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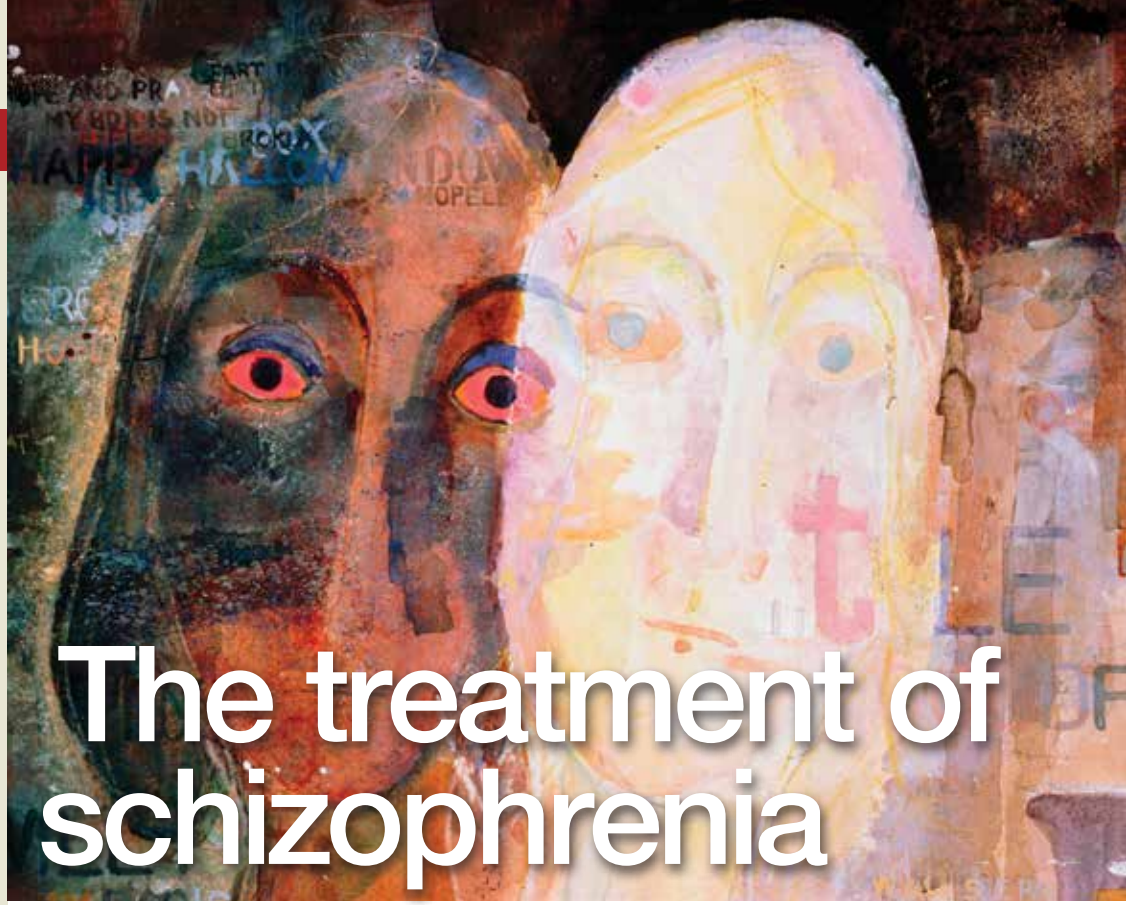

The treatment of schizophrenia

An overlooked 'duty to care'

ANTHONY HARRIS MB BS, PhD, FRANZCP

Schizophrenia remains a challenging illness causing high levels of chronic disability. Identifying the condition early is difficult, medication adherence is problematic, the availability of psychosocial interventions is limited and the poor physical health of people with schizophrenia is often overlooked.

