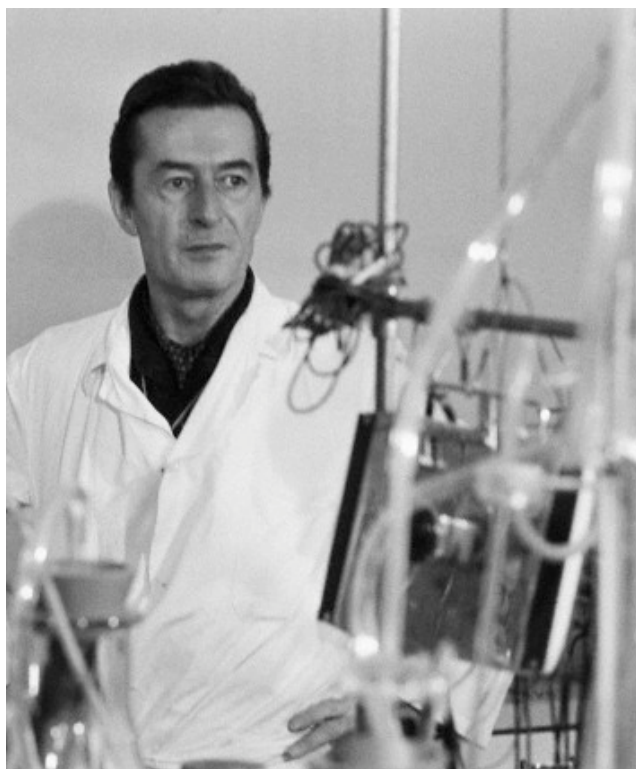


USING ANTIPSYCHOTIC MEDICATION FOR THE TREATMENT OF SCHIZOPHRENIA IN CHILDREN AND ADOLESCENTS

**Maite Ferrin, Helen Gosney, Arianna Marconi &
Joseph M. Rey**

Henri Laborit (1914-1995), a French physician, writer and philosopher, was the first to recognize the potential use of chlorpromazine in psychiatric disorders, which opened the door to the psychopharmacology revolution of the 2nd half of the 20th century.



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There is wide agreement that psychotic illnesses, including schizophrenia, are a group of heterogeneous conditions with multi-factorial causes (Howes & Kapur, 2009). A neurodevelopmental model hypothesizes that psychosis is the result of a deviation in neurodevelopmental processes that begins long before the onset of symptoms and is caused by a combination of environmental and genetic factors (Rapoport et al, 2005). In addition to prenatal insults, both late genetic and late environmental factors could explain the different ages of onset.

Symptoms of psychosis are typically classified in three clusters: positive (hallucinations, delusions), negative (poverty of thought and speech, impairment in social interactions, blunted affect) and cognitive (cognitive decline, impairment of executive functions).

This chapter complements and should be read in conjunction with chapter H.5 of the eBook ([Schizophrenia and Other Psychotic Disorders of Early Onset](#)). Early onset psychosis and very early onset psychosis are rare and differ from schizophrenia in several ways. For example, the early onset ones have a similar gender ratio and there is no difference between boys and girls in age at onset (Remschidt, 2002), while later onset schizophrenia is more common and has an earlier onset in men. There is much continuity between very early onset psychosis, early onset psychosis and schizophrenia in adulthood; however prognosis of the early onset disorders is poorer.

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The term “early onset psychosis” refers in this chapter to the presence of a psychotic episode before the age of 16, and “very early onset psychosis” when the psychotic episode occurs before the age of 13.

Table H.5.1.1 Core principles that should be included in intervention programs for early onset psychosis

PRINCIPLE	GOAL
Raising awareness	<ul style="list-style-type: none"> To raise knowledge about the importance of early detection and management
Specific early intervention training	<ul style="list-style-type: none"> To detect psychosis as early as possible
Assessment	<ul style="list-style-type: none"> To do a comprehensive assessment and ongoing assessment of comorbid disorders including depression and anxiety
Pharmacological treatment	<ul style="list-style-type: none"> Symptom reduction Careful titration Monitoring side effects
Care coordination	<ul style="list-style-type: none"> Rapid allocation of key workers/care coordinators Care plans focused on risk management, recovery and prevention of relapse
Psychosocial interventions	<ul style="list-style-type: none"> Identification Psychoeducation to young people and their families To make available family therapy and CBT To consider housing and income support
Education and employment	<ul style="list-style-type: none"> Undertake an education assessment Provide support into education, training and employment
Promoting recovery	<ul style="list-style-type: none"> Aspire to full recovery and support sufferers in regaining full participation in society

As highlighted in Chapter H.5, the treatment of psychosis in young people requires a coordinated and integrated approach based on different components of care tailored to the individuals' and their families' needs. Optimal management of young people with psychosis requires a multimodal approach that includes psychoeducation, psychotherapy, family therapy, specific rehabilitation and re-integration measures (Clark & Lewis, 1998; NICE, 2013). There is also growing evidence that treating individuals with first episode psychosis with a specific multimodal team-based, coordinated approach results in better clinical and functional outcomes than typical community care, particularly if this treatment begins soon after the onset of psychotic symptoms (Kane et al, 2015). The principles of treatment are summarised in Table H.5.1.1.

Pharmacotherapy is the mainstay of treatment (Meuser & McGurk, 2004; McClellan & Stock, 2013) and is the focus of this chapter. It is of note that many patients with first-episode psychosis still receive medications inconsistent with current guidelines, even in high income Western countries. For example a US study found that almost 40% of people with first-episode psychosis in community mental health clinics could benefit from changes to their medication (Robinson et al, 2015).

ANTIPSYCHOTIC DRUGS

Antipsychotic medications can be divided according to chemical structure, type of receptor binding, and clinical profile into two main groups: first generation and second generation. Some of the more commonly used antipsychotics are summarised in Table H.5.1.2.

MECHANISM OF ACTION

All antipsychotic drugs interact with a variety of neurotransmitter systems. First generation antipsychotics typically block dopamine receptors (especially D2 receptors). They reduce positive symptoms, such as delusions, hallucinations, formal thought disorder, as well as other non-specific symptoms such as agitation and aggressiveness. They are also associated with elevated prolactin secretion, extrapyramidal side effects such as tremor, dystonia and tardive dyskinesia, and with rare but potentially fatal side effects such as neuroleptic malignant syndrome. Figure H.5.1.1 shows the main dopamine pathways and effects of antipsychotic medication according to pathway.

Second generation antipsychotics vary in their receptor affinity, targeting mainly serotonergic (5HT_{2A}) as well as D2 and other receptors (e.g., M1, D4, D5). It was believed initially that second generation antipsychotics were effective in reducing negative symptoms. However, evidence of this is inconclusive. Because extrapyramidal symptoms can exacerbate negative symptoms and because second generation antipsychotics have fewer extrapyramidal effects, this can give the false impression of a reduction in negative symptoms with atypical antipsychotics. Second generation antipsychotics mainly cause weight gain, dyslipidaemia, and type II diabetes.



[Click on the image to view a 17-year-old high school student talk about his experiences with schizophrenia.](#)

WHO ESSENTIAL MEDICINES LIST 2015

The [WHO Model List of Essential Medicines](#) serves as a guide for the development of national and institutional essential medicine lists. It is updated and revised every two years. According to the WHO, essential medicines are drugs that satisfy the health care needs of the majority of the population. Thus, they should be available for prescription and at a price the community can afford. Medicines not in this list are less likely to be available in low and middle income countries.

Antipsychotic drugs included in the 2015 edition of the list are:

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Risperidone
- Clozapine

Table H.5.1.2 Dose range and main side effects of commonly prescribed antipsychotic medications (those included in the WHO essential medicines list 2015 are in bold)*

TYPE	NAME	DOSE (mg/day)	EPS	SEDATION	WEIGHT GAIN
FIRST GENERATION	Chlorpromazine	50-300	✓✓	✓✓✓	✓✓
	Fluphenazine	5-20	✓✓✓	✓	✓
	Haloperidol	1-10	✓✓✓	✓	✓
	Trifluoperazine	2-20	✓✓✓	✓	✓
SECOND GENERATION	Amisulpiride	800	✓	-	✓
	Aripiprazole	10-15	-	-	✓
	Asenapine	5-10	✓	✓✓	✓
	Brexpiprazole	1-4	✓	-	✓✓
	Cariprazine	1.5-6	✓✓	-	✓
	Clozapine	300-900	-	✓✓✓	✓✓✓
	Iloperidone	2-24	✓	-	✓✓✓
	Lurasidone	40-120	✓✓	✓	✓
	Olanzapine	5-20	-	✓✓	✓✓✓
	Paliperidone	3-12	✓	-	✓✓
	Quetiapine	200-800	-	✓✓	✓✓
	Risperidone	1-6	✓✓	✓	✓✓
	Sertindole	4-24	-	-	✓✓
Ziprasidone	20-80	✓	✓✓	✓	

- Very infrequent; ✓ infrequent; ✓✓ frequent; ✓✓✓ very frequent.

