Medical Interventions in Early Psychosis

A Practical Guide for Early Psychosis Clinicians

Orygen YOUTH Health Research Centre

EPPIC Early Psychosis Prevention and Intervention Centre

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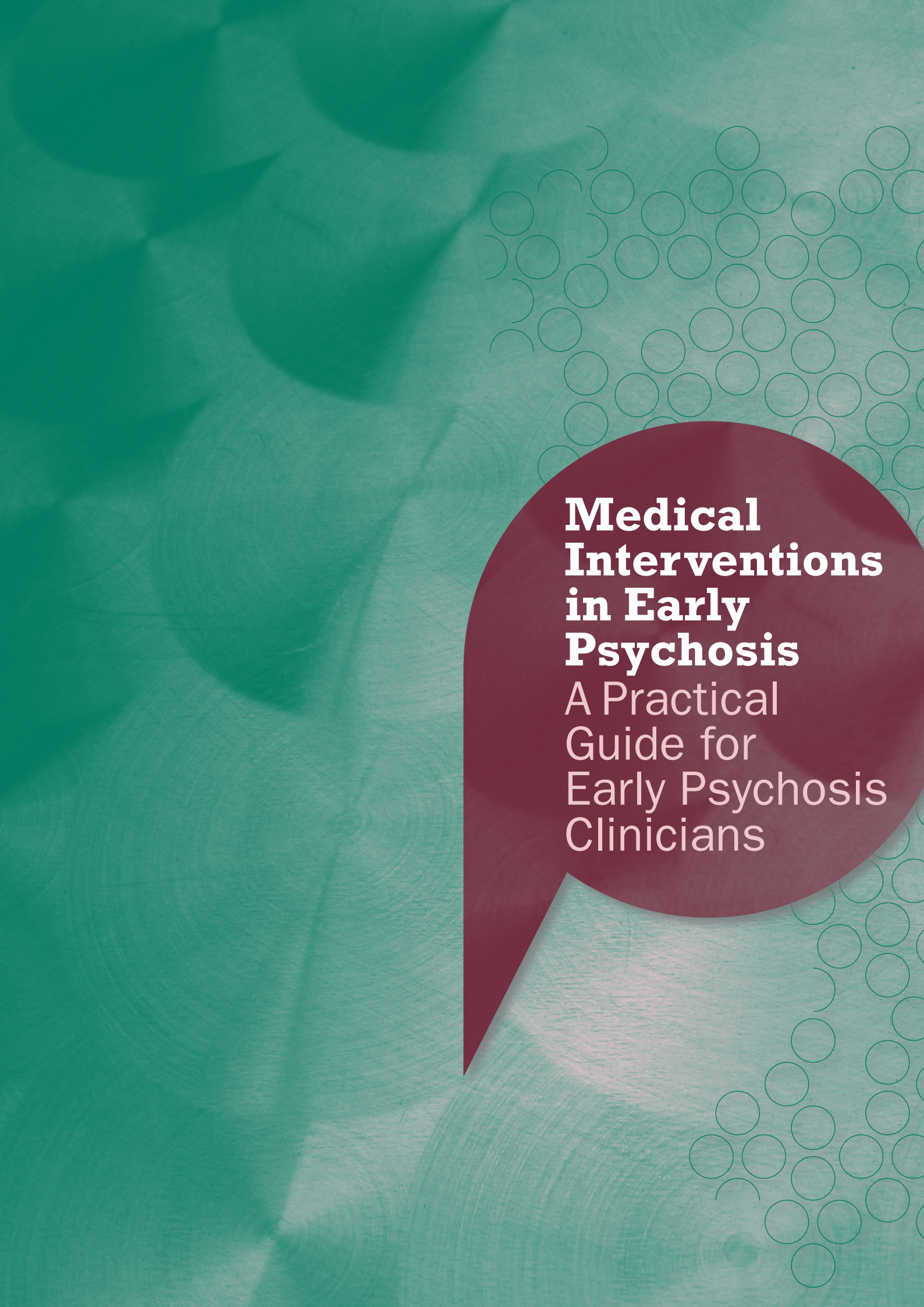

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Contents

Part 3
Introduction to pharmacological principles

Introduction

The period of peak onset of early psychosis – adolescence and early adulthood – paradoxically occurs at a time when most young people are experiencing the healthiest phase of their life. In this context, commencing an ongoing medical treatment regimen can be overwhelming for young people, who generally will have had little or no experience of needing to take medication. Adhering to a treatment regimen while dealing with side-effects, symptoms and trying to maintain a semblance of normal adolescent life, asks a lot of a young person, and they need to be supported throughout. The role of providing this support falls to all members of the treating team, and to provide the best possible support, all clinicians need to be aware of the impact of medication on a young person.

About this manual

Medical interventions in early psychosis: a practical guide for early psychosis clinicians is a manual designed to help non-medically trained clinicians gain a working knowledge of medical treatments for early psychosis. It is one of a series of manuals produced as part of the EPPIC National Support Program (ENSP) to help with implementation of the Early Psychosis Prevention and Intervention Centre (EPPIC) Model in early psychosis services. The EPPIC Model is a model of specialised early intervention in psychosis developed from many years experience within the clinical program at Orygen Youth Health and further informed by the National Advisory Council on Mental Health's *Early Psychosis Feasibility Study* (2011), which sought international consensus from early psychosis experts from around the world. Medical intervention is one of the 16 core components that make up the EPPIC Model.

How to use this manual

This manual has been developed as a resource for nurses and allied health professionals who work with young people in early psychosis. The material presented here should be valuable to clinicians new to early psychosis and those with specialised experience who are not familiar with medical interventions in the early psychosis setting.

The manual consists of three sections. The first, 'Prescribing principles and medications for early psychosis', covers principles for prescribing medication in young people with early psychosis, and gives an introduction to the four main classes of psychotropic drugs prescribed in this group – antipsychotics, antidepressants, mood stabilisers and benzodiazepines. The second, 'Medical management in early psychosis', details approaches to managing medication in young people, the role non-medical clinicians play in this, and strategies for addressing some of the challenges arising from medical treatments in early psychosis. The third section, 'Basic principles of pharmacology', is a basic overview of pharmacological principles that may be useful for clinicians to understand how drugs are processed by the body. Case scenarios and anecdotes from young people who have been treated in the EPPIC program at Orygen Youth Health are presented throughout to provide real-world context.

It should be noted that for the purposes of this manual, the term 'early psychosis' encompasses both young people who have experienced a first episode of psychosis and those who are at ultra high risk of developing psychosis (UHR). Further information specific to the UHR population can be found in the manual *A stitch in time: interventions for young people at ultra high risk of psychosis*.

Why use medical treatments for early psychosis?

Pharmacotherapy is considered first-line treatment for people with psychotic disorders, although it is by no means the only treatment recommended for these kinds of disorder. The *Australian Clinical Guidelines for Early Psychosis* (2010) recommend psychotropic medication, including antipsychotics, antidepressants and mood stabilisers, for treatment of various symptoms associated with first-episode psychosis (FEP).[1] The aim of using medication in young people who present with FEP is to reduce symptoms such as agitation,

anxiety, sleep disturbance, positive and negative psychotic symptoms and mood disturbance. Reducing symptoms allows the young person to then be engaged in psychosocial therapies to help with recovery from the psychotic episode, which may have been difficult prior to symptom relief.

It should be pointed out that antipsychotic medication is not recommended for young people who are UHR; however, medication might be used, if indicated, to treat psychiatric comorbidities such as depression. See 'Prescribing principles in early psychosis' on page 10 for more detail.

I'm not a doctor: why do I need to know this?

Although not responsible for prescribing medication, non-medical clinicians involved in a young person's treatment nevertheless need to have a practical knowledge of the medications used in early psychosis. Some clinicians may have a greater interest than others in the biological mechanics of how antipsychotics work, for example, and it is not expected that everyone learn the ins and outs of first-pass metabolism; however, all clinicians should be familiar at a minimum with how medications are prescribed, the side-effects they produce and even the long-term consequences of medication.

Case managers and other non-medical clinicians will often be the main source for information about medical treatments that young people and their families turn to. They therefore need to be able to provide clear and accurate information covering, for example, the role of medication in the overall treatment model for psychosis, side-effects and dosing regimens. As well as responding to concerns as they are raised by the young person or family, case managers need to be able to provide this kind of psychoeducation proactively, so that young people and families can make informed decisions about treatment.

After a young person has commenced medical treatment, case managers will often be the first to hear from the young person or family of any side-effects or difficulties adhering to medication. They will also be able to see for themselves how the young person is tolerating the medication. This observational information is vital to assessing and monitoring adherence to medication and side-effects, including metabolic side-effects. Reporting side-effects to medical staff is also a crucial role for non-medical clinicians.

Finally, given that part of their role will be to encourage young people to take medication, clinicians should ask themselves: 'How can I advocate for a young person to commence and adhere to medication if I am not myself aware of all the implications this has for that young person?'

PART 1

Prescribing principles and medications for early psychosis

Overview

This section provides a summary of the principles that should be followed when prescribing medical treatments for early psychosis, followed by an introduction to the psychotropic medications that young people with early psychosis may be prescribed. Before reading 'Introduction to psychotropic drugs' on page 16, clinicians may wish to review the section 'Basic pharmacology' at the back of this manual to familiarise themselves with how drugs interact in the body.

Prescribing principles for early psychosis

The highest relative risk period for the onset of a first episode of psychosis is between the ages of 15 and 24 years for females and 20 and 24 years for males.[2] One in five people with schizophrenia developed the illness before the age of 18 years. However, until recently, medical treatment guidelines largely reflected clinical studies in the adult population.[3] These facts highlight the need for an approach to the prescribing of medicines which takes into account specific principles oriented to working with young people.

The following guidelines and principles draw on the *Australian Clinical Guidelines for Early Psychosis, 2nd Edition* (2010), with reference to more recently published evidence where available.

Treatment guidelines for the pre-onset phase

Psychotic disorders are preceded by a prodromal or UHR phase, which has a relatively high transition rate to a psychotic disorder over a 1 to 5-year period.[4] Effective identification of young people who are in this phase and intervention during this period may reduce the risk of transition to first episode psychosis, delay its onset or minimise its impact.[4-6] Current problems such as comorbid depressive symptoms or anxiety should be treated.[6] Intervention during this UHR phase also ensures that, in the event that transition occurs, the individual is already engaged with treatment services; this will facilitate rapid and non-traumatic commencement of treatment of FEP.[6]

Comorbid diagnoses of depression, alone or in combination with anxiety, are common in people in the UHR phase.[7] The symptoms and associated functional disability may be more of a concern for people in the UHR phase than their sub-threshold psychotic symptoms.[7] Young people in particular are susceptible to impairment of social development during the period before the onset of psychotic symptoms.[8]

Options to manage this period include psychological and pharmacological strategies (see *Australian Clinical Guidelines for Early Psychosis, 2nd Edition* for a detailed discussion). Young people who seek help for distress and disability associated with their symptoms should be engaged, supported and offered specific treatment for comorbid conditions such as anxiety, depression and substance abuse.[1]

Antidepressants may also play a role in reducing the risk of transition to early psychosis.[9] By improving mood and perception of experiences and environmental stressors, antidepressants may reduce the risk of subsequent psychosis to a greater extent than antipsychotics.[10] However, the data available to date are from uncontrolled studies and should be interpreted with caution due to adherence being lower for antipsychotics than for antidepressants and the possibility of differences in baseline symptoms and functioning.[10]

As there is no significant benefit to antipsychotic use over more benign treatments such as CBT,[1] antipsychotic medication is not used as first-line therapy for young people who are at ultra high risk of psychosis.[4,11] In exceptional circumstances, antipsychotics may be considered as third-line treatment, for example: when rapid deterioration is occurring, when treatment of any depression has proved ineffective and there is a severe risk of suicide, or when there is increasing aggression or hostility that poses a risk to others.[1] Second-generation antipsychotics (SGAs) in low doses should be considered in these situations, as a therapeutic trial for a limited period.[1]

Omega-3 fatty acids have been found to have beneficial effects when taken during the UHR phase. Compared with placebo, omega-3 fatty acids prevented transition to psychotic disorder, with greater improvement in Global Assessment of Functioning (GAF) scores, and a time to onset of 4 weeks.[12,13] Larger trials are in progress to validate these findings.[5] Eicosapentoic acid (EPA) increases glutathione, the principal antioxidant defence of the brain, and its efficacy in recent-onset psychosis, but not chronic schizophrenia, may suggest differential pathophysiological pathways in early onset illness that may be amenable to intervention.[10] Omega-3 fatty acids have also shown a generalised positive effect on mental health, including major depression, that suggests that they may modulate mood, impulsivity and aggression.[10]

Principles of pharmacological treatment in young people with FEP

Pharmacotherapy is a first-line treatment for psychotic disorders. There are a number of differences between young people with FEP and people with established schizophrenia that should be considered when prescribing pharmacological treatments for FEP. This section outlines nine principles that should be followed when prescribing antipsychotic medication in the FEP population, as recommended by the *Australian Clinical Guidelines for Early Psychosis, 2nd Edition* (2010).[1] A summary of the issues particular to this group is presented in Box 1.

BOX 1. **PARTICULAR CONSIDERATIONS FOR PHARMACOTHERAPY IN THE FEP GROUP**

- Young people with FEP are often antipsychotic-naïve.
- A young person's first experience of antipsychotic medication (response and side-effects) will influence their engagement and adherence.[14-16]
- People with FEP often respond to much lower antipsychotic doses than those with established illness.[15,17]
- People with FEP generally show a more rapid improvement in symptoms than people with established schizophrenia.[15,17]
- Positive symptoms in people with FEP are generally responsive to treatment in terms of overall response rate and degree of symptom reduction.[18]
- People with FEP and young people may be particularly sensitive to antipsychotic-associated extrapyramidal side-effects.[16,18,19]
- People with FEP are more susceptible to antipsychotic-associated weight gain and metabolic side-effects than those with more chronic illness, due to their younger age and often being antipsychotic-naïve.[18,19]
- Diagnostic instability in FEP may require ongoing adaptation of pharmacological interventions.[15]

Principle 1. Take side-effect profiles into consideration

There is no convincing evidence to date that atypical, or second-generation antipsychotics (SGAs), have superior efficacy in young people to typical, or first-generation antipsychotics (FGAs),[3,20] with the exception of clozapine in treatment-refractory schizophrenia.[20] However, the tolerability of SGAs appears to be greater in this population, with fewer side-effects seen in the short term.[3] While there is little evidence to suggest that one SGA is preferable to another in this context, side-effect profiles of SGAs vary markedly, and these should be taken into consideration when prescribing antipsychotics to young people.[3] Young people appear to have a higher risk than adults for antipsychotic-associated weight gain, hyperprolactinaemia, extrapyramidal side-effects (EPSEs) and sedation, and possibly associated metabolic abnormalities.[21] At a time when young people are experiencing psychological and physical maturation, the impact of these side-effects may be different from that in adults.[21]

The main considerations when selecting an antipsychotic for FEP in young people should be their response to a trial of this medication and the most relevant side-effects for the each person.[3]

Principle 2. Treat psychiatric emergencies

The immediate goals of emergency management of aggression or agitation are to ensure the safety of the young person who is experiencing these symptoms and healthcare providers, and to help the young person manage their emotions and distress and control their behaviour, while minimising the psychological and physiological impact on them.[22,23]

Non-coercive psychological and practical attempts at 'de-escalation' of an aggressive or agitated person are strongly encouraged as first-line management.[23,24] If such strategies are not successful within a safe timeframe, then medication should be offered with the aim of achieving a state of calm.[25] Oral medication should be offered in the first instance.[26]

Antipsychotics or benzodiazepines are used to quickly alleviate distress.[27] Both FGA and SGA medications appear to be effective, but SGAs may have better tolerability.[28] Furthermore, the observed efficacy of SGAs may be dose-dependent.[29]

Despite being commonly used in clinical practice, the available data comparing the efficacy of benzodiazepines and antipsychotics in controlling psychosis-induced symptoms of aggression and agitation are limited and of poor quality (for a meta-analysis, see Gillies et al.[27]) Based on this information, benzodiazepines appear to be as effective as antipsychotics alone, but have fewer side-effects such as EPSEs. The combination of a benzodiazepine and an antipsychotic does not convey any advantage over either drug alone.[27]

If it is safe to do so, short-acting intramuscular (IM) benzodiazepines such as midazolam may be used in emergency situations where oral medication is not accepted or suitable. These have been used either alone or in combination with an antipsychotic.[30] IM antipsychotic medication is occasionally necessary,[26,30] and as with general medication principles in this group, the lowest possible dose to treat the symptoms should be used; the use of multiple antipsychotics is discouraged.[26] The young person should have regular medical monitoring following the IM injection.[26]

A recent meta-analysis[30] concluded that IM SGAs were as efficacious as IM FGAs, and in some studies showed a superior and more rapid response. Furthermore, SGAs were better tolerated with respect to EPSEs.[30] FGAs should therefore not be used in FEP psychiatric emergencies.

Principle 3. Distinguish between affective and non-affective psychosis

While differentiation between specific diagnostic entities may be difficult at initial presentation, a pragmatic approach in which pharmacotherapy is initiated according to a broad definition of 'affective' or 'non-affective' psychosis is recommended.[17] An early diagnostic distinction between affective and non-affective presentation is important in light of the different treatment recommendations for these subgroups in the acute phase, in particular the utility of adding a mood stabiliser to the treatment regimen for people experiencing manic psychosis.[17]

Principle 4. 'Start low, go slow'

Evidence suggests that there is a biological sensitivity to antipsychotics during the first onset of psychosis. People with FEP respond more rapidly to antipsychotic medication and have a greater response, and generally require lower doses to do so, than people with more established illness.[15] In addition, side-effects of antipsychotics can occur at substantially lower doses in the first-exposure population than in people re-exposed to antipsychotics.[15] Rapid titration may also increase the incidence of side-effects.[31] Accordingly, a 'start low, go slow' prescribing approach is recommended, using the lowest possible dose to control symptoms.[32]

Principle 5. Avoid antipsychotic polypharmacy

Although relatively common in clinical practice,[33,34] there is little empirical evidence to suggest that combining antipsychotic medications has superior efficacy to monotherapy in the treatment of psychosis.[33,34] Furthermore, combining antipsychotic medications is associated with an increased risk of side-effects, non-adherence and drug interactions.[33] The majority of international guidelines for schizophrenia and psychosis recommend against the use of more than one antipsychotic,[32,34,35] except when changing medications[32,35] or during augmentation with clozapine in treatment-resistant cases.[33] Although there have been no direct randomised controlled trials of antipsychotic polypharmacy in FEP populations, the increased propensity for side-effects in this population would not support this practice.

Principle 6. Monitor adherence

As mentioned, non-adherence to medication is particularly prevalent in young people,[36] and people with FEP who are non-adherent tend to be younger.[37] Strategies for managing non-adherence in young people have been outlined on page 32. Others that have been shown to be effective in people with established schizophrenia, and which may also be useful in FEP, include training for clinicians (nurses) in medication management, tailoring strategies to individuals and programs to compensate for cognitive deficits in people with schizophrenia, such as telephone intervention and Cognitive Adaptation training.[38] Intervention strategies that span a longer period of time are beneficial, particularly in FEP.[38]

Principle 7. Monitor and manage adverse events and side-effects

Antipsychotic medication may cause side-effects that are distressing or disabling for young people.[17] Well known side-effects of psychotropic drugs are discussed in the section ‘Introduction to psychotropic drugs’, on page 16.

There are consistently strong relationships between patients’ assessment of the impact of side-effects and non-adherence.[39] In addition to actively enquiring about side-effects and discussing their concerns, a validated self-rating tool to measure the young person’s perception of the side-effects they are experiencing (e.g. the Liverpool University Neuroleptic Side Effect Rating Scale[40]) may provide additional information on the tolerability of their treatment regimen.