Key points

- **Early identification and treatment of people with schizophrenia aims to change the longer-term course of the disorder.**
- **The poor physical health of people with schizophrenia is often overlooked.**
- **Adherence to treatment is especially problematic in people with schizophrenia and other psychotic illnesses, and involvement of the family and the local mental health team or the use of depot medication may be necessary.**
- **Initial treatments include second-generation antipsychotics and psychosocial interventions.**
- **Psychosocial interventions are effective but their availability is limited due to lack of funding and inequitable distribution of resources.**

Schizophrenia is a severe and persistent mental illness that still challenges us. It is the most severe of the psychotic illnesses and over a lifetime afflicts 7.2 people out of every 1000.[1]

The plight of people with schizophrenia has been explored in Australia in a nationwide epidemiological survey (the Survey of High Impact Psychosis; SHIP) that records our current underperformance in caring for people with a psychotic illness and also underlines the gap between the good intentions of our national mental health plans and the reality with which people with psychotic disorders, and schizophrenia in particular, live.[2]

This survey has shown that, as a group, people with schizophrenia remain overwhelmingly (85%) dependent upon government benefits. Few (13.1%) own their home, and a similar proportion (12.8%) have experienced homelessness at some stage over the past year. They remain isolated, with nearly 70% not attending any recreational activities. Importantly, many look to their GP for their care: 49.3% attending their GP for the care of their mental illness and 88.2% seeing their GP for any reason, underlining the need for GPs to understand schizophrenia and its treatment. And they have good reason to see their GP, with nearly half having a metabolic syndrome, although often this is

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not addressed.[3] This dimension of poor physical health in people with schizophrenia has frequently been ignored.

AETIOLOGY – GENETIC AND ENVIRONMENTAL

Although drug treatment is still based on the earlier serendipitous discovery of dopamine antagonists, our knowledge of the causes and treatments of schizophrenia has advanced. The polygenetic basis of the disorder is becoming clear, with evidence linking the disorder to genes active in neurotransmission, neural development, synaptic pruning and immunity.[4,5] There is significant overlap in some (but not all) of those genes with other psychotic disorders, such as bipolar disorder.[5] This genetic predisposition interacts with environmental stressors to cause schizophrenia.

Tracking this complex interaction is difficult, but as an example recent work has established plausible mechanisms for the long identified association of cannabis use and psychosis. Specific susceptibility single nucleotide polymorphisms (SNPs) of the catechol-O-methyltransferase (*COMT*) gene (the product of which helps regulate neurotransmitter levels in the prefrontal cortex) and the *AKT1* gene (which encodes a serine–threonine kinase important in regulating cell proliferation, differentiation and survival) both increase the risk of developing schizophrenia, a relationship that is affected by the frequency of cannabis use and possibly the age of its first use.[6,7] Although this story has a long way to go, it is clear that more than one group of neurotransmitters is involved, and that the expression of the disease is profoundly influenced by environmental factors.[8]

SYMPTOMS – THE FIVE DOMAINS

The symptoms of schizophrenia can be organised into five domains: positive, negative, excitement, cognitive and emotional, as discussed below.

- The positive symptoms are the well-known symptoms of delusions and hallucinations. These symptoms respond well to antipsychotic medications and do not tend to cause much long-term disability.
- The 'excitement' domain comprises the aggression and poor impulse control that is frequently a clinical problem in acute psychosis. This also responds well to medication.
- Negative symptoms describe lost functions – a loss of motivation, richness of thought, affect, sociality or emotional life. These symptoms respond less well to medication and are important when considering prognosis.
- Cognitive symptoms also substantially impact the ability of a person with schizophrenia to work, form relationships and socialise. They include problems with attention, concentration, memory, planning skills, speed of processing and social cognition. Social cognition is made up of abilities such as recognising emotions, 'theory of mind' (being able to think in other people's shoes), humour and empathy. These cognitive problems predate the onset of the disorder, deteriorate at the time of first presentation and thereafter tend to remain stable. Psychological treatments have proved to be useful in their treatment, but they have resisted medication.[9,10]
- Emotional symptoms such as anxiety and depression often form part of the clinical picture of schizophrenia. These can be treated with psychotherapy or medication.

