 1996). The finding that these advantages may be lost at 12 months underlines the need for such interventions to continue.

### *Maintenance in the community*

In maintenance treatment the simplest regimen of medication at the minimum effective dose is appropriate, ideally a neuroleptic taken once daily or by depot administration. Written instructions

may be useful for patient and carer. Tailoring the regime to patients' daily activities is advisable.

Depot injections are only advantageous compared with oral neuroleptics in out-patient studies; the advantage of decreased relapse is lost when in-patient groups are compared (Davis *et al*, 1994). Depot formulations may ensure that the patient who will not comply with oral treatment continues to receive a neuroleptic, but awareness that the patient has defaulted may be the only tangible benefit. Depot administration circumvents 'first pass' metabolism, which may result in worse side-effects; some patients find it painful and demeaning.

Patients should always be observed for, and questioned specifically about, unwanted side-effects. These (particularly Parkinsonism and akathisia (Anonymous, 1994), sexual dysfunction, sedation and weight gain) are a major cause of non-compliance. Side-effects should be managed by dose reduction (preferably), a change to a drug with milder side-effects such as an atypical neuroleptic, or the addition of a specific antidote.

It is important to give positive feedback when medication has been used appropriately.

## **Unresolved positive symptoms**

### *Differential diagnoses and simple solutions*

Poorly controlled positive symptoms constitute one criterion for treatment resistance. They may also be encountered in patients who cannot tolerate a therapeutic dose of neuroleptic without unacceptable side-effects (Box 1).

Other causes of psychosis, such as substance misuse, personality disorder, and organic psychosis, should be ruled out, as should the possibility of non-compliance. The impact of high levels of stress within the family and their repercussions should not be underestimated. Skilled nursing observation, urinary screening for drugs of misuse, serum prolactin levels,

#### **Box 1. Unresolved positive symptoms**

- Assess compliance
- Assess living situation
- Optimise medication
- Consider cognitive-behavioural strategies
- Consider family work to reduce stress

psychometric assessment and discussion with the patient and family may all contribute to accurate evaluation of unresolved psychosis.

A substantial minority of patients respond very poorly to medication, and this tends to be more of a problem with increasing chronicity. A thorough review of the patient's current and previous medication should take place, with the objective of rationalising over-medication or polypharmacy and identifying regimes which did or did not work previously. Simple adjustments, such as reducing neuroleptic treatments and dosages, dealing with troublesome side-effects (particularly akathisia) and drug interactions, can be worthwhile. Anticholinergics should be stopped if possible since they can antagonise the antipsychotic effects of neuroleptics. High-dose neuroleptics may worsen the patient's condition and may be unsafe (Mortimer, 1994).

Lithium has been shown to benefit up to half of all patients (Siris, 1993). Predictors of response to lithium include affective symptoms, aggression and family history of affective disorder; improvements are not limited to predictor symptoms. Benzodiazepines are likely to be helpful when psychosis is accompanied by marked anxiety, or to control behaviour disturbance in acute relapse. Evidence that other adjuvants are worth trying is much less convincing: carbamazepine may treat side-effects since it reduces circulating levels of neuroleptics by up to 50%, while propranolol may relieve akathisia that is being mistaken for psychotic agitation.

### *Atypical neuroleptics*

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Several atypical neuroleptics are now available (discussed in Kerwin *et al*, 1997). They aim to combine the same, or improved, efficacy as conventional neuroleptics with milder side-effects, particularly extrapyramidal side-effects (EPS). Pharmacologically, they fall into two categories: those which preferentially block dopamine (D<sub>2</sub>) and serotonin (5-HT<sub>2</sub>) receptors, and those which block multiple receptors (Gerlach & Peacock, 1995). The first group includes risperidone, sertindole and ziprasidone. At recommended doses, risperidone has few EPS and may be advantageous in the treatment of negative symptoms. Sertindole trials report EPS and prolactinaemia at placebo level, but owing to prolongation of cardiac conduction electrocardiogram monitoring is indicated. Efficacy is very similar to haloperidol for positive and negative symptoms, there being statistically significant advantages over haloperidol for

negative symptoms. Ziprasidone is still undergoing clinical trials: it may cause less EPS than conventional treatments.