Principle 8. Identify failure to respond but provide a sufficient period for treatment response and remission

Symptomatic response and remission may be measured in a number of ways, as reviewed in the *Australian Clinical Guidelines for Early Psychosis* (2010). Further details of prediction of response and management of non-response to medications are outlined in the ENSP manual *Medical management in early psychosis: a guide for medical practitioners*.[41]

Principle 9. Treat psychiatric comorbidities

Psychiatric comorbidities are common in people with FEP, and are often present before the first episode of psychosis occurs.[42] In addition, people with schizophrenia have a higher risk of anxiety or depressive disorders than the general population.[43] As many as 80–90% of people with FEP fulfil the diagnostic criteria for at least one comorbid psychiatric disorder.[17] Major depression, anxiety disorders

(including social phobia and post-traumatic stress disorders) and obsessive-compulsive disorder can occur concurrently with FEP. [17]

Depression and anxiety in people with psychosis are often associated with poorer outcomes such as increased hospitalisation rates and subjective assessment of psychosis-related difficulties.[44] Anxiety and depression levels are also related to rates of suicide and self-harm.[19,44,45]

Comorbid substance use, including nicotine and alcohol, is common in people experiencing first episode psychosis,[15] and may increase risk factors for relapse even in people who are adherent to their medication. Comorbid substance use is also associated with a worse prognosis in general, including more severe positive symptoms, longer periods of hospitalisation and poorer adherence to medication.[15]

Defining the boundaries of comorbid conditions may be difficult due to the interaction between the symptoms of the primary disorder and those of comorbid conditions.[17,19,43] Periodic reassessment in people with FEP is often required.[17,19] Therapeutic interventions are recommended when the presence of comorbidities impacts on the effective management of the primary psychotic disorder.[17,44] Pharmacological treatment of psychosis also has side-effects that can affect the young person's health or pre-existing medical comorbidities, as discussed in 'Physical health and monitoring', on page 49.

Prescribing considerations for special populations

Children

Children and adolescents are thought to be more susceptible than adults to extrapyramidal side-effects (see page 22) caused by FGA and the metabolic abnormalities associated with SGA, especially weight gain.[46] Onset of obesity in young people appears to carry a greater risk of future adverse cardiovascular outcomes than onset of obesity in adults.[47] For this reason, olanzapine is not considered a first-line antipsychotic medication in children and adolescents.[46]

Less information is available on the use of mood stabilisers in children.[47] The mood stabiliser lamotrigine is associated, in both adults and children, with the development of potentially life-threatening rashes, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis.[48] The risk of serious skin rashes is higher in children than in adults.[48]

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.[49] Close observation for any signs of increased risk of suicide should be maintained in children and adolescents with depression.[49]

Women of childbearing age, pregnancy and breastfeeding

In young women of child-bearing age, special consideration must be given to the risk of exposure of the foetus to psychotropic medication, balanced with the risk to the mother and child of deterioration or relapse without the medication.[50] This is of particular relevance to women with psychotic disorders, as there is in increased risk of unplanned pregnancy compared with the general population.[51,52]

Since the risk of foetal malformation is greatest in the first trimester, and possibly before the pregnancy is recognised, the risks associated with the use of psychotropic medications in pregnancy should be discussed with young women of childbearing age and a collaborative plan developed.[50] Women of childbearing age should receive counselling about effective forms of contraception if using these medications.

Mood stabilisers should not be used during pregnancy unless there is no other suitable therapeutic option.[50]

Antipsychotics and mood stabilisers are excreted in human breast milk and information on potential long-term effects on the infant is limited. Women should be counselled about the benefits of breastfeeding versus the risk of exposure to the infant. While in many cases the concentrations of drug in human milk is low, levels which approach clinical significance have been reported for some drugs.[53]

Young people with diabetes

Elevated blood sugar levels, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported with use of SGAs. Young people at risk of or who already have diabetes need to be monitored closely. See 'Physical health and monitoring' on page 49 for more information.

SUMMARY **PRESCRIBING PRINCIPLES FOR EARLY PSYCHOSIS**

- Typically, antipsychotic medication should be initiated at a low dose and titrated slowly to determine the lowest effective dose.
- Extra care needs to be taken when prescribing for special populations such as children and adolescents, women of child bearing age, pregnancy or breastfeeding and people with other physical health issues.

Introduction to psychotropic drugs

Psychotropic drugs are drugs that target neurotransmission, thus primarily affecting the central nervous system and brain function.[54] The medications prescribed for young people with early psychosis will vary according to the symptoms and characteristics of each person, including their level of risk for different adverse effects. Most young people with FEP will receive an antipsychotic, and they may also be prescribed antidepressants, mood stabilisers and/or benzodiazepines. Young people considered UHR should not be prescribed antipsychotics, but may be on other psychotropic medications for existing psychiatric disorders.

Psychosis is often classified according to the presence or absence of positive and negative symptoms. Positive symptoms include hallucinations (usually auditory), disturbed stream of thought, delusions, restlessness and aggression. Negative symptoms include social withdrawal, apathy and lack of emotional response. Some people with psychosis also experience affective (mood disorder) symptoms such as mania or depression.

It is important to identify whether a young person has affective or non-affective FEP, because the treatments for these conditions differ in some respects. Recommended treatments for affective and non-affective FEP are detailed in clinical guidelines.[1] However, the choice of medication(s) should also be based on clinical experience and tailored to suit each young person.

Antipsychotics

As mentioned on page 12, antipsychotic medications fall into two categories: typical/FGAs and atypical/SGAs. Most young people with FEP will receive an SGA, although FGAs are still used in some cases.[55]

How do they work?

Antipsychotics work by altering the effects of certain neurotransmitters in the brain. All available antipsychotics affect dopamine receptors, and some also target different serotonin (5HT), norepinephrine (noradrenaline) and/or acetylcholine receptors (see page 67 for more information).

Most antipsychotics will produce improvements in psychotic and manic symptoms within approximately 1 week after starting treatment, although it may take several weeks before their full effect on other symptoms is seen.[56] A reduction in psychotic symptoms is usually seen within 6–8 weeks.[57] However, the response to antipsychotics can be different for each person, and this time may be longer. In some cases there is insufficient response within the usual timeframes so a higher dose or switching to a different antipsychotic may be necessary.[1]

Young people with FEP generally have a good response to antipsychotic treatment, with up to 90% experiencing remission during the first 12 months.[58,59] However, the relapse rate is high, with 51% having a relapse during the first 2 years after the first episode and 78% at 5 years.[60] Based on these findings, current treatment guidelines recommend that maintenance treatment with antipsychotics be continued for at least 2 years after a response is achieved.[1] After this time, it may be possible for medication to be gradually withdrawn and restarted only when early signs of relapse are detected.

Mechanism of action

FGAs act as D2 receptor antagonists (that is, they block dopamine D2 receptors, preventing dopamine from binding to them). Their antipsychotic effect is caused by their blocking D2 receptors in the mesolimbic pathway.[61,62] However, by also blocking D2 receptors in other parts of the brain they can cause side-effects such as EPSEs, secondary negative symptoms and prolactin elevation.

Most SGAs block the D2 receptor and, with the exception of benzamides such as amisulpride, also block $5HT_{2A}$ to a similar degree.[56,61] However, aripiprazole acts as a partial dopamine agonist, meaning it reduces dopamine output when levels are high and increases it when levels are low. SGAs can have additional sites of action, including dopamine D1, D3 and D4, $5HT_{1A}$, $5HT_{2c}$, $5HT_6$ and $5HT_7$, and muscarinic, cholinergic and histamine receptors (see Table 1). Figure 1 shows the different binding properties of olanzapine.

FIGURE 1. **BINDING PROPERTIES OF THE ANTIPSYCHOTIC OLANZAPINE**[56]

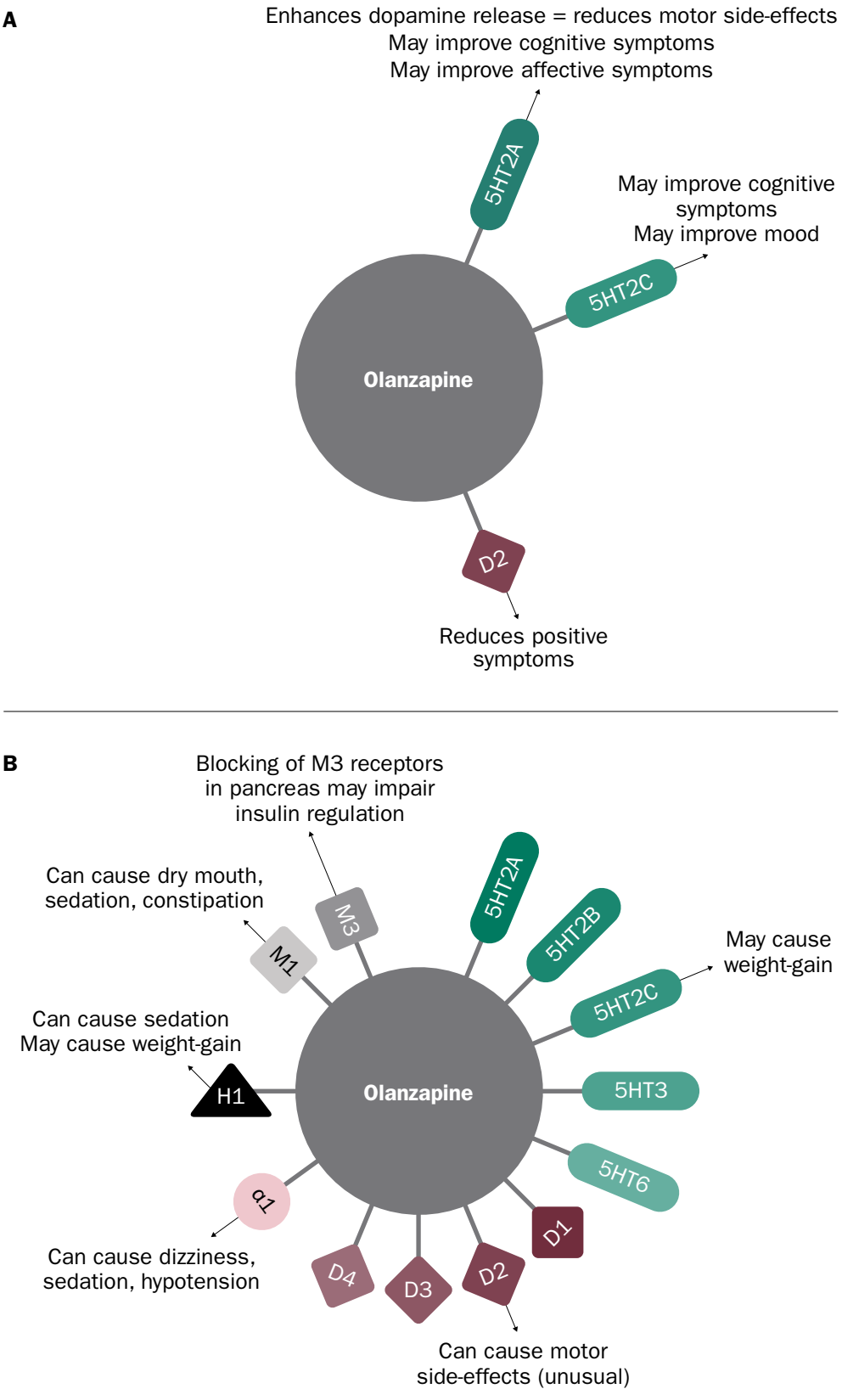


Figure shows binding properties of olanzapine that are (A) thought to improve symptoms in psychosis, and (B) thought to mediate side-effects associated with olanzapine.

Evidence of efficacy

The efficacy of FGAs and SGAs in schizophrenia has been demonstrated in clinical trials, although relatively few studies have focused on FEP. There is little evidence to suggest any one SGA is more effective than others in FEP.[63] Current treatment guidelines provide a summary of the available evidence supporting the use of these agents in FEP.[1]

SIDE-EFFECT PROFILE OF ANTIPSYCHOTIC MEDICATIONS

Given the generally similar efficacy of antipsychotic drugs, tolerability is a key consideration when choosing which drug to prescribe. Adverse events are associated with worsened quality of life and higher treatment discontinuation rates, reduce the likelihood of functional recovery, and have long-term effects on health.[1] Young people with FEP appear to be particularly sensitive to adverse effects of antipsychotic drugs.[1,64] Furthermore, it is important to remember that a young person's first experience with antipsychotic medication is likely to influence their engagement and adherence to treatment in both the short- and long-term. See also Table 1.

Common side-effects of antipsychotic drugs include

- EPSEs (movement disorders)
- prolactin elevation (which causes endocrine and sexual side-effects)
- weight gain
- diabetes and metabolic syndrome (which are associated with increased cardiovascular risk in the long-term)
- QTc interval prolongation (abnormal heart rhythm that can cause dizziness, fainting, cardiac arrest and occasionally death)
- sedation.[1,64-66]

Agranulocytosis and myocarditis

Agranulocytosis (a serious and potentially lethal condition of the blood) and myocarditis have also been reported with the SGA clozapine. Although these events are rare, because of this risk clozapine is used only in people with psychosis who have not responded to other antipsychotics.[67,68] See 'Treatment-resistant psychosis and clozapine' on page 58 for further information.

Sexual dysfunction

Sexual side-effects reported in people with schizophrenia taking antipsychotics include increased or decreased libido, gynaecomastia (breast growth in men), erectile dysfunction, infrequent menstruation, heavy or prolonged menstruation and premature ejaculation.[69,70]

Some of these are caused by hyperprolactinaemia, an increase in levels of the hormone prolactin that occurs frequently with FGAs and some SGAs (risperidone and amisulpride), but is rare with other SGAs (aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone).[71]

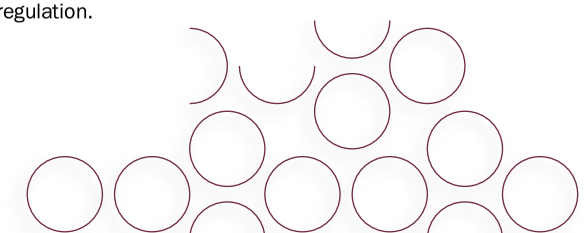
TABLE 1. **SGA MEDICATIONS USED TO TREAT FIRST EPISODE PSYCHOSIS IN YOUNG PEOPLE**[1,62,72,73]

AP	DOSE INFORMATION	RECEPTOR PATHWAYS INVOLVED IN AP EFFECTS	RECEPTOR PATHWAYS INVOLVED IN SEs	COMMON SEs	SEVERE SEs	COMMONLY REPORTED EPSEs
Amisulpride	Start with: 50–100 mg/day Initial target dose: 300–400mg/day Highest dose: up to 800 mg/day	Blocks D3 receptors Blocks presynaptic D2 receptors at low doses, postsynaptic D2 receptors at high doses (may have partial D2 receptor agonist activity)	Blocks D2 receptors in striatum (motor side-effects) Blocks D2 receptors in pituitary (prolactin elevation) Mechanism for weight gain and metabolic effects unknown	Insomnia Anxiety	Elevated prolactin levels Can cause EPSEs at higher dosage	Akathisia
Aripiprazole	Start with: 5–10 mg/day Initial target dose: 15–20 mg/day Highest dose: up to 30 mg/day	Partial D2 receptor agonist Partial agonist at $5HT_{1A}$ and blocks $5HT_{2A}$ at clinical doses	Blocks α1 receptors (dizziness, sedation, hypotension) Partial agonist of D2 receptors in striatum (motor side-effects) Partial agonist actions at D2 receptors (nausea, occasional vomiting, activating side-effects) Mechanism of any possible weight gain or metabolic effects unknown*	Restlessness Sleep disturbance Anxiety	Can cause EPSEs at higher dosage	Tremor Akathisia
Clozapine	Start with: 12.5–25 mg/day on day 1 then 25–50 mg/day on day 2 Initial target dose: up to 300 mg/day (within 2–3 weeks of starting) Highest dose: 600 mg/day	Blocks D2 receptors Blocks $5HT_{2A}$ receptors Interactions at $5HT_{2A}$ and $5HT_{1A}$ receptors may contribute to effects on cognitive and affective symptoms	Blocks H1 receptors in the brain (sedation, possibly weight gain) Blocks α1 receptors (dizziness, sedation, hypotension) Blocks M1 receptors (dry mouth, constipation, sedation) Blocks D2 receptors in striatum (motor side-effects – very rare) Mechanism of weight gain and metabolic effects unknown but insulin regulation may be impaired by blocking pancreatic M3 receptors	Hypersalivation Sedation Cognitive deficits	Weight gain Metabolic syndrome with possible diabetic complications Agranulocytosis Cardiovascular / respiratory arrest	Bradykinesia Akathisia
Olanzapine	Start with: 2.5–5 mg/day Initial target dose: 10 mg/day Highest dose: up to 20 mg/day	Blocks D2 and $5HT_{2A}$ receptors $5HT_{2C}$ antagonism may contribute to effects on affective symptoms and cognition	Blocks H1 receptors in the brain (sedation, possibly weight gain due to appetite stimulation) Blocks α1 receptors (dizziness, sedation, hypotension) Blocks M1 receptors (dry mouth, constipation, sedation)	Cognitive deficits Insomnia Anxiety Sexual dysfunction	Weight gain Metabolic syndrome with possible diabetic complications	Tremor Subjective akathisia

			Blocks D2 receptors in the striatum (motor side-effects) Mechanism of weight gain and metabolic side-effects unknown*			
Quetiapine	Start with: 25–50 mg/day Initial target dose: 300–400 mg/day Highest dose: up to 750 mg/day Rapid dose adaptation from starting dose recommended	Blocks D2 and $5HT_{2A}$ receptors Effects on $5HT_{1A}$ receptors may contribute to effects on affective symptoms and cognition	Blocks H1 receptors in brain (sedation, possibly weight gain) Blocks α1 receptors (dizziness, sedation, hypotension) Blocks M1 receptors (dry mouth, constipation, sedation) Blocks D2 receptors in striatum (motor side-effects – rare) Mechanism of weight gain and metabolic side-effects unknown	Somnolence Dizziness Orthostatic hypotension (mostly in elderly)	Moderate weight gain	Tremor Akathisia
Risperidone	Start with: 0.5–1 mg/day Initial target dose: 2–3 mg/day Highest dose: up to 6 mg/day	Blocks D2 and $5HT_{2A}$ receptors α-2 antagonist properties may contribute to effects on depression	Blocks α1 receptors (dizziness, sedation, hypotension) Blocks D2 receptors in the striatum (motor side-effects) Blocks D2 receptors in the pituitary (prolactin elevation) Mechanism of weight gain and metabolic side-effects unknown	Headaches Insomnia Anxiety Sexual dysfunction	Elevated prolactin levels Can cause EPSEs at higher dosage Moderate weight gain	Tremor Akathisia
Ziprasidone	Start with: 20–40 mg/day Initial target dose: 80–120 mg/day Highest dose: up to 160 mg/day	Blocks D2 and $5HT_{2A}$ receptors Interactions at $5HT_{2C}$ and $5HT_{1A}$ may contribute to improvements in cognition and affective symptoms Interactions with $5HT_{1D}$ and serotonin, norepinephrine and dopamine transporters may contribute to effects on affective symptoms	Blocks α1 receptors (dizziness, sedation, hypotension) Blocks D2 receptors in the striatum (motor side-effects) Mechanism of weight gain and metabolic side-effects unknown (uncommon with ziprasidone) and may be different from that of other antipsychotics	Somnolence Dizziness	Prolongs QT interval	Tremor Akathisia

AP, antipsychotic; EPSEs, extrapyramidal side-effects; SEs, side-effects; SGA, second-generation antipsychotic; 5HT, serotonin.

*The underlying mechanism(s) for weight gain, diabetes and dyslipidaemia with SGAs is unknown, and may be different for aripiprazole and ziprasidone versus other SGAs for which these events are more common. Blocking of pancreatic M3 muscarinic receptors may cause impairment of insulin regulation.



The use of anticholinergic agents to treat EPSEs

Young people are more likely than older people to develop EPSEs, especially with FGAs.[64] EPSEs are movement symptoms caused by the blocking of D2 receptors in the basal nuclei of the brain. The most serious of the EPSEs, tardive dyskinesia, involves asymmetrical involuntary movements and can occur with long-term and/or high-dose antipsychotic treatment. Tardive dyskinesia is difficult to treat and often incurable, so it is preferable to try to prevent it through the use of the lowest effective doses of antipsychotics and preferential use of SGAs.