DIAGNOSIS AND EARLY MANAGEMENT

The early identification of young people with psychosis has been a development in mental health pioneered in Australia by Professor Pat McGorry.[11] Although the precise role and effectiveness of the current treatment strategies is a topic of debate, the overall thrust of providing good care early in the course of the illness, with the intention of changing the longer term course of the disorder, remains clear.

Detecting the earliest manifestation of psychosis remains a challenge as it can express itself with a broad range of non-specific psychiatric symptoms such as anxiety, depression and social withdrawal. However, the identification of a young person with attenuated psychotic symptoms or brief time-limited psychotic symptoms or who has suffered a deterioration in their level of functioning and also has a family history of psychosis should trigger a referral to specialist services. Although the evidence base for optimal management of these early forms of psychotic disorders is still developing, treatment with agents other than antipsychotics (such as polyunsaturated fatty acids) or with psychological interventions have been trialled, although not with universal success.[12-14]

The clinical screening of a young person who has developed their first episode of psychosis requires the following:

- taking a careful history, including a detailed enquiry about their history of substance use
- assessing their level of premorbid functioning
- performing a physical examination.

Investigations recommended include the following:

- full blood count
- serum electrolyte levels
- calcium, creatinine and urea levels
- liver biochemistry
- fasting blood glucose concentration
- serum lipid level
- thyroid function tests
- urine toxicology
- CT/MRI of the brain.

Additional investigations may be relevant and could include an electroencephalogram (EEG), an electrocardiogram (ECG) or immunological investigations, including to brain autoantibodies (e.g. anti-N-methyl D-aspartate [NMDA]).

These investigations combine an examination of possible aetiological agents (including a toxicology and immunological

TABLE. ANTIPSYCHOTIC MEDICATIONS AVAILABLE IN AUSTRALIA

Medication	Dose (mg)	Adverse effects						
		Extra-pyramidal side effects	Sedation	Postural hypo-tension	Weight gain	Hyper-prolactin-aemia	Anticho-linergic side effects	Other
Second-generation antipsychotics								
Amisulpride	400–1200	++	++	+	+	+++	0	–
Aripiprazole*	10–30	+	+	+	+	0	0	Initial activation
Asenapine	10–20	+	+	++	++	+	+/–	–
Clozapine†	200–600	+/–	+++	+++	+++	0	+++‡	Agranulo-cytosis, myocarditis, seizures
Olanzapine	10–20	+	+++	+	+++	+	++	Insulin resistance
Paliperidone	3–12	++	+	++ (initial)	++	+++	+/–	–
Quetiapine	400–800	+	++	++	++	+	+	–
Risperidone	1–6	++	++ (initial)	++ (initial)	++	+++	+/–	–
Ziprasidone	80–160	+	++	+	+/–	0	+	Prolonged QTc interval
First-generation antipsychotics								
Chlorpromazine	200–600	++	+++	+++	+++	+++	+++	Hepatotoxicity, sun sensitivity, rash
Haloperidol	1.5–7.5	+++	+	+	++	+++	+	_
Trifluoperazine	5–20	+++	+	+	++	+++	+	–

screen) with relevant baseline and safety investigations (e.g. ECG and lipids levels). The inclusion of brain autoantibodies relates to the recent identification of a small group of patients with an autoimmune reaction targeting brain receptors or ion channel pathways. Although many patients with these autoantibodies develop a severe life-threatening illness, some may present with forms of a psychotic illness very similar to schizophrenia or a schizophreniform disorder.[15,16] Their treatment involves an immunological approach.