The second group includes olanzapine, quetiapine, zotepine and clozapine: seroquel and zotepine remain under trial. Olanzapine induces EPS at placebo rates: antipsychotic efficacy may be superior for negative symptoms. Seroquel appears equivalent in efficacy to conventional antipsychotics, while compared with conventional treatment EPS are reported as similar to placebo level. Zotepine may cause less EPS than conventional neuroleptics and has equivalent efficacy for positive symptoms.

Evidence of superior benefit is greatest for clozapine: 30–60% of treatment-resistant patients respond to this drug (Anonymous, 1994). EPS are conspicuous by their absence. There is a body of opinion that despite its drawbacks – the risk of neutropenia and inconvenience of white cell monitoring – clozapine should be used much earlier in the course of the illness than it generally is (Kerwin *et al*, 1997). Clozapine can be used safely with lithium, benzodiazepines and anticonvulsants (apart from carbamazepine). Sodium valproate may be given to patients on 600 mg or more per day owing to lowered seizure threshold at higher doses.

### *Cognitive therapies for positive symptoms*

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Cognitive-behavioural therapy (CBT) assumes that schizophrenia emerges in individuals who tend to employ dysfunctional cognitive models of themselves and their environment: these models may be amenable to interventions which utilise learning theory. CBT identifies and quantifies target symptoms and behaviours, examines their antecedents and consequences, intervenes in these if possible, and with the patient formulates alternative explanatory models for their target symptoms. Changes in symptoms and behaviour are evaluated (Turkington, 1996). For hallucinations, approaches include focusing on them or distraction from them, enhancement of coping skills and reducing the patient's belief in their omnipotence and omniscience (Chadwick & Birchwood, 1994). Patients who are able to respond more constructively to their voices, without the usual anger or withdrawal, may gain a degree of control over them. Critical collaborative analysis of voices (Turkington & Kingdon, 1994) explores their origin and rationale, supplanted by behavioural experiments such as the patient making a tape-recording when voices are heard, or the



patient taping his own rational responses which can be played back when voices are troublesome. Such interventions should not take place without adequate training and supervision.

Regarding delusions, it is well known that confrontation does not work. It may be possible to modify the belief through exploring the implications of the delusion as if it were absolutely true, and to test these out with behavioural homework. Reducing anger and anxiety associated with delusions is likely to be beneficial. However, there may be a risk of depression if delusions which preserve self-esteem are attenuated.

### *Importance of high expressed emotion and its management*

Aspects associated with relapse (critical comments, hostility and emotional over-involvement) have been widely enumerated: a review of prevalence reported by North American and European studies (Kavanagh, 1992) found the percentage of high expressed emotion (EE) families to be at least 45%. EE had substantial support as a predictor of positive symptoms. The median relapse rate in high-EE environments was 48%, versus 21% in low-EE environments.

Of seven studies which examined the effect on relapse of lowering EE in patients' relatives, five found a significant effect. The largest study followed 103 patients for two years. Four intervention groups were evaluated: routine care (including medication); routine care plus social skills training; routine care plus family psychoeducation and interpersonal problem-solving training; and routine care, social skills training, family psychoeducation and interpersonal problem-solving training. At two years the relapse rates for the four groups were 66, 42, 32 and 25%, respectively. The difference in relapse rate was found to depend on the lowering of high EE.

### *Conclusions*

Skilled medication management can make a large difference to the resolution of positive symptoms in schizophrenia. However, it is naive to assume that other factors have no influence: fraught, tense households are likely to be deleterious to all sorts of illnesses and this effect may be magnified in the case of mental illnesses. Questions remain concerning the specific therapeutic factors pertaining to these strategies. Is high EE a valid entity, or are reductions in relapse rate a result of increased time and attention being given to patients and their families, improving compliance

in drug-taking and other behaviours in all parties (including the doctor)? Regarding CBT, does improvement of isolated symptoms impinge on overall outcome? Unresolved positive symptoms afford such potential for relapse that these therapies are definitely worth trying, notwithstanding poorly understood mechanisms of action.