Although anticholinergic agents have been used to to treat EPSEs in people receiving long-term antipsychotic treatment, evidence from randomised double-blind controlled trials to support their use is lacking.[74] Moreover, anticholinergics are themselves associated with side-effects, including constipation, dry mouth, blurred vision and urinary retention, and may also lead to worsening of positive psychotic symptoms and cognitive function and the development of tardive dyskinesia. While anticholinergic agents may be acceptable for short-term treatment of acute EPSE when dose-reduction and treatment switching have not been effective, their long-term use is not recommended.[74]

FGAs versus SGAs

SGAs appear to be better tolerated than FGAs in young people with FEP overall, although there are notable differences between the side-effect profiles of individual SGAs (see Table 1). As a class, SGAs are associated with a lower discontinuation rate due to side-effects compared with the most commonly used FGA, haloperidol.[55,75-77] They do, however, appear to be less likely to cause EPSEs than FGAs, with the exception of high-dose risperidone.[61] However, weight gain and metabolic effects are more likely to occur with SGAs, particularly olanzapine.[61]

FGAs are not usually prescribed for young people with FEP. However, according to treatment guidelines for FEP, the use of low-dose FGAs may be considered in the following cases:[1]

- in non-affective FEP if there is insufficient response to two prior SGAs and the use of clozapine is not feasible (alone or as an add-on to an SGA)
- as a long-acting injectable depot formulation if adherence is an issue
- in manic or mixed psychotic episodes if there is no response to treatment with an SGA plus a benzodiazepine (alone or as an add-on to an SGA).

Long and short-acting injections

Most young people with FEP will be treated with oral antipsychotics. However, short-acting IM antipsychotics may be required in emergencies where oral antipsychotics are not accepted.[1] Medium-acting IM injections are generally used only in people with severe, ongoing psychotic symptoms and/or aggression who have insufficient response to other treatments and may otherwise need multiple short-acting injections.[1]

Long-acting injections (LAIs) may be considered for young people with FEP who have a lack of response due to difficulty with adherence to oral medications, and those who express a preference for this form of dosing.[1,78] LAIs offer the convenience of less frequent dosing and have the advantages of improved adherence and in-built contact with clinicians. The SGAs risperidone, olanzapine and paliperidone are

available as LAIs; however, there have been only a few studies in FEP, all of which used LAI risperidone.[79] The available evidence suggests that LAIs may be more effective than the oral formulation of the same drug in improving symptoms and relapse and remission rates, possibly due to improved adherence.[78,80] Furthermore, tolerability may be improved due to the lack of peaks and troughs in drug concentrations compared with oral antipsychotics. However, there is a shortage of data from randomised controlled trials regarding long-term outcomes for LAIs compared with oral antipsychotics in early schizophrenia.[78] Olanzapine LAI has been associated with cases of post-injection delirium/sedation syndrome (PDSS), a serious adverse event with similar symptoms to olanzapine overdose.[81-83]

Antidepressants

Antidepressants may be used in young people with FEP who have depression in addition to psychotic symptoms.[1] Depressive symptoms are common in people with FEP, although there is considerable variation in estimated rates (range 17–83%) depending on how depression is assessed and the study population.[84]

How do they work?

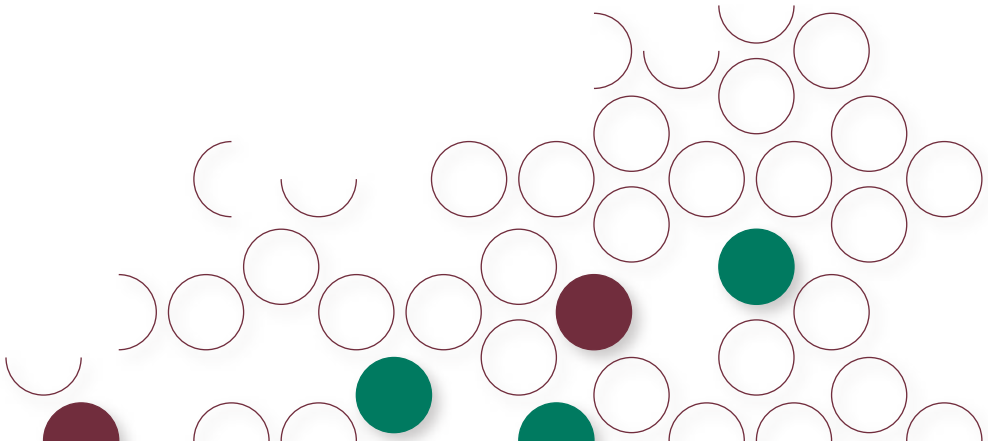
Antidepressants inhibit the reuptake of one or more of the monoamine neurotransmitters (serotonin, norepinephrine and dopamine) by binding or desensitising the neurotransmitter receptors or inhibiting monoamine oxidase, an enzyme responsible for degrading serotonin and norepinephrine.[56] This increases the concentration of the neurotransmitter(s) in the synaptic cleft.

Mechanism of action

Antidepressants of the selective serotonin reuptake inhibitor (SSRI) and selective norepinephrine reuptake inhibitor (SNRI) classes are used to treat depression in young people with FEP.[1] SSRIs, such as fluoxetine and sertraline, block the reuptake of serotonin into the neuron and increase its concentration at the synapse. SNRIs, such as venlafaxine, inhibit the reuptake of norepinephrine in addition to serotonin. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are two older classes of antidepressant that are not usually used to treat FEP in young people.

Evidence for efficacy

Although it has been established that antidepressants are effective in major depression, there is only weak evidence for their efficacy in treating depression in people with schizophrenia.[85] However, there is some evidence to suggest that adjunctive treatment with antidepressants is more effective than antipsychotics alone in improving negative symptoms.[86,87]



SIDE-EFFECT PROFILE OF ANTIDEPRESSANT MEDICATIONS

SSRIs and SNRIs are generally well tolerated. Common side-effects include:

- anxiety
- nausea
- vomiting
- headache
- tremor
- sleep disturbances
- sexual side-effects.

Most of these side-effects occur more frequently at the start of treatment.[56] SSRIs and SNRIs should not be discontinued abruptly due to the risk of serotonin withdrawal syndrome; gradual tapering of the dose is recommended.

Mood stabilisers

Treatment guidelines for young people with FEP recommend the use of a mood stabiliser alone or in addition to an SGA in those with manic or mixed psychotic episodes, and in combination with an SGA in people with bipolar depression and those with major depression who do not respond to treatment with an antidepressant plus an SGA.[1] Mood stabilisers used in FEP each have different side-effect profiles. Serious side-effects are possible with all of these drugs (see box on next page).

How do they work?

Lithium and the anticonvulsants sodium valproate, carbamazepine and lamotrigine improve manic symptoms, and lithium and lamotrigine have also demonstrated antidepressant effects.[88]

Mechanism of action

The mechanisms of action for these drugs as mood stabilisers have not been established.[88,89] However, recent evidence suggests that lithium enhances glutamatergic neural transmission in the hippocampus, and that lamotrigine and valproate also directly alter neural transmission.[88]

Evidence for efficacy

Mood stabilisers have demonstrated efficacy in bipolar mania,[90-92] although there is a lack of data on their use in FEP.

COMMON SIDE-EFFECTS OF MOOD STABILISERS

Lithium[93]

The occurrence and severity of adverse events with lithium is related to its serum concentration. Due to its small therapeutic ratio, monitoring of serumconcentrations of lithium is necessary as serious and potentially fatal toxicity can occur at concentrations of >1.5 mmol/L. Common side-effects associated with lithium include:

- leucocytosis
- nausea and vomiting
- diarrhoea
- constipation
- vertigo
- muscle weakness
- hand tremor
- muscle twitching
- fatigue
- thirst
- polyuria
- ECG changes
- mild cognitive impairment

Signs of chronic toxicity include slurred speech, tremor and increased reflexes – gastrointestinal problems are less likely.

Carbamazepine and lamotrigine[48,94]

Both carbamazepine and lamotrigine can cause skin reactions, which in some cases may be serious and life-threatening. Common side-effects in people taking carbamazepine include:

- blood cell disorders (leukopenia, eosinophilia, thrombocytopenia)
- ataxia (trouble with muscle coordination)
- dizziness
- somnolence (tiredness or drowsiness)
- diplopia (double-vision)
- headache
- blurred vision
- nausea and vomiting
- fatigue
- dry mouth

Lamotrigine has also been associated with:

- fatigue
- dry mouth
- nausea
- diarrhoea
- headache
- somnolence
- dizziness

Sodium valproate[95]

Sodium valproate is contraindicated in pregnancy and should not be prescribed in women of childbearing potential unless there is no suitable alternative due to its potential to cause birth defects, including neural tube defects. Other side-effects reported in trials of valproate include pain, asthenia (weakness), nausea, diarrhoea, vomiting, constipation, somnolence, sedation and fatigue.

Benzodiazepines

Benzodiazepines are commonly prescribed as monotherapy during the initial 24–48-hour antipsychotic-free assessment period for young people with FEP to treat symptoms such as agitation/aggression, anxiety, or sleep disturbance.[1] Benzodiazepines may also be used as an early add-on to an SGA in mixed or manic episodes.

How do they work?

Benzodiazepines are sedatives/hypnotics and anxiolytics that work by enhancing the effect of the neurotransmitter GABA at its receptor.[96]

Mechanism of action

Benzodiazepines bind to a benzodiazepine binding site on the GABA-A receptor and change its conformation so that GABA can bind.[96] Binding by GABA reduces the excitability of neurons, which has a calming effect on the brain.

Evidence for efficacy

There is limited evidence for the efficacy of benzodiazepines in psychosis either alone or with an antipsychotic, although a number of small studies suggest that their short-term sedating effects may be effective in calming acutely agitated people with FEP.[97]

SIDE-EFFECT PROFILE OF BENZODIAZEPINES

Common side-effects of benzodiazepines include:[96]

- fatigue
- drowsiness
- lethargy.

Prolonged use can cause cognitive impairment, including amnesia, disorientation, slurred speech and confusion. Benzodiazepines should only be used short-term due to the risk of tolerance, dependence, physical addiction and withdrawal symptoms with long-term use.

PART 2

Medical management in early psychosis

Overview

The following section details approaches to managing medication in young people and the role non-medical clinicians play in ensuring this done in the best possible way. It also addresses some of the practical issues and challenges that need to be considered in relation to medical treatments in young people with early psychosis, such as overdose, poor physical health, discontinuation of treatment and alcohol and other drugs.

Working with young people in relation to medical treatments

Collaboration and shared decision-making

The involvement of people in decision-making regarding their own medical treatment and inclusion of their preferences are becoming increasingly recognised as core components of practice in all areas of healthcare.[98]

Treatment for early psychosis often involves the initiation of an ongoing medication regimen, using medications that cause substantial side-effects. For young people experiencing a first episode of psychosis, this can be a particularly difficult and even frightening process. It is unlikely they have had much experience of having to take medicine on a daily, ongoing basis. Furthermore, there is significant stigma attached to antipsychotic medication, and this, along with physical side-effects, can affect a young person's development both socially and biologically. It is therefore not enough to prescribe medication and expect a young person to adhere to whatever regimen is given. The young person must be consulted and engaged in deciding what treatment they are to commence. This collaboration is essential to working effectively with young people in early psychosis.

Although not involved in prescribing medication, non-medical clinicians have a role to play in the collaborative process to ensure the young person and their family, where appropriate, are well informed about treatment options and feel consulted and listened to about their preferences for treatment. The collaborative process should ideally include the young person, their case manager, their family, the medical team, the multidisciplinary team and any other key people, professionals or services central to the young person's life.

Shared decision-making is a framework for medical decision-making that can help with effective collaboration. It involves a systematic collaboration between the young person and the treating clinician, with the aim of promoting the young person's involvement and satisfaction with treatment choice, by basing decisions on evidence and the young person's preference and needs.[99] A broad outline of shared decision-making processes is outlined in Box 2.

BOX 2. INVOLVING YOUNG PEOPLE IN THE DECISION-MAKING PROCESS

Collaborate about collaboration

Talk to a young person about what collaboration means and to what extent they want to be involved in decision-making regarding medical treatments. Acknowledge they are the experts when it comes to their own needs.

Psychoeducation and discussing treatment options

Talk about symptoms and explore questions the young person has, such as 'Why me? Why this problem, and why now?' Clinicians should emphasise that the young person has choices by discussing the range of treatment options (including mode of delivery) and asking what the young person's preferences are around delivery and receipt of information. Discussing the rationale for treatments and their possible outcomes should be central and based on sound evidence. The young person should also be given the opportunity to discuss personal preferences about treatment options.

Explore feelings

Address concerns, fears, anxieties and positive and negative expectations. This offers the young person opportunities to ask questions and clarify their knowledge or address any misconceptions regarding medication for psychosis. This is especially important in the FEP population, as this is likely their first experience of psychosis and related medical treatments.

Identify the young person's goals

Talking with the young person about their goals for the recovery process may help them to understand how medication can fit in with these goals, and to see how their priorities (e.g. completing their university qualification) might in fact align with those of the clinician (e.g. taking medication to stop symptoms coming back so the young person is well and can finish their studies). These goals may also influence the medical practitioner's consideration of medication options.

Check in

Continually checking in with the young person is a core feature of the shared decision-making model. It is important to remember that young people with early psychosis are experiencing a disruption to their normal brain functioning, and may find that their memory is not as good as it usually is. They are receiving a lot of new information about a possibly frightening illness, the service and medical treatments, and the way they view themselves and the world around them has changed dramatically.

Continued over page.

BOX 2. **INVOLVING YOUNG PEOPLE IN THE DECISION-MAKING PROCESS** CONTINUED

Clinicians therefore need to be clear that the young person has the information they need and, importantly, that they understand it so they can make the best decision for themselves as possible. It is also important that they are given time to think things through. Decision-making regarding medication and treatment is really important and can be intimidating. It is not a decision that should be taken lightly.

Make a decision

Once a decision has been made following this process, the reasoning for the decision should be reviewed by those involved, making sure everyone is comfortable with the decision and the process by which it was made. If no decision is reached, a plan can be made to decide later, and a time set to do this. Again, once a decision is made, it is important to make time to review it later.

Challenges to collaborative, shared decision-making

A collaborative, shared decision-making approach to medical treatments assumes that a young person *wants* to be involved in the decision-making process – it can therefore be challenging if a young person displays little interest or is keen to 'leave it up to the doctor'. However, this should not be a barrier to collaboration, and it is important to remember that the clinician, young person and their family may have differing opinions about what constitutes 'involvement'.[98] Involving the family, where appropriate, can assist in the decision-making process (see also the ENSP manual, *In this together: family work in early psychosis*). Clinicians should discuss expectations openly and ensure that the collaborative process is tailored to individual perspectives and needs. For example, young people or families from some cultural backgrounds may be more deferential to the role of the doctor and expect direction in the decision-making process, in which case, the collaborative process may look slightly different to that involving young people or families who are suspicious of health care services.

Time constraints are a common challenge to ensuring a young person is appropriately involved in treatment decisions. Clinicians may need to make designated appointment times to work through decision-making processes with the young person. However, the decision-making process does not only occur face-to-face in a room. Phone-calls or impromptu chats in the car on the way to appointments can be just as productive as set appointments. Clinicians should regularly check in with the young person throughout their episode of care with the service to ensure they are involved in decision-making; for example, making sure that they understand any new information they have received.

Factors related to psychotic symptoms (e.g. poor insight, cognitive difficulties) are often cited as reasons for not being able to involve young people in collaborative decision-making. Again, this highlights the importance of tailoring the process to each young person's needs and looking at what resources can be utilised (e.g. increased input from the family, creative delivery of information). Regardless of

symptom-related factors, young people are entitled to the most current, evidence-based information around medications. How this information is delivered and how the young person is engaged in shared decision-making may be need to be different, but this should not be a barrier to working collaboratively.

Encouraging treatment adherence

Medication non-adherence is a common in all areas of medicine. Rates of non-adherence to medical treatment in people with schizophrenia are high, having been shown to range between 43 and 74%, depending on which medication they are prescribed.[100] Prevalence in the FEP population is particularly high.[1] Studies focusing on adherence in FEP have indicated up to 60% of young people are not fully adherent within the first year of treatment.[101,102] This has been linked to poorer outcomes including an increase in positive symptoms, relapse, greater chance of hospitalisation, substance use and poorer quality of life.[103]

Adherence is a complex issue, influenced by numerous factors that are prone to change over the course of the illness.[104] Reasons for non-adherence are therefore multifactorial and intrinsically linked to each individual. Understanding *why* the young person is not taking their medicine as prescribed is the first step in addressing non-adherence. Table 2 outlines some known contributing factors to non-adherence.

TABLE 2. **FACTORS SHOWN TO CONTRIBUTE TO MEDICAL NON-ADHERENCE IN PSYCHOSIS**[100,102,104-106]

CONTRIBUTING FACTORS RELATED TO:	EXAMPLES
Disorder	Positive symptoms (e.g. paranoia) Substance use Negative symptoms Lack of insight Cognitive impairment
Treatment/medication	Adverse side-effects Efficacy/non-efficacy Dose requirements • e.g. side-effects resulting from commencement at a high dose, swallowing medication is unpleasant
Service/clinician	Engagement and quality of therapeutic alliance Pathways/access to care • e.g. voluntary/involuntary care Continuity of care

Continued over page.

CONTRIBUTING FACTORS RELATED TO:	EXAMPLES
Personal/young person	Age Developmental stage • e.g. medication regimen seen as 'controlling', or creating dependence at a point where independence is sought Past experience with medication or mental health services Stigma • e.g. medication seen as a sign of weakness, inability to cope, or reminder they are unwell Knowledge and attitudes
Family	Lack of insight into disorder Engagement with treating team member(s) Past experiences with mental health services and treatment Knowledge and attitudes
Social/cultural/ environmental	Financial burden Lack of peer or social supports Geographical access to services (e.g. pharmacy) Social stigma Family, cultural and religious beliefs Homelessness/unstable housing

Clinicians need to be mindful of these contributing factors so that they can begin to address potential adherence issues from the beginning of treatment. Collaborative and sensitive exploration of these factors with the young person, using a formulation-based approach to care, can help identify and target current and possible challenges to adherence, with the ultimate aim of improving adherence.

Along with considering these factors, it is important to define non-adherence as it relates to the individual. For example, whether the young person is fully or partially non-adherent to treatment, or whether they are intentionally or non-intentionally non-adherent. Gaining insight into these factors can assist with joint decision-making and guide treatment discussions and options.

Strategies to address non-adherence

The majority of direct clinical contact with a young person and their family will not involve medical staff at the same time. Therefore, clinicians need to possess knowledge of how, and with whom, to discuss, prioritise and implement a range of strategies to address non-adherence. At the same time, regular consultation with the medical team is essential to ensure that consistent strategies are used within the treating team.

As barriers to adherence are varied and individual, it makes sense that strategies for non-adherence will be multifactorial and tailored to the individual. Listed below are a variety of strategies to help address non-adherence.

Involve young people in treatment decisions

As outlined earlier in this manual, collaboration is central to working with young people. Collaboration offers the opportunity to gain knowledge around treatment and ensure young people are actively involved in treatment-related decision-making. This in turn encourages adherence through informed knowledge, self-empowerment and choice. Collaboration is also a defining component of the therapeutic alliance,[107] which in itself is a strong predictor of outcomes,[108] including treatment adherence in people with schizophrenia.[109]

> 'I think you need to set a clear plan [to manage side-effects] with your doctor that empowers you to decide whether you want to up or lower the medication depending on how you're feeling about it. Otherwise people will just do it [stop taking medication] and then they don't tell their case manager or doctor at all – they might just stop taking it.'
>
> – Young person
> EPPIC, Orygen Youth Health Clinical Program

Consider comorbidities

Comorbidities are common amongst those experiencing a first episode of psychosis.[1] Conditions such as persistent substance use are known to be associated with non-adherence.[110] Working collaboratively to identify and address comorbid conditions can be a useful strategy in understanding the reasons a young person may be non-adherent.

Address side-effects

Side-effects such as weight gain, sedation, cognitive dulling and others are strongly related to non-adherence.[39] Clinicians should try to address side-effects, or even anticipate them to reduce the chance of non-adherence (e.g. clinicians can anticipate weight gain by providing education about diet and exercise as soon as a young person is commenced on antipsychotics. See also 'Physical health monitoring' on page 49). Persistent endocrine and sexual side-effects may warrant a medical review by the young person's doctor to consider switching medication.[1]

Appendix 1 of this manual provides a list of side-effects that young people may experience while taking antipsychotic medication and suggested strategies to help manage them.