STARTING AN ANTIPSYCHOTIC MEDICATION

With the development of sustained psychotic symptoms (i.e. positive symptoms), it is reasonable to initiate antipsychotic medication .[17] Treatment should be started with a low dose of an oral second-generation antipsychotic other than clozapine (which is reserved for treatment-resistant patients) and the dose slowly titrated up until a response of the positive symptoms of psychosis is observed (Table). Initial agitation or insomnia can be treated with benzodiazepines (e.g. diazepam 5 to 10 mg twice daily) that is gradually withdrawn after the agitation comes under control. The treatment of schizophrenia is summarised in the flowchart and tips on treatment are listed in Box 1.

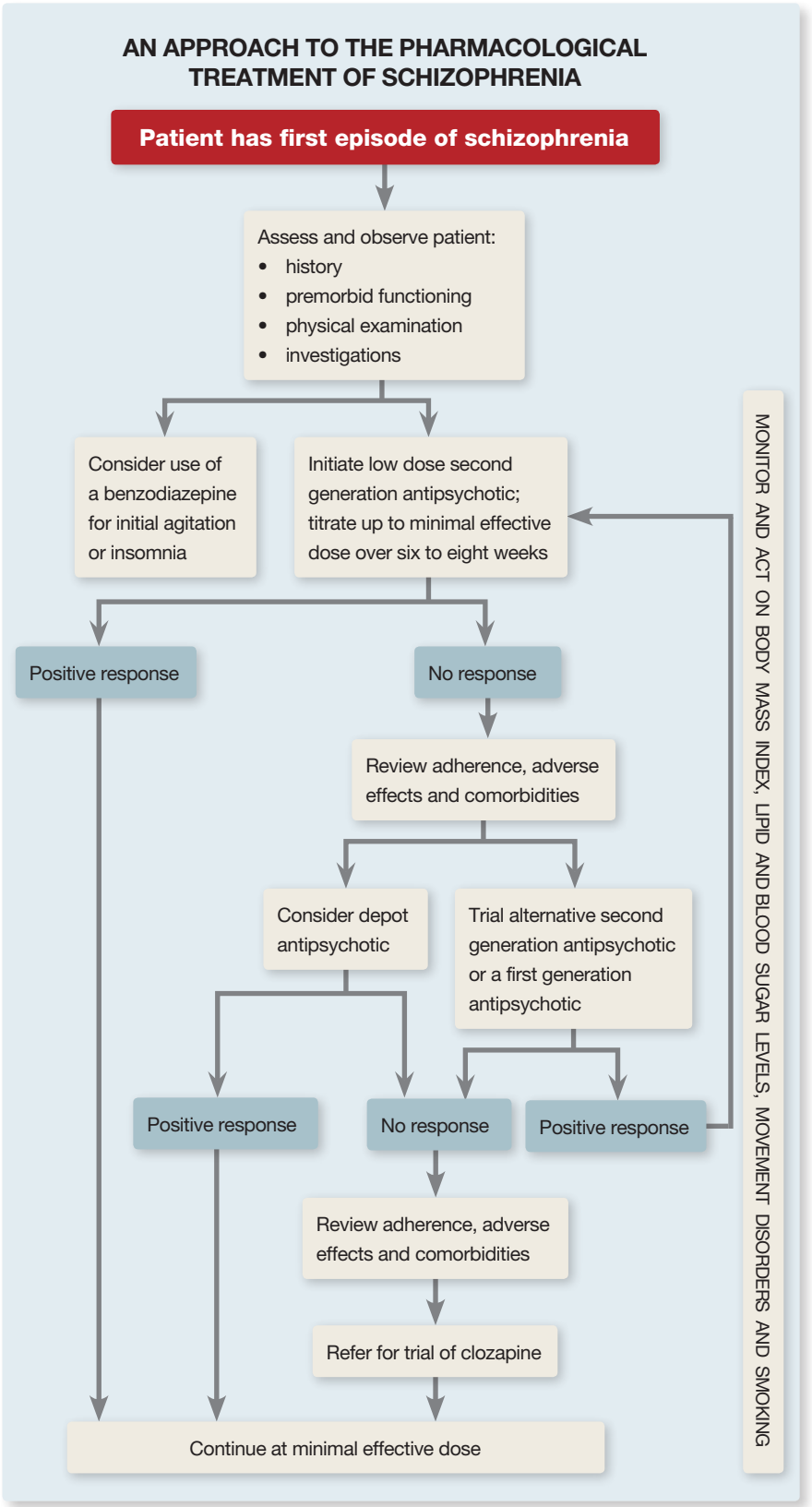
TABLE. ANTIPSYCHOTIC MEDICATIONS AVAILABLE IN AUSTRALIA continued