*Summarised from Leucht et al (2013) and other sources.

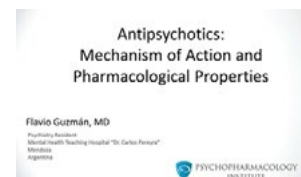
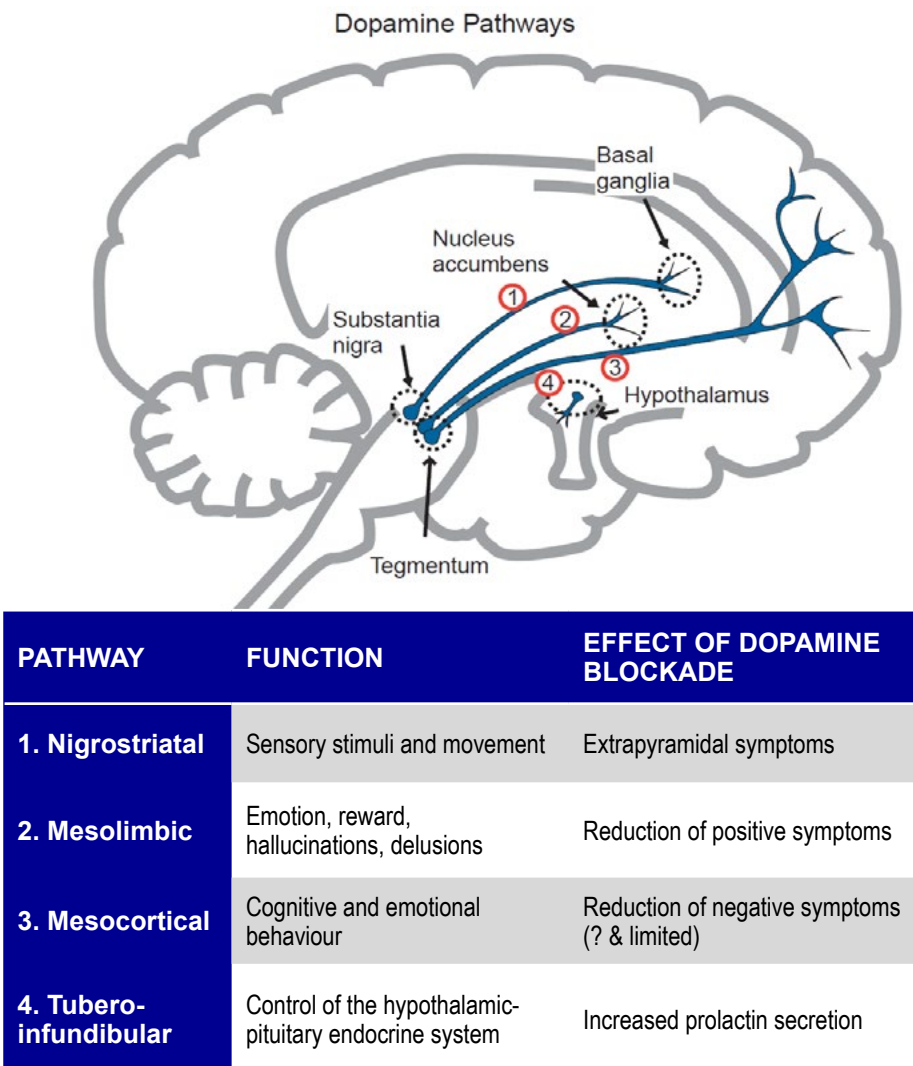
EPS: extrapyramidal symptoms.

The first antipsychotic drug, chlorpromazine, was introduced in 1952. Many other dopamine antagonists with antipsychotic properties were synthesized subsequently: between 1954 and 1975, about 40 new antipsychotic drugs were introduced worldwide—these were the **first generation, typical or traditional antipsychotics**.

A new group of antipsychotics (**second generation or atypical**) emerged in the 1980s. The second generation antipsychotics showed similar effectiveness but fewer extrapyramidal effects.

Clozapine, the first atypical antipsychotic, was introduced in Europe in 1971. It was withdrawn by the manufacturer in 1975 because it could cause agranulocytosis. Its use with the appropriate monitoring was approved in 1989 after having been shown to be effective in treatment-resistant schizophrenia and in reducing suicide rate in patients with schizophrenia.

Figure H.5.1.1 Main dopamine pathways and effects of antipsychotic medication according to pathway.



[Click on the image to view a presentation on the mechanism of action of antipsychotics \(9:33\)](#)

The lower propensity of second generation antipsychotics to cause extrapyramidal symptoms has been attributed to a weaker occupancy of D2 receptors—that rapidly falls off within 24 hours, in contrast to that for traditional antipsychotics (e.g., haloperidol), which maintains its D2 occupancy constant over 24 hours—or to 5HT2A blockade or both (Seeman, 2004). That is, one explanation of the difference in side effects between typical and atypical antipsychotics is that the atypical antipsychotics bind more loosely to D2 receptors than does dopamine itself (i.e., are displaced by dopamine), while the first generation antipsychotics bind more tightly than dopamine—and are less likely to be displaced by dopamine.

This has practical implications for treatment. Antipsychotic effect is achieved when 60% to 75% of D2 receptors have been blocked, while extrapyramidal side effects appear when 80% or more D2 receptors have been blocked (Figure H.5.1.2). This suggests that unnecessarily increasing the dose or using two antipsychotics concurrently is likely to result in more side effects rather than in symptom improvement.

EFFECTIVENESS

There are not much data regarding the efficacy and safety of pharmacological interventions in psychosis and schizophrenia in children, adolescents and young adults. A review of 27 trials including 3,067 participants found that antipsychotic treatment produced a large improvement in symptoms measured by the Clinical Global Impressions Scale, suggesting that efficacy of antipsychotics is similar in children, adolescents and young adults (Stafford et al, 2015). Nevertheless, much of the data about treatment is still extrapolated from studies in adults.

Recent meta-analyses have failed to find superiority in clinical efficacy between typical and atypical antipsychotic medication (Crossley, 2010). Yet different people respond to different antipsychotics. Currently we are unable to predict response of specific individuals to specific antipsychotics. That is, treatment is largely based on trial-and-error. However, up to 80% of patients with a first episode psychosis are expected to show a significant improvement with appropriate antipsychotic treatment. Of the 20% who do not improve, about one quarter is likely to respond to a different antipsychotic; the rest (15%) can be considered “treatment resistant”. A further three quarters of those resistant to treatment are likely to benefit from clozapine. This does not mean, however, that these outcomes persist over time; recurrence of symptoms due to relapse, poor adherence to treatment and to other factors is common. A meta-analysis including 65 trials comprising 6,493 patients found that antipsychotic drugs significantly reduced relapse at one year from 64% in those taking a placebo to 27% in those taking medication (number needed to treat to benefit = 3, see [Chapter A.6, page 7 of the eTextbook](#)) (Leucht K et al, 2012).

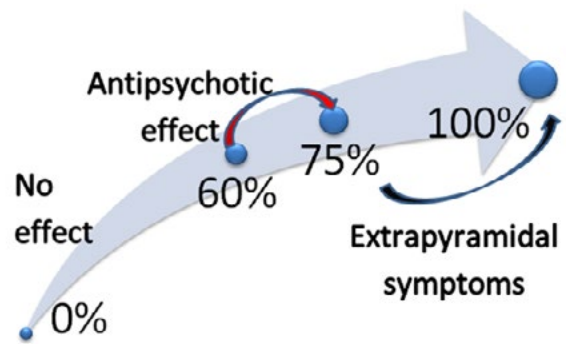


Figure H.5.1.2 D2 receptor occupancy and clinical effect

Antipsychotic effect is achieved when 60% to 75% of D2 receptors have been blocked, while extrapyramidal side effects appear when 80% or more D2 receptors have been blocked. This suggests that unnecessarily increasing the dose or using two antipsychotics concurrently is likely to result in more side effects rather than in symptom improvement.

Given that young people seem to have a higher risk of extrapyramidal side effects and more resistance to accept treatment, most guidelines recommend atypical antipsychotics as first line treatment. If second generation antipsychotics cannot be used because they are not available, for instance in some low income countries, first generation antipsychotics should be commenced at low doses (e.g., 1–2mg haloperidol or 100 mg of chlorpromazine) and titrated slowly UP to 4-6mg of haloperidol or equivalent in order to minimise undesirable extrapyramidal side effects (International Early Psychosis Association Writing Group, 2005). Antiparkinsonian medication can be considered/used if necessary (see “antiparkinsonian pharmacotherapy” below).