CASE SCENARIO **MARCUS**

Marcus was a young man in the early phase of recovery following recent onset of FEP with a marked affective presentation. He had continued to experience some ongoing thought disorder, paranoid thinking and unusual ideas around specific dietary requirements. Following a recent increase in his antipsychotic medication it was observed that Marcus's mental state was deteriorating. During an appointment he confirmed that he had ceased taking his medication in the context of tender chest/breasts, cognitive dulling and sexual dysfunction. Marcus was reluctant to tell his case manager he had ceased medication in case his dose was increased or he was put back in hospital.

The case manager made enquiries regarding the types of side-effects he was experiencing, validating his distress and concerns and normalising common side-effects associated with that medication. An urgent medical review and physical assessment was arranged along with pathology investigations. Marcus was switched to another antipsychotic medication and reported side-effects gradually abated and eventually he returned back to work.

Maximise engagement

Effective engagement is the foundation of treatment. McGlashan (1990) notes the core of all treatments, biological or otherwise, lies in the relationship that develops between clinicians and the people being treated.[111] There are many factors that might contribute to engaging young people in their treatment. It is essential that a young person feels listened to, understood and taken seriously by members of their treating team, and that they are being clearly and truthfully informed about treatments.[1] This will help them feel comfortable about expressing concerns relating to the proposed or prescribed treatments, which in turn can help case managers anticipate factors that may challenge adherence and discuss them with the young person.

For more detailed information around engagement in early psychosis, please see the ENSP manual *Get on board: engaging young people and families in early psychosis*.

Provide psychoeducation

Psychoeducation is the process of providing young people and their families with information and education about early psychosis. This may include diagnosis, treatments and side-effects, prognosis, coping strategies, rights, explanation of illness models and exploration into the impact of early psychosis on the sense of self and identity.[32,108] The provision of current, evidence-based information will equip a young person with the knowledge they require to make decisions about whether to take up treatment options and can encourage adherence.[98]

When delivering psychoeducation regarding medical treatment, clinicians will find they need to maintain a balance between realistic education about medication duration and side-effects and the need to engage the young person and family with the aim of enrolling them in treatment. Although mention of side-effects such as metabolic risk, cognitive dulling, sedation and more can be alarming, the young person needs to know so that they can make an informed decision.

For more detailed information on psychoeducation, please see 'Psychoeducation for medical treatments' on page 42.

Consider language used

Overly technical medical language and terms associated with psychiatry can feel stigmatising, overwhelming and confronting and be difficult to understand. Using carefully chosen terms and language that aligns with the young person and family's own experiences and explanatory models can increase understanding and help normalise and destigmatise the processes involved with medical treatments.

CASE SCENARIO **LANGUAGE USE REGARDING SYMPTOMS AND MEDICAL TREATMENTS**

Read the following two scenes. Consider the language used, and how Michael and his mother might feel after each of their visits to the doctor.

Michael is taken to his GP by his mother, Selma, who is concerned he is acting strangely and might have mental health issues. Michael appears to be experiencing paranoid symptoms. The GP tells Michael and his mother that Michael is delusional, experiencing 'ideas of reference' and 'loosening of association', and seems to be experiencing both positive and negative symptoms associated with schizophrenia. They are told that it is a medical condition that involves irregular levels of neurotransmitters in the brain, 'You know, things like dopamine and serotonin'. The GP proceeds to tell them that Michael will need to take a medication called 'antipsychotics' for the rest of his life if he wants to avoid additional relapses or 'a chronic outlook'.

Selma takes Michael to another doctor for a second opinion. This doctor tells them that it is likely that Michael is experiencing a lot of stress, and that this sometimes can affect our behaviour, how we think, and how we perceive the world, our environment and the behaviour of others. The doctor provides reassurance and recommends that Michael starts a medication called an 'antipsychotic', saying, 'This medication can help your thinking in a number of ways, help you worry less about things, feel clearer in your thoughts and hopefully help you feel more active and organised'. The GP emphasises the importance of taking the medication regularly to ensure a good recovery for better short-term (feeling better) and long-term outcomes (Michael's quality of life and ability to meet his goals).

Involve family and other supports

Studies have shown that young people whose families are actively involved in their treatment are more likely to adhere to medical treatment.[101] Families can support adherence in numerous ways. Examples include:

- reassuring young person, providing support, encouragement and understanding around medical treatments
- demonstrating to the young person 'we're all on the same page'
- modelling destigmatising behaviour
- monitoring, reminding or 'checking in' on medication adherence
- advocating for the young person
- active engagement in developing and implementing adherence strategies.

Clinicians should work with the family or significant others to develop what their role will be in supporting the young person to adhere to treatment. Any undue pressure felt by the family regarding monitoring the young person, or their role in supporting adherence, needs to be addressed.

Strategies that utilise peer support workers, FEP-related peer groups, support programs or the contribution and involvement of close and trusted friends in the support of the young person, can also be of benefit. Young people want to be accepted by their peers, and any perception that they are different from their peers could have an adverse effect on adherence to medication.[112] Engaging with others who have shared a similar experience can help normalise and destigmatise the use of medication.

Clinicians can also draw on previous clinical experience and knowledge to help reassure young people and families, by providing real life examples of actual recovery stories and hence providing simultaneously useful information and installing a sense of hope and optimism regarding treatment and outcomes.

Use compensatory strategies

As mentioned earlier, the reasons a young person might be non-adherent are varied. With this in mind, it is important to acknowledge non-adherence does not necessarily mean a person does not want to take their medication.

When a young person is having difficulty remembering to take medication, it can be useful to incorporate some compensatory, or external, strategies. Before compensatory strategies are implemented, exploration of reasons behind the forgetfulness is required to ensure strategies are appropriately selected.

Examples of compensatory strategies include:

- setting a phone alarm
- visual prompts (e.g. post-it notes on the fridge, bathroom mirror, near phone charger or on laptop)
- reminders from a family member
- establishment of a routine/activity-scheduling
- a daily checklist

- environmental modification (e.g. placing medication next to the bed or near toothbrush, using a dosette box such as Webster pack).

Consider long-acting injectable (depot) medication to prevent non-adherence

Traditionally, long-acting injectable (LAI), or depot, medication (see page 22) has been associated with known or suspected problematic adherence to oral medication, with guidelines generally outlining its role as a maintenance treatment.[113] This view of depot medication means it has generally been overlooked as an early treatment possibility, and is seen rather as a last-resort strategy for non-adherence. However, it has been suggested more recently that depot injections may be of benefit in FEP when preferred by the young person or when avoiding covert non-adherence is a clinical priority.[114] For example, a young person might prefer depot over oral treatment as it does not serve as a constant reminder of their illness, or because it is more convenient than having to take a pill every day. If clinicians and the treating doctor think it may be of benefit, depot medication should be presented to a young person as one of many early treatment options. It is important that the young person is also provided with appropriate information about depot medication to ensure a collaborative decision is made. Ultimately, the aim should always be to improve chances of a complete recovery.

Aside from LAIs, other strategies for reducing the complexity of treatment regimens should be considered, such as using slow-release oral formulations over bi-daily doses.

CASE SCENARIO **ANDY**

Andy is a young male living in a shared house and attending a TAFE carpentry course. He has previously recovered from an initial episode of psychosis while living at home with his family. Since moving into share accommodation, he has been socialising more, partying and using alcohol and other drugs. He subsequently has been erratically adherent to his oral medication, missing doses if he stays over at friends' houses and often going out on the weekends and forgetting to collect his scripts.

As a result of this period of non-adherence, Andy is beginning to experience a return of psychotic symptoms of disorganised thinking and poor motivation. He has stopped attending TAFE and is close to being suspended from his course. Andy's case manager has worked through additional psychoeducation with him, as well as trying to implement prompts to remind Andy to take his medication; however, these attempts to recommence oral medication have failed.

As Andy's issues with adherence seem to be related to disorganisation rather than refusal to take medication, his case manager and doctor suggest commencing a long-acting injectable (LAI) antipsychotic as a way to ensure that he has regular and consistent administration of antipsychotic medication. The case manager takes care to discuss the positive aspects of trialling an LAI (no need to collect a script, no daily reminder of illness, Andy won't need to take medication with him all the time) and the negative (momentarily intrusive, need to adjust dose initially, stigma regarding injections). Andy agrees to trial

Continued over page.

CASE SCENARIO **ANDY** CONTINUED

the LAI, and after several months notices a significant reduction in his symptoms and overall improvement in his thinking and motivation. He says to his case manager, 'Having the injection once a month is great. I even forget that I'm having it, I don't run out of tablets and don't need to worry about taking my medications in front of my friends or girls I see'.

Other strategies

Other effective strategies for non-adherence may include:

- utilising problem-solving skills (e.g. exploring better ways to remember to take medications and picking up scripts when memory is poor)
- direct instruction (e.g. family members telling the young person to take their medication at the set times)
- motivational interviewing approaches (e.g. using a 'stages of change' framework to motivate a young person to take medicine in order to meet their life goals).[1]

Involving families in medical treatment

As a large proportion of young people experiencing early psychosis are still living with their families, families play an integral role in the support and recovery of the young person. At the same time, the impact of psychosis can be very distressing for the family. They may experience feelings of guilt, fear, confusion and stigmatisation,[115,116] and often these feelings are compounded by anxiety that a loved one requires medication.

Families should be engaged in communication and psychoeducation about medical treatments as early as possible. Psychoeducation can help alleviate the family's distress, enhance their confidence in supporting and guiding the young person through their recovery and enhance their coping skills. As family attitudes to medication may predict adherence,[104] providing psychoeducation to families may also have a positive effect on treatment adherence.

Clinicians should provide accurate and up-to-date information on medical treatments and explore the family's current understanding of medication, its role in treatment, and their perceived role and expectations regarding medical treatment (for example, whether they will be involved in helping the young person adhere to treatment regimens). Information should be tailored specifically to each family in the context of their explanatory models. It should promote hope and optimism and allow the family opportunities to ask questions and raise any concerns. Table 3 outlines some common concerns families have regarding medication. Addressing these can help clear up misconceptions or unhelpful or uninformed expectations of medication.

TABLE 3. **COMMON FAMILY MEMBER CONCERNS ABOUT MEDICATION**

AREA OF CONCERN	COMMON QUESTIONS AND STATEMENTS
Stigma around taking medication	We don't want anyone to know they're on medication. Should we tell our friends and family? What will we tell our friends and family?
Treatment course	Will they need to take medication for the rest of their lives? How long will they need to take the medication? Can they stop the medication once they're well?
Treatment efficacy	Will the medication cure them? What if the medication doesn't work? Will they be the same as they were before they became unwell?
Treatment effects	Will the medication change their personality? Will the medication make them suicidal? Will the medication make them depressed? What are the side-effects and what can be done about them?

Note that communication of information regarding the young person's treatment to family members should be respectful of the young person's privacy. It is important to discuss confidentiality and expectations regarding what information might be shared with both the family and the young person. For more information regarding confidentiality, see the manual, *In this together: family work in early psychosis*.

Ultimately, families want to be able to best support their family member throughout their recovery. They should be seen as valued and respected members of the care team and encouraged to take an active role in the young person's recovery. Providing and sharing information around medication helps families to:

- improve their mental health literacy, and feel they have mastery of the topic
- take part in informed and shared decision-making (helping to ensure everyone's 'on the same page')
- dispel myths and misconceptions around medication and providing opportunity to discuss unrealistic, erroneous or anxiety-provoking expectations of medication
- support the young person in engagement in treatment
- identify side-effects early
- use an informed knowledge base to advocate for a young person who may not be well enough to advocate for themselves around medication decision-making.

It is important to understand that how a family supports the young person will be impacted upon by age and developmental stage. These factors should be considered when framing the family's role in supporting their young person to take medication.

SUMMARY **WORKING WITH YOUNG PEOPLE IN RELATION TO MEDICAL TREATMENTS**

- Working collaboratively with young people to make decisions about their treatment is important for engagement and adherence to treatment.
- The multidisciplinary team, including the doctor and primary clinician, the young person, the family and other key people or professionals should be included as part of the collaborative process.
- Discussing treatment options, exploring concerns or beliefs about treatment and identifying the young person's goals are important aspects of collaborative decision-making.
- There are challenges to collaborative decision-making; however, the young person should continually be encouraged to take part in the process as much as possible, and no individual challenge should be a barrier.
- Medication non-adherence is common across all areas of medicine, but rates of non-adherence in the FEP population are particularly high.
- Understanding why a young person has been non-adherent is the first step to addressing this issue.
- Strategies to address non-adherence should be discussed with the young person, family and amongst the multidisciplinary team to ensure a consistent understanding and approach.

Roles and responsibilities of non-medical clinicians in medical management

Communication within and outside the treating team

Case managers play a central role in a young person's care. A significant part of this role is to act as an advocate for the young person and communicate on their behalf – especially during clinical reviews or other meetings at which the young person is not present. This advocacy, along with effective communication, both within and outside of the team, can have a significant impact on reducing stress in the young person and family by ensuring consistent messages and information regarding medication are provided.

Ideally, each young person will be provided with consistent, multidisciplinary clinical management within a core treating team. However, there will be times when a young person is managed outside of this core team. This could include consultations with other clinicians or medical staff within the service, management by different parts of the service (e.g. the inpatient unit), or consultations with other health care providers, such as pharmacists, general practitioners or private psychiatrists.

Listed below are some practical strategies to help with communication regarding a young person's medical management:

- Ensure sufficient information about the young person and their medication history is available through clear and thorough documentation.
- Documentation regarding medical treatments can be included in file notes, risk assessments, mental state assessments, individual service plans (ISPs), assessment reports, referrals, treatment sheets, case formulations, crisis management and early warning signs documents.
- Information in file notes should include current treatment and the decision-making process behind this choice. Any changes to medication should be documented on the day of the change and any key people notified.
- Liaise regularly with the rest of the multidisciplinary team and ensure medical treatments are discussed at regular clinical reviews.
- Liaise with professionals outside of the team who have met with the young person to understand the context of the interaction, what was covered and actioned and what requires following up in regards to medical treatments.
- Provide regular updates to other professionals involved with the young person about their current status whenever there is a change in medication regimen.
- Work with medical staff to ensure treatment sheets are accurately filled in and up to date.

> 'It was very separate – seeing my case manager was nothing to do with seeing my doctor. So rehashing the same thing with your doctor once a month was really unhelpful.'
>
> – Young person
> EPPIC, Orygen Youth Health Clinical Program

There will inevitably be times when issues arise regarding a young person's medical management that are outside the scope of the case management role, but which cannot wait until the next clinical review to be raised. Clinicians need to be clear about their role and ensure they communicate directly with the medical team for advice and direction or arrange a medical review as required.

Instances where non-medical clinicians should involve the medical team include, but are not limited to:

- the young person is requesting a change of medication
- concerns are being expressed about side-effects
- the young person or family are reluctant to change or decrease medication
- the young person is indicating they no longer want to be on medication (heightening the risk of non- or partial adherence)
- the young person has self-initiated a dose change or ceased medication
- there is a clear deterioration in mental state in the young person

- there are identified significant risks to self or others
- the young person is planning or has become pregnant.

Note that medical staff should also be regularly involved in reviews to monitor a young person's physical health, including metabolic risk factors – not just for acute side-effects (see 'Physical health and monitoring' on page 49 for more information).

Delivering psychoeducation for medical treatments

Psychoeducation is the process of providing young people and their families with information and education about early psychosis, its diagnosis, treatments and side-effects, prognosis, coping strategies, rights, explanatory models and exploration into the impact of early psychosis on the sense of self and identity.[108] It aims to enhance the young person and family's understanding of early psychosis and promote coping, and should be delivered with the understanding that young people have the right to be fully informed about the nature of their condition.[1,117,118]

Ideally, psychoeducation enables young people to develop a knowledge base on which to form decisions and to take an active part in their medical treatment. It can provide a rationale for treatment[103] and offer a basic framework[108] for beginning to understand the 'how, what, why and where to next' in regards to their personal experience of early psychosis. Information about psychosis and treatment is especially important in the early psychosis population, as it is likely they have had very little prior experience of the disorder.[118] It can also reduce the distress and disability associated with early psychosis.[108]

The process of psychoeducation should involve more than having a chat about early psychosis, providing a few fact sheets and directing people to some appropriate web sites. It should be an ongoing, tailored process that draws upon a multitude of resources and methods of delivery.

> 'You shouldn't have to find out everything about the medication from reading that little pamphlet in the box or by looking it up on the internet. You should be told straight, face-to-face, to make sure you understand each and every symptom, what to do when you get the symptom, if you should panic and call, like, the ambulance or something or if you should just leave it be and just not take the medication or go to your doctor the next time you can.'
>
> – Young person
> EPPIC, Orygen Youth Health Clinical Program

It is likely that psychoeducation will be provided by both case managers and medical staff, though others can, and may, be involved throughout the course of care. As the contact case managers have with young people will not always involve medical staff, it is important that case managers are confident and competent in providing tailored psychoeducation regarding medical treatments. At the same time, they should regularly liaise with the multidisciplinary team to review psychoeducation, ensuring the ongoing appropriateness, accuracy and consistency of the message being delivered.

As it is beyond the scope of this manual to cover all aspects of psychoeducation, the next section will focus specifically on the role of non-medical clinicians in the provision of psychoeducation for medical treatments.

What should psychoeducation for medical treatments involve?

Psychoeducation should be provided to young people from the first contact they have with an early psychosis service and throughout their episode of care.

Tailoring the education towards a young person's own experience and explanatory model will ensure it contains meaning. If the information being presented, no matter how salient the clinician may believe it to be, holds no meaning for the young person, it is more likely to be rejected. Developmental stage and illness phase also need to be taken into account, as this it will affect how and to whom the information is delivered.

Broadly, psychoeducation regarding medical interventions should include information on:

- the broad range of indicated treatment options for the young person (e.g. second-generation antipsychotics, antidepressants, depot)
- how and why medications work
- the possible side-effects of medication, why these occur and strategies for reducing their impact
- dosage and titration and the importance of adhering to treatment regimens
- interactions between alcohol and other drugs and psychotropic medication.

Clinicians should also address any questions the young person or family have about expectations of medication: 'Will it help?' 'What if it doesn't?' 'How long will I need to stay on medication?' 'Do I need to take medication?' 'Can I change the dose myself?' They should also address any cultural issues, concerns or expectations regarding medication.

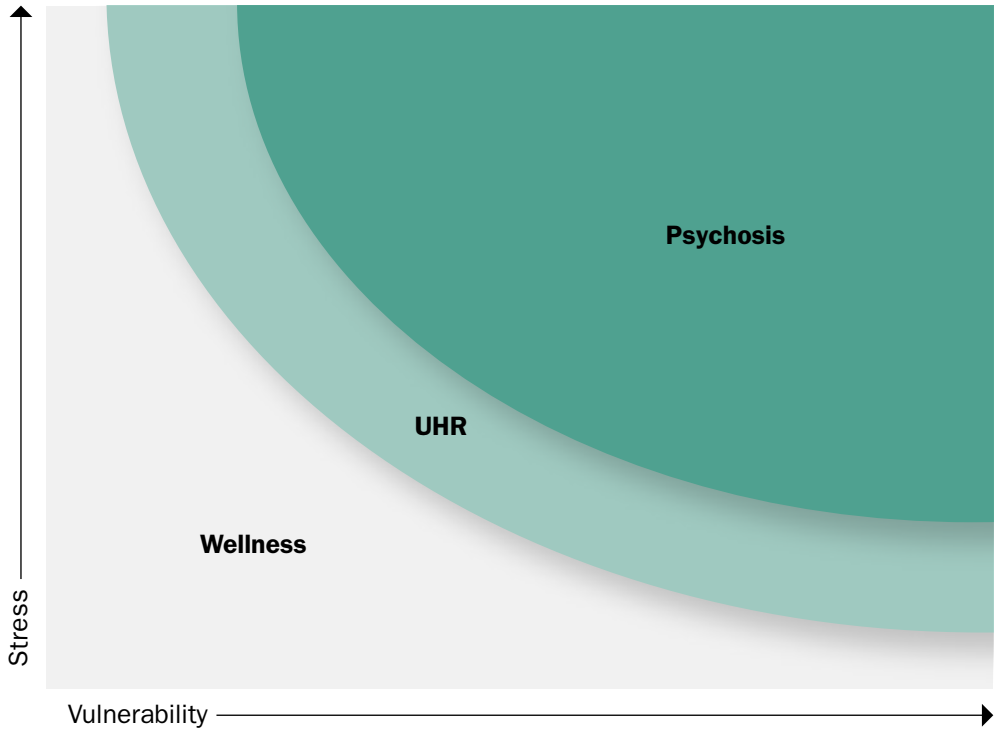
Models and conceptual frameworks to explain aspects of the underlying nature of early psychosis, how it comes about and the role of medication in treating it can be useful psychoeducative tools. Two of these models are described below.