Medication	Dose (mg)	Adverse effects						
		Extra-pyramidal side effects	Sedation	Postural hypo-tension	Weight gain	Hyper-prolactin-aemia	Anticho-linergic side effects	Other
Antipsychotic depot medications								
Flupenthixol decanoate	20–40 (every 2 weeks)	+++	++	+	++	+++	++	–
Fluphenazine decanoate	12.5–50 (every 2 weeks)	+++	+	+	++	+++	+++	–
Haloperidol decanoate	50–200 (every 4 weeks)	+++	+	+	++	+++	+	–
Olanzapine pamoate monohydrate	150–300[§] (every 2 to 4 weeks)	+	+++	+	+++	+	++	Post-injection syndrome – 3 h post-injection monitoring
Paliperidone palmitate	50–150[§] (every 4 weeks)	++	++ (initial)	+	++	+++	0	–
Risperidone depot	25–50 (every 2 weeks)	++	++ (initial)	+	++	+++	0	–
Zuclopenthixol decanoate	200–400 (every 2 weeks)	+++	++	+	++	+++	++	–

* An activation syndrome of agitation and restlessness can occur that requires low dose benzodiazepines for the first week of treatment.
† Prescription requires enrolment in compulsory monitoring program.
‡ Sialorrhoea commonly seen.
§ Loading dose strategy recommended.

Although small differences have been found on meta-analysis between the various second-generation antipsychotics, it is unclear how these translate to individual patients.[18] Selection is best guided, at least at this early stage, by an individual appreciation of the patient's presentation, the likely adverse effects of the medication and the availability of other services that can help develop a management plan with some depth. Even at this early stage it is advisable to have minimisation of adverse effects as central to the selection of antipsychotic agents. Although adverse effects such as movement disorders have been addressed to a great extent with the introduction of second-generation antipsychotics, other adverse effects such as sedation, weight gain and hyperprolactinaemia remain significant problems that need to be anticipated (see below).

Intensive integrated treatment, provided by specialist early psychosis or youth mental health teams, achieves a better return to function than does conventional care.[19] However, the persistence of this improvement after the patient's transfer from these more intense forms of treatment back to standard community care has not been demonstrated.[20]



TREATMENT ADHERENCE

Medication nonadherence is one of the key reasons for relapse in patients being treated for schizophrenia and as such is a focus of the therapeutic alliance. Adherence or concordance (a recently introduced term reflecting an agreement between the doctor and patient about the aims and means of treatment) is difficult in any area of medicine but is especially problematic in the treatment of psychotic illnesses because of the substantial burden of adverse effects associated with antipsychotic medications and lack of insight associated with these conditions.

Treatment concordance is based on a clear understanding by the patient of the illness, the treatments and the need for them. This can only be arrived at after extensive and repeated patient education and discussion. This should involve family members, especially for younger patients, as the agreement and support of the family should not be taken for granted. Patient education is not a one-off event but a virtuous cycle of informing and questioning involving the patient, their family and the doctor. The best questions usually come from a well-informed patient or family member. A list of online resources for patients and carers is provided in Box 2.