LONG-ACTING INJECTABLE ANTIPSYCHOTICS (LAIs)

Not taking antipsychotic medication is the single largest modifiable risk factor for the recurrence of positive symptoms of schizophrenia (Subotnik et al, 2015). Long-acting injectable antipsychotics (LAIs)—also known as depot antipsychotics—were developed to enhance adherence at a time of extensive psychiatric hospital deinstitutionalisation of patients and the need for an effective community-based treatment (see Table H.5.1.3). The first LAIs—fluphenazine enanthate and decanoate—were introduced in 1966. Yet, LAIs have been underused in the treatment of schizophrenia largely due to clinicians’ unjustified

Table H.5.1.3 Long-acting injectable antipsychotics

	ANTIPSYCHOTIC	TIME BETWEEN INJECTIONS (WEEKS)*	COMMENTS
FIRST GENERATION	Flupenthixol decanoate	2-4	<ul style="list-style-type: none"> May need concurrent antiparkinsonian medication
	Fluphenazine decanoate	1-4	
	Haloperidol decanoate	4	
SECOND GENERATION	Aripiprazole lauroxil	4-6	
	Olanzapine pamoate crystalline	2-4	<ul style="list-style-type: none"> Supplementation with oral olanzapine not required Monitor for post-injection delirium sedation syndrome, a risk with every injection (see Box)
	Paliperidone palmitate crystalline	4	<ul style="list-style-type: none"> No overlapping oral taper necessary
	Risperidone microspheres	2	<ul style="list-style-type: none"> Click here to access instructions for use

* Establish tolerability with the oral form of the medication first

negative perceptions and service barriers. Clinicians are often anxious about using LAIs because of:

- The belief that LAIs are associated with worse side-effects (despite lack of evidence supporting this)
- Concerns regarding patients' acceptance of LAIs (patients on this formulation often prefer it)
- Apprehension regarding reduced patient autonomy
- Worries about nursing staff involvement in administering LAIs, training and time pressures on staff—so that they can adequately and routinely monitor symptoms and side-effects
- Preferential attention to more fashionable medications
- Lower prescriber knowledge about and experience with LAIs
- Cost.

Oral formulations have advantages over LAIs such as rapid discontinuation in case of serious side-effects, enhanced sense of autonomy in patients, less frequent clinic attendance.

However, LAIs also have advantages over oral formulations in that they result in:

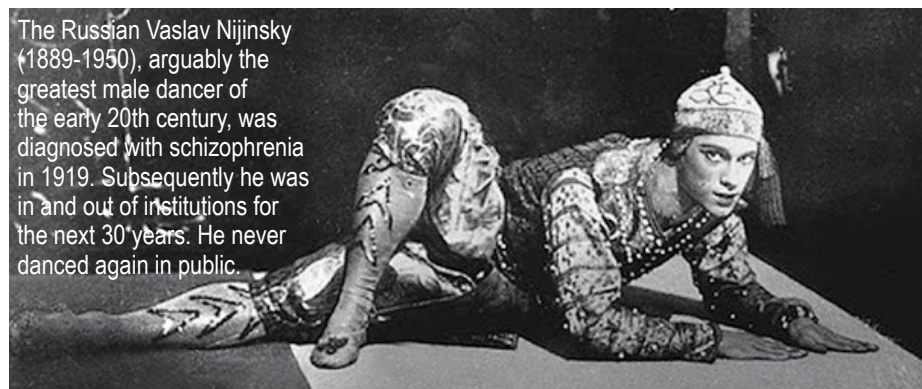
- Easier early detection of relapse
- Improved relapse prevention
- Reduced rehospitalisation rates
- More stable serum concentrations
- Reduced risk of accidental or deliberate self-poisoning
- Better ability to distinguish between lack of efficacy and poor adherence.

Effectiveness

LAIs are as effective as oral antipsychotics and efficacy of first and second generation LAIs is similar. However, clozapine rather than LAIs should be used for patients whose clinical instability is due to treatment-resistant illness rather than medication non-adherence (Castillo & Stroup, 2015).

LAIs in first episode psychosis

Traditionally the main reason for the prescription of LAIs was poor adherence to medication. However, it is being increasingly recognised that LAIs



The Russian Vaslav Nijinsky (1889-1950), arguably the greatest male dancer of the early 20th century, was diagnosed with schizophrenia in 1919. Subsequently he was in and out of institutions for the next 30 years. He never danced again in public.

OLANZAPINE POST-INJECTION DELIRIUM/ SEDATION SYNDROME

Post-injection delirium/ sedation syndrome (PDSS) is a potentially serious adverse event observed in about 7 per 10,000 injections of long-acting olanzapine. PDSS is characterized by excessive sedation or delirium that occurs shortly after the injection—similar to what is observed in an overdose of olanzapine.

The most likely explanation for PDSS is that a portion of the olanzapine pamoate injected accidentally enters the bloodstream resulting in an intravascular injection of a limited amount of the medication (McDonnell et al, 2014). It is recommended to monitor for alertness every 30 minutes for at least 3 hours after every injection.

“Psychotic exacerbation is undesirable for any patient, but it is particularly important to prevent psychotic exacerbations for recent-onset patients. Early relapse may disrupt important life tasks typically accomplished during adolescence or early adulthood, such as completing schooling, starting a career, and establishing social relationships outside one’s family of origin” (Robinson, 2011).

can have a place at various stages in the treatment of the illness and should be one of the options discussed with any patient requiring long-term treatment, even during the first episode. Patients with a first episode of schizophrenia who have responded well to antipsychotic medication, even if they understand that they have a mental disorder, very often doubt whether medication continues to be necessary, leading to stopping the medication prematurely, poor adherence and worse outcomes (Subotnik et al, 2015). For example, the French Association for Biological Psychiatry and Neuropsychopharmacology suggests that most patients that require long-term antipsychotic treatment should be offered a LAI (Llorca et al, 2013).

How to use LAIs

Long acting injectable antipsychotics are not indicated for short-term therapy (e.g., less than three months). The issues of patient consent (and/or family when appropriate) need to be dealt with carefully and sensitively to minimise harming the doctor-patient relationship. LAIs may be considered for patients with confirmed schizophrenia and with risk factors for medication non-adherence: history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medication, and poor insight. LAIs *are not* indicated in bipolar disorder.

When selecting a LAI, take into account patient's preferences, health status, experience with prior antipsychotic medication, and the side-effect profiles of different medications (Castillo & Stroup, 2015).

When using LAIs you should read about the specific recommendations for the use of each compound. In general, it is advisable to:

- Switch to the short-acting, oral preparation of the medication—if the patient is not already taking it—to establish response and tolerability
- Use the recommended injection technique for the particular drug—usually intramuscular injection in the gluteus maximus or deltoids
- Use an initial test dose and then an appropriate therapeutic dose while the oral medication is reduced and stopped.

SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS

While the efficacy of antipsychotics appears to be similar in children, adolescents and adults, side effects are greater in the young (Stafford et al, 2015). Preventing, minimising, and treating side effects are key elements in the management of these patients, which may result in treatment success or failure and their long-term consequences.

Extrapyramidal symptoms (EPS)

- EPS are particularly frequent with typical antipsychotics but can also be observed in second generation antipsychotics (e.g., risperidone; see Table H.5.1.2)
- EPS are more common in young people, especially if intellectually disabled, if there is central nervous system damage, and in drug-naïve individuals

- *Antiparkinsonian pharmacotherapy* (e.g., trihexyphenidyl or benzhexol, bentrropine) to reduce the incidence of extrapyramidal symptoms in people treated with first generation antipsychotics, antiparkinsonian pharmacotherapy should be considered at the start of treatment on a case by case basis, taking into account individual preferences, prior history of extrapyramidal side effects, characteristics of the antipsychotic medication prescribed, and other risk factors for both extrapyramidal and anticholinergic side effects (Buchanan et al, 2010). Prophylactic antiparkinsonian medication in people treated with second generation antipsychotics is not warranted. Anticholinergic drugs are not without peripheral (e.g., dry mouth, urinary disturbances, constipation, blurred vision) and central adverse effects (e.g., cognitive impairment) complicate management. The WHO recommends that anticholinergics should not be used *routinely* for preventing extrapyramidal side-effects in individuals with psychotic disorders treated with antipsychotics. This is an important issue to consider when choosing an antipsychotic—

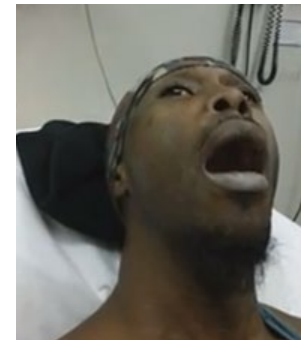
DYSTONIC REACTIONS THAT CAN BE CAUSED BY ANTIPSYCHOTIC MEDICATIONS

Dystonic reactions are not uncommon presentations in the emergency room, often seen in young patients taking metoclopramide, prochlorperazine (anti-emetics) or antipsychotic medications, particularly first generation ones. Clinical manifestations of acute dystonic reactions are listed below.