The stress–vulnerability model for describing psychosis

Shown in Figure 2, the stress–vunerability model is a simple and practical framework that allows the young person to take an active role in developing their understanding of psychosis.[108] It can be described this way:

- Each person possesses underlying vulnerabilities (e.g. genetic factors) that may pre-dispose them to an episode of psychosis.
- If enough stress is experienced (e.g. loss of a loved one, school stress, relationship breakup), the accumulation of stressors and vulnerabilities can result in the person becoming unwell.
- The more vulnerable a person is, the less stress is required to reach the threshold for an episode of psychosis.

FIGURE 2. **THE STRESS–VULNERABILITY MODEL OF PSYCHOSIS**



The role of medication within this framework is twofold.

Firstly, medication can help reduce symptoms. This will reduce stress and improve functioning and help the young person move into the recovery phase.

Secondly, medication acts as a protective factor after symptoms have subsided. Along with targeted biopsychosocial strategies that encourage coping, resilience building, healthy lifestyle choices and stress management, medication contributes to maintaining wellness in spite of ongoing stress and vulnerabilities.

The critical period hypothesis

The critical period hypothesis proposes that symptomatic and psychosocial deterioration occurs rapidly in the early years of psychosis and then plateaus.[119] The period of rapid deterioration is as a ‘critical’ period during which the disorder is more

responsive to intervention.[120] Therefore, targeted intervention, especially within the first 2–3 and even up to 5 years following a first episode of psychosis is considered crucial in the prevention of long-term symptomatic and psychosocial disability.[120,121]

This model can help explain the rationale for psychotropic intervention by:

- explaining the need for medication to reduce symptoms and duration of untreated psychosis early on, to prevent deterioration and resulting long-term disability, and to improve outcomes
- helping young people understand that even after their symptoms have gone away, medication, especially within this critical period, can still act as a 'safety net' to prevent relapse.

Psychoeducation doesn't always need to include detailed medical explanations; rather, clinicians should provide information in clear, easy-to-understand terms and check with the young person and family as they go to clarify information or address any questions. It is not a one-way process and relies on the sharing and discussing of information.

Psychoeducation should be flexible and guided by a comprehensive assessment and formulation. It should consider the young person's needs, developmental age, phase of disorder, personal experiences and explanatory models.

The role of the pharmacist

The importance of the pharmacist role in the medical management of young people can often be overlooked. Yet it is essential that case managers and other clinicians maintain regular contact with the pharmacist, whether hospital- or community-based. Clinicians and the medical team should ensure the pharmacist is aware of their role in the young person's medical management so that if concerns arise, the pharmacist knows who to contact and how.

The role of pharmacists can include:

- taking part in a medication management plan
  - this may include providing advice on medication dispensing (e.g. webster packs, dosette boxes)
- monitoring for adherence (e.g. that the young person is collecting their medication)
- supporting the team and young person in checking for any medication contraindications, ensuring the medication supply is accurate and cross-checking for any prescribing discrepancies.

Regular communication with the pharmacist, including ensuring treatment sheets are updated and congruent with scripts, will ensure consistent messages around medication are maintained.

SUMMARY **ROLES AND RESPONSIBILITIES OF NON-MEDICAL CLINICIANS IN MEDICAL MANAGEMENT**

- It is the treating team's responsibility to ensure clear and consistent communication with other service providers involved in the young person's care.
- The case manager plays a central role in advocacy for the young person and family.
- Clinicians should work closely with the medical team, especially if issues regarding medical treatment, adherence, or physical health arise.
- Medical treatments should be discussed regularly within the team, at clinical review meetings and with professionals outside the multidisciplinary team.
- Psychoeducation should involve providing young people and their families with information about psychosis, treatment and side-effects, prognosis, coping strategies, rights, explanatory models and explore the impact of psychosis on the young person and family.
- Psychoeducation should be tailored to the young person and their family, drawing on multiple resources and methods of delivery.
- The stress–vulnerability model and the critical period hypothesis can be used to assist the explanation of psychosis and the role of medication in treatment.
- Pharmacists are important contributors to ensuring safe medical management.
- Regular communication with the pharmacist can assist in medication management and help to monitor adherence.

Practical issues and challenges in medical treatments for early psychosis

Managing risk of overdose

Medication overdose is a risk factor within all areas of heath care where medication is prescribed. It is important to be aware of the risks from overdose in the FEP population, in regards to both prescribed and illicit drugs. Clinicians need to be aware not only of why a young person might overdose, but also strategies to prevent and, should overdose occur, appropriately manage and report it.

FEP populations are, more often than not, new to psychotropic medication. Add to this the stigma attached to experiencing a mental health issue that requires medication, the disruptive impact of early psychosis and the fact experimentation and use of illicit substances is characteristic of adolescence, and it is understandable that overdose presents a significant risk.

Where an overdose is unintentional, this may be for a number of reasons, such as the young person:

- taking an incorrect dosage (e.g. of prescribed medications)
- attempting to self-medicate to manage distressing symptoms (this could include illicit substances or prescription drugs)
- using illicit substances after a 'break', resulting in a lower tolerance level.

Other likely reasons for overdose are attempts by young people to suicide or self-harm. People experiencing early psychosis are at an increased risk of suicide, especially within the first few years following onset, and the most likely means is self-poisoning.[122] Likewise, the rate of self-harm in the FEP population has been found to be high, and overdose using antipsychotic medication found to be a relatively frequent method.[123]

Strategies to prevent overdose

Because of the serious risk posed by overdose to young people with FEP, it is extremely important to explore any risks (including triggers) relating to overdose during a young person's initial assessment. This should ensure appropriate preventative strategies to mitigate risk are prioritised and implemented. Some strategies that may help prevent overdose are presented here. Case managers and clinicians can take a major role in incorporating strategies within the young person's ongoing treatment.

Psychoeducation

As discussed earlier in the psychoeducation section, young people and their families/ significant others should be provided with clear and thorough information about medical treatments. Information about the role of any prescribed medication in treatment, its dosage and side-effects can help to avoid any method-of-use errors. Information regarding other drugs should also be provided as part of the ongoing psychoeducation process.

Risk management plans

A young person's risk management plan should cover a range of strategies and risks, including overdose, if indicated. Plans should identify possible triggers for overdose and provide strategies to address these (e.g. who the young person can call for help, stress management and coping skill strategies, environmental strategies [see below]). They should also include strategies to help the young person cope with ongoing symptomatology. It is essential that the most up-to-date contact details for the young person's supports is kept on file in case they need to be notified of an overdose.

Young people will present with varying risk profiles, so it is therefore important to understand the risk of overdose as it relates to each young person. Because young people are more likely to contact friends or family than clinicians when they seek help – especially prior to a suicide attempt[122] – incorporating these significant others in the risk management plan and its development is particularly important.

Environmental strategies

Environmental, or external, strategies can also be used to reduce the risk of overdose. These can include limited prescriptions (e.g. prescribing weekly to ensure only a small amount of medication is available at any time) or liaising with the pharmacy to limit the amount of medication that can be picked up at any given time. Strategies such as these should be included in the risk management plan.

Responding to overdose

If a young person presents having taken an overdose of medications or other substances, it is essential to arrange an urgent medical review and conduct an immediate risk assessment, which should determine:

- what the young person taken
- how much the young person taken
- how long ago it was taken
- whether the substance was taken in conjunction with anything else (e.g. alcohol, other drugs)
- whether any adverse reactions have occurred since the suspected overdose happened (e.g. vomiting)
- why the substance was taken and brief mental state assessment.

If there is difficulty obtaining the above information, and it is practicable and not putting the young person at further risk, it might be useful to gain collateral information from other people who were present at the time of overdose or who are with the young person at presentation.

If the young person's treating doctor is not available, a review by a duty doctor should be organised urgently. While this is being organised, someone must stay with and monitor the young person at all times – it may therefore be necessary to recruit the assistance of the rest of the multidisciplinary team.

Sending the young person straight to a hospital emergency department may be warranted. In this case it is useful to contact the emergency department to advise of the referral to allow crisis staff to anticipate and prepare for provision of the

young person's care. Hospital staff should be provided with any clinical information regarding the young person's medical history, side-effects and risk. If it is a clear emergency, call 000 and arrange an ambulance.

Sometimes an overdose may be reported to clinicians over the telephone, either by the young person or via a family member or other support. In this case an immediate risk assessment should be carried out over the phone with the young person, and action taken based on this assessment (e.g. phoning an ambulance, taking young person to hospital emergency department or arranging an urgent medical assessment either at home or at the service). While waiting for assistance, clinicians should stay on the phone with the young person if possible, monitoring their condition and guiding ambulance to them if necessary. It is also important to provide support and reassurance, as people can be highly distressed after an overdose and may have trouble following directions.

Documenting overdose

A young person's overdosing is considered a critical incident. It is essential that the incident is documented clearly and thoroughly in file notes as soon as possible. This documentation should include a risk assessment, mental state assessment, doctor's medical review, actions taken and any follow-up plans. Reports should be made according to each early psychosis service's reporting procedures (e.g. using 'Riskman' software). Clinicians therefore need to be aware of their service's policies and procedures around critical incidents.

Finally, a 'critical incident review committee' should review the incident. Committees can be locally established but it is important to ensure there is an appropriate governance structure that dictates who should be on the committee and to whom they report the outcomes to. The size and structure of the committee will depend on individual services. The purpose of such a committee is to objectively explore the incident whilst adopting 'no blame' attitude. This allows for an opportunity to review and learn from past experiences with the aim of improving future practice.

Physical health and monitoring

The majority of young people experiencing first episode psychosis will be prescribed an antipsychotic medication. The significant physical health side-effects that accompany antipsychotic medication, particularly SGA medication, can occur within weeks of beginning treatment, and they need to be acknowledged, understood and taken seriously.

As SGAs are seen as a first line treatment option for FEP, it is essential those involved with prescribing, managing and supporting the treatment of young people take responsibility in screening, monitoring and managing physical health side-effects of these prescribed medications. Young people themselves also need to be actively involved in this. A major goal of early intervention is to minimise the impact of early psychosis and prevent ongoing disability. Addressing and endeavouring to improve – not worsen – the physical heath of a young person should form a major part of this goal.

> ‘A lot of the time it’s like they’re focusing so much on your mind that they’re not really giving the attention to your physical wellbeing. So I really think that they need to include that aspect of your health more, because, you know, they put you on a medication and then six months later you’ve put on twenty kilos.’
>
> – Young person
> EPPIC, Orygen Youth Health Clinical Program

Evidence and rationale for the need to monitor and manage physical health issues

The physical health of people experiencing early psychosis is considerably worse than the general population, resulting in a reduction of life expectancy by 13–16 years.[124,125] This excess mortality is a result of physical health factors, such as cardiovascular disease, rather than suicide. Young people experiencing FEP are thought to be even more susceptible to weight gain and metabolic dysfunction.[1] Up to 60% of people experiencing early psychosis meet criteria for the metabolic syndrome,[126] a term used to describe a cluster of symptoms that can lead to serious life-shortening and threatening cardiovascular issues (see Box 3).

This poor physical health profile results from a mixture of both modifiable and non-modifiable risk factors. They include side-effects from antipsychotic medications and lifestyle-related factors such as sedentary behaviour and poor dietary habits.[127-129]

Weight gain is known to affect 80% of individuals treated with antipsychotic medication, with the rate of weight gain 3–4-fold greater in young people with limited previous antipsychotic exposure.[130] All antipsychotic medications and mood stabilisers may lead to weight gain, with second-generation antipsychotic medication frequently associated with clinically significant weight gain.[127,131-133] Some, especially olanzapine and clozapine, are known to have a greater propensity for significant weight gain.[134,135] (see Table 4).

The initial 12-months post initiation of antipsychotic medication has been identified as the critical period in which weight gain and metabolic changes occur.[130,136] Indeed, significant and rapid weight gain occurs within the initial 12-week period following the commencement of antipsychotic medication,[137,138] highlighting the need for early and preventative interventions that incorporate evidence-based lifestyle and pharmacological strategies.[139,140]

As a minimum, physical health screening should incorporate:

- waist circumference
- weight
- BMI (height required)
- blood pressure
- level of physical activity
- smoking (cigarettes per day)
- fasting pathology (lipid profile, glucose, liver function tests, vitamin D).

Routine monitoring of cardiometabolic health in all young people experiencing early psychosis is recommended in order to guide detection, prevention and intervention strategies and reduce future cardiovascular risk.[140] A number of metabolic algorithms exist, including those presented in Appendix 2 and Appendix 3.

BOX 3. **CRITERIA FOR THE METABOLIC SYNDROME**

As defined by the International Diabetes Federation, a person defined as having the metabolic syndrome must have:[141]

Central obesity (defined as waist circumference using ethnicity-specific values or BMI ≥ 30 kg/m^2)*

- Males ≥ 94 cm (South Asians ≥ 90 cm)
- Females ≥ 80 cm (South Asians ≥ 80 cm)

Plus any two of the following:

- Raised triglycerides
  - ≥ 1.7 mmol/L
  - or specific treatment for this lipid abnormality
- Reduced HDL cholesterol
  - < 1.03 mmol/L in males
  - < 1.29 mmol/L in females
  - or specific treatment for this lipid abnormality
- Raised blood pressure
  - Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg
  - or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose
  - ≥ 5.6 mmol/L
  - or previously diagnosed type 2 diabetes

*Age 16 years and over. Age 10–15 years ≥ 90th percentile cut-off if lower.

TABLE 4. **COMPARATIVE POTENTIAL OF ANTIPSYCHOTICS TO CAUSE WEIGHT GAIN**[134,135]

ANTIPSYCHOTIC	POTENTIAL FOR WEIGHT GAIN
Amisulpride	+
Aripiprazole	+
Clozapine	+++
Haloperidol	++
Olanzapine	+++
Paliperidone	++
Quetiapine	++
Risperidone	++
Ziprasidone	+

Don't just screen, intervene: strategies to target specific physical health issues

Interventions designed to prevent physical health issues arising in young people with FEP should be integrated as part of routine practice in an early psychosis service. The following interventions may involve the whole multidisciplinary team; while many treatments will be initiated by a doctor, it is necessary for case managers and other allied health clinicians to be proactively involved in medical and other interventions that can help to improve physical health.

Tobacco use

Young people with mental illness who smoke often want to and can quit. Interventions for smoking that can work for people experiencing early psychosis include:

- brief interventions
- motivational interviewing
- cognitive and behavioural strategies
- tools that show measurable improvement (e.g. FEV_1 tests, CO meters)
- consumer-led smoking plans that identify smoking triggers, withdrawal and ways of coping
- nicotine replacement therapy.

Success rates are often increased when psychological and behavioural therapies are combined with pharmacotherapies.

> 'I used to smoke a lot of cigarettes when I was being treated. I don't smoke any more, but I would have loved help to stop it at the time.'
>
> – Young person
> EPPIC, Orygen Youth Health Clinical Program

Blood pressure

Interventions including lifestyle components (structured exercise and dietetic therapy including salt reduction) can help with blood pressure. Often prescription of antihypertensives will be considered for patients where lifestyle interventions have been unsuccessful, preferably by a GP or specialist.

Blood lipids

Lifestyle interventions are the treatment of choice for lipid elevations in youth with psychosis with the aim of reducing obesity. For persistently elevated total blood lipid levels consideration is usually given to prescribing statins to reduce future cardiovascular risk.

Blood glucose

A fasting blood glucose sample above > 7 mmol/L is indicative of diabetes, and the young person needs to be referred to appropriate medical treatment (GP or diabetes clinic).

Physical activity

Insufficient physical activity is a key modifiable risk factor in the development of cardiometabolic abnormalities. Physical activity levels can be assessed via direct measurement utilising objective monitors such as pedometers and accelerometers, or more feasibly through simple self-report questionnaires. There is evidence supporting the use of the International Physical Activity Questionnaire – Short Form (IPAQ-SF) among people with schizophrenia.142 The IPAQ-SF consists of four questions, can be self-completed and takes less than five minutes to complete. The Australian Physical Activity guidelines encourage daily participation in physical activity and recommend adults accumulate 150 to 300 minutes of moderate intensity physical activity or 75 to 150 minutes of vigorous intensity physical activity, or an equivalent combination of both moderate and vigorous activities, each week. In addition, muscle-strengthening exercises are recommended at least two days per week.

All early psychosis clinicians have a role to play in promoting physical exercise to prevent or address metabolic problems. Basic education regarding healthy exercise levels and ways to achieve this are important. Interventions may include supporting access to local gyms or sport groups (e.g. local netball or football clubs). Education and exploration with the young person of other basic ways to improve exercise may be just as effective, for example, through ‘incidental’ exercise, such as using stairs rather than elevators, walking instead of driving, or taking up cycling as a means of transport. A useful fact sheet on physical health can be found at www.http://oyh.org.au/oyh-clients/fact-sheets.

Vitamin D

Vitamin D deficiency is seen in a high proportion of people with established psychotic disorders (see the ENSP manual *Medical management in early psychosis* for more information). Interventions to address vitamin D deficiency include:

- monitoring vitamin D levels twice yearly, including baseline
- promoting outdoor exercise (which may involve addressing underlying mental health problems)
- use of supplemented food sources (e.g. vitamin D-enhanced milk or margarine)
- use of pharmacological supplements.

Diet

People experiencing early psychosis consume more calories and saturated fat, and eat less fruit, vegetables and fibre when compared with the general population.[143] In addition, people with schizophrenia have diets lower in milk, potatoes and pulses and eat more take-away foods compared with the general population.[144] Diet can be assessed via 24-hour recall and comparison with the Australian Dietary Guidelines.[145] Another useful resource is the *Nutrition standards for consumers of inpatient mental health services in NSW hospitals*, which were developed to provide menus to inpatients that aim to achieve nutritional adequacy for key nutrients and prevent weight gain by moderating intake of foods of low nutritional value.[146]

Interventions to improve diet are important and may involve a variety of approaches. Education on types of healthy foods is essential, including providing young people with dietary guides to support this. An example of this is a 'traffic light' system that colour-codes foods so that people can easily recognise which foods are healthier than others. Where young people live at home, it is also important to include parents in education and support given they may be more likely to be the cooks of the house. Some young people living independently (or at home) may well not have developed healthy cooking skills and so there is a role for group work within the early psychosis service to develop these skills. The current Australian Dietary Guidelines and additional resources can be found at www.eatforhealth.gov.au.

> 'What would be awesome is if you do gain weight on your antipsychotics, your doctor steps in and explains to you healthy eating choices and other ways to really support you losing that weight again. I think they should be talking about these things before it gets too far, rather than when you've already gone from being a healthy BMI to medically overweight.'
>
> – Young person
> EPPIC, Orygen Youth Health Clinical Program

Sexual health

Sexually transmissible infections (STIs) are common amongst young people, with chlamydia the most prevalent STI affecting people aged 15–25 in Australia.[147] The majority of secondary students (69%) have experienced some form of sexual activity, with 59% of those young people reporting engaging in unsafe sexual behaviour.[148] Young people with emerging mental health issues or those experiencing a first episode psychosis have an added risk of adverse sexual health outcomes due to co-morbid vulnerabilities associated with mental health issues.[149]

Various factors contribute to the increased risk of engaging in sexual risk-taking behaviour for mental health young people, including impaired cognition negatively impacting on decision-making and judgment, the development of age-appropriate relationship skills and peer friendships, susceptibility to pressure to have sex, and pressure to not practise sex safely.[150] Unemployment can also significantly predict lack of condom use in young people,[149] while substance use is also a predictor for being sexually active and increased sexual risk-taking.[147]

The process of opportunistic screening involves ascertaining if a young person is sexually active and following a sexual health algorithm to determine which tests are required based on known risk factors. In NSW, some young people may be able to use the website www.stitest.org.au to screen for STIs. If testing cannot be completed at the early psychosis service, referral can be made to a youth-friendly sexual health clinic or GP.

Metabolic monitoring – who is responsible?

Clinical practice guidelines recommend regular monitoring of weight gain and metabolic indicators in those prescribed second-generation antipsychotics. Monitoring can help identify those who require early intervention for weight gain or metabolic disturbance in order to prevent long-term negative outcomes – but whose responsibility is this?