In addition to good information, patients need a way to influence their own treatment. Antipsychotics are not pleasant medications to take, having frequently occurring and difficult adverse effects. These adverse effects will be of differing levels of importance for different individuals, and their significance will change with recovery. For example, sedation may be useful initially to help with insomnia, but later may impede daytime function. Importantly, some adverse affects will need active enquiry: for example, few patients will volunteer sexual side effects to their doctor. A responsive attitude to these difficulties is important. Dose reduction or medication change can help with adherence.

Treatment adherence is also affected by the mode of administration. Probably all of the antipsychotics can be administered

1. SCHIZOPHRENIA: USEFUL TREATMENT TIPS

- Start low and go slow. Start antipsychotic medication at a low dose and increase slowly to avoid overwhelming new patients with adverse effects
- Simplify the treatment regimen. Most antipsychotics can be given once a day, reducing nonadherence; giving the medication at night can minimise difficulties with sedation
- Avoid polypharmacy. Most people with schizophrenia can be treated with a single antipsychotic
- Anticipate problems. The adverse effects due to antipsychotic medications are frequently observed and can be anticipated; for example, discuss increased appetite and weight gain before they occur, give dietary advice, avoid fast foods and soft drink, and encourage exercise
- If the medications are not working:
  - check for poor adherence. Medications can only work if they are taken!
  - check for substance abuse. Comorbid substance abuse is very common
- Look for and treat anxiety and depression
- Screen and treat physical illness as you would for any other patient

2. SCHIZOPHRENIA: ONLINE RESOURCES FOR PATIENTS AND CARERS

- Mental Illness Fellowship of Australia: www.mifa.org.au
- SANE Australia: www.sane.org
- Schizophrenia Fellowship of New South Wales: www.sfnsw.org.au

on a once daily basis, helping with patient forgetfulness and making a virtue out of sedation if given just before sleep. An increasing number of antipsychotics can be given as a depot injection (Table). Although this may meet with a degree of opposition at first, depot injection can become a preferred mode of administration that addresses forgetfulness and reduces arguments with family members and mental health staff. It has been tainted by its association with compulsory treatment but may be an option for some patients. Care must be taken to ensure that patients are on the lowest effective dose of the depot antipsychotic medication.

There are many behavioural interventions that can improve medication adherence, ranging from the using of a calendar medication pack to the synchronising of medication administration with other routines such as teeth brushing or the evening meal. At times the use of a community treatment order (CTO; also referred to as an involuntary treatment order or community management order) may be required to compel treatment. The requirements for a CTO differ from state to state in Australia, and referral to the local mental health team is appropriate.

CHANGING AN ANTIPSYCHOTIC

Patients often would like to change the antipsychotic they are using because they want fewer adverse effects. This requires a critical appraisal of the present burden of adverse effects against the risks of change. Will the change to a different medication just lead to another set of adverse effects that may be even less desirable? The need for change may be because symptoms are not improving (symptom resistance) – but if improved treatment effectiveness is desired, has the full dose range been explored with the present medication? If a change is to occur then the aim of the change needs to be determined and the potential cost of the change explored.

When the decision has been made to change antipsychotic medication, the steps below should be considered.

- Select another medication that addresses the concerns raised (e.g. sedation as an adverse effect).
- When that has been decided, the target dose and the mode of change should be determined:
  - changing to a dose substantially lower in drug equivalency than the present medication dose is likely to lead to a relapse and the rejection of the new medication as ineffective when the problem has been one of a substantial drop in dose
  - a slow cross taper transferring from one antipsychotic medication to another is almost always possible. There will be changes in adverse effect profiles, and this can lead to unexpected increases (or decreases) in level of sedation, changes in prolactin levels (leading to changes in the menstrual cycle, unexpected fertility and the need to consider contraception) or the occurrence of movement disorders
  - forewarn the patient about the possible effects of the treatment change.
- The dose of the new antipsychotic should be fine-tuned when the patient has settled on the new medication.
- When changing to a depot antipsychotic, other considerations come to the fore:
  - the dose will take many weeks or months to stabilise
  - some medications recommend a loading dose, e.g. olanzapine pamoate monohydrate and paliperidone palmitate
  - other medications, e.g. risperidone depot, have a delayed release requiring continued oral antipsychotic for three to five weeks.