SYMPTOM	DESCRIPTION
Oculogyric crisis	Spasm of the extra orbital muscles producing a deviation of the eyes upwards and outwards. Blefarospasm
Torticollis	Head becomes persistently turned to one side, often with painful muscle spasms
Opisthotonos	Uncomfortable forced extension of the neck. When severe, the back is involved and the patient may arch off the bed
Macroglossia	The tongue does not actually swell, but it protrudes and subjectively feels swollen
Buccolingual crisis	May present as trismus, <i>risus sardonicus</i> (a grinning expression produced by spasm of the facial muscles), dysarthria, and grimacing
Laryngospasm	Spasm of the vocal cords that temporarily makes it difficult to speak or breathe. The onset is usually sudden and can be quite frightening

Differential diagnosis of dystonic reactions include tetanus and strychnine poisoning, hyperventilation (carpopedal spasm is usually more prominent than in acute dystonic reactions), hypocalcaemia and hypomagnesaemia, neurological illnesses such as Wilson's disease, and catatonia (Campbell, 2001).

Dystonia responds promptly to anticholinergic drugs (e.g., bentrropine 1-2mg by slow intravenous injection) or antihistaminics (e.g., diphenhydramine). Children should be given parenteral bentrropine (0.02mg/kg to a maximum of 1mg), either intramuscularly or intravenously. Most patients respond within 5 minutes and are symptom-free by 15 minutes (see video clip). If there is no response the dose can be repeated after 10 minutes (or 30 minutes in children if intramuscularly). If the dystonic reaction does not improve, the diagnosis is probably wrong.



[Click on the image to view a dystonic reaction and its response to treatment \(4:28\)](#)

favouring the use of second generation medications

- Acute dystonias and akathisia are more frequent during the first weeks of treatment (see Box). Tardive dyskinesia tends to occur after long term use, especially with typical antipsychotics
- Extrapyramidal symptoms can be minimised by using the lowest effective dose of medication or antipsychotics that cause fewer EPS.

Neuroleptic malignant syndrome (NMS)

- This syndrome is characterised by hyperthermia, muscular rigidity, tachycardia, hyper- or hypotension, autonomic instability, rhabdomyolysis and altered mental state (confusion) (see Box)
- An elevation of creatine phosphokinase (CPK) and/or leucocytosis is usually observed. NMS should be suspected in any patient taking dopamine antagonists with raised CPK
- NMS is more common during the first weeks of antipsychotic treatment, but it can occur at any time and has been reported with both first and second generation antipsychotics (Masi et al, 2011)

NEUROLEPTIC MALIGNANT SYNDROME (NMS) AND SEROTONIN SYNDROME

Distinguishing between NMS and serotonin syndrome can be difficult, particularly in milder cases or in patients taking both dopamine antagonists and serotonergic drugs (including over-the-counter and alternative medicines such as St John's wort).

SYMPTOMS	NEUROLEPTIC MALIGNANT SYNDROME (NMS)	SEROTONIN SYNDROME
	A neurological disorder caused by an adverse reaction to neuroleptic or antipsychotic drugs. NMS usually develops within the first two weeks of treatment with a dopamine antagonist but it can occur at any time	A dose-related range of toxic symptoms which are largely attributable to increasing serotonin concentrations in the central nervous system. Although severe cases have been reported with an overdose of a single drug, they usually occur with a combination of two or more serotonergic drugs (even at therapeutic doses)
Behavioural	<ul style="list-style-type: none"> • Confusion, delirium or coma 	<ul style="list-style-type: none"> • Confusion, delirium • Agitation • Restlessness
Autonomic	<ul style="list-style-type: none"> • Hyperthermia • Sweating • Tachycardia • Unstable blood pressure • Tachypnoea 	<ul style="list-style-type: none"> • Hyperthermia • Sweating • Tachycardia • Hypertension • Mydriasis • Flushing
Neuromuscular	<ul style="list-style-type: none"> • Generalised muscle rigidity 	<ul style="list-style-type: none"> • Clonus (symmetrical and usually more marked in the lower limbs) • Hypotonia
Laboratory findings	<ul style="list-style-type: none"> • Elevated creatine phosphokinase • Leucocytosis 	

- Risks for NMS include higher doses of antipsychotics, multiple drugs, young age and male gender
- If not recognised, NMS can lead to loss of consciousness and even death
- Misdiagnosis can occur with catatonia, extrapyramidal side effects, serotonin syndrome or infectious diseases
- Management (preferably in an intensive care unit setting with cardio-respiratory monitoring) is mainly supportive. The main intervention is stopping the neuroleptic agents. The benefits of other interventions (e.g., dopamine agonists such as bromocriptine) are still unclear.

Sedation

- Sedation is a frequent and usually dose-dependent effect, although tolerance may be developed with time
- Table H.5.1.1 describes the relative sedating effects of commonly used antipsychotics
- Sedation may be a sought after effect in severely agitated patients; in these cases a more sedating drug (e.g., chlorpromazine, quetiapine) should be chosen.

Weight gain

- Weight gain is the most common long term adverse effect of atypical antipsychotics (see Table H.5.1.2 for the relative likelihood of weight gain)
- Compared with baseline, a weight gain of 5% during the first 3 months of treatment, or an increase of 0.5 in body mass index (BMI) in a longer period should raise concern (Masi et al, 2011)
- Negative effects associated with weight gain include dyslipidaemia, metabolic syndrome, diabetes mellitus, hypertension, polycystic ovary, and osteoarthritis
- Social withdrawal, treatment discontinuation and low self-esteem are some of the psychological consequences

Metabolic syndrome

- Metabolic syndrome is characterized by obesity, hyper-triglyceridaemia, low high-density lipoprotein (HDL) cholesterol levels, hypertension and hyperglycaemia
- Weight gain is probably the most important precursor of a general metabolic dysregulation, the metabolic syndrome. However, there may also be direct effects on insulin secretion in a dysregulated hypothalamic pituitary axes
- All antipsychotics are associated with metabolic syndrome, particularly clozapine and olanzapine (Masi et al, 2011).

Endocrinological

- Hyperprolactinaemia seems to be more common in children and adolescents than in adults. Post-pubertal girls may be more sensitive, as oestrogen stimulates prolactin synthesis

- The main effects of hyperprolactinaemia are amenorrhoea, menstrual cycle disorders, breast enlargement, galactorrhoea (both in males and females) and sexual effects (decreased libido, erectile difficulties)
- Hyperprolactinemia with antipsychotics is dose dependant and related to the drugs' affinity to D2 receptors. Overall, it is higher in first generation antipsychotics but there are second generation antipsychotics with a high potential for prolactin elevation (e.g., amisulpride, risperidone and paliperidone). Quetiapine has little effect on prolactin secretion. Aripiprazole may be associated with a small decrease of prolactin levels (Correll & Carlson 2006)
- If hyperprolactinemia becomes a concern, antipsychotic should be changed to quetiapine or aripiprazole.

Haematological

- All antipsychotics can induce a mild leukopenia, usually without clinical significance. Agranulocytosis and neutropenia are infrequent; if that happens, treatment with the same antipsychotic should be avoided
- Clozapine is associated with higher risk of agranulocytosis, especially during the initiation of treatment; however a late risk has also been described
- Regular monitoring by blood test is required when using clozapine (see clozapine on [Chapter H.5, p.16](#))

PREVENTING WEIGHT GAIN AND METABOLIC SYNDROME

Some young people taking antipsychotics can gain a substantial amount of weight very quickly. Once gained it is much harder to lose than to prevent it from happening in the first place. Because of the likelihood of significant weight gain with most second generation antipsychotics (see Table H.5.1.2) clinicians need to be proactive from the start by informing patients and families of this risk and ways of preventing it. The goal would be to achieve healthy eating, to maintain a body mass index (BMI) of less than 25 and an adequate level of physical exercise. Apart from regular monitoring of weight, waist circumference, fasting glucose and lipids (see Table H.5.1.4) clinicians ought to provide dietary and exercise advice, which should be monitored and reinforced at each consultation, recommending, for example to ([Women's and Children's Health Network, 2007](#)):

- Eat every 3 to 4 hours, with no more than 2 meals in the evening or at night
- Eat small portions at meals
- Eat breakfast every morning
- Eat slowly, drink an ample amount of water between bites and take second helpings only after a delay
- Eat no more than one fast food meal per week
- Avoid fried foods
- Replace all drinks containing sugar (e.g., soft drinks, cordial, juice), "diet" drinks, and whole milk with at least 2L of water a day and moderate amounts of unsweetened tea or low fat milk.
- Replace foods made with refined white flour and processed sugar and eat instead whole-grain foods and other food items that have a low [glycaemic index](#) (i.e. ≤ 55).
- Do not snack when full and replace high-fat, high-calorie snacks with fruit and vegetables
- Limit saturated fat intake
- Eat at least 25-30g per day of soluble fibre from fruits, vegetables and whole grains
- Limit watching television or playing computer/video games to less than 2 hours per day
- Perform moderate to vigorous physical activity for at least 30 to 60 minutes per day.