The short answer is that **everyone** is responsible for metabolic monitoring. This does not mean that each person involved in the care of a young person needs to take responsibility for every aspect, but that each person needs to be aware of their specific role in the monitoring process.

Non-medical clinicians should take an active role in psychoeducation around the physical side-effects of SGAs and the implementation of strategies to mitigate the harmful impact of these side-effects. With basic training, non-medical clinicians can also take a role in taking and recording measurements (e.g. weight, waist circumference) and feeding back these results to the medical team. However, it is the responsibility of medical staff to ensure these measurements are taken, reviewed and interpreted at the intervals recommended by appropriate clinical guidelines. Two recommended metabolic monitoring algorithms based on various Australian clinical guidelines are provided in the appendices of this manual. The responsibility of medical staff continues into developing collaborative management plans to manage and mitigate any ongoing metabolic side-effects, with input from the clinical team, young person and their family.

Though it is most beneficial to keep metabolic monitoring within the treating team, for reasons such as engagement and ensuring metabolic monitoring is completed, other, external, medical specialists may take a role in metabolic monitoring. Occasions where this might occur include when a young person is approaching discharge with care moving on to the GP or if a specialist opinion is warranted (e.g. through an endocrinologist).

Managing planned discontinuation of medicine

There is no clear evidence in FEP as to the period of time following remission that a young person should remain on medication.[1] Although between 80–90% of young people experience a remission of symptoms within the first year of treatment,[58,151] relapse rates in the FEP population are high, with almost 80% relapsing within 5 years.[152] For further discussion of the evidence about treatment duration and recovery, please see the chapter ‘Maintenance medication and discontinuation of treatment’ in the ENSP manual *Medical management in early psychosis*.

The idea of remaining on medication in the long-term can be challenging for young people and their families, especially if symptoms have remitted and the young person is maintaining a high level of functioning and quality of life. It is therefore likely that it will be the young person or their family who first brings up the possibility of discontinuation of medication.

Planning for discontinuation of medication should be a collaborative process with the young person and family (as appropriate; see Box 4). It may be useful to present them with a cost-benefit analysis of maintenance treatment versus discontinuation. This should include education around the possibility of relapse and its effects on function and behaviour and what the risks are of incomplete recovery and possible development of an ongoing disorder.

If a decision to discontinue medication is made, a plan should be put in place to manage the discontinuation process. Planned discontinuation should include the following:

- slow withdrawal of medication over a number of months[1]
- increased monitoring and contact during decrease and after discontinuation (including a period of observation if possible before discharge from the early psychosis service)
- close monitoring of mental state and risk factors during decrease and after discontinuation (it is best not to discontinue medication at times of expected increase in stress, such as discharge from service, beginning employment, etc.)
- monitoring of early warning signs (EWS) and development of an EWS management plan with the young person and family. Ensure all parties have a good idea about ‘what to look for’ and ‘what to do’ should symptoms re-emerge.

There will be times when a young person does begin to display EWS or relapses after discontinuing medication. At this point, it is important to arrange a medical review and examine the current symptom profile, including mental state, risk assessment and impact. Following this review, recommencement of medication may be indicated.

Not all discontinuations will be planned and there will be times when a young person either decreases or discontinues medication of their own accord. This highlights the importance of maintaining a strong therapeutic alliance and creating an environment where a young person feels comfortable to openly discuss when they might be thinking about discontinuing their medication. It also demonstrates the importance of regular contact with the young person and their family to keep across any problems or issues with adherence (see ‘Strategies to address non-adherence’, on page 32).

If a clinician becomes aware that a young person is decreasing or has ceased taking medication, they should establish how long the changes have been in place and explore the reasons behind the alteration. Assessment of mental state and risks is also warranted. These discussions should then guide the development of an informed and collaborative action plan for ongoing medical management.

BOX 4. **INVOLVING FAMILIES IN THE DISCONTINUATION PROCESS**

Families can play an important role in the discontinuation process. Where appropriate, families should be involved in discussion, planning and implementation of discontinuation. This can include:

- ensuring they are aware of the possibility of relapse not only as part of the natural course of the illness, but in the context of discontinuation
- focusing on their capacity to improve outcomes through understanding and identifying EWS and ensuring they have input and understanding into how to manage any emergence of EWS.

Nutritional supplements and potential interactions with pharmacotherapy

Supplement use appears to be relatively prevalent amongst young people, with studies finding anywhere between 10% and 74% of young people take some form of supplement.[154] Supplements might include vitamins, minerals, herbs, amino acids or energy drinks, some of which may interact with prescribed medications to either reduce efficacy or cause side-effects (see Box 5). As the majority of young people with FEP will be prescribed an antipsychotic, or other medication, during their episode of care, it is important that case managers and other clinicians are aware of any supplement use and potential interactions with pharmacotherapy.

Young people should be encouraged to discuss supplement use, and questions around this and what they have or are currently taking should be part of the initial assessment. It is also important to periodically review supplement use with a young person to monitor for any changes in use.

Should it become apparent a young person is using supplements, they need to be documented and the medical staff informed so they can check the interaction risks. Medical staff will be able to support the clinician in monitoring supplement use and providing education to the young person about any contraindications and possible side-effects (e.g. sleep deprivation and anxiety due to use of caffeine-laden energy drinks).[155]

BOX 5. **ADVERSE INTERACTIONS: ST JOHN'S WORT**

St John's wort has historically been used as a herbal, over-the-counter remedy for mild depression. Despite its apparent antidepressant effect, St John's wort should NOT be used by people taking antidepressant medication as it can increase side-effects, particularly those related to increased serotonin (e.g. confusion, agitation, tremor).[156]

Alcohol and other drugs

Substance misuse is common in people with FEP, with most studies showing anywhere between 60–70% report substance misuse at some stage prior to presentation. Cannabis and alcohol are the most widely used, with up to 70% of young people with FEP smoking tobacco.[1] Clinicians should therefore be prepared to accept substance misuse as the rule, rather than the exception, and the high prevalence in this population emphasises the importance of addressing and encouraging an open discussion around alcohol and other drug use.

Substance use and misuse should be screened for during assessment. Assessment should include substance use history, patterns of use, current use, risks, triggers, cravings and family history. Accurately identifying a young person's use of alcohol or other drugs as early as possible will enable interventions to improve outcome and may reduce the course of severity of both substance use and the FEP. [1] Some strategies to help with harm minimisation from alcohol and other drug use are outlined in Box 6.

Psychoeducation that focuses on alcohol and other drugs should be provided.This should include the fact that substance use is a predictor of poorer outcome and cover how alcohol and other drugs interact with medication and discussion of risks and harm minimisation. Examples might include

- explaining to young people that a drug they've been prescribed increases the effect of alcohol, so will take less alcohol than usual to become intoxicated (see Box 7)
- talking about safe methods of drug administration and using in a safe environment
- advising young people to avoid mixing substances if they can
- if a young person often goes out to take drugs, asking them to always let someone know where they are going and when they expect to be back.

For interactions between clozapine and tobacco, please see page 61.

BOX 6. **STRATEGIES TO REDUCE AND MINIMISE HARM FROM ALCOHOL AND OTHER DRUG USE**

Often, young people will continue to use alcohol and other drugs. In such situations, clinicians can take an active role in working with the young person and their family to discuss, develop and implement both substance use reduction and harm minimisation strategies. This might include:[1]

- setting realistic, well defined behavioural goals and a way to regularly monitor and review these goals
- utilising others – family, key supports – to assist in the plan to reduce substance use
- helping to maintain motivation by encouraging the young person to keep a list of reasons they want to change their substance use
- working around challenging cognitions associated with substance use (e.g. discussing positive drug expectancies)
- providing handouts tailored to the individual
- identifying triggers and high risk situations for substance use
- practising refusal skills
- education around cravings and withdrawal as well as practicing coping skills dealing with these.

BOX 7. **ADVERSE INTERACTIONS: ALCOHOL**

A specific example of the interaction between alcohol and medication is its amplifying effect on benzodiazepines. Benzodiazepines function by enhancing the effect of the neurotransmitter GABA at its receptor, resulting in sedation and a calming effect. Alcohol does the same thing – it increases the effects of GABA and acts as a CNS depressant. Combining alcohol and benzodiazepines amplifies the effects of each. This can result in slowing of the heart rate and respiratory system.[157]

Treatment-resistant psychosis and clozapine

In the FEP population, there is a high response rate to most antipsychotic medications, regardless of which one is used.[158] However, there is a subset of people with FEP who do not respond to first- or second-line antipsychotic treatment. Clozapine should be considered when remission does not occur despite the sequential use of two antipsychotic medications for a period of 6–8 weeks.[32,35] Clozapine may also be recommended in patients with a sustained or prominent suicide risk, either without depression, or when treatment for depression is ineffective.[35]

Clozapine is effective in treatment-resistant psychosis, producing improvements in positive and negative symptoms and having a low risk of EPSEs.[159] Despite these benefits, the use of clozapine is restricted to people who are either unresponsive or intolerant of other antipsychotic agents[160] because it may cause the potentially serious and life-threatening side-effect of agranulocytosis[161] (see Box 8).

The medical team will lead all aspects of clozapine management. Even so, non-medical clinicians need to possess sound knowledge of clozapine side-effects and the monitoring requirements for people who are taking clozapine. They particularly need to be alert to the signs that a young person may be developing agranulocytosis.

BOX 8. **CLOZAPINE SEVERE SIDE-EFFECTS**

Agranulocytosis is a severe drop in white blood cells. As white blood cells are essential components of the immune system, low levels can result in severe infections. If agranulocytosis is not identified early, it can be life-threatening. The majority of cases occur within the first 6 months of treatment, with the highest risk in the first 3 months. Between 0.5% and 2% of people prescribed clozapine may develop agranulocytosis.[161]

Agranulocytosis can be asymptomatic, but sudden fever, flu-like symptoms, mouth ulcers or sore throat may be early indicators of the condition, and should these arise, the medical team should be notified as soon as possible.[160]

Myocarditis is an inflammation of the heart muscle. The majority of cases occur early in treatment, with more than 85% of cases occurring in the first 2 months and 75% in the first 3 weeks. Prevalence has been reported between 0.015–0.188%, with an Australian study reporting 1.2% among those on clozapine. Presenting symptoms can include fever, tachycardia and chest pain.[162]

Monitoring requirements for clozapine

Due to these life threatening side-effects, people commenced on clozapine must undergo ongoing monitoring for blood-related, metabolic and cardiac side-effects. Monitoring requirements differ depending on the phase of treatment.

Blood tests should be carried out within the 10 days prior to starting clozapine, with repeat monitoring weekly after commencement for the first 18 weeks, then every 28 days thereafter. More frequent monitoring is required if moderate decreases in the white blood cell and/or neutrophil count are detected. Discontinuation is required when very low white blood cell and/or neutrophil counts are evident.[160]

Monitoring for cardiac and metabolic effects should be conducted, as described in Box 9.[160]

BOX 9. **SUGGESTED MONITORING OF PATIENTS PRIOR TO AND DURING THERAPY WITH CLOZAPINE**

Baseline

- Clinical history and examination
- Weight, blood pressure, heart rate
- ECG
- Transthoracic echocardiogram
- Troponin and CK-MB level
- Lipid profile and blood glucose level
- WBC count and differential (repeat in 1 week if in amber range)
- Liver function tests

0–18 weeks

- WBC count and differential (weekly if in green range or twice weekly if in amber range)
- Clinical evaluation, ECG, plasma troponin and CK-MB levels days 7 and 14

>18 weeks

- WBC count and differential (every 28 days if in green range or twice weekly if in amber range)

6 and 12 months

- Lipid profile
- Blood glucose level
- Liver function tests
- Transthoracic echocardiogram

Ongoing

- WBC count and differential (monthly)
- Blood glucose level (biannually)
- Transthoracic echocardiogram (annually)
- Lipid profile (annually)
- Weight, blood pressure, heart rate, troponin and liver function test (as required)

Continued over page.

BOX 9. **SUGGESTED MONITORING OF PATIENTS PRIOR TO AND DURING THERAPY WITH CLOZAPINE** CONTINUED

Additional

- Chest x-ray (if cardiac dysfunction suspected)
- Inflammatory markers (if myocarditis suspected)
- Selenium level (if cardiomyopathy suspected)

'Green range' = WBC count > 3.5x109/L and neutrophil count > 2.0x109/L

'Amber range' = WBC count between 3.0 and 3.5x10^9/L and/or neutrophil count between 1.5 and 2.0x10^9/L

'Red range' = WBC count <3.0 × 10^9/L and neutrophil count <1.5 × 10^9/L.
CK, creatine kinase; ECG, electrocardiogram; WBC, white blood cell.

Adapted from Berk et al. 2007.[160]

Clozapine use with other medications

Despite its efficacy in many treatment-refractory patients, over 50% of people may not respond adequately to clozapine.[66,67] The appropriate duration of a clozapine trial has not been fully clarified, with recommendations ranging from 3-6 months to as long as a year to identify later responders.[66,67]

When an adequate trial with clozapine fails, augmentation with a second antipsychotic medication is common clinical practice and it is possible that a small subgroup of clozapine-resistant people will respond to augmentation.

Again, the medical team will take the lead role in medical management, but case managers should be aware of the treatment possibilities for those taking clozapine, as it will assist in shared decision-making and psychoeducation processes.

Augmentation with SSRIs is often employed when negative or depressive symptoms are present, or with anxiety or obsessive-compulsive symptoms.[67] Mood stabilisers may be used to prevent seizures in high-dose clozapine treatment regimens, or for patients with mood instability.[66,67] Electroconvulsive therapy (ECT) has been investigated as an augmentation strategy for clozapine. The available literature has reporting and methodological concerns, which makes it difficult to draw conclusions.[66,67] However, limited clinical studies in clozapine-resistant schizophrenia suggest that ECT may be an option for clozapine-resistant schizophrenia (see page 63).[70-72]

Other interactions to be aware of

Consuming caffeine, which can be found in coffee, tea, coca cola and energy drinks, can cause the amount of clozapine in the blood to increase, as the active ingredient in caffeine inhibits the metabolism of clozapine.[163] Being aware of a young person's normal caffeine consumption and how caffeine can affect levels is important.

Tobacco speeds up the metabolism of clozapine, which results in regular smokers requiring higher doses to reach therapeutic levels.[164] Conversely, if a young person decreases or stops smoking tobacco, their clozapine levels may rise rapidly as a consequence. It is therefore important to be aware of a young person's usual smoking habits and advise them to notify the treating team should they decide to change them.

Delivering psychoeducation: how do we talk about starting clozapine?

Psychoeducation has been covered previously in this manual. Though the same principles and strategies should apply when discussing the option of clozapine with a young person, its side-effect profile, relatively intrusive and rigorous monitoring regimen and level of efficacy in comparison to other antipsychotics require particular attention and sensitivity.

Making sure that young people and families have heard about clozapine through psychoeducation delivered up to this point will ensure they are not shocked or surprised about the medication should it become a treatment option. More frequent medical reviews may need to be scheduled when considering clozapine, allowing for the young person and family to bring up questions or concerns as they arise.

Prior to entering into any reviews or discussion, it is useful for clinicians to reflect upon their own values and views about clozapine, as they may affect how they present information such as the pros and cons of clozapine treatment. When discussing or initiating clozapine, medical staff should take the lead role; however, the other clinicians should be aware of, and keep updated on, the current literature around clozapine and its role in early psychosis, as they will be involved in education, guidance and support regarding side-effects and monitoring.

The decision to commence clozapine can be a difficult one. When appropriate, allow the young person adequate time to digest the information and come to a decision. Information can be presented in a number of ways. Videos, pamphlets and brochures are widely available. These should be used as an adjunct to collaborative discussion and shared decision-making.

Psychoeducation regarding clozapine should include:

- a rationale for clozapine as a treatment option
- side-effects: clozapine is associated with very serious, life threatening side-effects, which can be immediately disconcerting. It is important to thoroughly address and not minimise these side-effects, but to also present the known benefits of clozapine through a balanced cost–benefits discussion
- monitoring requirements (see Box 9) when commencing and ceasing clozapine
  - provide information about the monitoring requirements for commencing clozapine, the importance of taking it at a regular time each day, and the dangers and possible consequences of ceasing clozapine suddenly
- clozapine and interactions with other substances.

ECT in treatment-resistant psychosis

It is possible that a small number of young people with FEP will benefit from ECT, for example in the case of psychosis that is resistant to treatment such as clozapine.[165] However, it should be viewed as a treatment of last resort for resolving a psychotic episode, not least because of the significant stigma attached to this treatment.

ECT is the practice of inducing seizure activity with an external electric current while the patient is under general anaesthesia. It is commonly used to treat major depressive disorder with or without psychosis, severe suicidality, catatonia, or in pregnancy where a rapid response is required. ECT may be recommended in patients who do not respond adequately to pharmacological treatment.[166]

The procedure is performed under general anaesthesia with short-acting induction agents. Neuromuscular blocking agents are also given to prevent injury during the seizure. Electrodes are placed either on one or both sides of the scalp and a pulse current is applied to induce a brief seizure of 30–60 second duration. Typically, ECT is delivered three times a week for 6–12 treatments, although more treatments are required in some patients.[166]

The exact mechanism of action of ECT is not fully understood; however, it does not alter the brain structure itself. It is thought to affect neurotransmitters and their receptors. ECT also alters hormone and neuropeptide concentrations, and possibly even enhances connectivity of the synapses in the regions of the brain associated with mood regulation.[167]

SIDE-EFFECTS OF ECT

Post-ECT, patients may experience headache, drowsiness or transient muscle pains. Short term memory impairment and confusion are relatively common after ECT, but normally resolve within 24 hours.[167]

ECT use in young people

ECT has been shown to be safe and effective in young people with FEP. Zhang et al. (2012)[168] found that young people treated with ECT in combination with antipsychotic medication had a significantly reduced hospital stay and a higher cumulative response rate over a 7-week period compared with antipsychotic medication alone.

More research is needed to clarify whether ECT conveys a long-term decrease in psychosis severity.[165] Importantly, there were no significant differences in clinical or neuropsychological variables at a 2-year follow up assessing long-term cognitive effects in adolescents with schizophrenia or schizoaffective disorder undergoing ECT compared with no ECT.[169]

SUMMARY **PRACTICAL ISSUES AND CHALLENGES IN MEDICAL TREATMENTS FOR EARLY PSYCHOSIS**

Managing medication risk

- Risks associated with medication include allergic reaction, severe adverse effects and intentional or unintentional overdose – each of these risks needs to be carefully managed.
- Risk management plans are a useful tool to address risk of overdose and should include a plan for what to do in the event of overdose.
- Serious adverse events such as overdose should be documented in the clinical file and reviewed by the multidisciplinary team or risk review committee.

Physical health monitoring:

- Physical health of people experiencing psychosis is considerably worse than the general population, resulting in reduced life expectancy.
- It is essential that all members of the multidisciplinary team are involved in physical health and metabolic monitoring of young people involved in the early psychosis service.
- Significant physical health changes are likely to occur in the first 12 months of treatment, with rapid weight gain most likely to occur in the first 12 weeks of antipsychotic treatment.
- Reducing tobacco use, increasing physical activity and exercise, improving diet and sexual health are interventions that should be initiated, provided or supported by the young person's treating team.
- Referral to external specialists or ongoing follow-up through the young person's GP may also need to be considered.

Managing discontinuation

- Planning discontinuation should be a collaborative process involving the young person, their family and the multidisciplinary team.
- Psychoeducation and a 'cost-benefit' analysis may assist the young person to make a decision about whether to remain on treatment long-term.
- Slow withdrawal, increased monitoring and an early warning signs management plan should be included as part of the planned discontinuation process.
- Not all discontinuation will be planned – unplanned discontinuation (non-adherence) should be discussed with the young person, and assessment of mental state and risk is also warranted.

Continued over page.