Treatment resistance should trigger a trial of clozapine (see the flowchart). Clozapine is a highly effective antipsychotic but is burdened with a large number

of adverse effects, some of which (such as agranulocytosis) are potentially fatal.[21] Patients taking clozapine should be closely supervised, and compulsory registration in a treatment program and treatment by certified staff is required. Although this is daunting, the benefits can be highly significant for the 30 to 50% of individuals who respond to clozapine. Conversely, continued treatment with clozapine is not warranted if the response is inadequate.

PSYCHOSOCIAL TREATMENTS

It is highly unlikely that someone with schizophrenia will recover through the use of medication alone, and a range of psychosocial interventions are essential to good health and recovery in these patients. The availability of these treatments is highly variable across Australia, even within metropolitan areas.

Many patients will already be referred to the local mental health team. The interventions provided by this team have differing degrees of effectiveness, but when care is provided in an assertive way, by a committed case manager and team, community treatment can be highly effective. Knowing the capabilities of the local mental health team can be very useful.

Having a family member develop schizophrenia places a tremendous strain on the workings of any family. This can reflect the lack of understanding for the change in behaviour, or the difficulties faced by the family in coping with that same behaviour even when they can appreciate the cause of the change. For example, how are parents to interpret the refusal of their son with schizophrenia to get out of bed until lunchtime every day? Is it to be seen as slothful, or perhaps due to oversedation by medication? Are continued persecutory beliefs restricting his ability to go outside, or is it a negative symptom of the disorder? Is he depressed, or is it helplessness in the face of an overwhelming diagnosis? These are but a few of the ways that this common problem behaviour can be interpreted. Family therapy, aimed at education, problem solving and changing the way family members communicate with each other, addresses this.

Cognitive behaviour therapy also has a place in the treatment of schizophrenia. Continued positive symptoms can be controlled by use of this therapy. It also remains an effective treatment for the anxiety and depression experienced by people with schizophrenia. Similar approaches using behavioural techniques can help organise the daily schedules of people with schizophrenia and help activate them. These simple techniques have been used to help improve self-care and basic interactions with others. This approach is formalised in social skills training, another evidence-based psychosocial intervention.

The cognitive deficits seen in people with schizophrenia, although relatively resistant to medication, can be treated using cognitive remediation. This treatment uses educational approaches to treat neurocognitive and social cognitive deficits. When combined with other psychosocial approaches, it also leads to improvements in overall community functioning.[9,10] However, few mental health staff are trained in these techniques as yet.

The interruption to education or work caused by schizophrenia can be addressed using a supported employment approach. With appropriate face-to-face support, many people recovering from schizophrenia can return to the workplace or education. This intervention, sometimes known as Individual Placement and Support (IPS), doubles the rate of return to work compared with conventional prevocational programs.[22]

Although these psychosocial interventions have been shown to be effective, they are rarely available in our communities. Funding and the equitable distribution of resources remain a problem in mental health. It is hoped that the recently announced Australian Government's 'Partners in Recovery' program will help co-ordinate, and at times provide, a broad range of community services for people with severe mental illnesses.

PHYSICAL HEALTH

The physical health of people with a severe mental illness such as schizophrenia remains a national disgrace. People with schizophrenia have a 2.5-fold increased risk of dying compared with other people in the general community and the gap has widened.[23]

Although part of this increased mortality rate is due to an increased risk of suicide, most of the risk is due to morbidity and mortality secondary to a broad range of physical diseases, including cardiovascular, endocrine, infective and respiratory disease, that have been brought under control in much of the rest of the community. Thus, while mortality rates for these diseases have dropped in the rest of the community they have remained stable, and may even be increasing, in people with psychotic disorders.[23]