Table H.5.1.4 Suggested monitoring for people taking antipsychotics

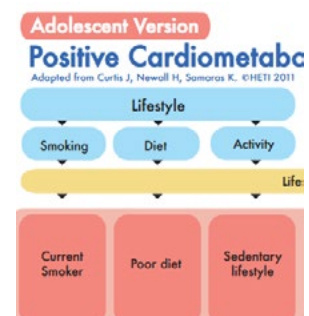
	BEFORE STARTING TREATMENT	AT 6 MONTHS	AT 12 MONTHS	EVERY 12 MONTHS AFTER
Weight and waist circumference	✓	✓	✓	✓
Blood pressure	✓	✓	✓	✓
Fasting serum lipids	✓	✓	✓	✓
Fasting blood glucose	✓	✓	✓	✓
Extrapyramidal symptoms, abnormal involuntary movements (i.e. tardive dyskinesia)	✓	✓	✓	✓
Ask about menstrual and sexual problems, gynecomastia and galactorrhoea (if positive: prolactin levels)	✓	✓	✓	✓

Seizures

- Antipsychotics may produce EEG abnormalities but risk varies widely among specific antipsychotics. Risk is particularly high with clozapine (up to 4% of the cases in studies with adolescents; Freedman et al, 1994) and olanzapine, moderate with risperidone and typical neuroleptics, and low with quetiapine
- Once other causes of the seizures are excluded, management may entail switching antipsychotic, stopping the medication briefly, reduce the dose or use an anticonvulsant.

Cardiovascular

- Cardiovascular adverse effects include orthostatic hypotension, increased heart rate, dizziness, and ECG changes (longer QTc interval, reduced ST interval)
- Adverse cardiovascular effects are more frequent with atypical antipsychotics, although ziprasidone has the greater risk (Masi et al, 2011)
- Transient increases in heart rate have been reported in children and adolescents but they have little clinical significance



[Click on the image to access an algorithm to monitor and achieve good cardiometabolic health in young people taking antipsychotic medication](#)

- Prolongation of the QTc interval (more than 500ms) is of greater concern because of the increased risk of ventricular arrhythmias and sudden death. Many drugs may lengthen the QT interval increasing the risk of torsade de pointes, which becomes more of a problem when patients are taking several medications concurrently
- An ECG at baseline and during follow-up is recommended if poly-pharmacy is used or if there is family history of sudden cardiac death as part of the monitoring process.

CHOOSING AN ANTIPSYCHOTIC MEDICATION

The first step is to define the goals of treatment in conjunction with the patient—and family when appropriate or if the patient is not well enough or old enough to participate in this process—and discuss the main options with their benefits and risks.

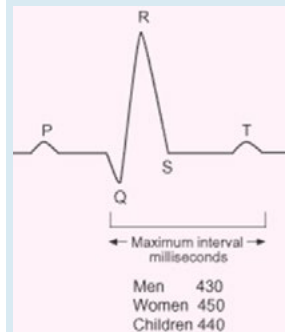
“Antipsychotic medications, other than clozapine and olanzapine (due to their side effects) are recommended as first-line treatment for persons with schizophrenia experiencing their first acute positive symptom episode” (Buchanan et al, 2010) . Overall, a second generation antipsychotic is preferred. The choice would be made taking into account:

- Their side effect profile
- The patient’s history of drug response (if known)
- The patient’s family history of drug response (if a family member has schizophrenia)
- Availability of the medication
- Clinician’s familiarity with the drug, and
- Price. Since schizophrenia is a chronic condition, in some countries price may be the most important factor to ensure or undermine adherence.

Dosage

People with a first-episode show better response to treatment and a greater likelihood of side effects than patients with multi-episode schizophrenia. The Schizophrenia Patient Outcomes Research Team (Lehman & Steinwachs, 1998) recommended that patients presenting with a first psychotic episode should be treated with lower doses of antipsychotic medication than those recommended for patients with multi-episode schizophrenia (see Table H.5.1.2). Available research suggests that lower doses of antipsychotics are as effective as higher doses in patients experiencing a first episode but are better tolerated. That is, the goal should be to maintain the medication at the lowest effective dose to minimise potential adverse events. Quetiapine is an exception; it often requires titration to 500–600 mg/day (Buchanan et al, 2010; Lachman, 2014). Evidence suggests that “starting low, and going slow” during the titration phase is the most effective approach to minimise side effects.

SOME DRUGS THAT CAN LENGTHEN THE QT INTERVAL



Antipsychotics

- Risperidone
- Fluphenazine
- Haloperidol
- Clozapine
- Ziprasidone
- Pimozide
- Droperidol
- Quetiapine

Antidepressants

- Amitriptyline
- Clomipramine
- Imipramine
- Dothiepin
- Doxepin
- Venlafaxine

Adequate antipsychotic trial

There is no consensus among experts about what constitutes an “adequate” trial. The majority agrees that treatment for 4-6 weeks (longer if dose increases are slow), achieving optimal dose and ensuring adherence would be an adequate trial.

It is expected that half to two-thirds of patients will experience a reduction in positive symptoms within three weeks at the initial dose; if not, the dose should be increased. In many countries, due to the need for hospital beds, lack of resources and the high cost of hospitalization, there is pressure on clinicians to achieve improvement or to discharge patients quickly. This often results in unnecessarily high doses of medication or a combination of drugs being used, which will not increase effectiveness but will cause more side effects, poor adherence to treatment, and poorer long term outcomes.

The patient does not get better

If after about 4 weeks at an adequate dose of antipsychotic medication there is no improvement, it would be appropriate to switch antipsychotics. Another antipsychotic from the same or a different type can be tried. A second generation antipsychotic should be the first choice in most young patients. While in general terms all antipsychotics appear to be similarly effective, some individuals may respond to some antipsychotics and not to others.

Treatment resistance

Patients who show no improvement with two adequate trials of antipsychotics are described as *treatment resistant* and should be treated with clozapine. Before concluding that a patient is treatment resistant, several issues need to be considered, namely:

- Adherence to antipsychotic medication. Up to half of the patients with schizophrenia are partially or totally non-adherent to their antipsychotic regimen. In cases of poor adherence a trial with long-acting injectable antipsychotics should be considered before using clozapine
- Engagement with and use of psychological treatments (family intervention, CBT)
- Other causes of non-response, which should be excluded: comorbid substance misuse (including alcohol), concurrent use of other prescribed medication or physical illness.

A trial of clozapine should last at least 8 weeks at a dosage from 300 to 800mg/day. If possible, clozapine levels should be obtained in cases of inadequate response. If the blood level is less than 350ng/ml, then the dosage should be increased as far as side effects are tolerated, to achieve a blood level above 350ng/ml (Buchanan et al, 2010).

A trial of clozapine should also be considered when, in spite of treatment, aggressiveness and hostility persist or if there are marked and persistent suicidal thoughts or behaviors (Buchanan et al, 2010). For further issues in the treatment with clozapine, please go to [Chapter H.5](#), page 16.

Antipsychotics and pregnancy

Antipsychotic medications cross the placenta. Neonates exposed to antipsychotic medications during the third trimester of pregnancy may be at risk for EPS and/or withdrawal symptoms following delivery. However, the current evidence is that taking antipsychotic medication during pregnancy does not independently increase risk for important short term maternal medical (e.g., gestational diabetes) and perinatal outcomes (Vigod et al, 2015).