## **Unresolved negative symptoms**

### *Definition and differential diagnosis*

Negative symptoms can be conceptualised as a failure to respond to stimuli, either externally or internally generated. Core negative symptoms are flatness of affect and poverty of ideation. Poverty of speech and drive, diminished expressive behaviour, self-care and personal function may be secondary to these core symptoms. They are considered prognostically unfavourable and relatively unresponsive to conventional neuroleptics. They may be an inevitable consequence of severe chronic illness, but differential diagnosis remains important.

Patients who are withdrawn owing to pre-occupation with positive symptoms may appear to have negative symptoms (Box 2). Useful clues include inappropriate affect, fragments of thought disorder, abnormal involuntary movements and hallucinatory behaviour. EPS, especially mask-like face and bradykinesia, are easily mistaken for real negative symptoms: other parkinsonian phenomena should be assessed. Over-sedated patients often have little drive, and complain about it or appear drowsy or asleep for long periods. Depressed patients may be misdiagnosed, although there is no correlation between depression and negative symptoms. These patients can be encouraged to convey distress, whereas the patient with truly flat affect will maintain indifference. Other useful clues are diurnal variation, early wakening and depressive ideation. Depression is very common in patients with schizophrenia, ranging from an insightful response to emerging disability, to a genuine schizoaffective state. Standard treatment for depression is indicated: the management of suicidal ideation requires particular care.

Many patients have a history of prominent schizoid traits of social inactivity, difficulty expressing emotion and eccentricity. Whether such a personality is a way station on the road to schizophrenia (part of the illness) or a risk factor for schizophrenia (causing experiences to be misconstrued) is unclear. These traits are unlikely to be modified by psychiatric treatment.

### Box 2. Differential diagnosis of negative symptoms

Excess medication – Parkinsonism/over-sedation  
 Unresolved positive symptoms  
 Depression  
 Schizoid premorbid personality

## *Treatment of negative symptoms*

One classic study of the effectiveness of rehabilitation (Wing & Brown, 1970) found that an increase in time spent by patients occupied in activities on wards was paralleled by clinical improvements in flatness of affect, social withdrawal and other negative symptoms. The implication is that patients retain some capacity to respond to external stimuli and give appropriate interaction. Every clinician will have come across patients who appear to be quietly institutionalised at home or in residential care: good outreach support for relatives and carers, respite periods and other rehabilitation provision perhaps constitute the best management strategy for the remediation of negative symptoms. However, there is evidence that clozapine and certain other atypical drugs do ameliorate negative symptoms. Patients should always be offered these drugs, particularly clozapine, as they may become much more amenable to rehabilitation as a consequence.

## **Behaviour problems**

### *Scope of behaviour problems*

Behaviour problems include self-harm, harming others, destroying property, sexual disinhibition, and socially embarrassing behaviours. Behaviour problems may ameliorate as part of the general process of getting better, in parallel with reduction of positive and negative symptoms: one study of patients on clozapine suggested this to be the case (Dye *et al.*, 1996).

### *Violence*

Violence, secondary to delusions, constitutes a particular danger. Patients who misuse drugs or alcohol are significantly more likely to commit

violent offences: very high rates of comorbid substance misuse have been reported in schizophrenia. A minority of patients are responsible for a disproportionate amount of violence: the best predictor of future violence is past violence. Such patients require more intensive monitoring of mental state and compliance than usual, and there should be contingency plans in case deterioration or defaulting from treatment occurs. Assessment of risk involves a consideration of not only the patient, but also his/her environment and potential victims.

## *Medication for specific problems*

The role of medication in the management of specific behaviour problems is not well defined. Lithium and anticonvulsants may be used for their anti-aggressive properties (Siris, 1993). The use of anti-libidinal drugs in sexually disinhibited men with schizophrenia has not, in my own experience, been valuable, as patients seem to have a normal amount of libido but direct it in ways which contravene social norms. This may be the case across a wide range of behaviour problems: the patient may have a vague awareness that their behaviour is undesirable, but does not understand that this matters in terms of its effects on other people.