SUMMARY **PRACTICAL ISSUES AND CHALLENGES IN MEDICAL TREATMENTS FOR EARLY PSYCHOSIS** CONTINUED

Nutritional supplements and alcohol and other drugs

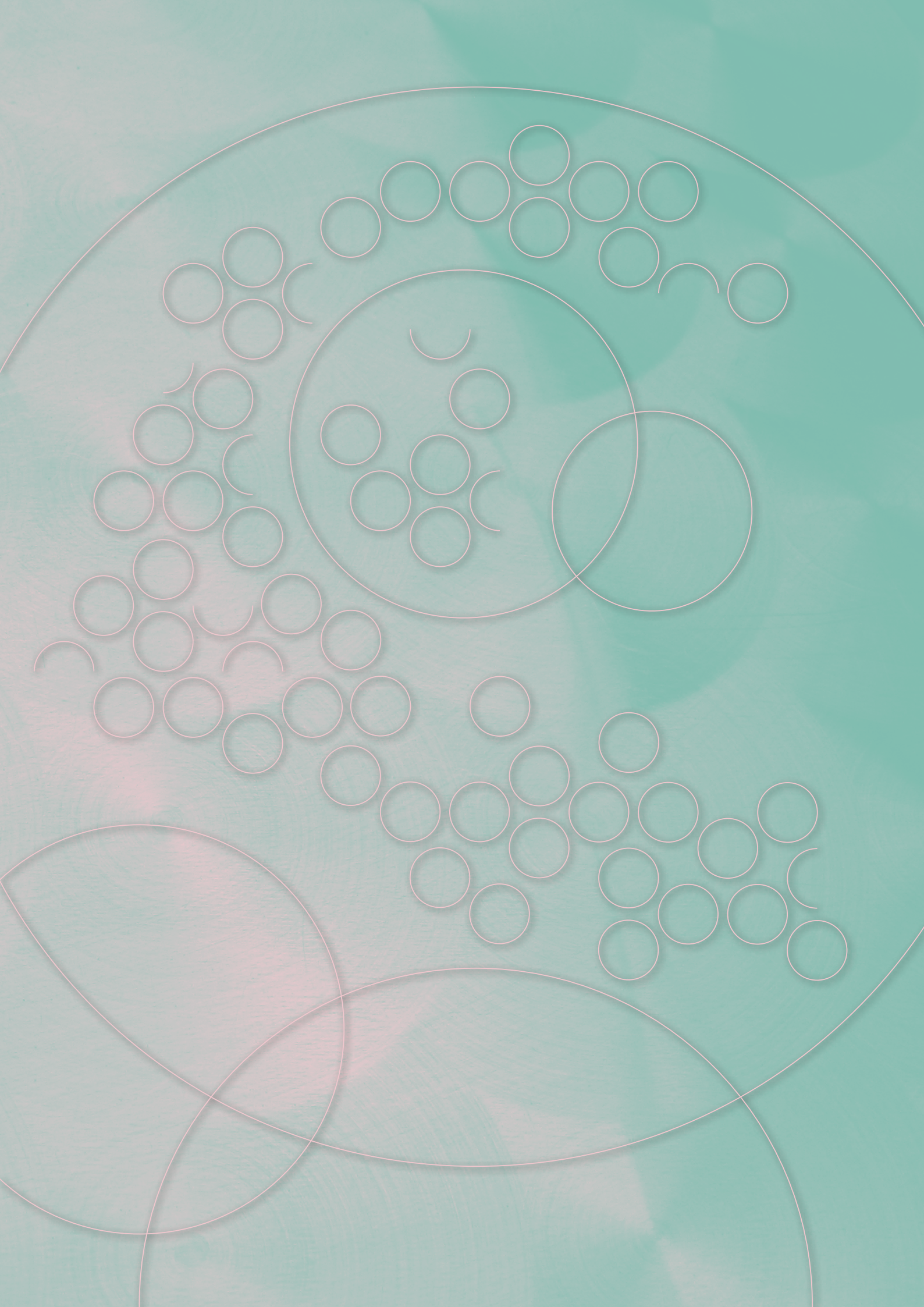
- Use of nutritional supplements (including vitamins and natural remedies) is relatively prevalent amongst young people, and many have the potential to interact with the medications that are prescribed by the treating team.
- Alcohol and other drugs also have the potential to interact with medications and affect mental state.
- Use of supplements, alcohol and other drugs should be routinely discussed and young people should be encouraged to talk about this with their treating team at any time.

Clozapine

- Clozapine may be considered if there has been an insufficient response or intolerance to two other antipsychotic medications.
- Clozapine may also be recommended in young people where there is sustained or prominent suicide risk.
- Clozapine can cause serious and life-threatening side-effects, and due to these effects ongoing monitoring of blood related, metabolic and cardiac side-effects is required.
- Case managers have an important role in discussing clozapine with young people and their families, as well as supporting monitoring in the short and longer term.
- In some cases, other medications may be used as an augmentation strategy for clozapine.
- Other substances, such as caffeine and tobacco can affect the amount of clozapine in the blood to increase or decrease.
- Psychoeducation is especially important for clozapine due to the risks as well as required monitoring, however the same principles of psychoeducation apply.

ECT

- A small number of young people with FEP may benefit from ECT.
- ECT has been shown to be safe and effective in young people with FEP.
- It has not, however, been shown to provide a long-term decrease in psychosis severity.



PART 3

Introduction to pharmacological principles

Overview

This section aims to give a brief overview of pharmacology as it applies to the drugs used to treat FEP in young people. Most young people with FEP will be prescribed an antipsychotic, and in some cases additional drugs, to treat their symptoms and prevent future episodes. A basic knowledge of pharmacology is important for clinicians working with young people with FEP to understand the how these drugs work, how they are processed in the body, why certain adverse effects occur, and the different treatment options available.

Receptors and neurotransmission

Psychotropic drugs, such as those used in FEP, target receptors for neurotransmitters, which are molecules that are involved in transmitting signals in the brain (and wider nervous system).[170,171] The effects of these drugs depend on the target and its location in the brain, as well as the properties of the drug itself.

Neurons are the signalling cells of the nervous system, and can both send and receive information. They have different functions depending on their location in the body, their size and shape.[171]

A neuron (see Figure 3) typically is composed of a cell body (soma) containing the nucleus, connected to thin, branched structures (dendrites) at one end and to a single long, slender projection (axon) with branched ends (axon terminals) at the other.[171] Neurons are connected by synapses, which form between the axon of the neuron ahead of the synapse (presynaptic neuron) and the dendrites, soma or axon of the neuron on the other side of the synapse (postsynaptic neuron).[171] The synapse is not a physical connection between the two cells, but contains a space, known as the synaptic cleft, across which chemical or electrical signals cross from one neuron to another.

FIGURE 3. **STRUCTURE OF A NEURON**

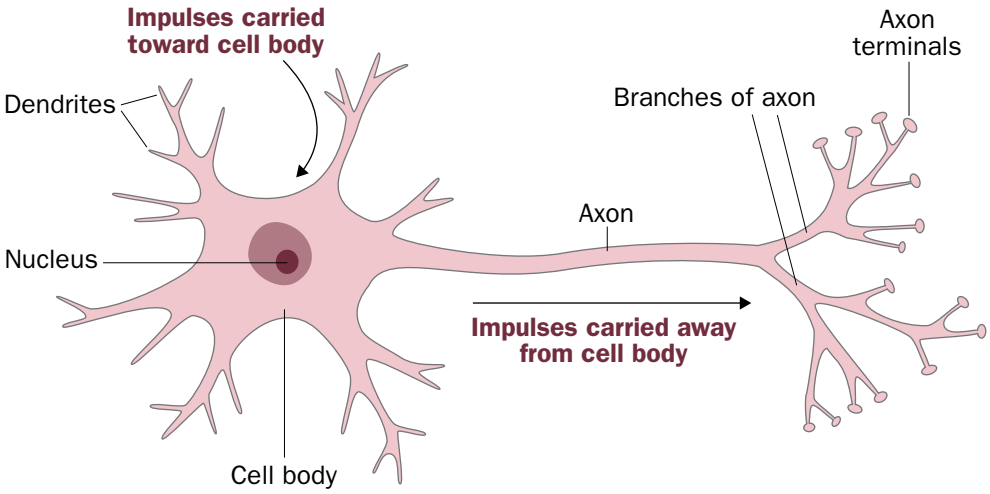
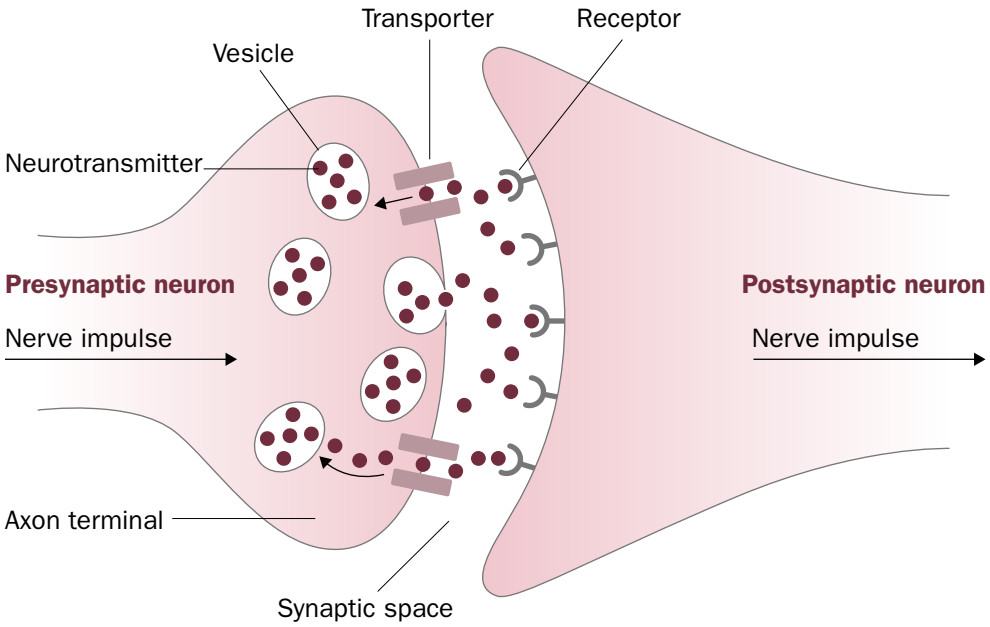


FIGURE 4. **RELEASE OF NEUROTRANSMITTERS IN RESPONSE TO A NERVE IMPULSE.**



Neurotransmitters are stored in presynaptic vesicles (left). The nerve impulse causes neurotransmitters to be released from the vesicles into the synaptic cleft; after diffusing across the synaptic cleft they bind to receptors on the postsynaptic neuron (right)

Stimulation of the presynaptic neuron by hormones, drugs, light or nerve impulses causes electrical impulses to be sent to its axon terminal,[171] which in turn cause the release of neurotransmitters into the synaptic cleft (see Figure 4). The neurotransmitters then diffuse across the synaptic cleft and bind to specific receptors in the membrane of the postsynaptic neuron and either stimulate or inhibit an electrical impulse in the postsynaptic neuron, depending on their function.

Binding of neurotransmitters to receptors is very brief. After binding, neurotransmitters are removed from the synaptic cleft, either through degradation by enzymes or by being taken back into the presynaptic neuron by a neurotransmitter transporter – a process known as 'reuptake'.[171] This prevents the accumulation of neurotransmitters in the synapse. By suppressing the activity of these neurotransmitter transporters it is possible to increase the activity of neurotransmitters in the synapse. Many psychotropic drugs, such as selective serotonin reuptake inhibitors (SSRIs), block monoamine transporters (transporters for neurotransmitters such as norepinephrine/noradrenaline, dopamine and serotonin) and thereby increase activity of these monoamines in the synapse.[170,171]

Abnormal neurotransmitter function is known to be involved in the development of psychoses; however, the precise roles of different neurotransmitters have yet to be established. The most studied are the monoamines dopamine and serotonin (5-HT), and the amino acid glutamate.

Pharmacodynamics: the effect of the drug on the body

The term 'pharmacodynamics' refers to the biological effects a drug has in the body. Broadly speaking, a drug is a substance that acts on a target that is implicated in a particular disease; for example, a receptor, an enzyme or a transporter molecule in a specific anatomical location. The aim of treatment with the drug is to restore normal function by either increasing or decreasing the activity of the target to counteract the underlying process that causes the disease. The way in which a drug produces this desired effect is referred to as its mechanism of action. In addition to its intended mechanism of action, a drug may have unintended activity, which can produce side-effects (see later).

The biological effects of a drug can vary between individuals and also in the same person at different times.[172] Some people will have a good response to a drug at a low dose but others may have little or no response, even at higher doses, and may need to switch to a different drug.

An important pharmacodynamic concept is the therapeutic ratio. Put simply, the therapeutic ratio compares the minimum amount of drug needed to produce a therapeutic effect to the amount that causes toxicity.[173] A larger ratio is preferable because it indicates that a drug is effective at doses well below those likely to cause unacceptable side-effects, and there is therefore a greater range of doses that can be used safely. Drugs with small therapeutic ratios, such as lithium, have a narrow range of doses that can be given safely and require careful monitoring of blood drug levels to avoid toxicity.

When prescribing a new medication, the aim is to use the lowest effective dose for that person. Treatment should be started at a low dose and the response assessed after an appropriate amount of time, and the dose increased only if the response is insufficient. However, for some medications, a 'loading dose' may be given for the first dose to produce a rapid initial response that is then maintained with a lower regular dose.

Pharmacokinetics: the effect of the body on the drug

Pharmacokinetic measures describe what happens to a drug in the body. This influences its biological effects, including the duration of its activity.[174-176]

Absorption is the process by which drugs are transported across the membranes of the body before they enter systemic circulation. Drugs used to treat FEP are usually given orally or by intramuscular (IM) injection.

Drugs that are given by IM injection diffuse between connective tissue or muscle fibres before they enter the blood. This can occur rapidly with short-acting formulations, or over a prolonged period with those used in long-acting injectable (LAI) antipsychotics (depot injections).

Oral drugs are absorbed primarily from the small intestine, and must pass through the stomach first. From the small intestine they enter the liver via the portal circulation, in the same way as nutrients absorbed from food would, and are then distributed to other parts of the body. Some of the drug will be broken down and inactivated by enzymes in the liver; the amount of activity lost to this 'first-pass metabolism' varies between drugs.

Absorption is affected by many factors, including the solubility and formulation of a drug, and the size and shape of the molecule (see Box 10). For oral drugs, the rates at which the stomach empties and the intestinal walls contract will also affect the absorption rate.

BOX 10. **SLOW-RELEASE ORAL MEDICATIONS**

Absorption should be taken into account in the case of slow-release oral medication. These are medications where the active ingredient is encased in such a way to allow for slow and steady release and absorption into the bloodstream. If slow-release tablets are split in half, the casing is disrupted and the tablet loses its slow-release effect, instead having an immediate release effect. It is therefore not recommended that slow-release tablets are split in half as this may lead to over or under dosing.

Distribution is the transfer of the drug from one part of the body to another after absorption. Effective distribution is critical because the drug needs to reach its target site as free drug (not bound to proteins) to have a pharmacological effect. The **volume of distribution** is the theoretical volume of blood that would be necessary to contain the total amount of drug present in the body at the same concentration as the current concentration in the blood. The volume of distribution can be larger than the actual total blood volume in the body. A large volume of distribution indicates that the drug has been distributed to the tissues, whereas a small volume of distribution means the drug has not been as extensively distributed and most of it has remained in the blood.

The volume of distribution is useful for estimating the dose required to achieve a particular concentration of the drug in the blood. A large volume of distribution means that plasma drug concentration of the drug for a particular dose will be lower than for a drug with a smaller volume of distribution. The volume of distribution varies between individuals, and is affected by characteristics such as height, weight, percentage body fat, pregnancy and kidney function. It may be necessary to adjust the dose for differences in the volume of distribution if it is important to achieve a particular drug concentration.

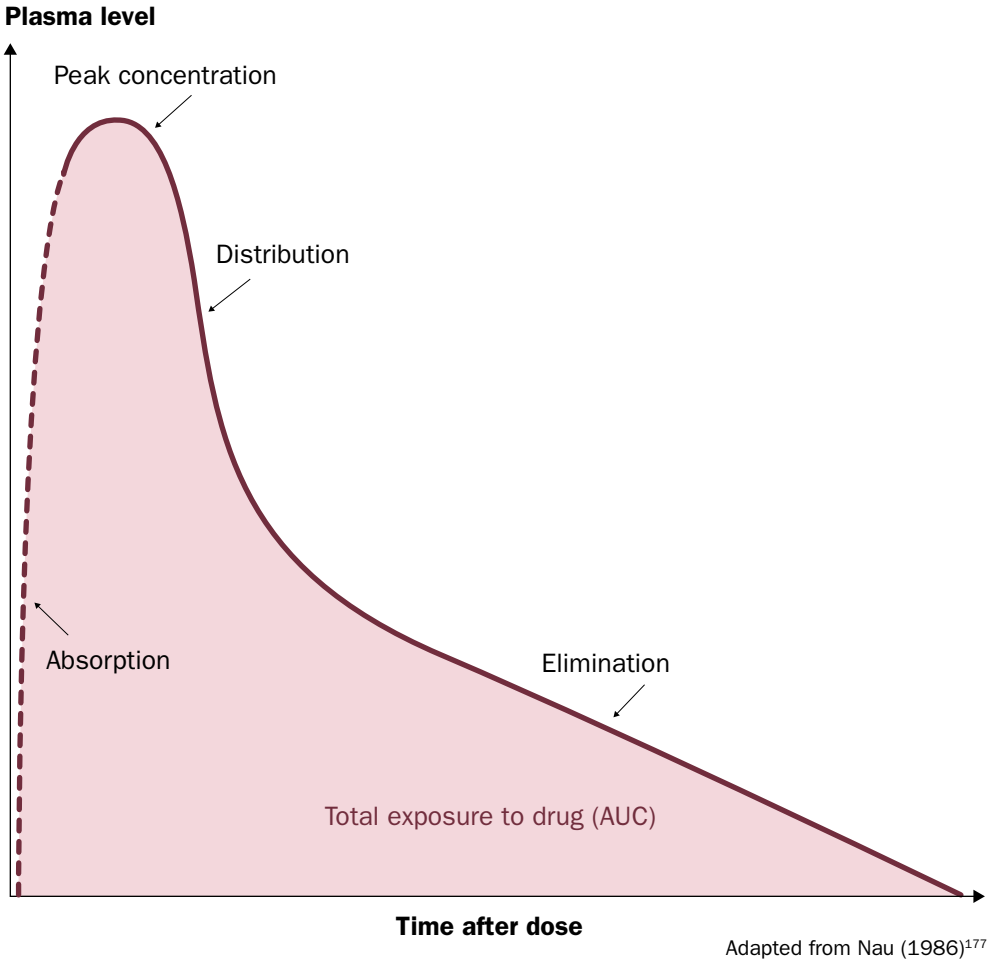
Metabolism is the chemical transformation of a drug in the cells by enzymes, converting it into one or more new molecules, known as metabolites. These metabolites may be more water-soluble to facilitate excretion by the kidneys, and are usually less active than the original drug; however, in some cases a metabolite may have equal or greater activity.

Metabolism of a drug may be affected by the activation or inhibition of the enzyme(s) involved by other drugs or certain foods, as well as by age and genetic differences between individuals. Excessive metabolic activity can cause reduced efficacy, whereas decreased metabolism can increase the risk of adverse events due to higher concentrations of the active drug accumulating in the circulation.

Elimination is the removal of drugs from the body, usually in the urine via the kidneys. The rate of excretion varies between individuals, and people with impaired kidney function will have a slower clearance rate. The most common alternative route of elimination is in the faeces; the proportions eliminated in the urine and faeces are different for different drugs. The **clearance** of a drug is defined as the volume of plasma that is cleared of the drug per unit of time, that is, the rate of elimination. The clearance determines the maintenance dose required to maintain a steady state concentration of the drug, because the drug must be given at the same rate at which it is eliminated.

The **elimination half-life** is the time it takes for half of the drug to be eliminated, which will affect the dosing frequency. Drugs with short half-lives will require more frequent dosing to maintain effective concentrations, whereas those with long half-lives can be given less frequently. Both the volume of distribution and the elimination clearance determine the elimination half-life, with a high clearance or small volume of distribution resulting in a short half-life. It takes around 5 half-lives for a drug to be almost completely eliminated from the body after it is discontinued.