[Click on the image to view a lecture by Dr Paddy Power on "Early intervention in psychosis" \(53:24\)](#)

ADJUNCTIVE TREATMENTS

A small proportion of people with a first episode of schizophrenia (more frequent among those with recurrent episodes) show an incomplete reduction of positive symptoms with antipsychotic monotherapy. In these patients, augmentation and adjunctive treatments are often used (Buchanan et al, 2010):

- There is no evidence that adding a second antipsychotic drug improves response (and increases the risk of unwanted effects)
- There is little evidence to support the benefit of adding lithium or anticonvulsants (e.g., carbamazepine, sodium valproate, lamotrigine) in the absence of clear bipolarity
- Benzodiazepines have been used to treat symptoms of anxiety, depression, or hostility in people with schizophrenia. There is no evidence supporting this use and there is considerable risk of dependence developing
- So far, there is insufficient evidence supporting the use of antidepressants for the treatment of co-occurring depression in schizophrenia
- ECT can be effective in reducing acute positive psychotic symptoms but shows no advantage compared with carefully chosen and administered antipsychotic medications
- Low-frequency rTMS (repetitive Transcranial Magnetic Stimulation), over the left temporoparietal cortex, has been found to be effective in the acute treatment of auditory hallucinations that have not responded to antipsychotics (Tranulis et al, 2008).
- There is growing evidence that concurrent psychotherapy, particularly CBT, is effective (NICE, 2009).

TREATMENT MAINTENANCE AND DURATION IN FIRST EPISODE PSYCHOSIS

Once psychosis has achieved a sustained remission, a slow reduction of antipsychotic medication should be tried in order to determine the minimal dose required by the patient. Maintaining antipsychotic medication reduces the risk of relapse in the early years after a first episode. Relapse is distressing, may interfere with social, family and educational/vocational outcomes, and may increase the risk of treatment resistance.

One of the most challenging issues that confront clinicians and patients is deciding for how long antipsychotic treatment should continue after a first psychotic episode. Although schizophrenia is a chronic illness, in about one quarter of the cases there is a complete recovery without further episodes (Stafford

et al, 2015). On the one hand, given the significant side effects of medication, pharmacological treatment should not be continued unless it is necessary. On the other hand, recurrence occurs in a substantial proportion of sufferers even if taking medication. The optimal duration of maintenance antipsychotic treatment to minimise the risk of recurrence remains controversial. In general, most guidelines recommend continuing treatment for 1-3 years (NICE, 2013; Royal Australian and New Zealand College of Psychiatrists, 2005). When making such a decision, clinicians should consider many factors, among others:

- The reliability of diagnosis: whether there is a high or low certainty about the diagnosis of schizophrenia
- Whether there is reasonable evidence suggesting the existence of a mood disorders (e.g., antipsychotic treatment may not need to be prolonged in cases of psychotic depression)
- The duration of the psychotic episode (e.g., if it was brief, shorter than one month, or more prolonged)
- The nature of the psychotic episode (e.g., a drug-induced psychosis)
- Whether complete recovery was achieved or whether symptoms, particularly negative symptoms, persist. Most patients with the so-called chronic schizophrenia may need lifelong medication treatment
- Patient's insight and adherence to treatment (e.g., if the patient is willing to be reviewed regularly and has a good understanding of the illness and of the initial symptoms of a recurrence)
- Presence of comorbid conditions such as depression or substance misuse
- Age at first episode (earlier onset has worse prognosis)
- Whether there have been previous episodes
- The life stage: it would be unwise to cease treatment during important life transitions (e.g., starting university) or stressful periods
- Whether there are relatives or social supports who can monitor early deterioration
- Severity of side effects of medication.

Medication should always be reduced gradually, over a period of weeks or months. Individuals who elect against advice to stop taking medication should continue to be monitored frequently and receive ongoing support. In all cases, families should be provided with continuing assistance and psychoeducation about the risks and possible manifestations of recurrence, accompanied by frequent review and support with unhindered access to early psychiatric treatment in the event of recurrence. Depression, suicide risk, substance misuse and social anxiety in the patient should be identified and actively treated.

MISUSE AND OVERUSE OF ANTIPSYCHOTICS

“Antipsychotic medication use in youth has been increasing since the mid-1990s. This development, most pronounced in the United States, has raised criticism about potential overuse because antipsychotics are prescribed mainly off-label, and their adverse effect burden for young people is worrisome [...] Who are these young people prescribed antipsychotic treatment? All signs suggest that SGA [second generation antipsychotic] use among children is chiefly in

those with aggression and behavioral dyscontrol, attention-deficit/hyperactivity disorder (ADHD), and disruptive behavior disorders (DBDs), but not for those with psychosis, bipolar mania, Tourette syndrome, or autism spectrum disorders” (Correll & Blader JC, 2015).

Misuse and overuse of antipsychotic medication in young people, often prescribed by professionals not trained in psychiatry, is becoming a growing problem globally. While antipsychotics are effective in reducing aggressive behaviours, their side effects, particularly with long-term use, are significant. Treating ADHD, disruptive behaviours, depression, and anxiety in youth with antipsychotic medications is problematic; other interventions with fewer side effects, when correctly used, can avoid the need for antipsychotic treatment (Correll & Blader JC, 2015). Frequently, antipsychotic drugs are also improperly used in people with intellectual disability.

THE COSTS OF A PSYCHOTIC EPISODE

The personal and financial costs of a psychotic episode for the sufferer, the family and society as a whole are considerable. For example, it was estimated in 2013 that the cost of treating one person with schizophrenia in the UK was £50,000 per year (NICE, 2013). Suicide rates are nearly 15% among people with schizophrenia, and their unemployment in Western countries varies between 50%-75%.

Figure H5.1.3 shows a comparison between different atypical antipsychotics and haloperidol according to the Regional Drug and Therapeutic Centre. The chart shows comparative costs of 1 year of treatment at a standard daily dose as of April 2015. Maintenance treatment in adults would usually require higher doses. In the UK a 1-month supply of haloperidol costs less than £2, compared with £100-£120 for atypical antipsychotics or £200 for clozapine.

ORGANIZATION OF SERVICES

Optimally, care for patients with a first episode of psychosis should be coordinated and individualized, provided through services that are specific for each phase of the illness (Ministry of Health, Province of British Columbia, 2010; International Early Psychosis Association Writing Group (2005). For example, minimising in-patient hospitalization during the acute phase should be a goal— young people often find their initial inpatient experience traumatizing (McGorry et al, 1991). Treatment should be provided in an outpatient setting or the home when possible. Ways to avoid hospitalization include:

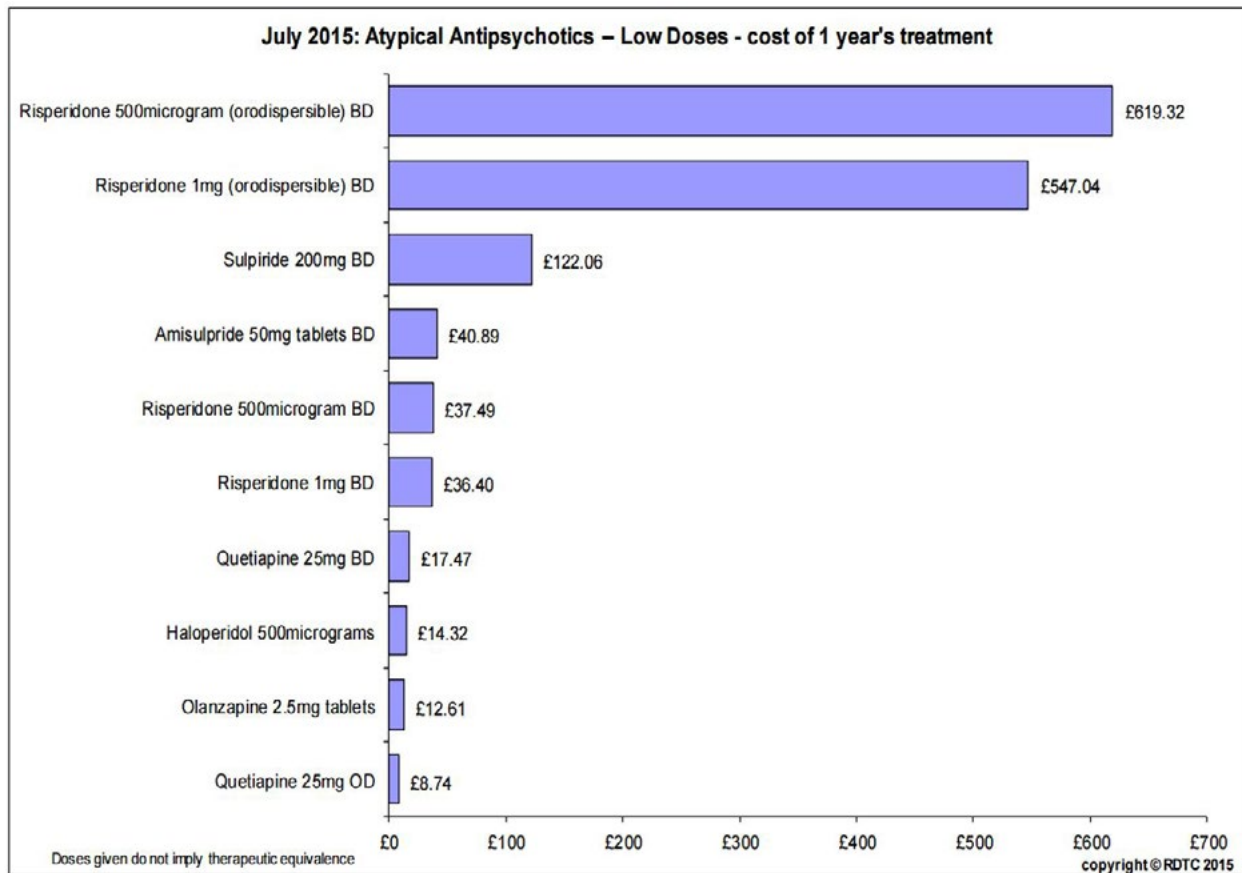
- Increasing the number of outpatient visits
- If available, outreach treatment team follow-up
- Access to emergency services when required, and
- Supported housing or residential care.