## *Behavioural management*

Behavioural treatment is apposite for the majority of patients. An assessment is made of the antecedents and consequences, which may be modified to make the behaviour less likely (Box 3). The reinforcements most valued by the individual patient are identified: these may be withdrawn for unacceptable behaviour, or the patient may earn extra reinforcements by refraining from the behaviour. Social disapproval by staff whom the patient respects may be a powerful means of modifying behaviour, but it is important

### Box 3. Behavioural treatment

Analyse antecedents, behaviours and consequences  
 Identify reinforcers  
 Practice desirable appropriate behaviours  
 Do not induce further disability  
 Prosthetic environment if necessary

that the patient must understand what are the alternatives to the behaviour that is being criticised. Formal behaviour programmes should be discussed with and understood by the patient, and must be structured so that the patient is not set up for demoralising failure. The value of unexpected kindness, in the form of occasionally bending the rules in the patient's favour, is much underestimated.

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## Loss of personal function

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### *Rehabilitation*

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Loss of self-care, communication and community skills is germane to loss of independence and increased resource uptake in schizophrenia. Overall, such deficits may reflect severity and chronicity of the disease, and be accompanied by negative symptoms and cognitive impairment. Positive symptoms may not be as relevant, but when the disorganisation syndrome is present or the patient is largely preoccupied with abnormal experiences, it may not be possible to engage them: the patient has no 'well part' which can be worked with.

Rehabilitation has much to offer once symptom management is optimised, and should be available in community settings. Skills which are lacking are identified and attempts made to teach the patient through repeated practice. Patients may need extra aids to do this, such as printed instructions about the stages of cooking a meal or using a washing machine. It is important that the patient appreciates why such activities are useful, and receives verbal and social reinforcement for improved performance. A behaviour programme may be set up in which the patient is rewarded for getting up, having a bath, doing laundry, etc. Social skills training, the use of role play, and opportunities to interact with the community outside the hospital are all useful ways of helping both the patient to function better and the team to monitor progress. Outside contacts with family, friends or volunteers should be encouraged. Sheltered work may help patients raise their self-esteem by achieving something, but exploitation should always be guarded against. As an overall aim, the patient should spend more time doing things which 'normal' people do, and less time doing nothing or 'mental patient-type' activities.

For patients unwilling to learn necessary skills, alternatives should be considered. Our own attitudes and values may not be appropriate. For instance, a patient who does not wish to cook may

be housed close to an inexpensive cafe. If lack of function is consequent on cognitive compromise, rehabilitation may prove impossible and a prosthetic environment supplied. However, patients should not be subject to over-provision, which may induce further disability.

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## Cognitive impairment

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### *Nature and importance of cognitive impairment*

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There is now virtually irrefutable evidence that schizophrenia is characterised by a compromise of intellectual function, ranging through specific deficits to frank dementia. Evidence of independent dementia pathology from post-mortem brain samples is, however, conspicuous by its absence, suggesting that the process is potentially reversible.

Memory and executive (frontal) functions are frequently impaired in patients with schizophrenia even when there is no significant general cognitive dysfunction. Such specific cognitive deficits are substantial correlates of psychiatric disability: a recent review (Green, 1996) found that verbal memory and certain aspects of executive performance were associated with outcome in terms of community functioning, social problem-solving and skills acquisition. By contrast, psychotic symptoms were not correlated with functional outcome in any study. Remediation of memory and executive deficits thus has the potential to overcome consequential rate-limiting steps in rehabilitation and to improve outcome. This is especially important given the enormous costs of long-term support for chronic dependent patients.

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### *Neuroleptics and cognition*

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Any drug which could remediate cognitive deficit – a 'smart drug' for schizophrenia – would have major advantages. Unfortunately, there is little evidence that conventional neuroleptics have any therapeutic effect on cognition (Mortimer, 1997). Atypical neuroleptics have not been adequately tested to date. Several studies on clozapine suggest that it may improve memory and frontal function (Mortimer, 1997). It has been suggested that dopaminergic and cholinergic agonists should be investigated as possible specific remedies for cognitive impairment, although this would risk antagonism of antipsychotic effects of neuroleptics and worsening of Parkinsonism.