FIGURE 5. **CHANGE IN DRUG CONCENTRATIONS DURING THE ABSORPTION, DISTRIBUTION AND ELIMINATION PHASES**



Adapted from Nau (1986)[177]

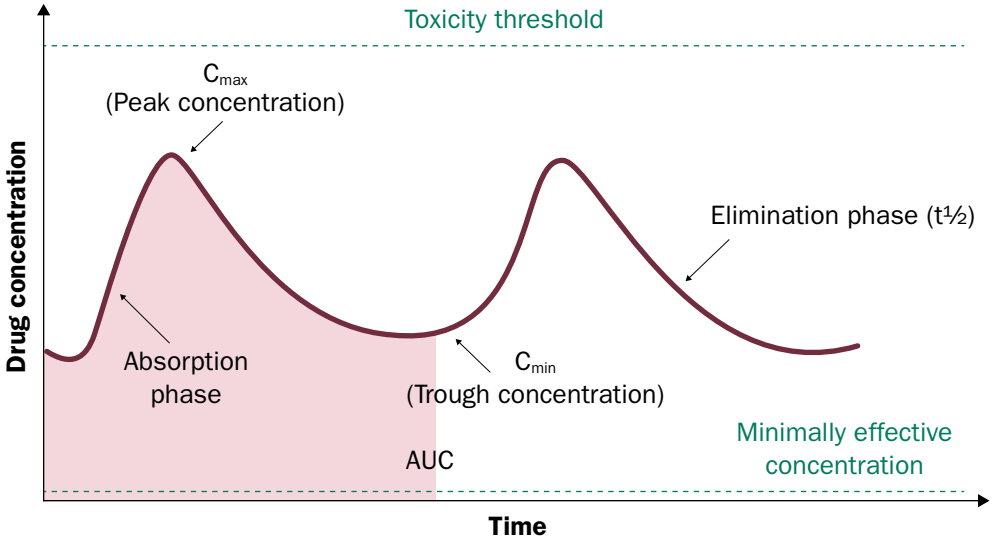
When a dose of a drug is given and it enters the circulation, the maximum (peak) plasma concentration (C_{max}) of the drug will be reached after a certain amount of time (t_{max}). The C_{max} needs to be below the toxicity threshold of the drug to avoid side-effects. A short t_{max} means that an effective concentration of the drug is reached more rapidly but can increase the risk of adverse events at the C_{max}, whereas a long t_{max} (such as with extended-release formulations) gives a more even drug concentration and effect over time. After the C_{max} has been reached, the concentration of the drug in the plasma declines as it is distributed to the tissues and eliminated. The changes in the plasma concentration of the drug over time are shown in the figure above. The area under the plasma concentration-time curve (AUC) represents the total amount of the drug entering the circulation, i.e. the body's exposure to the drug, after a dose. Increases or decreases in the AUC and/or C_{max} of a drug may occur as a result of interactions with other drugs or certain foods and these can lead to adverse effects or lack of efficacy.

Bioavailability refers to the amount of a drug dose that enters the circulation unchanged following absorption and the rate at which this occurs. Intravenously administered medication goes straight into the blood stream, and is therefore 100% bioavailable; oral medications, however, are not as bioavailable, as they need to go through absorption and first-pass metabolism prior to entering systemic circulation.

When people are taking medication on a regular basis, there is an ongoing process of the drug being absorbed, distributed, metabolised and eliminated (see Figure 5). Eventually there is a point where the amount of the drug going in is the same as the amount of the drug being eliminated; this is known as the 'steady state' (Figure 6). The time at which 'steady state' is reached is usually 5–6 half-lives of the drug.

The concentration of the drug in the blood should be maintained within the therapeutic range (above the minimum effective concentration and below the threshold for toxicity) to achieve the intended response and avoid side-effects. Excessive concentrations can suggest slow elimination or overdose, whereas concentrations that are too low may indicate non-adherence, poor absorption, excessively rapid elimination or that the prescribed dose is too low.

FIGURE 6. **PLASMA CONCENTRATION-TIME CURVE AT STEADY STATE**



Side-effects

Side-effects, or adverse reactions, are the unintended effects of a drug. These can sometimes be serious or severe, leading to hospitalisation or even death. Side-effects of medications have a negative impact on quality of life and can lead to reduced adherence or discontinuation of treatment.

All drugs have the potential to cause side-effects, particularly at high doses or when used incorrectly.[172] Most side-effects (around 70–80%) are dose-related and can be predicted.[178] These are caused by increases in the drug's intended activity or its unwanted effects, and are more likely to occur with drugs that have a steep dose-response curve and/or small therapeutic index. Side-effects that are not dose-related and are unrelated to a drug's mechanism of action, such as allergic reactions, are less common and harder to predict, and are potentially more serious.

Side-effects known to occur with psychotropic drugs used to treat young people with FEP are discussed separately for each drug class in the section 'Introduction to psychotropic drugs' on page 16.

Appendices

Appendix 1. Side-effects tables of SGA medications

TABLE 5. **SUGGESTED STRATEGIES TO MANAGE COMMON SIDE-EFFECTS OF ATYPICAL (SGA) ANTIPSYCHOTIC MEDICATIONS**

SIDE-EFFECT	DESCRIPTION	SUGGESTED INTERVENTIONS
Metabolic syndrome	A group of risk factors that increase risk of heart disease, diabetes and stroke: • Large waistline • High triglyceride level • Low HDL cholesterol level • High blood pressure • High fasting blood sugar	See 'Physical health and monitoring' on page 49
Sexual side-effects	Elevated prolactin levels have been shown to have profound effects on reproductive health and sexual function, including:[1] • hypogonadism • decreased libido in both sexes • amenorrhoea and infertility in women • low sperm count and reduced muscle mass in men.	• Reduce dose if possible while maintaining therapeutic dose • Switch to another antipsychotic with lesser sexual side-effect profile • Take a sexual history • Monitor prolactin levels • Rule out other reasons for sexual side-effects Young people are unlikely to report sexual problems or loss of libido, so education and active monitoring of these side effects is important.
Sedation	May include rapid onset of sleep, extended sleep duration and day time sedation. Peak effects of sedating medications are more likely to the cause of oversleeping. Sleep habits, lack of daytime activities and changes to lifestyle associated with illness can also contribute to more time spent in bed.	• A good sleep history • Reduce dosage if possible while maintaining therapeutic dose • Night-time administration only may help day time drowsiness • Slow release preparations (e.g. Seroquel SR) may help decrease rapid sleep onset • Switch to another antipsychotic with less somnolent profile

Continued over page.

TABLE 5. **SUGGESTED STRATEGIES TO MANAGE COMMON SIDE-EFFECTS OF ATYPICAL (SGA) ANTIPSYCHOTIC MEDICATIONS** CONTINUED

SIDE-EFFECT	DESCRIPTION	SUGGESTED INTERVENTIONS
Extrapyramidal side-effects (EPSEs) • **acute dyskinesias** • **dystonic reactions** • **Parkinsonism** • **akinesia** • **akathisia**	EPSEs are involuntary muscular movements, abnormal muscle tone, and posture. **Acute Dystonia** is often observed as sudden muscular contractions. It often produces neck or jaw spasms or cause eyes to roll up (oculogyric crisis). **Akathisia** is a sensation of motor restlessness, and may be observed as an inability to sit still or remain motionless. People with akathisia may appear to tremble nervously, shake their legs or keep getting up to walk around. Akathisia should be differentiated from agitation and restless leg syndrome. **Dystonias** are involuntary increases in muscle tone that result in sustained contortions that may cause the person to remain in a distorted position such as a flexed back or twisted neck. **Akinesia** is a marked reduction in accessory motor activity (e.g. arms swinging while walking) and in normal automatic movements (e.g. blinking, swallowing, periodic postural adjustment).	• Reduce dosage if possible while maintaining therapeutic dose. • Treat with anticholinergic medication (e.g. benztropine) • Propanolol • Clonazepam • Switch to another antipsychotic
Anticholinergic effects • **Constipation** • **Dry mouth** • **Blurred vision**		Constipation: • Recommend regular and increased fibre and fluid intake. • Consider short term laxative use. • Consult GP to rule out other causes. Dry mouth: • Chewing lollies or gum may help. • Rule out other causes. Blurred vision: • Consider reducing dose. • Check dose of anticholinergic agent used for EPSE.

TABLE 6. **SUGGESTED STRATEGIES TO MANAGE SERIOUS (RARE) ADVERSE EVENTS ASSOCIATED WITH ATYPICAL (SGA) ANTIPSYCHOTIC MEDICATIONS**

ADVERSE EVENT	DESCRIPTION	SUGGESTED INTERVENTIONS
Neuroleptic malignant syndrome (NMS)	Neuroleptic malignant syndrome (NMS) is a potentially fatal side-effect associated with antipsychotic drugs. Signs of NMS are hyperpyrexia (extremely high fever), muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine kinase, myoglobinuria (rhabdomyolysis) and acute renal failure. In such an event or with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs should be discontinued.	• Stop antipsychotic medication • Consider transfer to general medical ward for monitoring of vital signs, rehydration and other supportive measures
Tardive dyskinesia (TD)	Longer term use of anti-psychotic medications may result in tardive dyskinesia. Features of the disorder may include grimacing, tongue protrusion, lip smacking, puckering and pursing, and rapid eye blinking. Rapid movements of the arms, legs, and trunk may also occur. Involuntary movements of the fingers may be present. Symptoms of tardive dyskinesia may remain long after discontinuation of neuroleptic drugs. In many cases, the symptoms stop spontaneously, but in some cases they may persist indefinitely.	• Reduce dose if possible while maintaining therapeutic dose. • Switch to another antipsychotic. • Pharmacological management.
Leukopenia	An abnormally low level of white blood cells circulating in the blood. One or all types of white blood cells might be affected, leaving the person susceptible to physical illness and infection.	• May need repeat blood tests • May need urgent referral to a GP or specialist
QTc prolongation	A change in heart rhythm.	• Monitor ECG • Consider cardiology referral • Reduce dose if possible while maintaining therapeutic dose • Switch to another antipsychotic with less effect on QTc interval.

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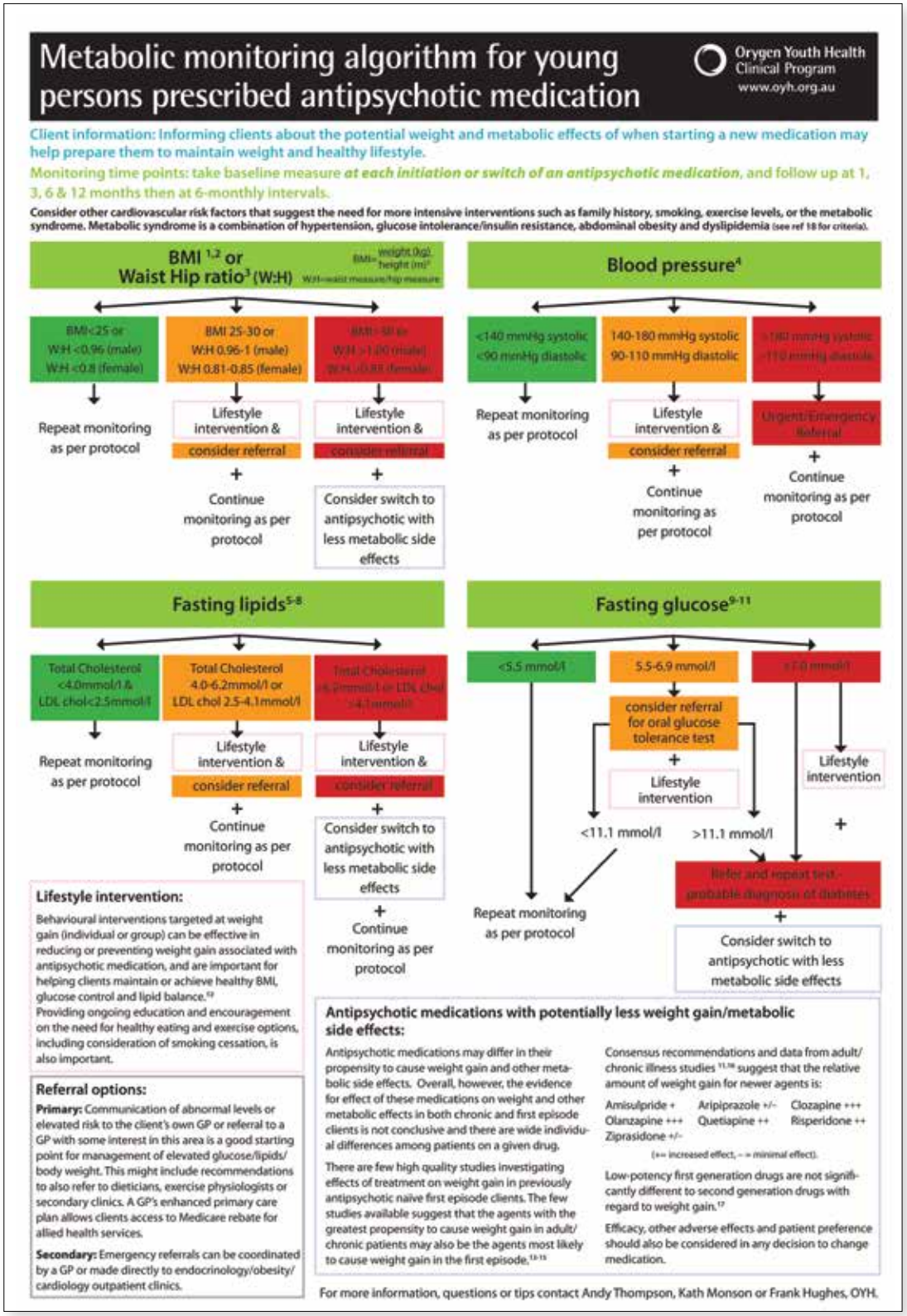
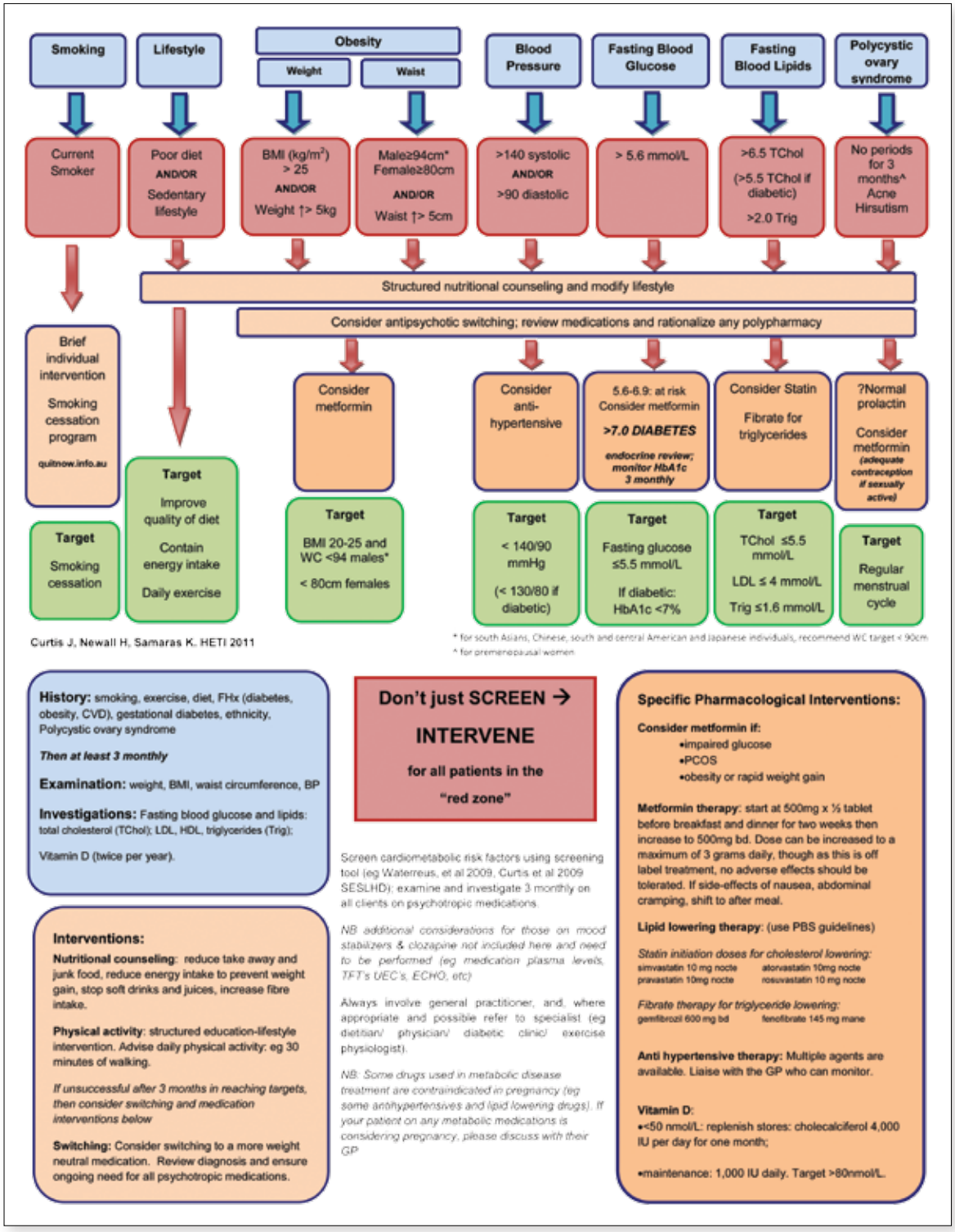
Appendix 2. Algorithm for monitoring metabolic side-effects in young people prescribed antipsychotics



Prepared by A. Thompson, K. O'Connor, W. Soong, Y.Yun, M. Willet for the Orygen Youth Health Metabolic Monitoring Project. 2010

Appendix 3. Algorithm for positive cardiometabolic health



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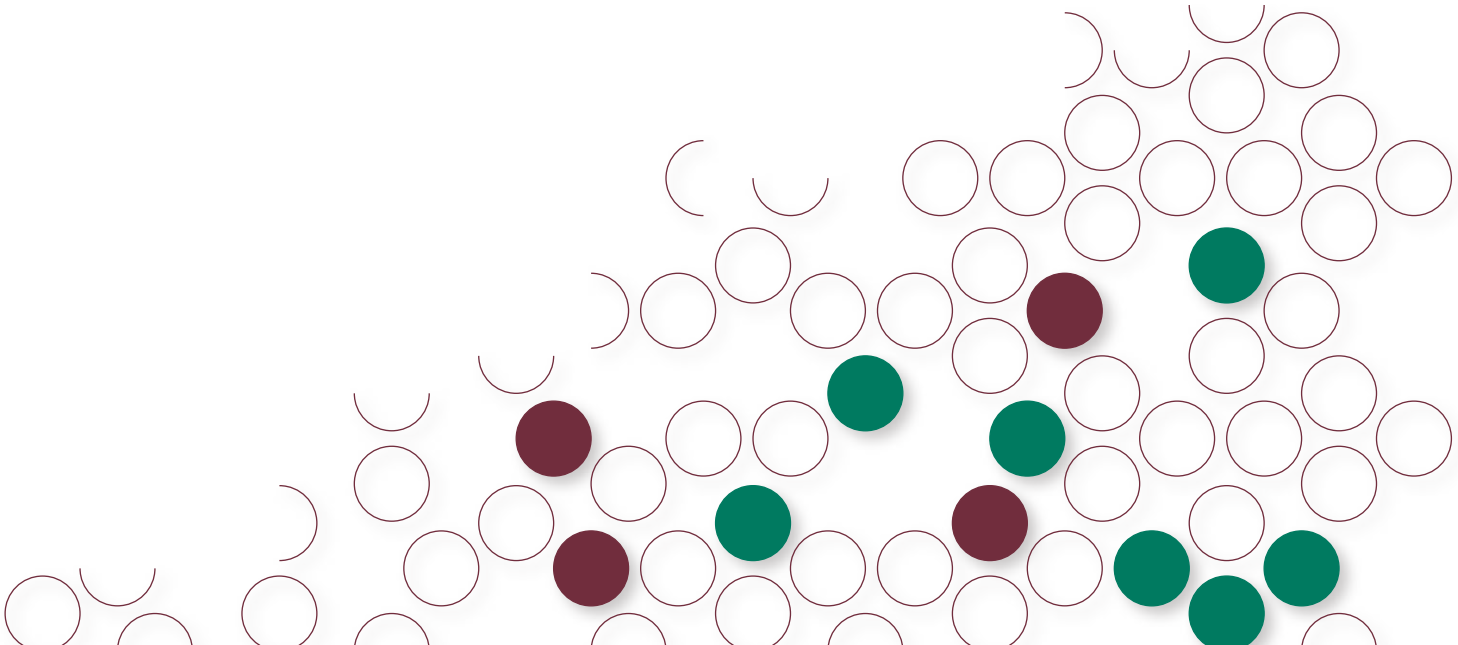

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