The level of intervention (inpatient, outpatient) depends largely on the degree of family, community and health services support rather than on the degree of psychopathology itself. Acute day-stay services and early intervention programs may be appropriate alternatives to in-patient care.

SEE “ONE CASE STUDY, TWO PATHWAYS” IN APPENDIX H.5.1.1

This vignette illustrates how patient’s and family’s beliefs and behaviour, bureaucratic barriers, organisation of services, and other factors impact on short and long term outcomes.

Figure H.5.1.3 Cost of atypical antipsychotics in the UK in April 2015 (according to the [UK Regional Drug and Therapeutic Centre](#))



Hospitalization may be required if there is a significant risk to self or to others, if the level of support in the community is insufficient, or if the severity of the crisis is too high for the family to manage. If the attempts to engage the youth in treatment fail and the young person remains actively psychotic, involuntary treatment should be considered according to the requirements of local mental health legislation. When hospitalization is necessary, it should be as short as possible (McGorry et al, 1991). Thus, adolescent inpatient units should be small in size and adequately staffed so that nursing of highly distressed or agitated young people is possible without locking the unit. A secure area is necessary so that care can be provided for aggressive or agitated patients without harming or disturbing others.

Early intervention programs seek to ensure continuity of care from the hospital to the community. These programs can reduce inappropriate use of emergency services or early re-hospitalization by increasing the frequency of contacts or adjusting medication dosage. Early intervention programs should also offer family education and support. The Ministry of Health Services Province of British Columbia (2010) recommends that in the first year the minimum frequency of contact with the young persons and their families should be once weekly during the acute or relapse phases; after that, once monthly. After acute symptoms

improve, it is recommended that young people not be transferred to primary care without the supervision of a specialist mental health team or professional.

FIRST EPISODE PSYCHOSIS IN RURAL COMMUNITIES AND LOW INCOME COUNTRIES

Service provision in rural areas and in low income countries differs significantly from those described. A number of issues must be considered, including:

- Geographic and demographic barriers (widely disperse rural communities, long distances to travel to access services, heterogeneity of the population)
- Limited resources (lack of trained mental health professionals in most low income countries, reduced staff and capacity of existing services, isolation of clinicians, less availability of employment, education and social opportunities for sufferers)
- Other barriers (stigma, lower tolerance of eccentricity).

These factors may result in longer duration of untreated psychosis, treatment discontinuation, higher stigma, and higher rates of alcohol and drug misuse (Welch & Welch, 2007; Kelly et al, 2007; Ministry of Health Services Province of British Columbia, 2010). These difficulties highlight the need for contemporary technologies (e.g., telemedicine), and for a close cooperation with primary care, drug and alcohol services, community supports and education (e.g., cooperation and education of elders and religious figures).

- Do you have questions?
- Comments?

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Adolescent inpatient units should be small in size and adequately staffed so that nursing of highly distressed or agitated young people is possible. A secure area is necessary so that care can be provided for aggressive or agitated patients without harming or disturbing others. Photo: ITV News

PREVENTION AND HIGH RISK FOR PSYCHOSIS

There is much interest and argument about whether young people who show some psychotic symptoms but who do not yet have a diagnosable illness can be identified and treated to prevent the development of schizophrenia. Psychotic episodes are usually preceded by a period of variable length in which a number of changes are detected—the “prodromal” phase—typically characterised by a sustained and clinically significant deterioration from the premorbid level of functioning, thinking, and behaviour. These changes include either subtle or more dramatic alterations in behaviour and emotions such as suspiciousness, social or family withdrawal, deteriorating self-care, and transient and attenuated hallucinations and delusions.

One model—the staging model—conceptualises two stages of the prodrome: a stage of mild or nonspecific psychotic symptoms, and a stage of increased symptom activity but which still does not fulfil criteria for diagnosis of a psychotic episode. This period is often called the “at risk mental state” rather than the “prodrome”, as this period can only be definitively identified as the prodrome in retrospect.

Another model seeks to identify individuals at “ultra-high risk” for psychosis. These young people would be aged 14 to 29 years and would:

- Experience positive symptoms or brief, limited, intermittent psychotic symptoms that are not severe or persistent enough to meet criteria for diagnosis of a psychotic disorder other than brief psychotic disorder, or
- Have a history of psychotic disorder or schizotypal personality disorder in a first-degree relative, and show a significant, persistent but non-specific decline in psychosocial functioning over the last year (International Early Psychosis Association Writing Group, 2005).

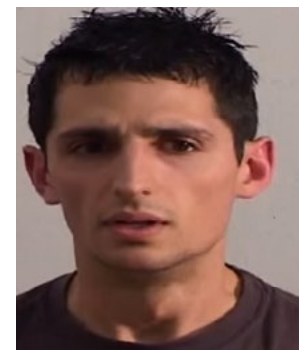
The purpose of identifying this high risk group is to prevent the development of a full-blown psychosis by early treatment. However, recent studies have found that the likelihood of transition to a full blown psychosis in this group of patients is only 16%, compared with earlier estimates of up to 60%.

A third approach focuses on the so called “basic symptoms”, such as subtle disturbances of thought, speech, and perception which may be altered years prior to the onset of frank psychosis. The Bonn Scale for the Assessment of Basic Symptoms (BSABS; Huber & Gross, 1989) has shown that presence of such basic symptoms predicts the development of schizophrenia with a probability of 70% over 10 years, while their absence excluded schizophrenia with a probability of 96%. Particular disturbances, such as thought interference, disturbances of receptive language, or visual distortions, predicted later schizophrenia with a probability of up to 91% (Klosterkotter et al, 2001). The BSABS is thought to detect individuals in an “early” prodromal phase characterized by the negative or deficit-like symptoms as well as neurocognitive deficits, while the “ultra-high risk” approach is more likely to identify youth in the late stage of the prodrome.

The possibility of a psychotic disorder should be considered in a young person who shows a deteriorating psychosocial functioning, is becoming socially withdrawn, performing worse for a sustained period at school or at work, or who is becoming more distressed or agitated without an adequate trigger. However,



[Click on the image to view a 2013 lecture by Patrick McGorry on “Early intervention for psychosis: A new architecture and culture of care” \(1:03:34\)](#)



[Click on the image to view a video clip questioning the validity of the “ultra-high risk of psychosis” model \(2 parts\)](#)

evidence of the effectiveness of different treatments, including antipsychotics, in reducing the likelihood of transition to psychosis is still lacking. Evidence is growing that psychological treatments, particularly CBT, may prevent or delay transition to psychosis in identified high risk populations. Given the limited evidence and the risks of antipsychotic treatment, the use of antipsychotics is not recommended in at risk youth. In some cases, for example if there is a rapid deterioration, severe suicide risk, or if there is severe aggression or hostility, a time-limited “therapeutic trial” may be appropriate.

A trial has shown that omega-3 fatty acid administration reduces the rate of transition from prodromal stage to a full psychotic episode (Amminger et al, 2010). Given this is a treatment with minimal side effects it is hopeful but requires replication (NICE, 2013).

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Appendix H.5.1.1

EMILY: ONE CASE STUDY, TWO PATHWAYS

This vignette intends to show how different care pathways—the result of patient’s and family’s beliefs and behaviour, bureaucratic barriers, organisation of services and other factors—may impact on short and long term outcomes.