In the SHIP study, four out of five subjects with a psychotic illness met criteria for abdominal obesity, 28.6% had an elevated blood glucose level and 49.9% met criteria for metabolic syndrome.[2] When this is combined with high rates of smoking, with 66.1% of the study participants reporting continued tobacco use compared with 25.3% of the general population, the basis of the poor heath outcomes can be understood.[2] This picture is compounded by poor nutrition and high rates of sedentary lifestyle, with only 3.3% of study participants having moderate or high levels of physical activity compared with 27.9% of the general community.[2]

The opportunity for intervention is there. However, we diagnose physical conditions in these patients less rigorously and then intervene less forcefully than for other patients. This is despite high rates of contact with medical services, including GPs. Aggressive programs in exercise and dietary interventions are bring trialled but, as in many other areas of medicine, prevention is better and more practical. Early action is, therefore, an essential partner to the careful monitoring of weight and other indices of good physical health (e.g. waist circumference, blood pressure, blood sugar

levels and lipids) for any person treated with an antipsychotic. If a patient begins to gain weight while taking an antipsychotic, changing the antipsychotic to one that is less likely to cause weight gain (such as aripiprazole, amisulpride or ziprasidone) may help the patient before he or she has to battle a major weight problem.

Other significant health problems can be caused by antipsychotic medications. The movement disorders that bedevilled the use of first-generation antipsychotics have been reduced by the adoption of second-generation antipsychotics, but they still do occur and monitoring of patients for these adverse effects is still important. An acute dystonia is best handled with an anticholinergic agent such as benztropine. Akathisia, an inner sense of restless that can force a person to move continually, can be very disabling. This is best handled by a reduction in the dose of the antipsychotic, and more immediately with a benzodiazepine, an anticholinergic or a beta-blocker. Occasionally other movement disorders, such as tardive dyskinesia, are still seen. People with tardive movement disorders require referral for specialist care.

Hyperprolactinaemia is also common in people prescribed medications with a higher propensity to block dopamine D2 receptors, such as amisulpride, risperidone, paliperidone and most first-generation antipsychotics.[24] High levels of prolactin have consequences such as disturbance of the menstrual cycle, galactorrhoea, gynaecomastia and sexual dysfunction. These adverse effects can be very disturbing to the individual who suffers them, but will rarely be disclosed unless specifically enquired about. Longer-term risks of the disturbance of the hypothalamic–pituitary–gonadal axis due to increased secretion of prolactin are uncertain.

HOW LONG TO TREAT?

Schizophrenia is a chronic and relapsing disorder, so the withdrawal of medication from an individual who has established some degree of stability in their lives should be approached carefully. Earlier research looking at relapse after the first episode of schizophrenia suggested that 80% of people with schizophrenia would relapse in the first five years after diagnosis, mostly after ceasing medication.[25] No satisfactory method has been developed to identify the small proportion of patients who would not relapse after ceasing medication.

Guidelines are varied in their recommendations about how long to continue treatment, but a trial cessation after treatment for two years after the first episode of psychosis would be seen as reasonable, and after five years of treatment if the patient has a further relapse of the illness. What constitutes remission is always a vexed issue, particularly when considering negative symptoms. Although this has been linked with scores on research instruments, the consensus for the working clinician would be that there should be no more than mild fleeting symptoms across both positive and negative symptom domains for a minimum of six months. This prolonged period, much longer than was required in the past, underlines the necessity to reduce adverse effects from treatment to a minimum if patients are to continue to take the medication.

CONCLUSION

Schizophrenia remains a challenging illness causing high levels of chronic disability. Our increased understanding of the illness has not yet translated into improved medication, but there has been progress in a range of psychosocial treatments although their availability is limited. Recent research has demonstrated poor physical health for this group despite high levels of contact with health practitioners, including GPs. Significant improvements in both mental and physical health outcomes can be achieved with the application of known interventions. MT

FURTHER READING

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