## Direct cognitive remediation

Attempts have been made to correct specific cognitive abnormalities through practice at tasks or tests which employ the intellectual skills found to be lacking. It has been shown that test performance can be improved, but unfortunately these new skills do not generalise to everyday behaviour, and symptoms do not seem to benefit either (Lieberman *et al*, 1995). Social skills training, role play and similar rehabilitation strategies are perhaps more valid in terms of the relevant executive and memory abilities required by patients.

## Care programmes and management of the stable patient

The CPA is the recommended model for management of psychiatric patients. It formalises good professional practice (Kingdon, 1994) (Box 4). CPA has the potential to assess patients' needs comprehensively, to improve communication between professions and to match patient requirements with appropriate interventions and facilities.

Patients who are stable and whose problems are largely resolved may no longer require CPA. Such patients should still be reviewed at least annually by a mental health care professional, preferably working in primary care. The review should include a general health care check, assessment of mental state, compliance and side-effects, personal function and cognition, with the views of an informant if possible.

## The future

Clozapine has been joined by a choice of alternative atypical neuroleptics. Long-term studies of relapse

### Box 4. Care Programme Approach

Multi-disciplinary assessment of health and social needs  
Named keyworker  
Written care plan  
Regular reviews of needs and progress

### Box 5. Essentials of long-term treatment

Maximise compliance to prevent relapse  
Address unresolved positive symptoms  
Manage unacceptable negative symptoms  
Deal with behaviour problems  
Assess cognitive status  
Evaluate rehabilitation needs

rates, quality of life and economic benefits are favourable (e.g. Guest *et al*, 1996). Family intervention and CBT have gained a foothold. The importance of investing resources in the psycho-education of first-episode patients and families, and of compliance counselling, is slowly becoming established. Despite these hopeful advances, for many patients their benefits appear to be as far away as ever. Regarding drugs, the situation has been termed "a revolution waiting to be prescribed" (Kerwin, 1995).

The demand for psychological interventions may rise, if treatment of new patients with atypical drugs creates a cohort who have milder symptoms and who are eminently suitable for such input. Trusts should be encouraged to invest in appropriate training of nurses, for instance for the Thorne diploma.

There is perhaps more potential now than at any time since the introduction of conventional neuroleptics for psychiatrists to make a real difference to the outcome of patients with long-term schizophrenia. These patients should not continue to suffer from the low expectations of their doctors, as well as from their illness.

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3. Differential diagnosis of negative symptoms includes:
  - a non-compliance with medication
  - b depressive symptoms
  - c akathisia
  - d disorder of personality
  - e use of excess sedating medication.
4. Important elements of behaviour therapy in schizophrenia include:
  - a absolute adherence to agreed programmes
  - b identification of reinforcements
  - c psychodynamic exploration of behavioural rationale
  - d specific pharmacological treatment
  - e verbal and social reinforcement.
5. Treatment options for negative symptoms include:
  - a high-dose conventional neuroleptics
  - b high-dose atypical neuroleptics
  - c clozapine
  - d tricyclic antidepressants
  - e behavioural therapy.
6. Cognitive function in schizophrenia is characterised by:
  - a a decline in IQ
  - b visuo-spatial dysfunction
  - c language dysfunction
  - d working memory impairment
  - e classic amnesic syndrome.

## Multiple choice questions

1. Chronic schizophrenia is characterised by:
  - a elation of mood
  - b negative symptoms
  - c obsessional phenomena
  - d loss of self-care skills
  - e clinically significant cognitive impairment.
2. Differential diagnosis of unresolved positive symptoms includes:
  - a non-compliance with medication
  - b alternative diagnosis to schizophrenia
  - c depressive symptoms
  - d substance misuse
  - e disorder of personality.

MCQ answers					
1	2	3	4	5	6
a F	a T	a F	a F	a F	a T
b T	b T	b F	b T	b F	b F
c F	c F	c F	c F	c T	c F
d T	d T	d T	d F	d F	d F
e T	e F	e T	e T	e T	e T