Background

Emily is a 15 year old girl at the time of her first consultation. She had a normal birth following an uneventful pregnancy and an unremarkable early childhood, although she was regarded as intense and highly strung. She often preferred to be with her horses or boys rather than girls or her age. When she was 14, her family noticed that she was increasingly spending more time alone or with her horses and seemed preoccupied. They assumed she had had another argument with her female friends and just gave her some time and space. However, this pattern of behaviour persisted. Her parents then heard from other parents that Emily had blocked all her friends on social media and had completely stopped texting and phoning them. Emily’s parents tried to support her to rebuild some friendships by making suggestions and offering help (e.g., by driving a few of them to get a pizza or to see a film together), but Emily became irritated with her parents and told them to keep out of her life. At the end of the school term, Emily’s parents were informed by several teachers that Emily had become disorganised and disinterested, and that her academic performance had declined. None of the teaching staff were aware of conflicts with peers, on the contrary, Emily’s peers were also concerned about her and had tried to be supportive and understanding. School staff thought that there were family problems which impacted on Emily’s life. At this point, Emily’s parents also became concerned about the situation. Then, Emily told her parents that she could no longer trust them and that she might need to move to live somewhere else.

Optimal care

Due to the recent events, parents sought medical help. After a preliminary assessment, the family doctor stated that Emily could be psychotic and referred her to the child and adolescent mental health team and the early intervention in psychosis service (EIP). The EIP team assigned a support worker to spend time with Emily, at first in her bedroom, later going out for walks, and after to a café. As the worker gained Emily’s trust, she spoke about her fears—she knew that there was a plot against her. The support worker carefully validated Emily’s feelings and experiences but did not say they were real and repeatedly suggested that stress or illness might be causing some of these experiences. After 4 months of weekly or twice weekly engagement sessions Emily had a good enough relationship with her support worker to accept her suggestion that she meet some colleagues, a doctor and an occupational therapist who might be able to help her.

Emily did not allow her parents to be present at the assessment but agreed that the team could speak with them separately. After the assessment, Emily was diagnosed as having a psychotic episode. She was advised to have blood tests and an ECG and then commenced on a low dose of risperidone. Emily did not believe that this would help, but she accepted that she was struggling to cope with her current experiences and that even if medication did not help, it might not do her any harm, and she would appreciate sleeping better. After several long discussions with her support worker Emily agreed to try risperidone for 3 or 4 weeks, as long as she could stop it if she felt worse.

Two weeks after starting taking risperidone Emily's beliefs became less rigid, she began to open to alternative explanations and thought that maybe she had been affected by exam stress, and stated she had only been considering existential issues about what is reality and who controls destiny, rather than being certain of anything. She gradually started communicating more with her parents who did not challenge her as she regained insight and reframed her past behaviour, so that she did not feel humiliated. Over the next 6-8 weeks, she largely returned to be her old self and functioned better. She dropped some subjects and used the time to catch up on what she had missed in the other areas. Both Emily and her family were informed about the diagnosis, and they attended psychoeducation sessions at the EIP service.

Less optimal care

Emily refused to attend the family doctor stating that she was not unwell, and would be fine if she was "not being forced to be a part of all of this stuff". Her parents attended without her. The doctor advised that he could not help without seeing Emily, and that child and adolescent mental health team would not accept a referral unless he sent a six-page referral with consent signed by both one of the parents and Emily. He advised them to monitor for signs of cannabis use and to try and persuade Emily to come and see him at the surgery.

Her parents felt despondent after the appointment and very isolated with their worries. They continued trying to communicate with Emily, but she remained irritable and guarded in her interactions. Her self-care gradually deteriorated and she was increasingly difficult to wake up for school. Four months later, she stopped attending school altogether. She stayed in the house without going out at all for two months. However, she did not fulfil the family doctor's criteria for a home visit. When her parents contacted social services, they were advised that it was a "health issue". After another 2 months Emily made a suicide attempt ("the only way to escape from the plot against me"). Her parents found her drowsy in bed and took her to the hospital's emergency. After medical treatment of her overdose in a paediatric ward she was detained under the mental health act for treatment.

Appendix F.5.1.2

SELF-DIRECTED LEARNING EXERCISES AND SELF-ASSESSMENT

- Read the case vignette In Appendix H.5.1.1 (Emily) and write one page about the factors you believe are relevant in causing the less optimal care in the second part of the vignette.
- Find a medical record of a patient who has been treated for a first psychotic episode and comment on the quality of the care provided, specifically:
 - Were baseline tests conducted and appropriate?
 - Was the medication prescribed appropriate and why?
 - Was the patient given several concurrent medications? If yes, why?
 - Were side effects of medication reported and dealt with appropriately?
 - Would you have treated the patient differently? If yes, how and why?
- List four unjustified concerns that some medical practitioners have about long acting antipsychotic medications (answer: see pages 7 and 8).

MCQ H.5.1.1 Which one of the symptoms below is characteristic of the so called negative symptoms of schizophrenia?

- Hallucinations
- Delusions
- Illusions
- Flat affect
- Thought disorder

MCQ H.5.1.2 Which one of these neurotransmitter receptors plays the key role in schizophrenia?

- Dopamine D1
- Dopamine D2
- Muscarinic M2-4
- Serotonin 5-HT1A
- Alpha1 adrenergic

MCQ H.5.1.3 Which of the following antipsychotics is less frequently associated with weight gain?

- Olanzapine
- Quetiapine
- Aripiprazole
- Clozapine
- Haloperidol

MCQ H.5.1.4 Which of the following antipsychotics is less likely to cause extrapyramidal symptoms?

- Haloperidol
- Risperidone
- Ziprasidone
- Clozapine
- Chlorpromazine

MCQ H.5.1.5 Compared to first generation antipsychotics, second generation antipsychotics:

- A. Bind less strongly to D2 receptors
- B. Bind less strongly to 5-HT₂ receptors
- C. Do not bind to D2 receptors
- D. Do not bind to 5-HT₂ receptors
- E. Do not cause extrapyramidal side effects

MCQ H.5.1.6 Extrapyramidal symptoms are associated with D2 receptors blockade in?

- A. Mesocortical pathway
- B. Mesolimbic pathway
- C. Nigrostriatal pathway
- D. Tuberoinfundibular pathway
- E. Amygdala

MCQ H.5.1.7 What is the percentage of D2 receptor occupancy commonly associated with the antipsychotic effect?

- A. 30%-45%
- B. 45%-60%
- C. 60%-75%
- D. 75%-90%
- E. 90%-100%

MCQ H.5.1.8 Which antipsychotic has most likely to produce seizures?

- A. Risperidone
- B. Quetiapine
- C. Clozapine
- D. Olanzapine
- E. Haloperidol

MCQ H.5.1.9 Treatment resistance in schizophrenia is defined as:

- A. Patients' refusal or resistance to treatment
- B. Not showing improvement with two adequate trials of antipsychotics
- C. Not showing improvement with 2 or more antipsychotics simultaneously
- D. Not showing improvement after 4-6 weeks of treatment
- E. Not showing improvement with one antipsychotic drug and concurrent CBT

MCQ H.5.1.10 Neuroleptic malignant syndrome differs from serotonin syndrome in that patients with neuroleptic malignant syndrome show:

- A. Hyperthermia
- B. Confusion
- C. Sweating
- D. Elevated creatine phosphokinase
- E. Tachycardia

MCQ H.5.1.11 In a 6-week double-blind, randomized, placebo-controlled trial (Findling RL et al. Am J Psychiatry 2008; 165:1432-1441) 302 patients aged 13 to 17 years with a diagnosis of schizophrenia were randomly assigned to placebo or 10 or 30 mg/day of aripiprazole. Results showed that 54% of the patients taking 10 mg/day of aripiprazole and 36% on placebo had responded at 6 weeks. What is the number needed to treat (NNT)?

- A. 2
- B. 3
- C. 4
- D. 5
- E. 6

MCQ H.5.1.12 *The same study (Findling RL et al. Am J Psychiatry 2008; 165:1432-1441) showed that 58% of the patients taking 30 mg/day of aripiprazole and 36% on placebo had responded at 6 weeks. What is the number needed to treat (NNT) in this case?*

- A. 2
- B. 3
- C. 4
- D. 5
- E. 6

MCQ H.5.1.13 *Which one of these drugs is typically used in the treatment of antipsychotic-induced extrapyramidal side effects?*

- A. Anticholinergic drugs (e.g., benztropine)
- B. SSRI's (e.g., sertraline)
- C. L-dopa
- D. Naltrexone
- E. Benzodiazepines (e.g., diazepam)

ANSWERS

- MCQ H.5.1.1:** Answer: D
MCQ H.5.1.2: Answer: B
MCQ H.5.1.3: Answer: C
MCQ H.5.1.4: Answer: D
MCQ H.5.1.5: Answer: A
MCQ H.5.1.6: Answer: D
MCQ H.5.1.7: Answer: C
MCQ H.5.1.8: Answer: C
MCQ H.5.1.9: Answer: B
MCQ H.5.1.10: Answer: D
MCQ H.5.1.11: Answer: E
MCQ H.5.1.12: Answer: D
MCQ H.5.1.13: Answer: A